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EFFECTS OF BRIEF-INTENSE MODE AND ACUPUNCTURE-LIKE TENS IN THE RELIEF OF CHRONIC LOW BACK PAIN

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Abstract

Background: Transcutaneous electrical nerve stimulation (TENS) is a physical modality used in the management of pain using various treatment modes. However, the optimal mode of application for the treatment of chronic low back pain appeared not to be well studied.
Aim: The study aimed to determine and compare the effects of Brief-intense mode and Acupuncture-like TENS in the relief of chronic low back pain.
Materials and Methods: Twenty-seven (27) participants were recruited using a consecutive sampling technique. Participants were randomly allocated into three groups (Brief-intense, Acupuncture-like TENS and Control group) using simple balloting. Participants in brief-intense group and acupuncture-like TENS group received TENS treatment using different current intensities, pulse duration and frequency in addition to conventional physiotherapy treatment for low back pain. However, participants in control group received only conventional physiotherapy treatment for low back pain. Each group received treatment two times a week for six weeks. Outcome measures assessed were pain intensity and functional disability using Numerical Pain Rating Scale (NPRS) and Roland Morris Questionnaire (RMQ) respectively. Data collected at baseline, week three and six were analyzed using using one-way ANOVA and independent T test. Alpha level was set at < 0.05.
Results: There was a significant reduction in pain intensity and functional disability in the three groups across the three time frame for measurement ($p < 0.05$). However, there was no significant difference between the effects of Brief-intense mode and Acupuncture-like TENS on pain intensity and functional disability ($p > 0.05$).
Conclusion: Both modes of TENS (brief-intense group, acupuncture-like TENS) produced a significant effect in the reduction of pain as well in the improvement of functional disability in all participants with chronic low back pain. However, no one seems to be more effective than the other in the treatment of chronic low back pain.

Keywords: *low back pain, Transcutaneous electrical nerve stimulation, Brief-intense TENS*

Introduction

The low back with regards to anatomy of the human body is defined as extending from the 12th rib to the iliac crest[1]. Krismer & van Tulder[2] also referred to Low back pain as pain located between the 12th rib and the inferior gluteal folds, with or without leg pain. Back pain will affect 75–85% of persons at some point in their lives[3]. Low Back Pain (LBP) can be caused by a several factors such as: trauma, degenerative conditions, body anthropometrics, work conditions, disease conditions, posture as well as lifestyle and psychological factors. Typically, mechanical and nonspecific causes of low back pain exist. Intrinsically, the intervertebral disks, spine, or the nearby soft tissues might cause mechanical low back pain. Clinical signs which are usually referred to as red flags, can be used to spot cases of non-mechanical LBP and recommend additional testing or imaging. LBP is divided into three broad categories according to how long the symptoms last. A back pain can be referred to as acute when it has been present for not more than six weeks while sub-acute back pain usually lasts between six to twelve weeks[4] . Chronic LBP is defined as that which lasts for 12 weeks or longer[5].

LBP is an extremely common issue that most people encounter at some point in their life[6] . The burden of low back pain is increasing along with the aging and expanding populations since it is the main cause of years lost to disability worldwide[7]. LBP, which is rated as the number one cause of disability worldwide, is thought to affect adults of working age more than any other group[6]. Epidemiological data reveals that improving social and economic conditions in low and middle income countries could decrease the prevalence of LBP, as the practice of seeking for low-value healthcare among people living with LBP can lead to increase in the risk of long-term back-related disability[8]. LBP is the number one contributor to the overall burden of musculoskeletal conditions with 570 million prevalent cases worldwide, responsible for 7.4% of global years of healthy life lost to disability[9]. Some risk factors for developing low back pain include; lifting at work, Obesity, depressive symptoms and lifestyle factors such as smoking[10]. In a global review by Hoy *et al.,*[11] after accounting for methodological variability, it revealed a point prevalence of 11.9% ±2.0%, its one month prevalence was 23.2%± 2.9%, the annual prevalence was 38.0%, its overall lifetime prevalence revealed 39.9% and the mean prevalence was 31.0%± 0.6% overall. According to studies, it has been established that Africa has a 47% lifetime prevalence of LBP, a 57% one-month prevalence, and a 39%-point prevalence[12]. LBP is thought to affect between 32.5% and 73.5% of Nigerians on a yearly basis with a mean prevalence of 55.39% [13]. The occurrence of neuropathic pain in LBP is commonly estimated to be around 5%, however some research indicates that up to 16–55% of patients with chronic LBP may have potential neuropathic pain components[14] .

Transcutaneous electrical nerve stimulation (TENS) is a low-cost non-pharmacological method used to treat disorders including both acute and chronic pain[15]. Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage[16]. To trigger mechanisms that relieve pain, several TENS approaches are employed to selectively activate populations of nerve fibers. Conventional TENS with stimulation parameters such as low intensity and high frequency, Acupuncture-like TENS with stimulation parameters such as high intensity and low frequency, and Brief-intense TENS with stimulation parameters

such as high intensity and high frequency are some of the common modes TENS deliveries[17]. In a study by Melzack *et al*., [18] it was found that Transcutaneous electrical stimulation was efficient in relieving LBP when compared to therapeutic massage. According to a randomized study by Yannick *et al.,*[19] the application of acupuncture-like TENS induced a clinically significant analgesia in all participants with chronic LBP. In another randomized study by Ilhanli,[20] the application of acupuncture-like TENS induced analgesia in all participants with chronic LBP following lumbar disc herniation. However, analgesia was found to be starting earlier in treatment regimen. In a review by Flowerdew & Gadsby,[21] it was reported that there was limited statistical evidence that acupuncture-like TENS was effective in inducing analgesia in participants with chronic LBP. In a randomized trial by Ilhanli, [20] the application of brief-intense TENS mode induced analgesia in all participants with chronic LBP and lumbar disc herniation.

LBP is a widespread problem that affects millions of people worldwide. TENS is a popular non-invasive therapy for the management of chronic LBP. However, there is a lack of consensus on the most effective mode of TENS for pain relief. Specifically, there is a need to compare the effects of brief-intense TENS mode and acupuncture-like TENS mode in the relief of low back pain. This study therefore aims to address this gap in the literature by investigating and comparing the effects of Brief-intense mode of TENS and Acupuncture-like mode of TENS in the relief of low back pain. The specific objective of the study was to identify the TENS mode that would result in a more significant reduction in pain intensity and functional disability among patients with chronic low back pain.

Materials and methods

Ethical approval for this experimental study was obtained from ethical review committee of the University of Benin Teaching Hospital (UBTH) (protocol number ADM/E 22/A/VOL.VII/148301176). Participants in this study included male and female patients with a history of Low back pain who are currently being managed at the physiotherapy clinic in the University of Benin Teaching Hospital (UBTH). Participation in this study was voluntary and decision not to participate in this study had no repercussion however, the following categories of patients were excluded: patients with major mental health condition (i.e. schizophrenia), patients with skin sensation impairment and other contraindications to TENS therapy.

A simple randomization technique using simple balloting technique was used to assign participants into group A (brief-intense group), group B (Acupuncture-like TENS) and group C (control/no TENS). The sample size was determined by Cohen's table of sample size determination using power of 80% (0.80) with the effects size of 1 (d=1) while setting the alpha level at 0.05. The sample size therefore was 17 per group, while the total sample size for the 3 groups was 51. Taking 10% attrition rate into consideration, the overall total estimated sample size was 56. However, a total of 33 participants who were available and met inclusion criteria were randomly assigned into the three groups i.e (Acupuncture-like TENS group n=12, Brief intense group n=9 and the Control group n=12). 6 participants did not complete the six weeks' treatment sessions and their data were therefore excluded in the final data analysis while only 27 participants completed the six weeks' treatment sessions (Acupuncture-like

TENS n=8, Brief-intense n=9 and Control n=10).

The Numerical Pain Rating Scale (NPRS) was used to grade the pain intensity of participants while Roland Morris Questionnaire was used to evaluate their level of physical disability as a result of low back pain at baseline, week 3 and week 6 of the study.

Interventions:

Group A (Brief-intense mode): The participants were given a proper explanation on the procedure followed by proper assessment to check for contraindications to the application of TENS. Participants in this group were positioned in prone lying on a treatment couch and were treated with brief-intense mode of TENS with a pulse duration of 155μs and a frequency of 85Hz for 10 minutes, twice a week for 6 weeks as well as their conventional treatment for Low back pain which includes; manual therapy such as soft tissue mobilization, mobilization and/or manipulation of the lumbar spine, specific trunk muscle training; Infrared radiation to the low back and patient education. Data were collected using the NPRS at baseline, 3 weeks and at 6 weeks of intervention. Similarly, Roland Morris Questionnaire was used to assess level of functional disability at baseline, 3 weeks and at 6 weeks of intervention.

Group B (Acupuncture-like TENS): Similar procedure was followed as for participants in group A. However, participants in this group were treated with Acupuncture-like TENS mode with a pulse duration of 155μs, frequency of 5Hz and a tolerable level of intensity for 10 minutes, twice a week for 6 weeks as well as their conventional treatment for Low back pain which includes; manual therapy modalities such as soft tissue mobilization, mobilization and/or manipulation of the lumbar spine, specific trunk muscle training; Infrared radiation to the low back and patient education. Data were collected using the NPRS and Roland Morris Questionnaire at baseline, 3 weeks and at 6 weeks of intervention.

Group C (Control/no TENS): Participants in this group did not receive any TENS treatment, however, they were only treated with the conventional treatment for Low back pain which includes; manual therapy modalities such as soft tissue mobilization, mobilization and/or manipulation of the lumbar spine, specific trunk muscle training; Infrared radiation to the low back and patient education. Data were collected using the NPRS at baseline, 3 weeks of intervention and at 6 weeks of intervention. Using the Roland Morris Questionnaire, data were collected at baseline, 3 weeks and at 6 weeks of intervention.

Data was compared within the groups at baseline, at three weeks and at six weeks using one-way ANOVA, and compared between group using independent T test. Alpha level was set at 0.05.

Results

The main purpose of this study was to compare the effects of Acupuncture-like and brief intense TENS mode in the management of patients with Low Back Pain in the University of Benin Teaching Hospital. A total of 27 participants were recruited from the out-patient clinic of physiotherapy Department, University of Benin Teaching Hospital (UBTH).

Shown in figure 1 is the participant flow chart. 33 participants who met inclusion criteria were randomized into Acupuncture-like TENS group (12), Brief-intense TENS group (9) and Control group (12). 4 patients dropped out of Acupuncture-like group, while 2 dropped from the Brief-intense

group. A total of 27 patients with LBP completed the study.

Presented in table 1 is the sociodemographic characteristics of the participants. A total of twenty-seven (100%) patients with low back pain participated in this study. 8 (29.6%) in acupuncture like TENS group, 9 (33.33%) in brief intense TENS group and 10 (37.0%) in control group. 14 (51.90%) were males while 13 (48.10%) were female. Majority of the participants 26 (96.30%) were Christians. The most represented ethnic group in this study were Benin (22.20%). Majority of the participants 12 (44.4%) had a low back pain diagnosis of about 1 year duration.

Table 2 shows the clinical characteristics of the participants: In the acupuncture-like TENS group, the age of the participants ranged from 40 to 60 with a mean age of 51.38 ± 8.63. The mean duration of low back pain was 2.63 ± 1.59. The mean pain score of the participants at baseline, week 3 and week 6 were 6.00 ±2.83, 5.13 ± 2.85 and 3.75 ± 2.12 respectively. The mean Roland Morris Questionnaire score of the participants at baseline, week 3 and week 6 were 9.38 ± 5.99, 6.38 ± 5.15 and 7.75 ± 4.77 respectively.

In brief intense group, the age of the participants ranged from 42 to 72 with a mean age of 57.33 ± 8.88. The mean duration of low back pain was 2.33 ± 1.32. The mean pain score of the participants at baseline, week 3 and week 6 were 6.44 ±1.81, 5.22 ± 1.85 and 4.22 ± 1.64 respectively. The mean RMQ score of the participants at baseline, week 3 and week 6 were 11.33 ± 4.69, 9.77 ± 4.09 and 8.00 ± 4.00 respectively.

In the control group, the age of the participants ranged from 37 to 75 with a mean age of 50.88 ± 13.18. The mean duration of low back pain was 2.00 ± 1.33. The mean pain score of the participants at baseline, week 3 and week 6 were 4.90 ±1.59, 4.00 ± 1.41 and 2.70 ± 1.25 respectively. The mean RMQ score of the participants at baseline, week 3 and week 6 were 8.30 ± 6.52, 7.30 ± 6.25 and 6.30 ± 5.91 respectively.

Presented in table 3 is the result of One way ANOVA showing comparison between age, duration of LBP, pain rating and functional disability at baseline. The result shows, there was no significant difference in age, duration of low back pain, pain intensity and functional disability at baseline (p=0.365, p=0.649, p=0.272, and p=0.528 respectively (see Table 3).

The result of a paired t test for significance difference in pain rating scores and RMQ scores within the three groups at baseline, week 3 and week 6 of the study is as shown in table 4.

In the Acupuncture like treatment group, the results revealed a statistically significant decrease in pain scores from baseline (6.00 ± 2.83) to week 3 (5.13 ± 2.85) p =0.006. There was also a statistically significant decrease in RMQ scores from baseline (9.38 ± 5.99) to week 3 (8.37 ± 5.15) p =0.018. Similarly, between, there was a statistically significant decrease in pain scoresfrom baseline (6.00 ± 2.83) to week 6 (3.75 ± 2.12) p=<0.001 and a statistically significant decrease in RMQ scores from baseline (9.38 ± 5.99) to week 6 (7.75 ± 4.77) p=0.014.

In the brief intense treatment group, there was a statistically significant decrease in pain scores from baseline (6.44 ± 1.81) to week 3 (5.22 ± 1.85) p =0.002. There was also a statistically significant decrease in RMQ scores from baseline (11.33 ± 4.69) to week 3 (9.77 ± 4.09) p =0.001. Similarly, there was a statistically significant decrease in pain scores from baseline (6.44 ± 1.81) to week 6 (4.22 ± 1.64) p =<0.001. There was

also a statistically significant decrease in RMQ scores from baseline (11.33 ± 4.69) to week 6 (8.00 ± 4.00) p =<0.001.

In the control group, the result showed that there was a statistically significant decrease in pain scores from baseline (4.90 ± 1.59) to week 3 (4.00 ± 1.41) p =0.001. There was also a statistically significant decrease in RMQ scores from baseline (8.30 ± 6.52) to week 3 (7.30 ± 6.25) p =0.001. Between baseline and 6 weeks, there was a statistically significant decrease in pain (t=6.000, p=<0.001) and a statistically significant decrease in RMQ scores (t=11.000, p=<0.001).

Table 5 shows the result of One way ANOVA comparison of pain rating and functional disability across the three groups (acupuncture-like TENS, brief intense and control) at baseline, week 3 and 6 of the study. A one way ANOVA across group tests was conducted to explore the effect of acupuncture like TENS, Brief intense TENS and the control group on pain intensity and functional disability at baseline, week 3 and week 6. The result revealed that, there was no statistically significant difference in pain intensity scores across all the three groups at baseline, week 3 and week 6 of the treatment period (p=0.272; p=0.374; p=0.148 respectively). Furthermore, the result also revealed no statistically significant difference in functional disability scores across all three groups at baseline, week 3 and week 6 (p=0.528; p=0.601; p=0.729).
Table 6 shows result of One-way ANOVA comparing the pain and disability scores across baseline, week 3 and week 6 within the three groups. The result shows a statistically significant difference across baseline, week 3 and week 6 within the brief intense group (p=0.045) and in the control group (0.026) while there was no significant difference within the Acupuncture like treatment group across the three-time frame (p= 0.247). The result also revealed no significant statistically difference in the functional disability scores across baseline, week 3 and week 6 within the three groups. A post hoc analysis using Bonferroni analysis showed that there was a statistically significant decrease in pain rating scores between baseline and week 6 in the control group (p=0.022) and brief intense group (0.041) as shown in table 7.

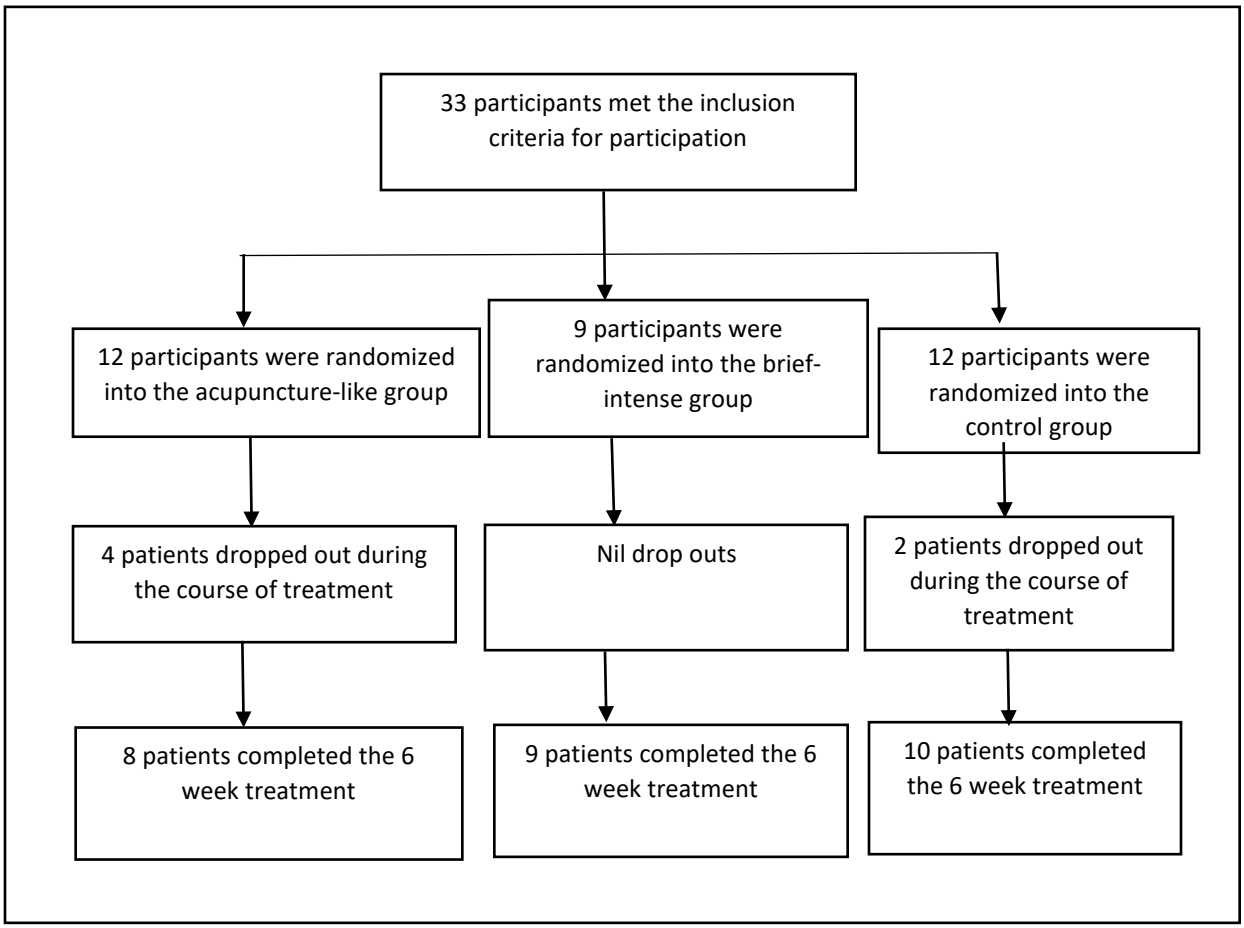

Figure 1: Participants flow chart

Table 1: Sociodemographic Data of the Participants (n=27)

Variable	Acupuncture-like TENS N (%)	Brief intense TENS N (%)	Control N(%)	Total N(%)
Gender				
Male	4(14.81)	3(11.11)	6(22.22)	14 (51.90)
Female	6(22.22)	5(18.51)	4(14.81)	13 (48.10)
Marital Status				
Single	0(0.00)	0(0.00)	3(11.11)	3 (11.10)
Married	8(29.63)	9(33.33)	7(25.93)	24 (88.90)
Religion				
Christianity	8(29.63)	8(29.63)	10(37.04)	26 (96.30)
Islam	0(0.00)	1(3.70)	0(0.00)	1 (3.70)
Ethnicity				
Benin	1(3.70)	1(3.70)	4(14.81)	6 (22.20)
Ibo	4(14.81)	4(14.81)	0(0.00)	8 (29.60)
Yoruba	1(3.70)	2(7.41)	1(3.70)	5 (18.5)
Others	2(7.41)	2(7.41)	4(14.81)	8 (29.60)
Occupation				
Civil Servant	3(11.11)	0(0.00)	1(3.70)	4 (14.81)
Business	1(3.70)	2(7.41)	2(7.41)	5 (18.52)
Retired	1(3.70)	2(7.41)	2(7.41)	5 (18.52)
Others	4(14.81)	5(18.51)	5(18.51)	14 (51.85)
Level of Education				
Primary	1(3.70)	0(0.00)	0(0.00)	1 (3.70)
Secondary	4(14.81)	3(11.11)	1(3.70)	8 (29.6)
Tertiary	5(18.51)	5(18.51)	8(29.63)	18 (66.7)
Duration of low back pain (years)				
1	3(11.11)	3(11.11)	6(22.22)	12 (44.4)
2	1(3.70)	2(7.41)	0(0.00)	3 (11.1)
3	1(3.70)	3(11.11)	2(7.41)	6 (22.2)
4	2(7.41)	0(0.00)	2(7.41)	4 (14.8)
5	1(3.70)	1(3.70)	0(0.00)	2 (7.4)

Table 2: Clinical characteristics of the Participants (n=27)

Group		Minimum	Maximum	Mean ± S.D
Acupuncture-like (n=8)	Age	40.00	63.00	51.38 ± 8.63
	Duration of LBP (years)	1.00	5.00	2.63 ± 1.59
	NPRS Baseline	2.00	10.00	6.00 ±2.83
	NPRS Week 3	1.00	9.00	5.13 ± 2.85
	NPRS Week 6	1.00	7.00	3.75 ± 2.12
	RMQ Baseline	2.00	18.00	9.38 ± 5.99
	RMQ Week 3	2.00	16.001	6.38 ± 5.15
	RMQ Week 6	2.00	15.00	7.75 ± 4.77
Brief Intense (n=9)	Age	42.00	70.00	57.33 ± 8.88
	Duration of LBP (years)	1.00	5.00	2.33 ± 1.32
	NPRS Baseline	3	9	6.44 ± 1.81
	NPRS Week 3	2	8	5.22 ± 1.85
	NPRS Week 6	1	7	4.22 ± 1.64
	RMQ Baseline	6	20	11.33 ± 4.69
	RMQ Week 3	6	17	9.77 ± 4.09
	RMQ Week 6	4	15	8.00 ± 4.00
Control (n=10)	Age	37.00	75.00	50.80 ± 13.18
	Duration of LBP (years)	1.00	4.00	2.00 ± 1.33
	NPRS Baseline	3.00	9.00	4.90 ± 1.59
	NPRS Week 3	2.00	7.00	4.00 ± 1.41
	NPRS Week 6	2.00	6.00	2.70 ± 1.25
	RMQ Baseline	3.00	22.00	8.30 ±6.52
	RMQ Week 3	2.00	21.00	7.30 ± 6.25
	RMQ Week 6	2.00	20.00	6.30 ± 5.91

Table 3: One way ANOVA showing comparison between age, duration of LBP, pain rating at baseline and functional disability at baseline (n=27)

	Acupunture Like	Brief Intense	Control	F	P value
Age	51.38 ± 8.63	57.33 ± 8.88	50.80 ± 13.18	1.051	0.365
Duration of LBP (years)	2.63 ± 1.59	2.33 ± 1.32	2.00 ± 1.33	0.440	0.649
NPRS Baseline	6.00 ±2.83	6.44 ± 1.81	4.90 ± 1.59	1.377	0.272
RMQ Baseline	9.38 ± 5.99	11.33 ± 4.69	8.30 ±6.52	0.657	0.528

Table 4: Paired t test showing the difference in pain rating scores and RMQ scores within the three groups at baseline, week 3 and week 6 of the study. (n=27)

	Baseline – Week 3 Baseline – Week 6	**Mean ± S.D**	**T value**	**p-value**
Acupuncture like (n=8)	NPRS Baseline – Week 3	0.875± 0.641	3.862	0.006*
	NPRS Baseline – Week 6	2.25 ± 0.87	7.180	<0.001*
	RMQ Baseline – Week 3	1.00 ± 0.926	3.055	0.018*
	RMQ Baseline – Week 6	1.63 ± 1.41	3.27	0.014*
Brief Intense (n=9)	NPRS Baseline – Week 3	1.22 ± 0.833	4.400	0.002*
	NPRS Baseline – Week 6	2.22 ± 0.67	10.00	<0.001*
	RMQ Baseline – Week 3	1.56 ± 0.88	5.29	0.001*
	RMQ Baseline – Week 6	3.33 ± 1.12	8.944	<0.001*
Control (n=10)	NPRS Baseline – Week 3	0.900 ± 0,57	5.014	0.001*
	NPRS Baseline – Week 6	2.00 ± 0.632	6.000	<0.001*
	RMQ Baseline – Week 3	1.00 ± 0.667	4.8743	0.001*
	RMQ Baseline – Week 6	2.00 ± 1.05	11.000	<0.001*

Table 5: One way ANOVA comparing pain rating and functional disability across the three groups (acupuncture-like TENS, brief intense and control) at baseline, week 3 and 6 of the study (N=27)

	Time frame	Acupuncture like (Mean ± S.D)	Brief Intense (Mean ± S.D)	Control (Mean ± S.D)	F	p-value
NPRS	Baseline	6.00 ±2.83	6.44 ± 1.81	4.90 ± 1.59	1.377	0.272
	Week 3	5.13 ± 2.85	5.22 ± 1.85	4.00 ± 1.41	1.026	0.374
	Week 6	3.75 ± 2.12	4.22 ± 1.64	2.70 ± 1.25	2.070	0.148
RMQ	Baseline	9.38 ± 5.99	11.33 ± 4.69	8.30 ±6.52	0.657	0.528
	Week 3	6.38 ± 5.15	9.77 ± 4.09	7.30 ± 6.25	0.521	0.601
	Week 6	7.75 ± 4.77	8.00 ± 4.00	6.30 ± 5.91	0.320	0.729

Table 6: One way ANOVA comparing pain rating and functional disability at baseline, week 3 and week 6 within acupuncture-like TENS, brief intense and control group. (N=27)

	Time frame	Acupuncture like	Brief intense	Control
NPRS	Baseline	6.00 ±2.83	6.44 ± 1.81	5.74 ± 2.12
	Week 3	5.13 ± 2.85	5.22 ± 1.85	4.74 ± 2.07
	Week 6	3.75 ± 2.12	4.22 ± 1.64	3.52 ± 1.74
	P value	0.247	0.045*	0.026*
RMQ	Baseline	9.38 ± 5.99	11.33 ± 4.69	9.63 ± 5.73
	Week 3	6.38 ± 5.15	9.77 ± 4.09	8.44 ± 5.19
	Week 6	7.75 ± 4.77	8.00 ± 4.00	7.30 ± 4.87
	P value	0.829	0.272	0.578

Table 7: Post hoc analysis using Bonferroni post hoc test showing difference in pain rating scores across baseline, week 3 and week 6 in control and brief-intense group (N=27)

		Mean Difference	Std. Error	p	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
Control (NPRS)						
Baseline	Week 3	0.8272	0.654	0.652	-0.844	2.498
	Week 6	1.949*	0.673	0.022*	0.230	3.658
Week 3	Baseline	-.8272	0.654	0.652	-2.498	0.844
	Week 6	1.122	0.688	0.344	-0.635	2.879
Week 6	Baseline	-1.949*	0.673	0.022*	-3.668	-0.230
	Week 6	-1.122	0.688	0.344	-2.879	0.6353
Brief Intense (NPRS)						
Baseline	Week 3	1.222	0.835	0.469	-0.927	3.371
	Week 6	2.222*	0.835	0.041*	0.072	4.372
Week 3	Baseline	-1.222	0.835	0.469	-3.371	0.927
	Week 6	1.000	0.851	0.729	-1.149	3.149
Week 6	Baseline	-2.222*	0.835	0.041*	-4.371	-0.007
	Week 6	1.000	0.851	0.729	-3.141	1.114

Discussion

The results of this study showed that the Brief intense mode had a significant effect in reduction of pain and functional disability in individuals with chronic LBP, similarly, the Acupuncture-like TENS mode was also found to produce a significant reduction in pain and functional disability in individuals with chronic LBP. The finding is similar to a study carried out by Rajfur *et al.,* [22] that compared the efficacy of different selected electrical therapies including TENS on chronic LBP. It reported that TENS was effective in elimination of pain and improvement of functional abilities of patients suffering from LBP, although findings of Rajfur *et al*.,[22] and the finding in this study should be compared with caution as two different TENS modes including; conventional mode and acupuncture-like TENS mode were both used concurrently in the study by Rajfur *et al.,* [22] without any distinction on which exact mode had the most effect on the participants with chronic LBP. Further, the results of a systematic review by Khadilkar *et al.,*[23] where the standard modes of TENS including; conventional, acupuncture-like, brief intense, burst mode and modulation mode were compared to placebo TENS, showed that there was conflicting evidence on the benefits of TENS in reducing LBP intensity. Again, caution should be observed when comparing the findings from the review by Khardilkar *et al*.,[23] and the finding in this study as several other standard modes of TENS were included in the study of Khardilkar et al[23].

It was observed from this study, that there was statistically significant improvement in pain rating score as well as on functional disability in all participants in the brief intense, acupuncture-like TENS and the control treatment groups. This finding is in tandem with a study carried out by Moseley[24] on the efficacy of combined physiotherapy i.e. manual therapy, specific exercise training and education in chronic LBP patients on dependent variables such as pain and functional disability as majority of the components making up the combined physiotherapy and education treatment approach were part of the treatment given to all the participants in the three different treatment groups i.e. brief-intense group, acupuncture-like TENS group and the control group. The result of the study carried out by Moseley[24] revealed that after four weeks of treatment and at follow up, there was significant improvement in pain rating scores as well as on functional disability in all participants randomized into the combined physiotherapy and education treatment group when compared to the control group.

Although, both modes of TENS were seen to be effective in the reduction of pain on the low back among participants in this study, there was no significant difference in the effect between the brief intense mode, acupuncture-like TENS mode and in the control group. This finding is in tandem with a study carried out by llhanli[20] that revealed no significant difference at the end of the treatment regimen in the effects of three modes of TENS including conventional, acupuncture-like and brief-intense modes of TENS in participants with chronic LBP following lumbar disc herniation. However, the findings of the study carried out by llhanli,[20] may not be suitable for direct comparison with the finding in this study as that of llhanli,[20] was delimited to patients diagnosed of chronic LBP following lumbar disc herniation, hence caution should be observed when comparison are being made with respect to this project. This observed insignificant difference between the effects of brief-intense mode, acupuncture-like TENS and in the control group could be

attributed to the short duration of treatment sessions adopted for treating participants in the three treatment groups i.e. brief-intense group, acupuncture-like TENS group and the control group throughout the course of the study as well as the inability to stimulate to the point of visible muscle twitching in the participants within the acupuncture-like TENS group.

Conclusion

From this study, both modes of TENS (brief-intense group, acupuncture-like TENS) proved to have statistically significant effect in the reduction of pain as well in the improvement of functional disability in all participants with chronic LBP. However, no one seems to be more effective than the other in the treatment of chronic LBP.

Recommendations

Further studies on the effect of TENS on chronic LBP should be researched into. Similar studies should also be carried out with a larger population, a longer duration, more importantly, each treatment session using the acupuncture-like TENS mode should be long enough to produce visible muscle twitching. Other standard modes of TENS should be explored in the treatment of chronic low back pain.

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Conflict of interest

The authors declare no conflict of Interest in this study.

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ELEVATED PRE-TREATMENT NEUTROPHIL-TO-LYMPHOCYTE AND NEUTROPHIL-TO-LYMPHOCYTE-PLATELET RATIOS ARE ASSOCIATED WITH A HIGH RISK OF IN-HOSPITAL DEATH AMONG PATIENTS WITH PROSTATE CANCER IN SOUTHEASTERN NIGERIA

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Abstract

Background: There is an increasing mortality rate among patients diagnosed with prostate cancer (PCa) in West Africa. To identify the causes of the high mortality rate, this study analyzed the occurrence of high-grade tumours and presence of BRCA2 gene loss. It also assessed the utility of systemic inflammatory indices as prognostic tools in low-resource settings.

Methods: This study included 72 cases of PCa diagnosed from Jan. 2017 to Dec. 2020. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelets- neutrophils-to-lymphocytes ratio (PNLR), and neutrophils-to-lymphocytes platelets ratio (NLPR) were assessed and analyzed accordingly. Significance was set at $p< 0.05$.

Results: The prevalence of Gleason grades (G) 1 to 5 was 9.3%, 16.3%, 16.3%, 25.6, and 32.6%, respectively. There was a high frequency of BRCA2 loss (58.3%) and frequency was higher among patients with G4/5 tumours (59.5%) than in patients with G1-G3 tumours (46.7%) at $p= 0.347$. A high frequency of G4/5 tumours was observed among patients within the age group of 50-59 years (n= 7/8; 87.5%) and patients with castration-resistant PCa (n= 12/17; 70.6%). The pre-treatment PLR and calcium concentration were higher among patients with G4/5 tumours compared to patients with G1-G3 tumours ($p= 0.046$ and < 0.001, respectively.) There were direct relationships between BRCA2 expression and age ($p= 0.019$), tumour grade and calcium ($p= 0.000$), BRCA2 and calcium expression ($p= 0.027$), unemployment and G4/5 ($p< 0.001$), and education status and G4/5 ($p= 0.020$). The pre-treatment NLR and NLPR were 2.0 and 4.7 times higher in in-hospital deaths than in stable discharges at $p= 0.005$ and 0.001, respectively.

Conclusion: This study revealed high frequencies of BRCA2 loss and high-grade PCa in Southeastern Nigeria. It also revealed elevated pre-treatment NLR and NLPR in cases of in-hospital death. It suggests that pre-treatment PLR could be used to identify patients with G4/5.

Keywords: *Systemic inflammation, Gleason grade, castration-resistant, calcium, BRCA2 mutation*

Introduction

Globally, prostate cancer (PCa) is the third most common cancer.[1] The odds of developing PCa are 1 in 52 and 1 in 9 for countries with low and high sociodemographic index (SDI), respectively.[2] However, the age-standardized incidence rate (ASIR) to age-standardized mortality rate (ASMR) is 2.4 times higher in countries with low SDI such as African countries than in countries with high SDI, especially countries in North America and Europe.[1] Felay et al. also reported that PCa is the most common cancer and the leading cause of cancer-related deaths among males in West Africa.[3] From 2018 and 2020, the ASIR and ASMR increased by 1.2% and 1.6% in West Africa, respectively.[1,4] The risk for developing PCa includes age, smoking, high BMI, family history of malignancy, BRCA1/2 mutations, and Lynch syndrome.[1] Although studies show that rapid disease progression and higher mortality are higher among BRCA2 mutation carriers compared with BRCA1 mutation carriers,[5,6] other reasons for the increase or variation in incidence and mortality rates are yet to be elucidated and extensively investigated. Identifying individuals at risk of death using a less invasive and affordable approach could improve the survival rates of patients diagnosed with PCa in West Africa. Inflammatory response involving neutrophils, lymphocytes and platelets plays a crucial role in tumour initiation and metastasis.[7] In Asia, high pre-treatment systemic immune inflammation indices (SIII) are associated with ethnicity, tumour type, poor overall survival, and poor progression-free survival.[8] Man and Chen also reported that high neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are associated with poor prognosis, especially among patients with metastatic castration resistance PCa.[9] In this study, to identify prognostic tools among Nigerian men, we assessed SIII in high and low-grade prostate tumours as well as in-hospital deaths and patients stable on discharge. For the first time, this study showed that NLR and NLPR could be used as prognostic tools, especially among patients with low-grade tumours.

Materials and Methods

Study Population and Ethics

This retrospective study included 72 cases of prostate cancer diagnosed from January 2017 to December 2020 at the Department of Gynaecology, Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, Nigeria. This study was approved by the NAUTH ethics committee (NAUTH/CS/66/VOL.14/VER.3/116/2021/078). The patient's medical records were accessed for socio-clinical demographics such as age, gender, comorbidities, and presentation time. Only two patients received docetaxel as platinum chemotherapy. All analyses were performed by the ethical standards in the Declaration of Helsinki.

Sample collection and handling

Two samples, 5 ml of veinous whole blood, were collected from each patient and discharged into EDTA containers: a week before the first chemotherapy and a week before discharge. Full blood counts were carried out on the whole blood samples using a Haemo-autoanalyzer. Following ultrasound investigations, biopsy, and surgery, resected tissues were sent to the Department of Morbid Anatomy and Forensic Medicine for histological investigation. Two pathologists evaluated the tissues for evidence of malignancy based on the Gleason pattern of grading (G). The total white cell count (TWBC) ($10^{\wedge 9}$/L), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelets-neutrophils to lymphocytes ratio (PNLR; [Platelet count x Neutrophil count]/Lymphocyte count), and neutrophil-to-lymphocyte-platelet ratio (NLPR; [Neutrophil count x 100]/Lymphocyte count x platelet count]) were calculated for the subgroups.

Procedure for Immunohistochemistry:

The sections were first dewaxed and hydrated. The Epitopes in sections were then retrieved. Sections were treated with peroxidase blocker and subsequently washed in phosphate Buffered Saline (PBS). The sections were treated with the primary antibody (Breast Cancer gene 2; BRCA2) for 60 minutes in a humidity chamber, washed in PBS, and treated with the secondary antibody accordingly. The slides were then washed in PBS for 2 minutes. The sections were treated with Horseradish peroxidase and washed in 2 changes of PBS. The sections were stained with 3,3′-Diaminobenzidine (1 drop in 1 ml of Substrate), washed in PBS, stained with Haematoxylin, washed in PBS, and distilled water, dehydrated, cleared, and mounted with a DPX. BRCA2 staining intensity or expression in the tissues was scored using a scale of 0, +1, +2, and +3. For BRCA2 and Iron expressions, scores 0 and +1 were considered negative (mutation) while scores +2 and +3 were considered positive.

Statistical analysis

Chi-square/Fisher was used to determine the association between the socio-clinical demographics of patients 50 years and those > 50. Pearson's correlation was used to determine the relationship between the SIII before and after the last treatment. T-test was used for comparing data of 1. Patients aged ≤ 50 years and > 50 years, 2. Chemotherapy naïve and experienced patients, 3. Patients who received 1-3 cycles and 4-6 cycles of chemotherapy, 4. Herbal medicine experience and naïve patients, and 5. Patients with and without metastatic tumours. ANOVA was used to compare data of patients who presented at ≤ 6 months and > 6 months, and patients who were stable, unstable, and dead at discharge (in-hospital death). Significance (p) was set at p≤ 0.050.

Result

Socio-clinical features of PCa cohort

In this study, the frequency of PCa peaked in the age group of 70-79 years (figure 1). The prevalence of Gleason grades 1 to 5 was 9.3%, 16.3%, 16.3%, 25.6, and 32.6%, respectively. The mean (± SD) age of patients with Gleason grades 1 to 5 was 70.3 ± 6.9, 77.3 ± 6.2, 75.6 ± 12.6, 72.8 ± 7.8, and 67.4 ± 9.8, respectively (p= 0.191). There was an inverse relationship between tumour grade and age (p= 0.108). A higher frequency of G4/5 tumours (n= 7/8; 87.5%) was observed among patients aged 50-59 years (p> 0.05). Most of the patients were self-employed, and a higher frequency of G4/5 (high-grade) tumours was observed among patients who were unemployed (p< 0.05). Most of the patients had only basic education and the frequency of high-grade PCa decreased with increasing education (p< 0.05). The frequency of G4/5 tumours was also high among patients with a history of alcohol and tobacco use, and positive for DM (p> 0.05). Patients who were positive for BRCA2 loss and herbal-experienced had a higher and a lower frequency of high-grade tumours, respectively (p> 0.05 and < 0.05). This suggests that BRCA2 loss is associated with higher grade of prostate cancer. It also suggests that a history of herbal intake reduces the risk of developing higher grade of prostate cancer.

The frequency of high-grade tumours was higher among patients who presented within 6 months of symptom manifestation (p> 0.05). Among men who had bilateral orchidectomy, the frequency of castration-resistant PCa (CRPCa) was 47.2% (17/36). A higher frequency of grade 4/5 tumours was observed among patients with CRPCa (70.6%; 12/17) compared with their castration-sensitive PCa (42.1%; 8/19) counterparts (p= 0.315). Approximately 6% of the patients received chemotherapy (table 1). The prevalence of BRCA2-negative and positive

tissues was 65.1% and 34.9%, respectively (figure 2) whereas the prevalence of calcium-negative and positive tissues was 48.7% and 51.3%, respectively. The frequency of high-grade tumours was higher than G1-G3 (low-grade) and the age of the former was lower than the latter at $p< 0.05$ and > 0.05, respectively. The expression of BRCA2 and calcium was higher in high-grade than in low-grade at $p> 0.05$ and < 0.05, respectively. The lymphocyte and platelet counts were 1.3 times and 1.2 times higher while the neutrophil count was 1.2 lower in high-grade than in low-grade tumours at $p= 0.122$, 0.342, 0.054, respectively. There were direct relationships between BRCA2 expression and age ($p= 0.019$), Calcium and age ($p= 0.281$), tumour grade and Calcium ($p= 0.000$), and BRCA2 and Calcium expressions ($p= 0.027$). Higher frequencies of BRCA2 and calcium positivity were observed in high-grade compared with low-grade at $p< 0.001$.

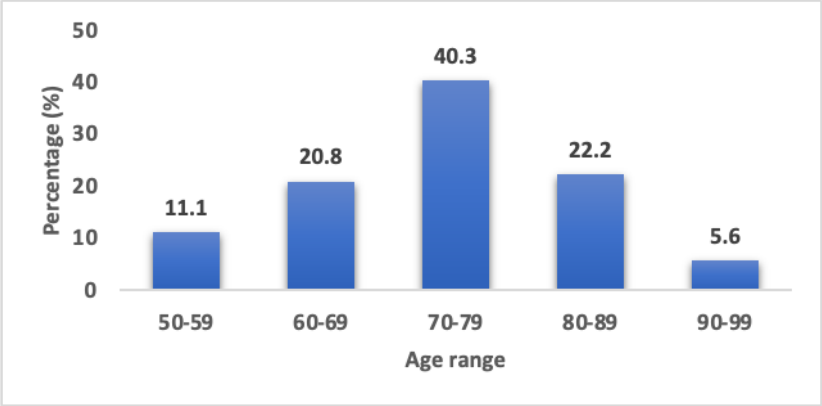

Figure 1: Frequency of prostate cancer across age groups

Figure 1 shows a high frequency of early-onset PCa among patients aged 50-59 years.

Table 1: Socio-clinical characteristics of patients diagnosed with PCa

Variables	Total N= 72	G4/5 n= 42 (%)	p- value
Level of Education:			
No formal education	10 (13.9)	7 (70.0)	0.020*
Basic education	57 (79.2)	35 (61.4)	
Tertiary education	5 (6.9)	0 (0.0)	
Employment status:			
Civil servant	19 (26.4)	3 (15.8)	< 0.001*
Self employed	40 (55.5)	29 (72.5)	
Unemployed	13 (18.1)	10 (76.9)	
Alcohol consumption:			
No	25 (34.7)	12 (48.0)	0.329
Yes	47 (65.3)	30 (63.8)	
Tobacco Use:			
No	40 (55.6)	23 (57.5)	> 0.999
Yes	32 (44.4)	19 (59.4)	
History of Hypertension:			
No	33 (45.8)	20 (60.6)	0.812
Yes	39 (54.2)	22 (56.4)	
Diabetes Mellitus			
No	54 (75)	30 (55.6)	0.582
Yes	18 (25)	12 (66.7)	
History of Herbal medicine:			
No	45 (62.5)	31 (68.9)	0.027*
Yes	27 (37.5)	11 (40.7)	
TSMP			
≤ 6 months	41 (56.9)	25 (61.0)	0.636
> 6 months	31 (43.1)	17 (54.8)	
BRCA2 loss			
No	30 (41.7)	17 (56.7)	0.815
Yes	42 (58.3)	25 (59.5)	
Chemotherapy experience:			
No	68 (94.4)	38 (55.9)	0.135
Yes	4 (5.6)	4 (100)	
Bilateral Orchidectomy			
No	36 (50.0)	19 (50.0)	0.474
Yes	36 (50.0)	23 (67.6)	

Keys:
TSMP= Time of symptom manifestation to presentation.
Descriptive analysis and Chi-square/Fisher's exact test.
*Significance was set at $p \leq 0.05$.

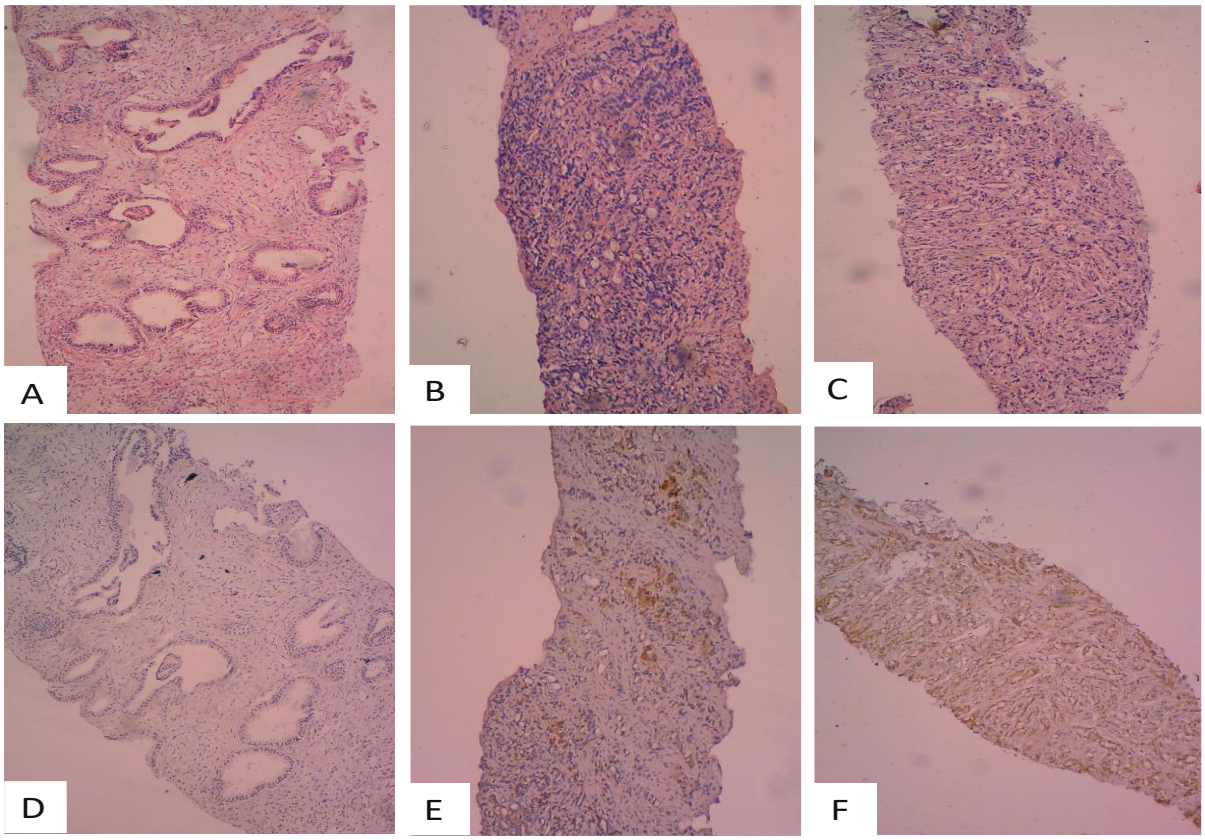

Figure 2: Sections of Prostate cancer tissues

Figures A-C were stained by the H&E technique while figures D-F were stained by the immunohistochemical technique. Figures D (control), E and F show negative, mild, and high staining intensity for BRCA2 protein, respectively. X200 magnification.

Variation of Haematological indices based on socio-clinical characteristics

The median value of NLR, PLR, PNLR, NLPR, TPSA, and %FPSA of the patients was 2.27, 123.5, 434.8, 1.29, 129.7, and 10.20, respectively while their mean ± SD was 4.22 ± 1.13, 137.2 ± 16.27, 911.5 ± 306.10, 2.36 ± 0.59, 391.10 ± 26.00, and 12.09 ± 2.26, respectively. Pre-treatment PLR was higher among patients with high-grade tumours compared to low-grade at $p< 0.05$ whereas lower pre-treatment TWBC, NLR, PNLR, and NLPR were lower among the former than the latter at $p< 0.05$, $p> 0.05$, > 0.05 and < 0.05, respectively (figure 3). The pre-treatment TWBC, PLR, NLR, PNLR, and NLPR were 1.1, 1.1, 1.2, 1.2, and 1.7 times higher among patients who presented at the clinic after 6 months of symptom manifestation compared to patients who presented within 6 months of symptom manifestation ($p> 0.05$). The pre-treatment TWBC/PLR of herbal medicine-

experienced patients was 1.2 and 1.7 times higher than that of herbal medicine-naïve patients (7.62 ± 1.27/194.2 ± 38.69 vs 6.13 ± 0.38/116.0 ± 10.83 at p= 0.161 and 0.019, respectively). The NLPR is 1.7 times higher among patients with CRPCa compared to patients with castration-sensitive PCa (0.94 ± 0.17 vs 1.59 ± 0.39, respectively; p= 0.087). The pre-treatment NLR and NLPR were 2.0 and 4.7 times higher in in-hospital deaths (IHD) than in stable discharges at p< 0.05 (table 2). Interestingly, PLR, TWBC, and PNLR were 0.8, 0.9, and 0.9 times lower in in-hospital deaths than in stable discharges (p> 0.05).

Table 2: Comparative analysis of Haematological indices based on patient's condition on discharge.

Parameters	Stable OD n= 26 Mean ± SD	In-Hospital death n= 29, Mean ± SD	p-value
TWBC (10^9/L)	8.29 ± 1.43	6.43 ± 0.34	0.266
NLR	1.84 ± 0.23	3.73 ± 0.58	0.005*
PLR	137.8 ± 15.25	106.3 ± 8.20	0.085
PNLR	470.9 ± 61.15	416.3 ± 63.32	0.543
NLPR	0.73 ± 0.13	3.44 ± 0.72	0.001*

Keys:

OD; On discharge.

Statistics: T-test and ANOVA.

*Significance was set at $p \leq 0.05$.

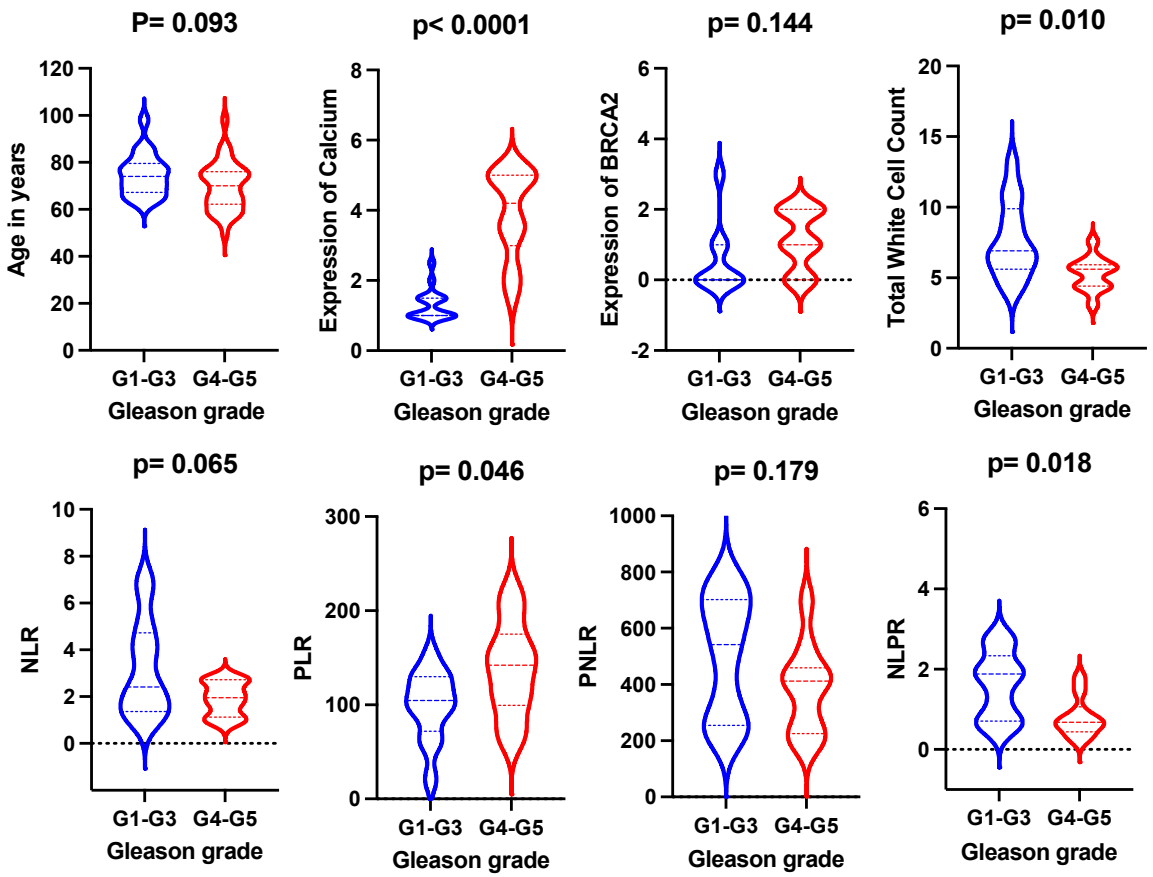

Figure 3: Comparison of age, Calcium and SIII profile based on tumour grade

Figure 3 shows a higher frequency of early-onset G4-G5 tumours marked by high PLR, and high expression of calcium and BRCA2 protein at p< 0.05, < 0.05 and > 0.05. It also revealed a high TWBC, NLR, NLPR and PNLR among patients with G1-G3 (low-grade) tumours than in patients with G4-G5 (high-grade) tumours at p< 0.05, < 0.05, < 0.05 and > 0.05, respectively.

Discussion

To identify affordable biomarkers for identifying individuals at risk of PCa-related death, this study evaluated the pre-treatment NLR, PLR, PNLR and NLPR in different clinical outcomes. The frequency of PCa in the age group of 50-59 years in this study is lower than the pooled frequency of 18.4% recorded among West African men.[2] The difference may be attributed to improved awareness and uptake of screening exercises. The frequency of high-grade tumours in this study is also higher than the pooled frequency (48.8%) earlier recorded in West Africa.[2] It is also higher than the frequencies recorded in the United States of America (USA; 13.0%) and Asia (25.3%).[10] Evidence shows that germline mutation in the BRCA2 gene is a major predictive factor of aggressive prostate cancer and poor survival.[6] This might explain why there was a higher frequency of high-grade tumours among patients with BRCA2 mutation in this study. The frequency of BRCA2 gene mutation in this study is also higher than the frequency recorded among African Americans (14.3%) and Caucasians (3.6%).[10] Taken together, the high ASMR in West Africa could be attributed to high BRCA2 mutation and high-grade tumours. It could be argued that the BRCA2 mutation was responsible for the defective calcium (Ca^{2+}) channel resulting in the high concentration of calcium in high-grade tumours.[11] The defective Ca^{2+} channel has been linked to malignant transformation, tumour proliferation, metastasis, and treatment resistance.[12] This also suggests that calcium concentration in prostate tissues could be used for solving cases of intra-observer variability.

For the first time, this study showed that NLPR could be used as a prognostic tool, especially among patients with low-grade tumours. In this study also, a high NLR was observed in IHD cases even though only 33.3% of IHD were associated with grade high-grade tumours. There was also an insignificant difference in NLR between low-grade and grade high-grade tumours. This is supported by an earlier study that did not show any significant association between the Gleason score and the pathological stage.[13] This suggests that NLR is more strongly associated with treatment outcomes than diagnosis. This is supported by two meta-analyses, which show that elevated NLR predicts poor prognosis and could be used for risk stratification among patients with PCa.[14,15] The lower PLR observed in IHD compared to stable discharge, and the high PLR among patients with high-grade tumours compared to low-grade tumours suggests PLR could be used to monitor disease progression. This is at variance with the findings of Huszno et al. who did not observe any significant association between PLR and clinicopathological factors among men with PCa in Poland.[16]

Conclusion

This study revealed a high prevalence of high-grade and aggressive PCa in Nigeria. This might be an explanation for the high mortality rate among West African men who were diagnosed with the disease. The study also revealed elevated pretreatment NLR and NLPR among patients with poor outcomes and suggests that they offer predictive advantages in low-resource settings where cancer care is borne by the patients. The study suggests that patients aged 50-59 years should be closely monitored for improved survival.

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DEVELOPMENT AND ANALYTICAL VALIDATION OF AN ENZYME–LINKED IMMUNOSORBENT ASSAY FOR THE MEASUREMENT OF SERUM S100A12 AND SERUM CALPROTECTIN IN INFLAMMATORY BOWEL DISEASE

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Abstract

Background: Inflammatory bowel disease (IBD) is characterized by prolonged symptomatic episodes of risk of relapse and remission. Current diagnosis of IBD rely heavily on use of faecal biomarkers such as faecal calprotectin (fCAL) which has been noted to have certain limitations. Quantitative determination of levels of fCAL through the application of enzyme–linked immunosorbent assay (ELISA) technique is well–established**.**

Aim: the primary goal of this study was to develop and validate S100A12 ELISA (Immunodiagnostik™ AG, Stubenwald–Allee 8a, D–64625 Bensheim, Germany) for the determination of S100A12 in serum (sA12), and to validate MRP8/14 Calprotectin S100A8/A9 ELISA (Bühlmann Laboratories AG, Baselstrasse 55, CH–4124 Schönenbuch, Switzerland) and IDK® Calprotectin ELISA (Immunodiagnostik™ AG, Stubenwald–Allee 8a, D–64625 Bensheim, Germany) for the determination of calprotectin in serum (sCAL).

Method: The assay was validated by determining sensitivity, linearity, recovery, imprecision, carry over, analytical interference and stability. A two–site sandwich enzyme–linked immunosorbent assay (ELISA) was developed and analytically validated using faecal and serum samples from healthy controls and patients presenting with inflammatory bowel disease directed against commercially available ELISA kits manufactured by Bühlmann Laboratories AG, Schönenbuch, Switzerland and Immunodiagnostik™ AG, Bensheim, Germany. To accomplish this goal, a two–site sandwich ELISA for serum S100A12 and faecal calprotectin was set up and validated by evaluating faecal S100A12 ELISA assay for

use with serum S100A12 samples, and faecal calprotectin ELISA assay for use with serum calprotectin samples.
Results: Linearity versus recovery data for BMN®-Cp (100.8 vs. 82.1%), IDK®-Cp (98.4 vs. 89.5%) and IDK®-A12 (103.7% vs. 107.8%) are within the target of between 80–120% acceptance criteria for immunoassays. %CV for intra–assay versus inter–assay variability for BMN®-Cp (3.1 vs. 3.2), IDK®-Cp (2.9 vs. 4.7) and IDK®-A12 (7.0 vs. 3.8) are <20% acceptable criteria for imprecision study.ULMR for BMN®-Cp, IDK®-Cp and IDK®-A12 were $2.4x10^6$, $2.5x10^4$ and $5.4x10^2$ ng/mL respectively. LoB versus LLoD were 577 vs. 597, 0.673 vs. 1.119 and 1.145 vs. 1.633 ng/mL for BMN®-Cp, IDK®-Cp and IDK®-A12 respectively. LoQ was 3615, 2880 and 522 ng/mL for BMN®-Cp, IDK®-Cp and IDK®-A12 respectively. No significant assay drift, carry over or instability was observed for the assays.
Conclusion: The assays described are sufficiently sensitive, linear, accurate, precise and reproducible for routine clinical laboratory application. Further studies to evaluate the clinical utility of the assays in assessing IBD are needed.
Key words: *ELISA, inflammatory bowel disease, faecal calprotectin, faecal biomarkers*

Introduction

Inflammatory bowel disease (IBD), a lifelong gastrointestinal disorder that is characterized by prolonged symptomatic episodes of risk of relapse and remission, is categorised majorly as Crohn's disease (CD) and Ulcerative colitis (UC). Unexpected frequent flare–ups and poor clinical management cast significant burden on quality of life of IBD patients.[1,2] Crohn's disease (CD) is transmural, and affects not just the colon and small intestine but any segment of the gastrointestinal tract, existing or occurring across the entire wall of any organ or blood vessel from the mouth to the anus. Ulcerative colitis (UC), however, affects only the colon and the rectum.[3–5] Inflammatory bowel disease (IBD) symptoms may include but not restricted to diarrhoea, nausea, vomiting, constipation, fever, sweats, malaise, fatigue, arthralgia, reduced appetite, abdominal pain, cramping, blood in stool and weight loss. The complications could lead to severe bleeding and dehydration, bowel obstruction, anal fissure, colon cancer, ulcers, fistulas, osteoporosis, liver disease etc.[6–8]

Current diagnosis of IBD rely heavily on results of faecal biomarkers as heterogeneous groups of biomolecules that either drip from, or are actively released by inflamed mucosal cells, activated neutrophils or fast separating cells following the divergent episodes of inflammation of the gastrointestinal tract.[1,2,9,10] S100A12 and calprotectin (S100A8/A9 heterodimer) are calcium–binding, low molecular weight S100 proteins that are predominantly expressed in activated granulocytes under conditions of chronic inflammation.[11–13] S100 protein family are soluble in 100% saturated solution of ammonium sulphate at neutral pH.[14] Both S100A12 and calprotectin, released by neutrophils in the gut of IBD patients, are pro–inflammatory proteins that trigger important extracellular activities that contribute towards immune responses.[15–17]

Faecal calprotectin (fCAL) has been used in IBD studies as the 'gold standard' against which most faecal biomarkers are

benchmarked.[1] Some studies showed that fCAL has higher sensitivity and specificity, and compared to serum C–reactive protein (CRP) and erythrocyte sedimentation rate (ESR), fCAL is consistently a better diagnostic biomarker in the assessment of IBD.[18–20] IBD may be distinguished from irritable bowel syndrome (IBS) by using fCAL and faecal S100A12 (fA12).[19] These biomarkers avoid invasive and expensive endoscopy as the latter is not required for patients with suspected IBS. However, the fact that an ideal biomarker that is simple, easy to perform, non–invasive, inexpensive, quick and reproducible is non–existent implies that relying on fCAL as the 'gold standard' is doubtful for wide application in the assessment of IBD.[15,21]

Like most biomarkers[2], fCAL is not immune to certain limitations,[20–23] lacking specificity, a validated and an optimal cut–off threshold to characterize active inflammatory disease, distinguish IBD from IBS, forecast clinical remission, mucosal healing and assess response to treatment. This encourages a default to different application of the specific assay based on clinical situations.[1,2,9] Thus, fCAL levels are dependent on age and clinical comorbidities that could vary considerably every 24 hours. The problem of significant overlap that exists in fCAL levels (50–150 µg/g) in IBD and IBS patients presents an ambiguous situation regarding the decision to refer or not to refer a patient to endoscopy. The reluctance with which patients are receptive of providing stool samples for analyses limits the robust application of fCAL in assessing intestinal inflammatory diseases.

Quantitative determination of levels of fCAL through the application of enzyme–linked immunosorbent assay (ELISA) technique is well–established[24] and commercially prepared ELISA kits are now available for routine clinical laboratory investigations. Diagnostic accuracy of these kits are still subject to manufacturers' claim to the validity of their performance characteristics which must be confirmed by a user–laboratory prior to routine use. Some variations in kit performance characteristics have been reported.[25] Immunoassays that employ monoclonal testing technology posted superior performance in terms of accuracy, imprecision, sensitivity, recovery, linearity, assay drift, stability, interference etc compared to those with polyclonal technology in screening patients to identify those with organic intestinal disease of abdominal discomfort.[25,26]

High inter–individual biological variation has been reported for levels of fCAL and there are issues of spot variability during multiple sampling from the same faecal collection.[26] These issues may be overcome by using serum samples.[11–15] However, further work is needed to ascertain whether serum may be an alternative matrix for measuring concentrations of fCAL and fA12 in assessing IBD. Therefore, the primary goal of this study was to develop and validate S100A12 ELISA (Immunodiagnostik™ AG, Stubenwald–Allee 8a, D–64625 Bensheim, Germany) for the determination of S100A12 in serum (sA12), and to validate MRP8/14 Calprotectin S100A8/A9 ELISA (Bühlmann Laboratories AG, Baselstrasse 55, CH–4124 Schönenbuch, Switzerland) and IDK® Calprotectin ELISA

(Immunodiagnostik™ AG, Stubenwald–Allee 8a, D–64625 Bensheim, Germany) for the determination of calprotectin in serum (sCAL). When validated, both sA12 and sCAL will provide a prologue for evaluating their utility as alternative biomarkers to fA12 and fCAL in current and future IBD studies.

Materials and methods

Patient recruitment and study design

Forty patients included in this study were those that presented at the twice weekly IBD Clinic at New Cross Hospital Wolverhampton, West Midlands, United Kingdom scheduled for fCAL measurement. Inclusion criteria were based on symptoms contained in the guidelines set out in New Cross Hospital's standard operating procedure for requesting fCAL measurement to exclude IBD. These are symptoms associated with long–term diarrhoea and rectal bleeding (> 6 weeks) in patients > 45 years old, unplanned weight loss, presence of abdominal or rectal mass and anaemia. Exclusion criteria were current therapy with non–steroidal anti–inflammatory drugs (NSAIDs), intestinal infection accompanied by bloody diarrhoea and clinical signs indicative of IBD and IBS.

Healthy controls (HC) were included in the study. These were twenty patients that are asymptomatic of the criteria listed above and in whom there were no chronic diseases that have been known or postulated to increase systemic concentrations of calprotectin or S100A12. HC were selected from among those requests from primary care practices scheduled for routine annual general check–up that met the exclusion criteria. In addition, their CRP results were < 4 mg/L.

Sample collection

Serum samples used in this study were obtained from patients (n = 40) who were confirmed as positive IBD cases based on the result of their fCAL assay and from HC patients (n = 20). New Cross Hospital Wolverhampton uses Bühlmann fCAL™ ELISA kit for in–house measurement of fCAL. This method reports a result of greater than one hundred microgram per gram stool (> 100 µg/g) for a positive IBD case.

Five millilitres (5 mL) of serum were collected from both patient groups for this study. Unless indicated otherwise, all serum samples were stored away at –80°C on reception until analyses on them were required. They were however, allowed to thaw slowly and equilibrate at ambient (room) temperature for at least two hours prior to being assayed for sCAL or sA12 on the Diamedix™ Dynex DS2™ Automated ELISA (DS2) System (Diamed Corporation, Hialeah, Florida, USA). Although variations in ambient temperature in the laboratory did not occur throughout the duration of this study, it was still important to define ambient temperature as 18–25°C. All serum samples used in this study met the above stated criteria.

Laboratory methods

The in–house method at New Cross Hospital Wolverhampton was used to measure fCAL. The Immunodiagnostik™ method for the determination of fA12 was adapted to measure sA12 in this study. Storage and preparation/reconstitution of reagents was performed according to manufacturers' instructions. Although the assay protocol from each kit varied slightly in terms of the wash buffer, sample/incubation buffer, incubation timings, washing steps, choice of

conjugate, substrate and stop solutions, they were nevertheless based around the same principle framework detailed in the kit inserts made available for this study by Biohit Healthcare UK Limited.

Development and Optimisation of a two–site sandwich ELISA technique

A two–site sandwich ELISA was developed. The principle of this assay allows the binding of the antigen or antibody to a solid surface or a latex particle. ELISA plates were coated with the capture antibody, and non–specific binding sites were blocked identically for all plates. First, 96–well flat–bottom ELISA plates (manufactured by Bühlmann Laboratories AG, Baselstrasse 55, CH–4124 Schönenbuch, Switzerland and Immunodiagnostik AG, Stubenwald–Allee 8a, D–64625 Bensheim, Germany) were coated with 100 microlitre (µL) per well affinity–purified monospecific anti–calprotectin/anti–S100A12 and 200 nanogram (ng) per well carbonate–bicarbonate buffer (pH 9.4). The assay was run on the DS2 System. All routine maintenance of the instrument was performed as recommended in the owner's operating manual provided by Diamed Corporation, Hialeah, Florida, USA.

The assay protocol used disposable tips for sample and reagent pipetting steps. The rest of sample loading and on–board dilution steps used 5 mL fraction collection tubes (Sarstedt Aktiengesellschaft & Co., Germany). All the results of sCAL and sA12 were reported in nanogram per millilitre serum (ng/mL). The standard and control materials were prepared by dissolving different lyophilised calprotectin and S100A12 standards (calibrators) and control materials in 500 µL of deionised water. However, Immunodiagnostik™ recommends the use of Ultra–Pure Water (Water Type 1; ISO 3696), which is free of undissolved and colloidal ions and organic molecules free of particles > 0.2 micrometre (µm) with an electrical conductivity of 0.055 µS/cm at 25°C (≥ 18.2 MΩ cm). The vial content were allowed to stand for 10 minutes at 18–25°C and mixed thoroughly by gentle inversion to ensure complete reconstitution before use.

Sample/incubation buffers supplied by Bühlmann and Immunodiagnostik™ were used for blank preparation. Serum samples of unknown concentrations of calprotectin and S100A12 were initially prepared in a 1:100 (calprotectin) and 1:10 (S100A12) dilution with sample/incubation buffer before measurement.

For calprotectin measurement using the Immunodiagnostik™ assay (IDK®-Cp), a two–step dilution process was carried out, i.e., 50 µL sample + 450 µL SAMPLE BUFFER (Cat. No. K 6935 SAMPLEBUF) = Dilution I (1:10); followed by 50 µL Dilution I + 450 µL SAMPLE BUFFER = Dilution II (1:10), to give a final dilution factor of 1:100.

For calprotectin measurement using the Buhlmann assay (BMN®-Cp), a single step dilution of 10 µL sample with 990 µL INCUBATION BUFFER (Code: B–MRP8/14–IB) gave a dilution factor of 1:100.

For S100A12 measurement using the Immunodiagnostik™ assay (IDK®-A12), a single–step dilution of 50 µL sample with 450 µL SAMPLE BUFFER (Cat. No. K 6938 SAMPLEBUF) gave a dilution factor of 1:10.

During optimization the influence of several parameters was analysed. Different concentrations of primary antibody, secondary antibody and horseradish–peroxidase–labelled streptavidin were compared. Different wash buffers and washing protocols were analysed and the effects of using different buffers to dilute the reagents were studied. Various incubation times and protocols for standards and samples were also evaluated. In the interest of space none of the results of these experiments are presented here, and only the optimized ELISA procedure is described.

Measurement of calprotectin and S100A12 in serum with ELISA technique

All the plates were set up in the same fashion. Each well of the microtitre plate was loaded with 100 µL of the designated solution. For S100A12 only, the plate was first washed 5 times with IDK® ELISA Wash Buffer (Cat. No. K 6938 WASHBUF) prior to application of standards, controls and samples. Standard (or calibrator) solutions were applied in duplicates beginning with the highest to the lowest concentration of calprotectin or S100A12 as appropriate. This was followed by application of blank samples, then two control samples with different concentrations of calprotectin (or S100A12), and finally test samples. The plates were then incubated for 40 minutes (60 minutes for S100A12 with shaking at medium speed) at 18–25°C and washed 5 cycles, plate–wise with constant timing by purging the washer with 9999 µL of IDK® ELISA Wash Buffer (Cat. No. K 6935 WASHBUF for IDK®-Cp assay and Cat. No. K 6938 WASHBUF for IDK®-A12 assay) or a 3–cycle wash, plate–wise, with constant timing by purging the washer with 3000 µL of BMN® EK–Cal Wash Buffer (Code: B–MRP8/14–WB for BMN®-Cp assay).

For the detection of captured antigen in the standards, controls and samples, microtitre plates were incubated with antibody solution containing 100 µL per microtitre well of secondary antibody–enzyme conjugate. The respective antibody–enzyme conjugate include a monoclonal detection antibody (anti–MRP8/14 Ab) conjugated to horseradish peroxidase (HRP) streptavidin for BMN® EK–Cal Enzyme Label (Code: B–MRP8/14–EL for BMN®-Cp assay), monoclonal human anti–calprotectin peroxidase–labelled conjugate (Cat. No. K 3695 CONJ for IDK®-Cp assay) and polyclonal horseradish peroxidase–labelled anti–S100A12 Ab conjugate (Cat. No. K 6938 CONJ for IDK®-A12 assay)

After incubation for 40 minutes (60 minutes for S100A12 with shaking at medium speed) at 18–25°C, the plates were washed 5 cycles as described previously and then developed for 12 minutes (14 minutes for BMN®-Cp assay with shaking at low speed) with 100 µL per well of 3,3’,5,5’–tetramethylbenzidine (TMB) dihydrochloride substrate solution in citrate buffer with hydrogen peroxide (Cat. No. K 3695 SUB for IDK®-Cp assay, Code: B–TMB for BMN®-Cp assay and Cat. No. K 3698 SUB for IDK®-A12 assay). The reaction was stopped by promptly adding to each microtitre well 100 µL of a solution of 0.25M Sulphuric Acid (Cat. No. K 3695 STOP for IDK®-Cp assay, Code: B–STS for BMN®-Cp assay and Cat. No. K 3698 STOP for IDK®-A12 assay).

Following an initial orbital shaking at medium speed that lasted three seconds, the absorbance of each well was measured immediately by the microtitre plate reader on the DS2 System at two wavelengths. Absorbance measured at 450 nm served as the primary test filter wavelength while the absorbance measured at 620 nm served as the primary reference filter wavelength. It was important that the absorbance was read within 5 minutes of developing the colour taking into consideration that the intensity of the colour change is temperature sensitive.

ELISA calibration curve representation

Standard curves were calculated with the use of a 4–parameter curve fit: $y = (A – D)/[1 + (x/C)^B] + D$, where D is the *y* value corresponding to the asymptote at high values on the *x* axis, A is the *y* value corresponding to the asymptote at low values on the *x* axis, C is the *x* value corresponding to the mid–point between A and D, and B describes how rapidly the curve makes its transition from the asymptotes in the center. All 4–parameters were calculated with an algorithm based on the Levenberg–Marquardt method (SOFTMAX PRO; Molecular Devices).

Assay working range

Samples with concentrations of the assay above the kit's measuring range (defined by the concentration range of the calibrators) were further diluted and re–assayed. The result obtained was multiplied by the dilution factor used. Samples with concentrations of the assay below the kit's measuring range cannot be clearly quantified. *However, the upper limit of the measuring range (ULMR) can be calculated as: highest concentration of the standard curve multiplied by sample dilution factor to be used while the lower limit of the measuring range (LLMR) can be calculated as: limit of the blank (LoB) multiplied by sample dilution factor to be used.*

Validation of ELISA for measurement of calprotectin and S100A12 in serum

Each assay was validated by determining sensitivity, linearity, recovery, intra– and inter–assay variability. Linearity, recovery, and intra– and inter–assay variability were determined with serum samples and calibrators provided by Immunodiagnostik™ and Bühlmann. All serum samples used for assay validation were stored at –20°C until used.

Analytical sensitivity: limit of the blank (LoB) and lower limit of detection (LLoD)

Assay sensitivity was determined by calculating the mean concentration of 10 sets of blank samples and evaluating the mean plus 2 standard deviations (i.e., mean + 2SD) on the standard curve.[27] The lower limit of the working range was defined as the sensitivity. The upper limit of the working range was determined by the apparent value of an absorbance, which equals the mean maximum absorbance minus 2SD, as determined from the mean absorbance in 10 duplicate wells containing approximately 100 µg/L of calprotectin or S100A12.

LoB is the highest analyte concentration expected to be found when replicates of a sample containing no analyte are tested.[28] LoB was derived by measuring replicates of a blank sample or dilution buffer (zero concentration of analyte) and calculating the mean result and SD. Five aliquots of sample/incubation buffer containing zero concentration of analyte (blank solution)

was each measured in duplicates (n = 10) on the same ELISA microtitre plate according to assay protocol. The mean concentration of analyte (calprotectin/S100A12) and SD was calculated and used to calculate the LoB according to the following formula: LoB = Mean($_{BLANK}$) + 2(SD_{BLANK})

LLoD was determined by using the calculated LoB and test replicates of a sample known to contain a low concentration of the analyte under consideration[28]. LLoD is estimated as the sum of the LoB and 2SD of low concentration of sample. Five aliquots of sample/incubation buffer containing zero concentration of analyte were spiked with a small known concentration of calprotectin/S100A12 taken from the manufacturer's supplied calibrators. Concentrations of calprotectin/S100A12 in the spiked samples were chosen based upon the manufacturer's claimed analytical sensitivity. These were 400, 3.9 and 0.66 ng/mL for BMN®-Cp, IDK®-Cp and IDK®-A12 assays respectively.

The spiked samples were analysed five consecutive occasions in duplicates (n = 10) on the same ELISA microtitre plate as per assay protocol used for LoB samples. Subsequently, the mean concentration of analyte and SD were calculated as described as per assay protocol used for LoB. The LLoD was calculated using the following formula: LLoD = LoB + 2($SD_{LOW\ CONCENTRATION\ OF\ SPIKED\ SAMPLE}$).

Functional sensitivity: Limit of quantitation (LoQ)

LoQ was determined as part of the imprecision experiments by evaluating the coefficient of variation expressed as a percentage (%CV) of the intra–assay and inter–assay imprecision experiments conducted with pooled HC samples and pooled serum samples from IBD patients whose concentrations of calprotectin and S100A12 were moderately and highly elevated respectively, to identify the lowest concentration of calprotectin or S100A12 at which the %CV was < 20%.

Linearity

Linearity was determined by evaluating each sample at its initial strength (1:1) and at serial dilutions of 1:2, 1:4, 1:8, 1:16, 1:32, 1:64 and 1:128.

Recovery

Recovery was determined for each assay by adding known concentrations of calprotectin or S100A12 to four (4) sample buffer aliquots in equal volumes to give the sample matrix and then each aliquot measured in duplicate runs (n = 8). Calprotectin or S100A12 was taken from the calibrators supplied by the manufacturer.

Imprecision

Intra–assay variability was determined by evaluating a minimum of 5 aliquots each of pooled serum samples from HC and IBD patients, a minimum of 10 times within the same assay run using the formular: *%CV* = (*SD/Mean*)*100, where *CV* = coefficient of variation. Inter–assay variability was determined by evaluating 2 levels of control material (low and high), aliquots of pooled serum samples (n ≥ 10) from HC and IBD patients severally (n ≥ 10) in consecutive assay runs using the formular: *%CV* = (*SD/Mean*)*100.

Assay carry over

In order to determine the concentration of calprotectin or S100A12 carried over into the blank sample (incubation or sample buffer), each of the serum samples with increased concentrations of calprotectin or S100A12 were individually placed in the microtitre well preceding the two neighbouring wells that contained the blank sample in the following sequence: HBB, where H is the serum sample with high calprotectin or high S100A12 concentration and B is the blank sample according to an established protocol.[29,30] Measurements were repeated in duplicate (n = 4). Consequently, any significant cross–contamination (carry over) of calprotectin or S100A12 between the wells during the ELISA washer–purge step and plate–wash cycle could be detected in the blank sample. Any cross contamination was regarded as being significant when the mean calprotectin or S100A12 concentration measured in the two blank replicates (i.e., BB) was greater than the previously calculated LoB for the assay.

Assay drift

To investigate assay drift, low– and high–quality control materials (supplied by ELISA kits manufacturers) used in this study were allocated to different positions at the beginning and towards the end of the microtitre plate for each particular run of calprotectin and S100A12.

Reference intervals

Reference intervals for serum calprotectin and S100A12 was not established as part of the study because enough HC ($n \geq 75$) that could meet the exclusion criteria were not recruited into the study. sCAL and sA12 values obtained in this study were compared with values obtained with previously described works.[31,32]

Statistical analysis

Data processing and statistical analyses were performed using SPSS version 26 (IBM SPSS Statistics Software, Armonk, New York, USA). Functional sensitivity was determined as the lowest concentration of calprotectin and S100A12 that could be measured with optimum reproducibility at <20%CV. fCAL assay was linear between 20 and 1932 µg/g and results <20 and >1932 µg/g were arbitrarily assigned a value of 20 and 1932 µg/g respectively, for statistical purposes. Since the data were non–parametric as determined by Kolmogorov–Smirnov (KS) and Shapiro–Wilk (SW) tests, data are expressed as medians with interquartile ranges. Spearman's rank–order coefficient of correlation (*r*) was used to measure the degree of association between variables, and *r*–values between 0.5 and 1.0 indicate a good correlation. Significant statistical relationships were defined as a *p*–value less than 0.05 (i.e., $p < 0.05$).

Result

The development of two–site sandwich ELISA resulted in a typical reproducible standard curve (figure 1). The upper limit of the measuring range for BMN®-Cp, IDK®-Cp and IDK®-A12 were 2.4 x 10^6, 2.5 x 10^4 and 5.4 x 10^2 ng/mL respectively.

Analytical sensitivity: LoB and LLoD

The calculated results of LoB and LLoD for the three assays are set out in table 1. Unlike the results of IDK®-Cp and IDK®-A12 assays, the LoB and LLoD values for BMN®-Cp assay were deliberately reported in µg/mL as against ng/mL for easy and quick comparison with the decision threshold provided by the assay manufacturer.

Functional sensitivity: LoQ

The intra–assay and inter–assay imprecision results for the moderately and highly elevated fractions for BMN®-Cp, IDK®-A12 and IDK®-Cp assays (tables 2 and 3) showed %CVs of <20%. The LoQ derived from the moderately elevated pooled concentrations were 3615 and 522 ng/mL for the BMN®-Cp and IDK®-A12 assays respectively, and from pooled HC samples to be 2880 ng/mL for the IDK®-Cp assay. All imprecision was at an acceptable %CV criterion of <20% and the LoQ > LLoD.

Linearity

The results from the serially diluted serum samples containing elevated concentration of calprotectin or S100A12 for each assay are shown in table 4. The mean of Measured to Expected ratios for linearity (n = 7) for the BMN®-Cp assay was 100.8% (range: 92.7–108.3%). For the IDK®-A12 assay, mean = 103.7% (range: 71.4 – 148.8%) and for the IDK®-Cp assay, mean = 98.4% (range: 89.2–112.3%). Linear regression was also carried out on the plot of the Expected and Measured results of the dilutions (n = 7) for each assay (figure 2). The slope, intercept and square of regression coefficient (r^2) were: 0.9390, +73.061, 0.98 (BMN®-Cp); 1.1103, –22.615, 0.98 (IDK®-Cp) and 1.5107, –20.998, 0.98 (IDK®-A12) respectively. In each case, the dilutions were linear over the range tested and the results met the >80% of target acceptance criterion for immunoassays. A summary of the linear regression fits characteristics of the assays are shown in table 5.

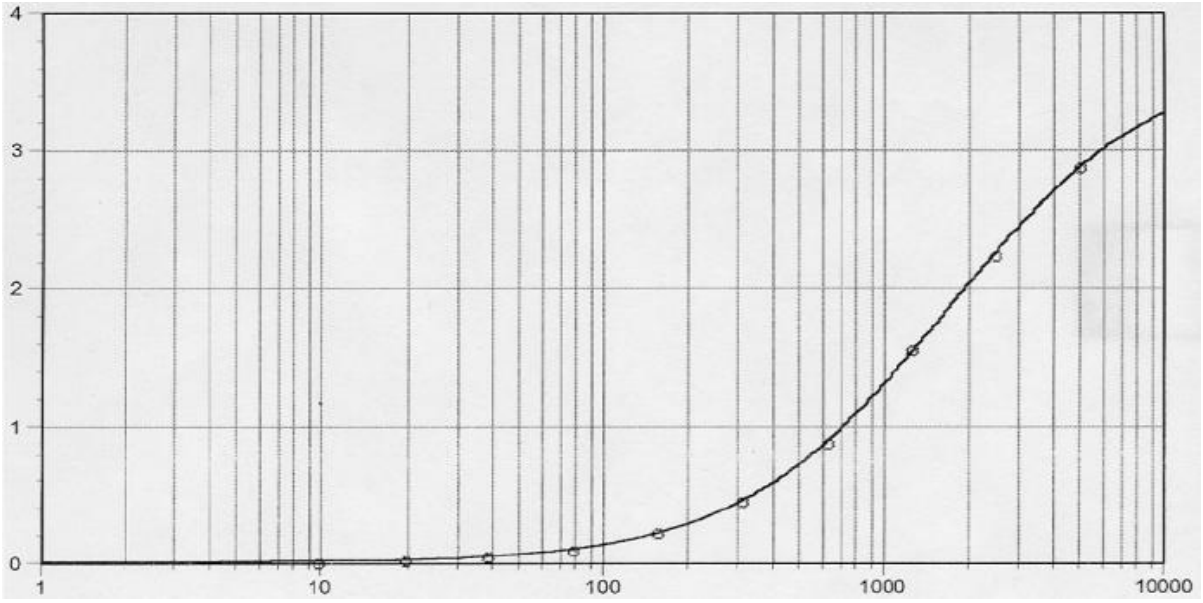


Figure 1 – A representative calibration curve for the estimation of calprotectin and S100A12 by the two–site sandwich ELISA. This method utilises two selected monoclonal antibodies that bind to human calprotectin and S100A12 respectively. The standard curve was calculated using the 4–parameter curve fit: $y = (A - D)/(1 + [x/C]^B) + D$; where A = 0.002, B = 1.055, C = 18.669 and D = 3.531. The y–axis displays the absorbance at a dual wavelength mode of 450 nm(s) and 620 nm(s). R–Squared (r^2) = 1.000

Table 1 – Analytical sensitivity data. Calculated values of the mean and SD for limit of the blank (LoB) and the lower limit of detection (LLoD); n = the number of replicates

Assay	n	Mean BLANK (S100A12 CALPROTECTIN)	SD BLANK	LoB (CALCULATED)	Mean (LOW CONC. OF SPIKED SAMPLE)	SD (LOW CONC. OF SPIKED SAMPLE)	LLoD (CALCULATED)
IDK®-A12 (ng/mL)	10	0.319	0.177	0.673	0.517	0.223	1.119
IDK®-Cp (ng/mL)	10	0.539	0.303	1.145	0.436	0.244	1.633
BMN®-Cp (µg/mL)	10	0.545	0.016	0.577	0.533	0.010	0.597

Table 2 – Intra–assay (within–batch) imprecision data for the ELISA for serum BMN®-Cp assay, IDK®-A12 and IDK®-Cp assays using pooled highly elevated IBD samples (#1), pooled moderately elevated IBD samples (#2) and pooled HC, i.e., non–IBD samples or controls (#3). * = Functional sensitivity (LoQ) for the assay indicated.

n = Number of replicates; SD = Standard Deviation; CV = Coefficient of Variation

Intra–assay Imprecision	**BMN®-Cp (ng/mL)**			**IDK®-A12 (ng/mL)**		**IDK®-Cp (ng/mL)**		
Sample #	#1	#2	#3	#1	#2	#1	#2	#3
N	10	10	10	10	10	10	10	10
Mean (ng/mL)	9691	4553	3940	1257	535	15184	3038	**2880***
SD (ng/mL)	278.8	86.3	179.4	115.8	25.8	156.1	119.9	111.3
CV (%)	2.8	1.8	4.6	9.2	4.8	1.0	3.9	3.8
Mean CV (%)	**3.1**			**7.0**		**2.9**		

Table 3 – Inter–assay (between–batch) imprecision data for the ELISA for serum BMN®-Cp, IDK®-A12 assay and IDK®-Cp assays using pooled highly elevated IBD samples (#1), pooled moderately elevated IBD samples (#2), low internal quality control (#3) and high internal quality control (#4) provided by the kit manufacturers. * = Functional sensitivity (LoQ) for the assay indicated. n = Number of replicates; SD = Standard Deviation; CV = Coefficient of Variation

Inter–assay Imprecision	**BMN®-Cp (ng/mL)**				**IDK®-A12 (ng/mL)**				**IDK®-Cp (ng/mL)**			
Sample #	#1	#2	#3	#4	#1	#2	#3	#4	#1	#2	#3	#4
N	10	10	8	8	12	12	8	8	10	10	8	8
Mean (ng/mL)	18748	**3615***	1526	5158	723	**522***	0.7	6.6	13489	2901	7.8	38.1
SD (ng/mL)	1109.9	245.9	2.2	42.7	16.6	6.1	0.1	0.5	874.8	122.4	0.3	1.5
CV (%)	5.2	6.8	0.1	0.8	2.3	1.2	4.3	7.6	6.5	4.2	4.1	3.9
Mean CV (%)	**3.2**				**3.8**				**4.7**			

Table 4 – Linearity of dilution (parallelism) data for the ELISA for serum BMN®-Cp assay, serum IDK®-A12 assay and serum IDK®-Cp assay shown for elevated concentration of neat serum at serial dilutions of 1 in 2, 1 in 4, 1 in 8, 1 in 16, 1 in 32, 1 in 64 and 1 in 128. The Measured to Expected ratios are given in %

Assay	n	Range: (Measured/Expected)*100	Mean	SD	%CV
BMN®-Cp (ng/mL)	7	92.7 – 108.3	100.8	6.2	6.1
IDK®-Cp (ng/mL)	7	89.2 – 112.3	98.4	9.3	9.4
IDK®-A12 (ng/mL)	7	71.4 – 148.8	103.7	29.6	28.6

Table 5 – A summary of the linear regression fits analysis of the results of Measured (M) and Expected (E) concentrations of serum BMN®-Cp assay (A), serum IDK®-Cp assay (B) and serum IDK®-A12 assay (C) from serial dilutions (n = 7) of the analyte for the respective ELISA kits. ¶The relationship between the Measured and Expected concentration of the analyte is expressed in the form of the equation: $y = mx + c$ where x and y represents the Expected and Measured result respectively. SEM = Standard error of the mean

Assay	Slope	Intercept	Linear Fit	Relationship of M to E	Line Equation (y = mx + c)¶	r^2	*P*	SEM
A	0.9390	+73.061	73.06 + 0.939*x*	M = 73.06 + 0.939E	y = 0.939*x* + 73.061	0.98	0.0001	68.9
B	1.5107	–20.998	–21 + 1.511*x*	M = –21 + 1.511E	y = 1.5107*x* – 20.998	0.98	0.0001	14.7
C	1.1103	–22.615	–22.62 + 1.11*x*	M = –22.62 + 1.11E	y = 1.1103*x* – 22.615	0.98	0.0001	29.9

Table 6 – Spiking recovery data for the ELISA for serum BMN®-Cp, IDK®-A12 and IDK®-Cp assays shown for 4 spiking concentrations of calprotectin and S100A12 in 4 serum matrices. The Measured to Expected ratios are given in %

Assay	n	Range: (Measured/Expected)*100	Mean	SD	%CV
BMN®-Cp (ng/mL)	4	65.5 – 95.5	82.1	10.7	13.0
IDK®-Cp (ng/mL)	4	84.7 – 93.8	89.5	3.2	3.6
IDK®-A12 (ng/mL)	4	107.7 – 155.9	126.5	18.4	14.5

Recovery

The results of recovery experiment for the assays were expressed as the ratios of Measured to Expected concentration of the analyte in the sample matrix. These are set out in table 6. The Measured to Expected ratios for recovery for the BMN®-Cp assay was: mean = 82.1%, range: 65.5–95.5%, SD: 10.7% and %CV: 13.0%. For the IDK®-Cp assay, mean = 89.5%, range: 84.7–93.8%, SD: 3.2% and %CV: 3.6%. For IDK®-A12 assay, mean = 126.5%, range: 107.7–155.9%, SD: 18.4% and %CV: 14.5%. Overall, the assays exhibited acceptable individual analytical performance judged by the mean %Recovery of 104 ± 22%. However, the BMN®-Cp assay demonstrated 65.5–68.9% under recovery at the lowest spiked concentration of 1200 ng/mL calprotectin in serum.

Intra–assay (within–run) Imprecision

The results of the intra–assay (within–run) imprecision experiment varied between 1.0 and 9.2% as set out in table 2. %CV for intra–assay variability for pooled highly elevated IBD samples, pooled moderately elevated IBD samples and pooled HC samples for the BMN®-Cp assay were 2.8, 1.8 and 4.6% respectively. %CV for intra–assay variability for pooled highly elevated IBD samples, pooled moderately elevated IBD samples and pooled normal samples for the IDK®-Cp assay were 1.0, 3.9 and 3.8% respectively. %CV for intra–assay variability for pooled highly elevated IBD samples and pooled moderately elevated IBD samples for the IDK®-A12 assay were 9.2 and 4.8% respectively. The observed mean of intra–assay imprecision for S100A12 and calprotectin was <10% for each assay: (BMN®-Cp: 3.1%; IDK®-A12: 7.0% and IDK®-Cp: 2.9%) to indicate a good performance characteristic. The IDK®-Cp assay posted the best overall intra–assay performance with a demonstrable lowest mean %CV and narrowest %CV range.

Inter–assay (between–run) Imprecision

The results of inter–assay (between–run) imprecision experiment varied between 0.1 and 7.6% as set out in table 3. %CV for inter–assay variability for pooled highly elevated IBD samples, pooled moderately elevated IBD samples, low IQC and high IQC for the BMN®-Cp assay were 5.2, 6.8, 0.1 and 0.8% respectively. %CV for inter–assay variability for pooled highly elevated IBD samples, pooled moderately elevated IBD samples, low IQC and high IQC for the IDK®-Cp assay were 6.5, 4.2, 4.1 and 3.9% respectively. %CV for inter–assay variability for pooled highly elevated IBD samples, pooled moderately elevated IBD samples, low IQC and high IQC for the IDK®-A12 assay were 2.3, 1.2, 4.3 and 7.6% respectively. The observed mean of inter–assay imprecision for S100A12 and calprotectin was <10% for each assay: (BMN®-Cp: 3.2%; IDK®-A12: 3.8% and IDK®-Cp: 4.7%) to indicate a good performance characteristic. The BMN®-Cp assay posted the best overall inter–assay performance with a demonstrable lowest mean %CV and narrowest %CV range.

Assay carry over

A significant level of assay carry over from one microtitre well to a neighbouring one is confirmed if the mean calprotectin or S100A12 levels in the blank (sample or incubation buffer) solution expressed as LoB of carry over assay (LoB^{C}) are greater than the LoB of sample or incubation buffer ($LoB^{§}$) for the particular assay. As

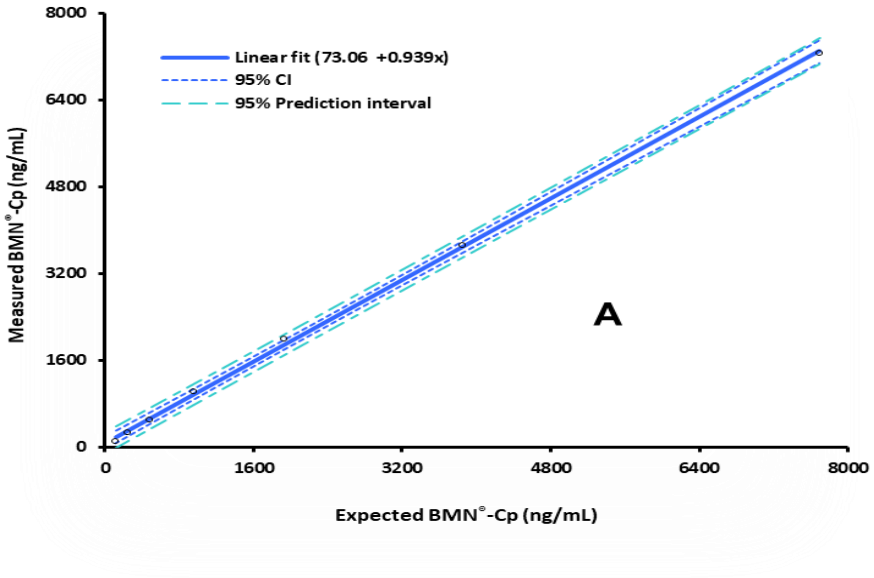
shown in table 7, no concentration of calprotectin or S100A12 was detected at or above the respective LoB[§] in the neighbouring wells that followed the elevated samples. This confirms that no significant carry over was detected (LoB[C] < LoB[§]) in the assays.

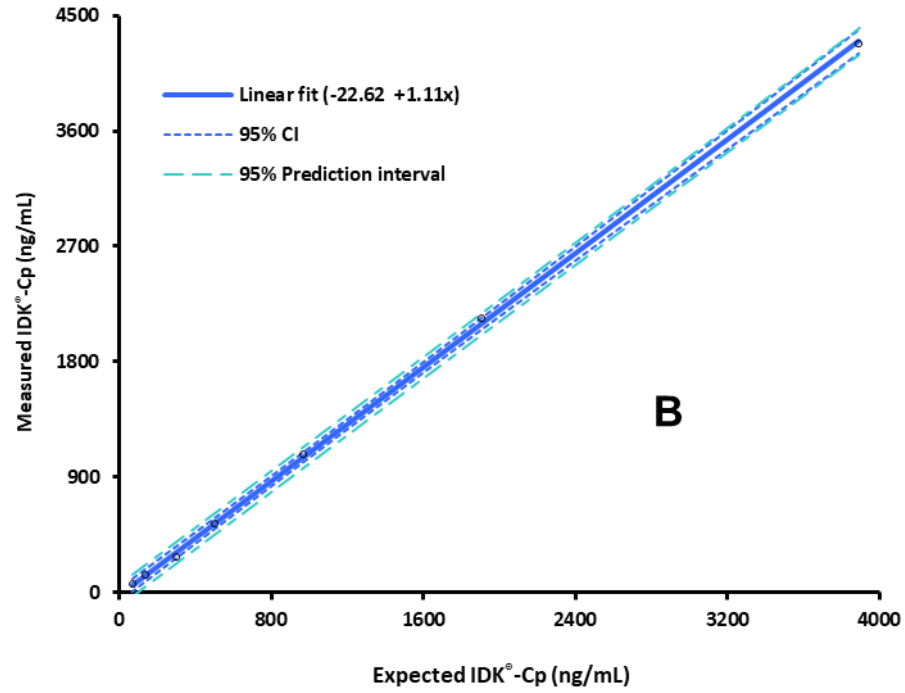
Assay drift

There was no drift in the results of both levels (low and high) control materials recorded after a particular run for calprotectin and S100A12.

Method comparison: BMN®-Cp versus IDK®-Cp

The results of the cross–kit comparison for fCAL, serum BMN®-Cp, IDK®-Cp and IDK®-A12 assays in 40 patients with IBD are presented in table 8. Median fCAL was 297 µg/g (IQR: 102–1454 µg/g). Median sCAL measured with the BMN®-Cp assay, 5428 ng/mL (IQR: 3728–8603 ng/mL) was higher (p = 0.0001) than median sCAL determined with the IDK®-Cp assay, 3254 ng/mL (IQR: 2085–4606 ng/mL). Median sA12 measured with the IDK®-A12 assay was 412 ng/mL (IQR: 321–565ng/mL). The Spearman's rank–order coefficient of correlation (r) test for non–parametric data showed close correlation between BMN®-Cp and IDK®-Cp values for the common set of 40 IBD samples (Spearman's, r^2 = 0.9852, p < 0.0001) (figure 3). The strong, positive linear correlation between the BMN®-Cp and IDK®-Cp assays is described by the line equation: $y = 1.6885x + 190.02$, where y = BMN®-Cp and x = IDK®-Cp as measured by both assays.


8000
6400
4800
3200
1600
0
Measured BMN®-Cp (ng/mL)
Linear fit (73.06 +0.939x)
95% CI
95% Prediction interval
A
0
1600
3200
4800
6400
8000
Expected BMN®-Cp (ng/mL)



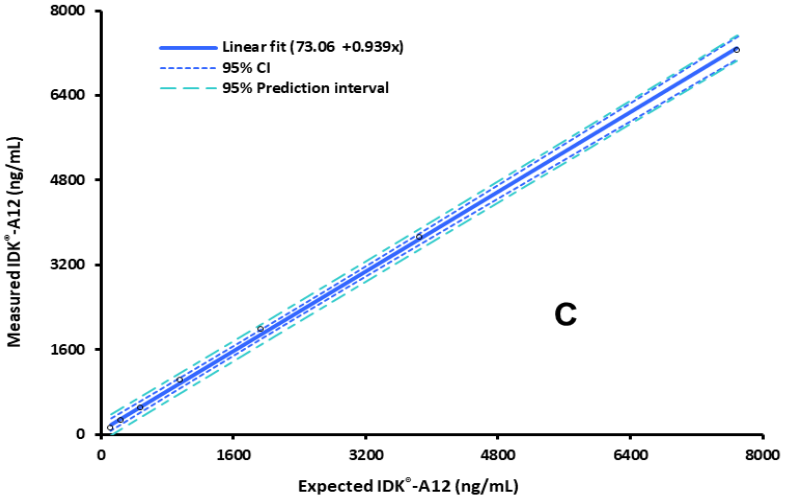


Figure 2 – Scatter plot with fit for serum BMN®-Cp, IDK®-Cp and IDK®-A12 assays. Measured and Expected results for the elevated sample dilutions (n = 7 for each assay) demonstrate reliability of:

(A) BMN®-Cp assay: 95% CI = –15.02 to 161.15 (Intercept), 0.913 to 0.965 (Slope) and t–statistic = 2.13 (Intercept), 92.00 (Slope);

(B) IDK®-Cp assay: 95% CI = –61.12 to 15.89 (Intercept), 1.09 to 1.13 (Slope) and t–statistic = –1.51 (Intercept), 125.63 (Slope);

(C) IDK®-A12 assay: 95% CI = –40 to –2 (Intercept), 1.408 to

Table 7 – Limit of the blank (calculated from sample/incubation buffer) versus limit of the blank (determined from the carry over assay). The mean concentration of serum calprotectin and serum S100A12 of low spiked sample and 'carry over blank', SD of 'carry over blank' (SD^C), their respective calculated LoB above and results. LoB^C = Limit of the Blank of carry over assay; $LoB^§$ = Limit of the Blank of sample/incubation buffer as was previously determined above for the particular assay protocol; n = the number of replicates.

Assay	n	Mean Concentration		SD^C	Calculated Value		Result
		LOW CONCENTRATION OF SPIKED SAMPLE	CARRY OVER BLANK (S100A12/CALPROTECTIN)		LoB^C	$LoB^§$	
IDK®-A12 (ng/mL)	4	0.517	0.251	0.086	0.424	0.673	$LoB^C < LoB^§$
IDK®-Cp (ng/mL)	4	0.436	0.778	0.095	0.968	1.145	$LoB^C < LoB^§$
BMN®-Cp (µg/mL)	4	0.533	0.517	0.026	0.569	0.577	$LoB^C < LoB^§$

Table 8 – Faecal calprotectin, serum calprotectin and serum S100A12 concentrations for 40 IBD patients. [a]In–house reference method. [b]Reference range supplied by kit manufacturer. [c]Reference range quoted in a published study by Larsen et al[35].

Parameters	fCAL™ (µg/g)	BMN®-Cp (ng/mL)	IDK®-Cp (ng/mL)	IDK®-A12 (ng/mL)
N	40	40	40	40
Minimum	47	1290	675	202
Maximum	1932	22743	12808	1285
Median	297	5428	3254	412
Interquartile range (IQR)	102–1454	3728–8603	2085–4606	321–565
Reference range	> 200[a]	400–3900[b]	< 3000[b]	35–1570[c]

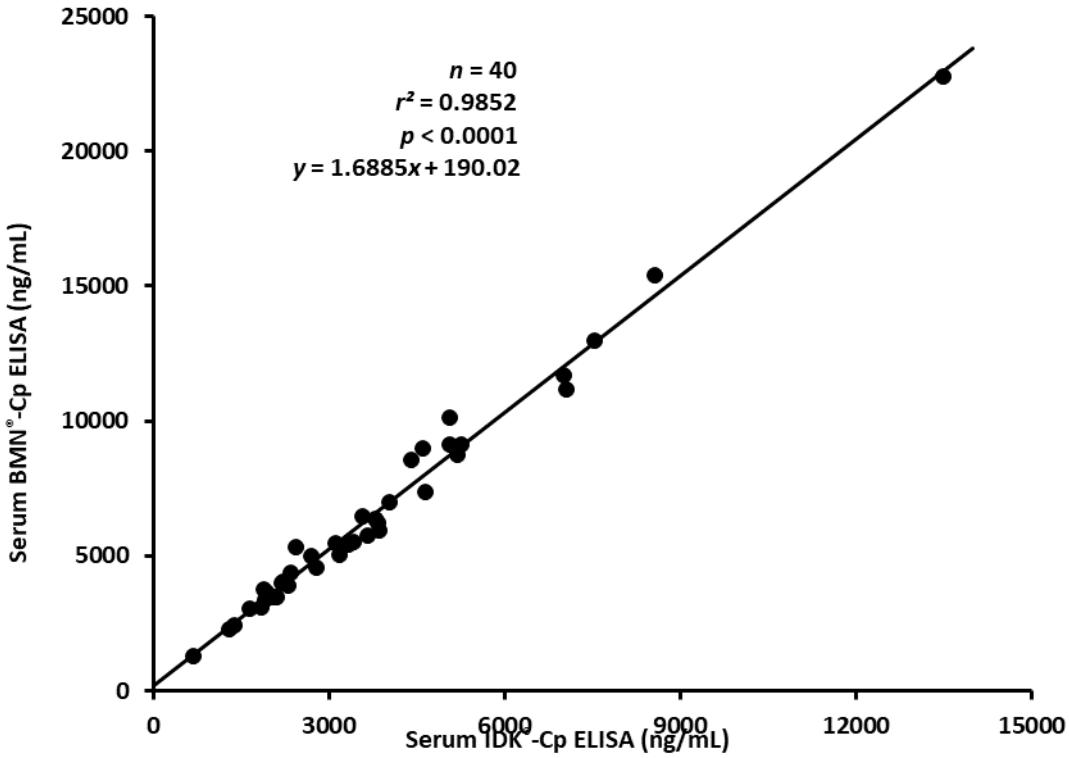


Figure 3 – Serum BMN®-Cp versus serum IDK®-Cp in IBD. Calprotectin concentrations measured in 40 serum samples from patients presenting with IBD using the IDK®-Cp ELISA (Cp^{Ω}) and the BMN®-Cp ELISA (Cp^{ϕ}). Both assays showed a strong, positive correlation (Spearman's, r^2 = 0.9852, p < 0.0001) as given by the equation of the straight line: $y = 1.6885x + 190.02$, for the data set. A gradient of 1.6885 indicates a good relationship between the two assays where Cp^{ϕ} [ng/mL] = 190 + 1.689 Cp^{Ω} [ng/mL].

Discussion

In this study, a two–site sandwich ELISA for the quantitation of sCAL and sA12 was developed, and optimised. During optimization, it was established that incubation of standards and samples with orbital shaking at low–to–medium speed did not result in much lower and more variable reactions. It may be that there was not higher density of macromolecules in serum samples than in standard solutions and that with orbital shaking at low–to–medium speed, no other macromolecules push for antigen molecules from a favourable position for antibody binding before a bond can be determined. This meant that shaking during incubation of controls, standards and samples was not discontinued.

The three assays: BMN®-Cp, IDK®-Cp and IDK®-A12 that were developed, optimised and validated for use in serum were analytically sensitive and specific, linear, precise, accurate, reproducible with a wide working range, and have the ability to discriminate between patients with or without an inflammatory disease such as IBD. All three assays demonstrated good analytical performance on validation.

It may appear counterintuitive that concentrations of sCAL measured by the BMN®-Cp and IDK®-Cp assays are significantly different. However, as noted elsewhere[27–30,33,34], immunoassay methods are not truly analytic in that different immunological procedures for the same analyte or substance could produce different results. More importantly in this study, the results from the BMN®-Cp and IDK®-Cp assays correlated closely, with a Spearman's rank–order coefficient of correlation, r^2 = 0.9852, $p < 0.0001$, indicating that both assays do evaluate the same function (figure 3).

Concentrations of sCAL measured with the BMN®-Cp assay were 1.7–fold higher than those measured with the IDK®-Cp assay. This is consistent with other studies that reported between–assay variability of ELISA kits[31,32]. Reasons for this include a possible difference in assay antibodies and assay format. The BMN®-Cp and IDK®-Cp assays use the same type of capture antibody made of monoclonal anti–human antibody. Whilst the detection antibodies are monoclonal in structure, they are however, of different origins (horse vs. human respectively) and different assay format (sandwich vs. two–site sandwich respectively). The lack of agreement in the results of sCAL determined by the BMN®-Cp and IDK®-Cp assays indicate that absolute results of sCAL are not interchangeable. The upper reference ranges of the BMN®-Cp (>3900 ng/mL) and IDK®-Cp (>3000 ng/mL) assays, however, reflect this 1.7–fold difference and therefore, sCAL results from both assays relative to their reference ranges may be usefully compared.

Measurement of S100A12 in serum was adapted from the S100A12 ELISA kit for the in–vitro determination of S100A12 in stool. Concentrations of sA12 in this study was not compared with fCAL levels as part of assay application in clinical studies of IBD since there was no reference range provided by Immunodiagnostik™ AG, Bensheim, Germany. We did not determine reference range for sA12 either as this was beyond the scope of this study. The performance characteristics of the IDK®-A12 assay was however, validated against other criteria provided by Immunodiagnostik™ AG, Bensheim, Germany.

Analytical sensitivity or LLoD for IDK®-A12 (1.119 ng/mL), IDK®-Cp (1.633 ng/mL) and BMN®-Cp (597.0 ng/mL) were calculated with a working range of 6.73 – 540 ng/mL for IDK®-A12, 114.5 – 25000 ng/mL for IDK®-Cp and 57700 – 2400000 ng/mL for BMN®-Cp. The lowest standard of 0 ng/mL, however, was not consistently detectable by IDK®-Cp and IDK®-A12 assays. The next higher standard for IDK®-Cp (3.90 ng/mL) and IDK®-A12 (0.66 ng/mL) were consistently measurable. Thus, the practical sensitivities of the assays were set at 4.0 ng/mL for IDK®-Cp and 1.0 ng/mL for IDK®-A12, and the working ranges were defined as 4 – 250 and 1 – 54 ng/mL for IDK®-Cp and IDK®-A12 respectively.

Taking into account the dilution of serum samples to a factor of 1:100 for IDK®-Cp and 1:10 for IDK®-A12, this translates into a practical working range of 400 – 25000 ng/mL (IDK®-Cp) and 10 – 540 ng/mL (IDK®-A12) for serum samples. Similarly, the lowest standard of 4 ng/mL was not consistently detectable by the BMN®-Cp assay, while the next higher standard of 12 ng/mL was consistently measurable and therefore the practical sensitivity of the BMN®-Cp assay was set at 12 ng/mL and the working range was defined as 12 – 240 ng/mL for serum samples. Considering that the serum samples were diluted to a factor of 1:100, this translates into a practical working range of 1200 – 24000 ng/mL for serum samples.

These adjusted or practical working ranges for the IDK®-Cp, IDK®-A12 and BMN®-Cp assays show a wide range suitable for routine clinical laboratory practice. The LLoD for the IDK®-Cp and BMN®-Cp assays are adequate when considered against their respective upper limit of the manufacturer's provided reference intervals (>3000 ng/mL for IDK®-Cp and >3900 ng/mL for BMN®-Cp). As previously stated, the reference interval for the IDK®-A12 assay was neither supplied by the kit manufacturer nor determined as part of the analytical validation process for the ELISA kits in this study.

The standards (calibrators) used in this study include the same lyophilised materials in five ampoules of varying concentrations of calprotectin (i.e., 0.0, 3.9, 15.6, 62.5 and 250.0 ng/mL for the IDK®-Cp assay; 0.4, 1.2, 4.0, 12.0 and 24.0 µg/mL for the BMN®-Cp assay) that had been used to calibrate the BMN®-Cp and IDK®-Cp assays, and the practical working range in this study is comparable to that reported by their respective manufacturers, making the data comparable, thus facilitating data analysis and interpretation.

Functional sensitivity or LoQ is the lowest concentration of an analyte that may be discriminated from zero with a high degree of confidence and it is reported as the lowest analyte value whose %CV is < 20.[28,33] In all cases and at an acceptable criterion of < 20 %CV, the LoQ is greater than LLoD (LoQ > LLoD). In this study, the LoQ was reported as 3615, 2880 and 522 ng/mL for the BMN®-Cp, IDK®-Cp and IDK®-A12 assays respectively, and this satisfied the 'fit for purpose' criteria of analytical methods as the corresponding values for LLoD were 597.0 , 1.633 and 1.119 ng/mL for the BMN®-Cp, IDK®-Cp and IDK®-A12 assays respectively. All three assays were linear between 840 and 15380 ng/mL, which will provide robust comparison within the analytical range of between 10 and 25000 ng/mL that cut across the linearity bracket provided by the

commercially available ELISA kit manufacturers.

A mean value of 103.7%, 98.4% and 100.8% for Measured to Expected ratios for linearity for the IDK®-A12, IDK®-Cp and BMN®-Cp assays respectively, compared favourably with the kit manufacturers provided mean data of 91.8%, 95.8% and 97.8% for the IDK®-A12, IDK®-Cp and BMN®-Cp assays respectively, and these values are within the targeted Measured to Expected ratios of between 80% – 120% acceptance criteria for immunoassays.

Measured to Expected ratios for linearity ranged from 71.4% to 148.8% for the three assays. Some values were outside the range of 80% – 120% acceptance criteria for immunoassays. The two highest values of 148.8% and 134.8% were observed for the sample with the lowest sA12 concentration of 840 ng/mL (i.e., 1:1 or neat dilution), suggesting that the IDK®-A12 assay has a limited linearity in the lower limit of the working range (i.e., 10 – 540 ng/mL). Nevertheless, for the assessment of IBD, it would be expected that sA12 values would be in the upper rather than the lower area of the working range and therefore, would not affect the clinical usefulness of sA12. In conclusion, the assays are linear within the analytical range for clinical application, with decreased linearity for extremely low and extremely high concentrations of sCAL and sA12.

Recovery for the IDK®-Cp (89.5%) and BMN®-Cp (82.1%) assays were within accepted target criteria of 80% – 120% for immunoassays. Recovery for the IDK®-A12 assay (126.5%) was acceptable even though just outside the target criteria (table 6). These recoveries compare favourably to those provided by the assay manufacturers. Recovery of calprotectin with the IDK®-Cp assay was adequate at all concentrations studied. Recovery at low concentrations of calprotectin with the BMN®-Cp assay was just outside the target criteria but acceptable because it would not affect the clinical utility of the assay in detecting inflammation due to IBD. Similarly, over–recovery of sA12 at low concentrations with the IDK®-A12 assay would not affect the clinical utility of the assay in detecting inflammation due to IBD.

It is generally recognized that intra–assay (within–run) and inter–assay (between–run) variability for immunoassay of less than 20% are acceptable. In the present study, intra–assay and inter–assay variability were all less than 10% and compared favourably to manufacturers' supplied imprecision values. This reinforces the accuracy of the three assays for clinical usefulness.

Serum samples may be haemolysed, icteric or lipaemic. The potential effects of these were not investigated but icteric, lipaemic and haemolysed samples were excluded. The assay protocols, however, require dilution of samples which may provide protection from these interferences. The shelf–life of the ELISA kit components used in this study was over 12 months of refrigerated storage. The fact that the values of the calibrator for calprotectin and S100A12 remained constant during the course of the over 12–month shelf–life of the assays indicated that the reagent and assays were stable. The effect of sample stability and repeated freeze–thaw cycles on calprotectin and S100A12 assays was not investigated in this study. Previous studies have been reported that calprotectin and S100A12 are stable in serum samples when stored frozen at –20ºC for at least 6 months.[31,32,35] However, storage at ambient

temperature may give a 6–fold or greater increase in calprotectin and S100A12 concentrations[35]. Caution must, therefore, be exercised in analysing old samples not appropriately stored. Furthermore, repeated freeze–thaw cycles did not alter the analytes concentrations in blood[35]. This was supported from good inter–assay (between–run) imprecision reported in this study.

A limiting factor in the evaluation of performance characteristics of the assays was the smaller than desired number of samples available for measuring sCAL and sA12, and high ELISA kit costs. All assays, however, were fully validated for the quantitation of sCAL and sA12, and showed good performance characteristics that compared favourably with assay parameters of commercially prepared kits. Linearity, recovery and imprecision studies indicate the assays to be linear, accurate and reproducible. Due to unavailability of calprotectin and S100A12 analogues, analytical specificity of the ELISA kits for calprotectin and S100A12 assays could only be demonstrated by linearity and recovery of calprotectin and S100A12. However, as more S100 protein family and/or analogues may become available in future, analytical specificity of calprotectin and S100A12 ELISA assays may need to be further evaluated.

Conclusion

This study has shown that the BMN®-Cp, IDK®-Cp and IDK®-A12 assays are suitable serum assays for routine application in a clinical laboratory. The performance characteristics were robust and sensitive from LoB, LLoD or LoQ and carry over studies. The three assays are reliable from the results of imprecision, reproducibility, recovery and linearity experiments, and compared favourably to manufacturer's provided performance characteristics. The large difference in numerical values between sCAL concentrations measured with the BMN®-Cp and IDK®-Cp assays indicate that the results and any derived cut–offs between the assays are not directly inter–changeable. Further studies are required to evaluate the clinical utility of the validated BMN®-Cp, IDK®-Cp and IDK®-A12 assays in serum in the assessment of inflammatory disorders, in particular IBD.

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KNOWLEDGE OF THE MANAGEMENT OF EXTRAPYRAMIDAL SYNDROMES OF NEUROLEPTIC DRUGS AMONG NURSES IN NEUROPSYCHIATRIC HOSPITALS OF ANAMBRA AND ENUGU STATES

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Abstract

Background: Many patients on antipsychotic medication have reported experiencing Extrapyramidal Syndrome (EPS). Due to high rate of EPS developed in patients, antipsychotic medication guideline and rating scale were developed for the management of EPS while caring for patients on antipsychotic drugs.

Aim: The aim of this study was to determine the knowledge and management of Extrapyramidal syndrome of Neuroleptic Drugs among Nurses in Neuropsychiatric Hospitals of Anambra and Enugu State**.**

Materials and methods: A descriptive cross-sectional survey was carried out among 221 Nurses from Neuropsychiatric Hospital in Anambra State and Federal Neuropsychiatric Hospital in Enugu state. Data was collected using questionnaire adopted from a similar study. The data was summarized frequencies, percentages and Chi-square with level of significance set at < 0.05.

Results: More than half of the nurses in Federal Neuropsychiatric Hospital Enugu 164 (83.25%) had good knowledge of EPS, while 14 (66.67%) of Nurses in Neuropsychiatric Hospital Anambra State also had good knowledge of EPS and its management. While 197 (100%) and 21 (100%) in Federal Neuropsychiatric Hospital Enugu and Neuropsychiatric Hospital Nawfia Anambra respectively agreed that their hospitals had no policy/guideline for EPS management. There was a significant association between years of working as a registered nurse (p=<0.001), current grade level (p=0.001) and knowledge of EPS among nurses.

Conclusion: Most of the participants had good knowledge of Extrapyramidal Syndrome; none of them used American Association guideline and rating scale in management of EPS.

Recommendation: As EPS continues to pose problem to psychiatric patients, nurses who are the ones administrating these medications need to adopt the standard guidelines stated for management of EPS to ensure its reduction.

Keywords: *Extrapyramidal Syndrome, Knowledge, Management, Psychiatric patients, Antipsychotics, Nurses*

Introduction

Extrapyramidal Syndrome have been identified as a medical and societal issue facing patients taking antipsychotic therapy[1]. All hope is placed on antipsychotic drugs because of the debilitating characteristics of the condition, the fundamental issue with these medications is their propensity to have extremely negative effects to the point that it can make it difficult to understand why they were prescribed in the first place. These undesired effects have an impact on the patients' motor skills, daily living activities, social functioning, loss of employment, re-hospitalization and finally make them dependent on their family members[1]. There are several strategies of administering antipsychotics to patients that will help to reduce the development of EPS and these involve the of a rating scale, World Health Organisation (WHO) guidelines, and use of American Psychiatric Association Guideline [2,3]

Studies suggest that nurses generally lack adequate pharmacological knowledge and this has frequently resulted in suboptimal care to patients[4]. Medication errors had been made by 64.55% of nurses[5]. Begum et al.,[6] assessed the antipsychotic medication side effects knowledge amongst registered mental health nurses in England and found that many nurses had a suboptimal working knowledge of antipsychotic medication side effects which has the potential to compromise care. Stomski[7] revealed that only one quarter of the respondents (26.5%) studied were currently using an assessment tool to identify antipsychotic medication side effects by nurses. However, in Nigeria, there are limited studies with regards to the knowledge and management of Extrapyramidal syndrome of Neuroleptic drugs among nurses[5]. Nurses spend most of their clinical time with patients, therefore must possess a wealth of knowledge and competencies while caring for the psychiatric patients. However, it is disheartening to note that psychiatric patients come up with EPS under the nurses' watch. Therefore, this study aimed to assess the knowledge and management of EPS of neuroleptic drugs among nurses in Neuropsychiatric hospitals of Anambra and Enugu States, southeastern Nigeria.

Materials and methods

Study design: A cross descriptive design was adopted for the study. This was used to assess the Knowledge and management of Extrapyramidal syndrome of Neuroleptic drugs among nurses in Neuropsychiatric hospitals of Anambra and Enugu States.

Study setting: The study was conducted at Neuropsychiatric Hospital Nawfia Anambra State and Federal Neuropsychiatric Hospital Enugu. The first hospital is a state government-owned institution while the latter is a Federal institution located in the two different states, in the South –East geopolitical zone of Nigeria.

Population for the study: The target population consisted of all registered nurses practicing at Neuropsychiatric Hospital Nawfia Anambra State and Federal Neuropsychiatric Hospital Enugu. The total number of registered nurses in Neuropsychiatric Hospital Nawfia Anambra was 21 (Nurses'

Annual Report, 2022) while the number of nurses in Federal Neuropsychiatric Hospital Enugu was 200 (Nurses' Annual Report, 2022). The study involved the total population; thus, there was no sampling carried out. All the 221 Nurses in both hospitals were recruited for the study.

Instrument for Data Collection: Data was collected using questionnaire designed by the researcher in accordance with the set objectives of the study on Knowledge and Management of Extrapyramidal Syndrome of Neuroleptic Drugs among Nurses in Neuropsychiatric Hospitals of Anambra and Enugu States. The questionnaire has 6 sections containing seventeen (16) items. Section A has three (3) items which elicited information on participants' demographic characteristics. Section B contains five (5) items, which elicited information on Nurses' knowledge of EPS. Section C contains six (6) items, which elicited information on Relationship between years of experience with Knowledge and management of EPS. Section D contains four (4) items which elicited information on Location of facility. Section E contains one (1) item which elicited information on management of EPS and finally, Section F contains one (1) item which elicited information on factors affecting management of EPS. Face and content validation of the instrument was carried out by research experts in research ethical committee Federal Neuropsychiatric hospital Enugu and also by the research committee Neuropsychiatric Hospital Nawfia Anambra state and finally by a Data and Research consultant Flourish Data Analytics School Nnewi. Their inputs were utilized in modifying the tool before actual field use. The reliability of the instrument was ensured by collecting pilot data at Synapse Psychological center Awka Anambra State which has similar characteristics with the study population. Ten percent of the total population was used. The internal consistency of the items was established using Cronbach's Alpha method at value of 0.83 which shows high consistency.

Data Collection: Data was collected with the aid of a questionnaire during all shifts for a period of one month.

Ethical Consideration: Ethical approval was obtained from the Research and Ethics Committee Neuropsychiatric Hospital Nawfia Anambra State and Research and Ethics Committee Federal Neuropsychiatric Hospital Enugu. Informed oral consent was obtained from respondents before administering the instrument and confidentiality of the data collected was ensured.

Data analysis: Descriptive statistics of frequency, percentages, mean, standard deviations and chi-square was used. The results were presented in tables. Level of significance was set at < 0.05.

Results

Socio-demographic characteristics of the participants showed that majority of the participants involved in the study were from Federal Neuropsychiatric Hospital Enugu (90.37%) most of who were in the 41-50years age range (31.65%) and most had a degree in Nursing (56.88%).

Most of the nurses from Enugu facility had a higher level of good knowledge than their counterparts in Nawfia (83.25% as compared to 66.7%). Also,

moderate knowledge was higher in Enugu than Nawfia. There was a statistical association between Years of work experience and Knowledge of EPS, while there was a statistically significant relationship between akathisia lower dose (p=<0.001), Switch to antipsychotic with lower risk (p=<0.001), Anticholinergic agent and benzodiazepines (p=0.006) and facility (Federal Neuropsychiatric Hospital). Results from table 4b showed that there was a statistically significant relationship between Parkinsonism lower dose (p=<0.001) and facility (Federal Neuropsychiatric Hospital). Results (table 5) showed that there was a statistically significant relationship between Negligence of the nurses (p=<0.001), Non-management of EPS according to American Psychiatric Association guideline (p=0.002) and facility (Federal Neuropsychiatric Hospital.

Table 1: Socio-demographics of study participants

Variable	Frequency	Percent
Age (yrs.)		
21-30yrs	32	14.68
31-40yrs	60	27.52
41-50yrs	69	31.65
51-60yrs	57	26.15
Facility		
Federal Neuropsychiatric Hospital Enugu	197	90.37
Neuropsychiatric hospital Nawfia	21	9.63
Highest level of Education		
BNSC	124	56.88
MSC	4	1.83
RN	8	3.67
RPN	82	37.61

Table 2: The knowledge of nurses in Neuropsychiatric hospitals Anambra and Enugu on EPS

Variable	Federal Neuropsychiatric Hospital		Total (%)	X^2-value	p-value
	Enugu (n=197)	Nawfia (n=21)			
Knowledge					
Good Knowledge	164 (83.25)	14 (66.67)	178 (81.65)	9.75	0.008*
Moderate Knowledge	29 (14.72)	4 (19.05)	33 (15.14)		
Poor Knowledge	4 (2.03)	3 (14.29)	7 (3.21)		

/-Statistically significant (p-value <0.05)/*

Table 3: Impact of years of experience on the knowledge and management of EPS

Variable*	Federal Neuropsychiatric Hospital		Total (%)	X^2-value	p-value
	Enugu (n=197)	Nawfia (n=21)			
Years of working as a registered/working mental nurse					
Less than 1year	-	2 (9.52)	2 (0.92)	47.24	<0.001*
1-2yrs	-	2 (9.52)	2 (0.92)		
3-5yrs	28 (14.21)	6 (28.57)	34 (15.60)		
6-10yrs	51 (25.89)	7 (33.33)	58 (26.61)		
11-15yrs	65 (32.99)	4 (19.05)	69 (31.65)		
15 and above	53 (26.90)	-	53 (24.31)		
Current Grade Level					
Grade level 7	-	4 (19.05)	4 (1.83)	47.56	<0.001*
Grade level 8	28 (14.21)	7 (33.33)	35 (16.06)		
Grade level 9	51 (25.89)	6 (28.57)	57 (26.15)		
Grade level 10 and above	118 (59.90)	4 (19.05)	122 (55.96)		

/-Statistically significant (p-value <0.05)/*

Table 4a: The management regimen that the study participants use for EPS

Variable	Federal Hospital Enugu (n=197)	Neuropsychiatric Nawfia (n=21)	Total (%)	X^2-value	p-value
Dystonia					
1st choice use of anticholinergic medication like biperiden					
No	7 (3.55)	-	7 (3.21)	0.77	0.380
Yes	190 (96.45)	21 (100.0)	211 (96.79)		
2nd choice the use of antihistamine					
No	33 (16.75)	2 (9.52)	35 (16.06)	0.74	0.391
Yes	164 (83.25)	19 (90.48)	183 (83.94)		
Yes	164 (83.25)	19 (90.48)	183 (83.94)		
3rd choice benzodiazepine					
No	41 (20.81)	5 (23.81)	46 (21.10)	0.10	0.749
Yes	156 (79.19)	16 (76.19)	172 (78.90)		
Akathisia					
Lower dose					
No	-	2 (9.52)	2 (0.92)	18.94	<0.001*
Yes	197 (100.0)	19 (90.48)	216 (99.08)		
Switch to antipsychotic with lower risk					
No	-	2 (9.52)	2 (0.92)	18.94	<0.001*
Yes	197 (100.0)	19 (90.48)	216 (99.08)		
Concomitant use of beta –blocker like propranolol					
No	8 (4.06)	1 (4.76)	9 (4.13)	0.02	0.878
Yes	189 (95.94)	20 (95.24)	209 (95.87)		
Anticholinergic agent and benzodiazepines					
No	79 (40.10)	2 (9.52)	81 (37.16)	7.60	0.006*
Yes	118 (59.90)	19 (90.48)	137 (62.84)		

/-Statistically significant (p-value <0.05)/*

Table 4b: The management regimen that the study participants use for EPS

Variable	Federal Neuropsychiatric Hospital		Total (%)	X^2-value	p-value
	Enugu (n=197)	Nawfia (n=21)			
Parkinsonism					
Lower dose					
No	-	4 (19.05)	4 (1.83)	38.23	<0.001*
Yes	197 (100.0)	17 (80.95)	214 (98.17)		
Change antipsychotic					
No	68 (34.52)	3 (14.29)	71 (32.57)	3.54	0.060
Yes	129 (65.48)	18 (85.71)	147 (67.43)		
Use of anticholinergic agent					
No	44 (22.34)	6 (28.57)	50 (22.94)	0.42	0.518
Yes	153 (77.66)	15 (71.43)	168 (77.06)		
Tardive dyskinesia					
1st choice Lower dose					
No	2 (1.02)	1 (4.76)	3 (1.38)	1.96	0.161
Yes	195 (98.98)	20 (95.24)	215 (98.62)		
2nd choice Use of Valbenazine or deutetrabenazine					
No	177 (89.85)	21 (100.0)	198 (90.83)	2.35	0.125
Yes	20 (10.15)	-	20 (9.17)		
3rd choice use of Gingko					
No	6 (3.05)	-	6 (2.75)	0.66	0.417
Yes	191 (96.95)	21 (100.0)	212 (97.25)		

/-Statistically significant (p-value <0.05)/*

Table 5: Factors militating against the management of EPS among study participants

Variable	Federal Neuropsychiatric Hospital Enugu (n=197)	Nawfia (n=21)	Total (%)	X^2-value	p-value
Negligence of the nurses					
No	186 (94.42)	8 (38.10)	194 (88.99)	61.44	<0.001*
Yes	11 (5.58)	13 (61.90)			
Non-management of EPS according to American Psychiatric Association guideline					
No	-	1 (4.76)	1 (0.46)	9.42	0.002*
Yes	197 (100.0)	20 (95.24)	217 (99.54)		
Poor knowledge of Psychopharmacology					
No	34 (17.26)	3 (14.29)	37 (16.97)	0.12	0.730
Yes	163 (82.74)	18 (85.71)	181 (83.03)		
Yes	163 (82.74)	18 (85.71)	181 (83.03)		
Lack of seminars and/continue education					
Yes	197 (100.0)	21 (100.0)	218 (100.0)	-	-
Employment of non-psychiatric nurses in psychiatric hospital					
Yes	197 (100.0)	21 (100.0)	218 (100.0)	-	-

/-Statistically significant (p-value <0.05)/*

Table 6: Relationship between Years of working as a registered/working mental nurse, current grade level and knowledge

Variable	Knowledge			Total (%)	X^2-value	p-value
	Good Knowledge (n=178)	Moderate Knowledge (n=33)	Poor Knowledge (n=7)			
Years of working as a registered/working mental nurse						
Less than 1year	2 (1.12)	-	-	2 (0.92)	34.46	<0.001*
1-2yrs	-	1 (3.03)	1 (14.29)	2 (0.92)		
3-5yrs	24 (13.48)	9 (27.27)	1 (14.29)	34 (15.60)		
6-10yrs	42 (23.60)	11 (33.33)	5 (71.43)	58 (26.61)		
11-15yrs	62 (34.83)	7 (21.21)	-	69 (31.65)		
15 and above	48 (26.97)	5 (15.15)	-	53 (24.31)		
Current Grade Level						
Grade level 7	2 (1.12)	1 (3.03)	1 (14.29)	4 (1.83)	22.40	0.001*
Grade level 8	23 (12.92)	9 (27.27)	3 (42.86)	35 (16.06)		
Grade level 9	43 (24.16)	11 (33.33)	3 (42.86)	57 (26.15)		
Grade level 10 and above	110 (61.80)	12 (36.36)	-	122 (55.96)		

/-Statistically significant (p-value <0.05)/*

Discussion

On the knowledge of the participants about EPS, the result from the findings showed that more than half of the participants (164 nurses) in Federal Neuropsychiatric Hospital Enugu and Neuropsychiatric Hospital Nawfia 14(66.67) had good knowledge of EPS and its management although none have undergone any form of training on EPS. This result supported the findings of Sheela[8], which stated that 80 percent of caregivers had average knowledge on EPS. Also, in a study conducted by Benedicta et al[9] in India, result showed that 45% of the participants had good knowledge, same was reported by Idah[10], there is a similarity in sample studied. This result contradicts a report from Begum[6] which stated that many nurses have suboptimal working knowledge of antipsychotic side effects. Also Davis[11] reported that the knowledge level of EPS increased in post-test examination.

On the management of EPS using rating scale and guideline, all the participants stated that they were not aware of guidelines or hospital policy for management of EPS, but they managed EPS generally using medications .The options that were highly applied by more than 70% of the participants were the use of biperiden for management of dystonia, propranolol for management of Akathisia, lowering of dosage for management of Parkinsonism and finally lowering of dosage as the first choice for Tardive dyskinesia. The other elements were implemented by less than 50% of the participants. This findings were in line with the results of Celeste et al[12] in which 55% of staff believed that medications worked well to manage resident behaviour. Wubeshet et al[13] reported that 51 respondents accepted dose reduction as the first line treatment of every EPS and most of the participants' side effects were not managed according to American Psychiatric Association guideline 178 (82.4%). This contradicts the report of Haddad et al[14], in which anticholinergics received greater use (five trials) and beta-blockers (two trials).

Most of the sociodemographic characteristics of the participants influenced the knowledge of EPS and its management. However, work experience had more influence on the knowledge of EPS; there was a significant relationship between years of working as a nurse, current Grade level and Facility type. This findings were contradicted by the findings of a similar study by Begum et al[6] in which the years of clinical experience and clinical banding were directly related to knowledge of antipsychotic medication side effects.

Extrapyramidal Syndrome is one of the major challenges facing patients on antipsychotics and there is no way the psychiatric patients can do without the antipsychotic drugs. It can be reduced if some strategies like usage of American psychiatric Association guideline, rating scale and WHO guideline are been implemented by the nurses while caring for psychiatric patients. In this study, results showed that the participants had good knowledge of EPS and there is an association between years of work experience and level of knowledge. The two hospitals are not using the various EPS

rating scales in the assessment and management of EPS but all the drug of choice mentioned for treatment of EPS (except Valbenazine) are being used in the treatment of EPS. None of the guidelines stated by America Psychiatric Association were used in the management of EPS, yet they still have good knowledge Of EPS. Some of the barriers to effective management of EPS are: Nurses Poor knowledge of Psychopharmacology, lack of seminars /continue education and employment of non-psychiatric nurses in Psychiatric Hospitals. Therefore, it is important to improve knowledge as one progresses in his work for effective management of EPS, and this can be achieved through attending of training workshops/seminars on EPS management, encouraging the use of rating scales, American Psychiatric Association Guideline and Employment of Psychiatric Nurses in Psychiatric Hospitals.

Conclusion

Most of the participants had good knowledge of Extrapyramidal Syndrome; none of them used American Association guideline and rating scale in management of EPS.

Recommendation

As EPS continues to pose problem to psychiatric patients, nurses who are the ones administrating these medications need to adopt the standard guidelines stated for management of EPS to ensure its reduction.

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KNOWLEDGE OF THE APPROACHES TOWARDS CANCER PAIN MANAGEMENT IN PATIENTS CARE AMONG NURSES IN SELECTED HOSPITALS IN AKWA IBOM STATE

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ABSTRACT

Background: Cancer-related pain can be acute or chronic and related to tumour, treatment, or both. Cancer pain has a debilitating effect and, if left untreated or poorly managed, can have a significant impact on a patient's physical, emotional, and mental well-being, thus impairing the patient's quality of life. Immediately a comprehensive assessment of a patient's pain is concluded, different treatment approaches should be considered before treatment planning is developed.

Aim: This study examined knowledge and approaches used in managing cancer pain in cancer patients among nurses in selected hospitals in Akwa Ibom State, Nigeria.

Materials and methods: A cross-sectional descriptive survey was carried out among 88 registered nurses purposely recruited from selected hospitals in Akwa Ibom State. Data was collected using Observational checklist and revised Nurses Knowledge and Attitudes Survey Regarding Pain (NKASRP) questionnaire. The obtained data were summarized using frequencies, Percentages and chi-square.

Results: More than half of the nurses 64 (73.70%) had adequate knowledge about cancer pain management while only 3 out of 10 cancer pain management approach was satisfactorily utilized by the participants in the care of cancer patient aimed at relieving pain.

Conclusions: Although more of the nurses had adequate knowledge on cancer pain management, the approach used was sub-optimal.

Keywords: *cancer pain, management approach, nurses***.**

Introduction

Cancer is one of the leading causes of death worldwide, killing nearly 10 million people annually[1]. Lung cancer, stomach cancer, colon cancer, liver cancer, and breast cancer cause the highest number of cancer-related deaths each year. Cancer accounts for nearly one in six deaths worldwide[2]. According to National Cancer Institute[3],cancer is a disease in which cells in the body grow out of control and spread to different parts of the body, cancer is a genetic and physical disease. When cancer develops, permanent changes in DNA are propagated to daughter cells[4]. Cancer appearance varies a lot from what is seen in tissue. The previously homogenous tumour tissue becomes heterogeneous as a result of the mutation[5].

Despite the overall trend of declining cancer incidence, the number of cancer patients is increasing, with an estimated 1 million new cases each year, more than half of them in developing countries[2]. About 60-70% of cancer cases in Nigeria are in an advanced stage. At least 30% of these cases suffer from one or more types of pain, which are mostly characteristic of the pathognomy of the illness state[6]. According to National Cancer Control plan Nigeria[7], 72,000 people die from cancer each year in Nigeria and an estimated 102,000 new cases of cancer are diagnosed each year.

Cancer patients usually suffer from different types of pain, including acute, chronic, episodic, breakthrough, procedural, neuropathic and nociceptive pain. Cancer pain, if not properly managed, can affect patients' physiological, psychological, social and mental functioning, causing great distress and placing a heavy burden on families and society[6]. Cancer patients experiencing persistent pain can become desperate, believing that the pain is a complication and an exacerbation of a deadly disease.

Pain is a complex experience of discomfort consisting of physiological and psychological responses to noxious stimuli and is primarily associated with injury or fear of injury[8]. Pain in cancer patients usually begins at the time of diagnosis and persists throughout the course of the disease. Although pain is subjective, physical pain remains a major source of suffering and can be easily assessed using validated equipment. Reports from developed countries indicate that the prevalence of pain at cancer diagnosis and early in the disease course is generally estimated at about 50%, rising to 75% in advanced stages[9]. Pain in cancer patients has a prevalence of 64% in patients with metastatic, advanced or terminal disease, 59% in patients undergoing cancer treatment, and 33% in patients after curative treatment. Study showed that people over the age of 60 were more than twice as likely to be hospitalized for persistent pain-related conditions as those under the age of 59[8].

Quality of life is greatly affected by pain in almost all cancer patients, and physical activity primarily affects sleep, appetite, relationships, emotions, and visual activity[10]. Cancer pain causes a great deal of suffering for patients, but it also places a heavy burden on families and society as a whole[4].

Pain in cancer patients should be managed in a multidisciplinary setting with a combination of pharmacological and non-pharmacological interventions by team members from different disciplines. The study therefore focuses on aspects of the nursing team as part of a multidisciplinary team in cancer pain management[11]. As part of a multidisciplinary team, nurses play a key role in cancer pain management. They need to actively intervene to fully control and relieve pain through non-

pharmacological approaches and be aware of pharmacological treatments, indications, contraindications and side effects[12].

The main goals of cancer pain treatment are pain control and relief, reduction of side effects and costs, increased autonomy and performance in activities of daily living, including psychological aspects, and improved quality of life. Clinical practice guidelines recommend that pain assessment and management in cancer patients is of critical importance at all stages of the disease[13]. The nurse's approach to cancer pain begins with an assessment. Accurate and consistent pain assessment using validated assessment tools is the first step towards effective and individualized treatment[12]. Three tools have been suggested for use in assessing pain intensity that is Visual Analogue Scales, Oral Rating Scales, and Numerical Rating Scales. However, if cognitive function is severely impaired. Self-reporting pain becomes difficult when people are old, have poor communication skills, or are at the end of life[14]. Observations of pain-related behaviour and discomfort can be used as a surrogate assessment tool for pain, although this has not been validated in this case[10].

This assessment will include a comprehensive pain assessment to determine a treatment plan, including discomfort for neuropathic pain symptoms (burning, tingling, numbness)[10]. Assessment-based interventions; reassessment of pain, and adjustment of treatment plans as needed. Pain prevention is another step in cancer pain management, involving continuous monitoring of pain levels and physical function, use of multimodal analgesia, and appropriate analgesics to prevent episodes of severe pain. Intervention-based research is another approach to treating cancer pain: that is conducting studies to test pharmacological and non-pharmacological strategies, elucidate patient perspectives through qualitative research, and assess practices through quality improvement studies.[14] Evidence-Based Practice; utilize current best evidence to guide practice, Consistent use of clinical practice guidelines for cancer pain and palliative care, Educate and encourage colleagues to incorporate evidence-based practice into their daily practice. Family-centered care and education: Encourage self-management and involve family members in patient-centered pain care, Assess educational needs and barriers to pain management[17]. Utilize interventions such as coaching, counselling, and knowledge-based approaches to improve pain control palliative care, identification and management for syndromes pain such as breakthrough and neuropathic pain, use alternative therapies to improve pain management, and support patient/family with psychosocial needs and resolution with end-of-life processes[11]

Materials and methods

Cross-sectional descriptive survey was adopted for the study. This was used to access knowledge and approach on cancer pain management among nurses, The study was conducted in 3 secondary health care facilities in Akwa Ibom State which include: Immanuel General Hospital, Ikot Ekpene General Hospital and Ibom Specialist Hospital. The target population consisted of all registered nurses that were working in oncology related department of the selected facilities with a total of 88 nurses. The study involved the total population, thus there was no sampling carried out. All the 88 registered nurses were consecutively recruited for the study.

Instrument for data collection: The study obtained data through the use of revised Nurses Knowledge and Attitudes Survey Regarding Pain (NKASRP) and observational check list. The instrument was divided into

three (3) sections: A–C. Section A was designed to gather information relating to the socio demographic and educational background of the respondents. The revised Nurses Knowledge and Attitudes Survey Regarding Pain (NKASRP)[15] was adapted in section B for knowledge assessment of nurses. However, this instrument was modified by the researchers in order to fit the study similar to Nega, Tachbele and Kassa[16]; who used same approach. Observational check-list developed by Smeltzer, Bare, Hinkle and Cheever[17] was used in Section C to observe and assess the approach used by nurses in managing cancer pain and had been previously used by Attahir[18] to determine nurse approach on elderly patient in cancer pain management. Face and content validation of the instrument was carried out by experts in the field of Nursing, oncology, their input were utilized in modifying the tool before the actual field use. The reliability of this instrument was pre-tested on nurses at General Hospital Iquita, Oron, Akwa Ibom State, which has similar characteristics with the study population. to test for the internal consistency and reliability, Cronbach alpha was used. This yielded a value of 0.833 which showed a high consistency

Data collection: Data was collected over a period of 4 weeks.

Ethical Approval and consent to participate: Ethical approval was obtained by the Akwa Ibom state Ministry of Health ethics and research committee, informed oral consent was obtained from the respondents before administering the instrument and observations and confidentiality of the data collected was ensured

Data analysis: Data were summarized and analysed using descriptive statistics of mean, frequency and percentage and chi-square was used to compare the approaches render by nurses for cancer pain management and the result were presented in tables. Level of significant was set at less than 0.05.

Results and Discussion

Findings from this study shows the many (25%) of the respondents were aged 46 years and above; majority (89.8%) of the nurses were females: predominantly Christians (97.7%) and mostly married (79.6%). About 39 (44.3%) of the nurses working experience were between 5-10 years. The educational qualifications of Nurses that participated in the study; majority had Registered Nurse and Midwife qualification (RN/RM) with 42%, followed by Bachelor of Science Degree (BSc) with 33%. However, most (35.2%) of the nurses did not have additional cancer/pain related training and majority(35.2) of the respondent had only basic nursing knowledge.

Findings shows that majority (72.70%) of the participants had adequate knowledge of cancer pain management. The highest correct responses (97.70%) by nurses is on the item number 8 which asked about if the patients' spiritual beliefs may condition their minds to believe that pain and suffering are necessary experience of life. The decision table (table 3); which was showed nurses' level of knowledge toward cancer pain management. Poor knowledge (27.30%) was recorded in less than one third of the participants.

Findings from the study shows 2 out of 10 approaches were carried out satisfactorily; 5 approaches were utilized but not with satisfaction. Three approaches were not utilized by majority of the respondents.

The level of knowledge of nurses based on the study revealed that more than half of the nurses (72.70%) have adequate knowledge on cancer pain management in the care of cancer patients. Although, majority of the nurses has only basic nursing training and no further training on general or cancer pain management. This is contrary to previous

findings by Elumelu et al[19] in which only 2 (2%) nurses out of 119 could give a good account on the management of cancer pain. This finding agreed with that of Attahir[18] which opined that nurses are required to possess knowledge regarding pain management generally and on cancer. This will be of great benefit for the nurses to effectively plan nursing activities so as to ensure that pain is fully managed according to its subjective occurrence.

On the approaches employed by nurses during cancer pain management, the participants demonstrated unsatisfactory utilization of the approaches in managing cancer pain in cancer patient. Nevertheless, some approaches were optimally applied than some. Those that were most utilized by more than 70% of the participate included administering balanced and analgesic agent as prescribed, obtaining additional prescriptions as needed and instructing patient and family about potential side effects of analgesic agent. Other approaches which were carried out by less than 50% satisfaction included reassuring patient that pain is real, using pain assessment scale, assessing and recording pain characteristics, re-administering pain assessment scale after administration of pain medication, identifying and encouraging patients to use strategies and teaching patient additional strategies to relieve pain and discomfort. Management of cancer pain protocol should always be practised while taking care of cancer patient experience pain. Nurses should ensure pain assessment are made and the strategies components of the cancer management are well established.

Table 1: Socio-demographic and Professional Characteristics of the Nurses

Variable	Frequency	Percentage
Age (Years)		
21-25	2	2.3
26-30	22	25
31-35	20	22.7
36-40	19	21.6
41-45	14	15.9
46+	11	12.5
Gender		
Female	79	89.8
Male	9	10.2
Religion		
Christianity	86	97.7
Others	2	2.3
Marital Status		
Divorced	1	1.1
Married	70	79.6
Separated	2	2.3
Single	13	14.8
Widowed	2	2.3
Highest Qualification		
BSc	29	33.0
MSc	12	13.6
Registered Nurse	1	1.1
Registered Nurse and Midwife	37	42.1
Others	9	10.23
Cadre		
ACNO	19	21.6
AD	1	1.1
CNO	6	6.8
NO1	10	11.4
NO11	1	1.1
PNO	31	35.2
SNO	20	21.7
Years in Service		
Below 2 years	-	-
3 – 10 years	39	44.3
11 – 20 years	24	27.3
21 – 30 years	17	19.3
31+ years	5	5.7
Additional cancer and/or pain management and assessment training		
General Pain Management	30	34.1
Oncology	21	23.9
Palliative	6	6.8
None	31	35.2

Table 2: level of knowledge of cancer pain management among Nurses

S/N	Variable	Response (%)		
		True	False	Answers
1	Vital signs are always reliable indicators of the intensity of a patient pain.	32 (36.4%)	56(63.6%)	F
2	Patients who can be distracted from pain usually do not have severe pain.	42 (47.7%)	46(53.3%)	F
3	Aspirin and other non-steroidal anti-inflammatory agent are not effective for painful bone metastases.	27(30.7%)	61(69.3%)	F
4	Patients may sleep in spite of severe pain.	68 (77.3%)	20(22.7%)	T
5	Respiratory depression rarely occurs in patients who have been receiving stable doses of opioids over a period of months.	63 (71.6%)	25 (28.4%)	T
6	Combining and analgesic that work by different mechanism (e.g., combining an NSAID with an opioid) may result in better pain control with fewer side effects that using a single analgesic agent.	71 (80.7%)	17 (19.3%)	T
7	The usual duration of analgesia of 1-2 mg morphine IV is 4 to 5 hours.	19(21.6%)	69 (78.4%)	F
8	Patient spiritual beliefs may condition their mind to believe that pain and suffering are necessary experience of life.	86 (97.7%)	2 (2.3%)	T
9	If the source of the patient's pain is unknown, opioid should not be used during the pain evaluation as this could Mask the ability to correctly diagnose the cause of pain.	39 (44.3%)	49 (55.6%)	F
10	Elderly patient cannot tolerate opioids for pain relief.	18 (20.5%)	70 (79.6%)	F
11	Giving patients sterile water by injection (placebo) is a useful test to determine if the pain is real.	22(25.0)	66(75.0%)	F

Table 2B: decision table- Rating Nurses level of knowledge toward cancer pain management.

Variable	Frequency	Percent (%)
Poor Knowledge	24	27.30
Excellent Knowledge	64	72.70
Total	**88**	**100.0**

Table 3: Observational check list on Nursing care approach for a patient with cancer pain

Variable		Frequency	Percent	Mean	p-value
Reassure patient that pain is real	Not Done	25	28.41	2.95	<0.001*
	Done not Satisfactorily	47	53.41		
	Done Satisfactorily	16	18.18		
Use pain assessment scale	Not Done	14	15.91	1.11	<0.001*
	Done not Satisfactorily	62	70.45		
	Done Satisfactorily	12	13.64		
Assess and record pain characteristics	Not Done	-	-	2.05	<0.001*
	Done not Satisfactorily	51	57.95		
	Done Satisfactorily	37	42.05		
Administer balanced and analgesic agent as prescribed	Done not Satisfactorily	2	2.27	3.0	<0.001*
	Done Satisfactorily	86	97.73		
Re-administer pain assessment scale	Not Done	70	79.55	1.0	<0.001*
	Done not Satisfactorily	14	15.91		
	Done Satisfactorily	4	4.55		
Document severity of patient pain on chart	Not Done	9	10.23	2.14	0.001*
	Done not Satisfactorily	25	28.41		
	Done Satisfactorily	54	61.36		
Obtain additional prescriptions as needed	Not Done	2	2.27	1.27	0.001*
	Done not Satisfactorily	5	5.68		
	Done Satisfactorily	81	92.05		
Identify and encourage patients to use strategies.	Not Done	53	60.23	1.68	0.030
	Done not Satisfactorily	22	25.00		
	Done Satisfactorily	13	14.77		
Teach patient additional strategies to relieve pain and discomfort.	Not Done	64	72.73	1.82	0.740
	Done not Satisfactorily	16	18.18		
	Done Satisfactorily	8	9.09		
Instruct patient and family about potential	Not Done	9	10.23	1.78	0.047

side effects of analgesic agent.			
	Done not Satisfactorily	15	17.05
	Done Satisfactorily	64	72.73

Conclusion

In this study, there were knowledge gaps although the nurse had excellent knowledge but there was suboptimal utilization of cancer pain management approach among nurses in the health facilities. Cancer pain management is one of the major problems faced by cancer patient and the need of pain reduction cannot be overemphasized. The pains can be managed if the approaches are duly followed.

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Competing interest

There exists no conflict of interests

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CROSS-CULTURAL ADAPTATION, RELIABILITY, AND VALIDATION OF THE INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE SHORT FORM IN LANGUAGES IN AFRICA: A SYSTEMATIC REVIEW

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Abstract

Background: The African population consists of diverse cultures and languages whose first language is not English. To address the challenges of using the English version of the International Physical Activity Short Form (IPAQ-SF), encourage physical activity (PA) participation/research, and curb non-communicable diseases (NCDs) in developing countries in Africa, there is a need for cultural adaptation of the questionnaire.

Aim of the study: This study aimed to conduct a Systematic Review on cultural adaptation, reliability and validation of the IPAQ-SF into African languages and to proffer probable reasons for differences between the versions.

Materials and Methods: We searched PubMed, Google Scholar, and AJO from inception to August 14, 2022. Studies were recruited if they conducted a cultural adaptation, validation and reliability of IPAQ-SF into the African language. The data analysis included descriptive statistics, ANOVA, and Student's t test using SPSS version 23, and a $p<0.05$ was used as the level of significance.

Results: A total of 453 healthy adult subjects (Hausa, *n* = 102 & Yoruba, n = 351) who met the inclusion criteria were documented. The mean age and BMI were 29.3±6.255 years and 24.1±4.335 (kg/m^2), respectively. Majority of the subjects were male (*n* = 293) and single (*n* = 375) than married (*n* = 74) and female (*n* = 160). The reliability and concurrent validity of the Yoruba and Hausa IPAQ were acceptable. The total scores obtained from the concurrent validity in the males in the Hausa (*r* = 0.844) IPAQ-SF were significant (*r* = 0.022) and more than that of the Yoruba (*r* = 0.640) version. The ICC total and female was significantly higher in the Hausa than the Yoruba IPAQ-SF.

Conclusions: Overall, not many studies reported the cultural adaptation of English IPAQ-SF into African languages. Both Hausa and Yoruba IPAQ-SF have acceptable concurrent validity and test-retest reliability for assessing PA. The total score for the concurrent validity male, ICC total and female were significantly higher in the Hausa than the Yoruba IPAQ-SF. We recommend that the English IPAQ-SF be culturally adapted to the Africa languages such as Igbo, pidgin, Swahili, Ajagam, Boki, and Effik.

Keywords: *international physical activity short form, cross-cultural adaptation, Africa, Validation, reliability*

Introduction

Morbidity and mortality as a consequence of a sedentary lifestyle have long become a global concern owing to the resultant debilitating effect on vital body systems, such as the cardiovascular and musculoskeletal systems, predisposing individuals to noncommunicable diseases (NCDs)[1-5]. Physical activity (PA) participation, on the other hand, has a magnitude of health benefits, as evident in several studies across the populations[6-10]. A PA lifestyle is presumed to be uncultivated by many people, it requires self-discipline to keep and adhere to and often habituated[6].

Having posed a challenge in the past, numerous methods of assessing the level of PA and participation have been developed over the years and adapted among diverse cohorts[11-14]. Generally, PA assessment tools are grouped into objective and subjective measures. For example, accelerometers, pedometers, computer-based activity monitors, motion sensors, and armbands, made up the objective methods[15-16] but are not readily accessible and affordable by the low socioeconomic class of persons who seem to make up a major fraction of the population in developing countries[17-20]. Simple affordable subjective measures, such as the International Physical Activity Questionnaire (IPAQ), have been validated to suit populations in developed and developing countries.

The IPAQ is a universally reliable and valid self-report questionnaire with a 9 and 31-item short/long form. Both forms of the questionnaire assess PA on a 7-day recall with the long form assessing PA in the domains of occupational PA, housework/house maintenance/care for family, transportation PA, time spent sitting and leisure-time and recreation/sport PA. For example, the short form assesses PA in the domains of walking, vigorous-intensity activity (e.g., aerobics), sitting, and moderate-intensity activity (e.g., leisure cycling)[19]. The IPAQ was first validated with studies pooled from populations across 12 countries, recommendations from which led to increased utilization of the IPAQ-SF for assessing PA compared with other existing questionnaires[21]. Lee et al.[22] carried out a systematic review of 21 validated studies pooled from the US, Europe, Asia, and Africa, with Africa having one study validating IPAQ-SF among populations in South Africa. They found a lot of inconsistency in methodology, but all 21 studies had similar findings. The correlation between objective measurement of PA level and the IPAQ-SF utilized in the studies ranged between 0.09 to 0.39, which is less than the minimal acceptable standard of PA according to the literature (objective measurement = 0.50 and measurement for fitness = 0.40). Second, there was even greater variability in the correlation between domains of the IPAQ-SF (moderate or vigorous PA) compared to objective standards (-0.18 to 0.76), but the majority of the correlation was up to the minimum acceptable standard. Additionally, a comparison between PA level as assessed by IPAQ-SF and an objective criterion was provided by only six of the 21 studies. There was also an overestimation of the PA level by 36 to 173% in IPAQ-SF and an underestimation of PA by 28%.

The cultural adaptation of the IPAQ-SF consists of a step-by-step process of translation of the original English version into a different language and ends with assessing the validity and reliability of the new version and correlating it with the original version. In most cultural adaptation of outcome measures, the guideline by Beaton et al.[23] is mostly used. Some researchers have translated and adapted the IPAQ-SF into languages that are alien to African culture. For example, the Spanish version by Craig et al.[19] has been recommended by Medina et al.[24] and used by Medina[25] among Mexicans. Additionally, the Greek and Chinese versions of the IPAQ-SF have been reported in the literature[26-27]. The degree to which the IPAQ-SF obtains similar results when compared to another instrument is label validity[28-29], while the capacity of the IPAQ-SF to obtain similar scores in consecutive measurements is labelled reliability[28]. For example, in a study by Oyeyemi et al.[30], the construct validity of the IPAQ-SF was assessed by testing it with the rate pressure product (RPP), while the reliability was tested by administering the questionnaire within consecutive intervals with a time lapse of one week[30-31]. Additionally, to strengthen efforts to encourage PA participation and curb NCDs in developing countries in Africa, a review of the reliability of the conclusions

drawn from validation studies assessing the level of PA among the continent's populations is warranted.

The African population is made of a diverse group of cultures and languages whose first language is not English. To address the challenges with using the English IPAQ-SF, there is a need for cultural adaptation of the questionnaire. Additionally, systematic reviews (SR) of studies on cultural adaptation of IPAQ-SF in languages in Africa are lagging in the literature, since none was found from our search. We therefore sought to conduct this SR of studies on cultural adaptation, reliability and validation of the IPAQ-SF in African languages and to identify probable reasons for differences between various versions. Second, we compared the reliability and validity of the different language versions of the IPAQ-SF.

Materials and Methods

Criteria for eligibility

The criteria for inclusion were as follows: 1) Studies that cross-culturally translated and adapted the English version of the IPAQ-SF into languages in Africa. 2) Studies that reported the psychometric property─ reliability and validity of the IPAQ-SF. 3) Studies whose subjects were healthy adults 18-65 years.4) Studies that followed the prescribed guidelines of translation and cultural adaptation of the IPAQ-SF as specified by the guideline of IPAQ for data processing found at http://www.ipaq.ki.se[32] ─ synthesis, backwards translation, subjection to review by expert committee, and pretesting. 5) Studies whose PA data underwent a cleaning process to make sure that the various domains of IPAQ-SF fell in the range of 10 and 180 MET-min/week-[1] for all subjects as prescribed by the guideline of the IPAQ core group found at http://www.ipaq.ki.se[32]. 6) Studies published in the English language whose full text can be freely assessed.

The criteria for exclusion were as follows: 1) Studies whose subjects were18 - 65 years but not on African descent.2) Studies that followed the stepwise process for culturally adapting the IPAQ-SF into languages other than Africa. 3) Studies whose full text cannot be openly assessed. 4) studies on cultural adaptation of PA questionnaire other than IPAQ-SF into African language.

Included source information

The idea to commence this study surfaced in 2022, and the systematic search for relevant studies (keywords) was carried out on August 14, 2022, and was carried out from January 2000 to August 14, 2022. To retrieve relevant studies on the validation, reliability, and cross-cultural adaptation of the IPAQ-SF in languages in Africa, search engines such as PubMed and Google Scholar were employed. Additionally, we searched the website of the Africa Journal online. Therefore, our search was consistent with the guidelines for SR/MA as recommended by AMSTAR[33].

The strategy utilized in searching

We searched PubMed using keywords and Boolean operators (AND; OR), after which we applied the same strategy to Google Scholar and AJO. A researcher (PAE) searched keywords linked to the reliability, validation, and cross-cultural adaptation of the IPAQ-SF in languages in Africa. Therefore, the search (MeSH) terms included "cross-cultural adaptation" OR "cultural adaptation" AND "reliability" OR "Validation" AND "short international physical activity questionnaire" OR "international physical activity questionnaire" OR "IPAQ-SF" AND "Africa languages".

Selection of study

The researchers (PAE, ID) independently reviewed the retrieved studies to ascertain whether the abstracts or titles of the prospective included studies met the criteria for eligibility. Therefore, only articles with full-text that met the inclusion criteria were selected for this systematic review. Additionally, the authors used discussion to reconcile any misunderstandings in choosing an appropriate article. The data from the included studies were manually extracted into Excel and then into SPSS by one researcher (PAE), and another researcher checked to ensure that there were no errors during extractions. The extracted data were cleaned by the researcher PAE in the extraction sheet in a form that can be read by

analytical software. The NIH quality assessment for the included studies is presented in table 5.

Measures of outcome

Weight and height were used to measure subject BMI, and sociodemographic data such as age, sex, gender, marital status, ethnicity, employment status, educational level and health status were collected from the subjects in the included studies. Parameters such as heart rate and systolic blood pressure were used to measure the rate pressure product (RPP)—an index of cardiorespiratory fitness, while the IPAQ-SF was used to determine the amount of time spent in PA and measures sitting, walking, vigorous-intensity activity, and moderate-intensity in MET minutes per week 7 days ago. PRISMA guidelines for systematic review were adopted for this study (figure 1).

Assessment of reliability and validity

To assess concurrent validity, the researchers of the included studies administered the two versions of IPAQ-SF with a time lag of 1 hour and then compared the scores obtained by the subjects in Min week^{-1} in the original English IPAQ-SF with the language-translated version. In contrast, the construct validity was assessed by either comparing the scores obtained by the subjects in Min week^{-1} in the language translated version by RPP or by comparing the total PA in Min week^{-1} of the language version with one of its constructs, for example, walking in Min week^{-1}. Additionally, the reliability was assessed by administering the language-translated version of the IPAQ-SF on 2 occasions separated by 7 days.

Data analysis

The statistical analysis utilized in the recruited studies included descriptive statistics and independent t-tests. The validity of the questionnaire was evaluated by Spearman and Pearson correlation coefficients (r), while single measure intraclass correlation coefficient (ICC) was adopted to determine the reliability. The suggestion by Landis and Koch[34] was utilized in interpreting the reliability. For example, the level of agreements was rated as follows: *almost perfect* = 0.8-1.0, *substantial* (0.6-0.8), *moderate* = 0.4-0.6, *fair* (0.2-0.4), and *poor* = 0-0.2. The heteroscedasticity of the data was indicated by Bland–Altman analysis to describe the total error (95% limits of agreement) between the language-translated IPAQ and the retest English version. Additionally, the difference between the Yoruba and Hausa IPAQ-SF was determine using independent t test, while ANOVA was used to compare the Yoruba, Hausa, and meta-data (combined mean for both versions) IPAQ-SF, and $p < 0.05$ was set as the level of significance.

Results

Our search yielded 65 hits on PubMed, 1 study from AJO, and 14 on Google Scholar. Following an elaborate assessment, approximately 9 relevant articles were identified, and only 2 studies carried out on 453 (n = 102 IPAQ-SF Hausa & n = 351 for Yoruba) apparently healthy adult subjects who met the criteria for inclusion were documented (figure 1). Additionally, these studies were conducted in Africa (Nigeria)**.**

The study by Awotidebe et al.[31], conducted in Obafemi Awolowo University (OAU) Ile-Ife, Osun state, Southwest, Nigeria, purposively sampled a cohort of undergraduate students (age 22.4 ± 3.01 years, mostly male and singles) culturally adapted the IPAQ-SF into the Yoruba language. The prefinal version was tested on 15 subjects (mean age = 21.3±4.7 years; female: n = 6; male: n = 9) who were recruited for the pilot study, after which the final version (Yoruba) was developed and used to collect data in the main study. Additionally, based on the outcome of the pilot, some modifications were made; for example, the word “digging” translated to “gbígbẹ́ kòtò”, “vigorous aerobics and PA and was replaced with “hard running and PA”, and “serious farm work” and “cutting grass around the house and fetching of water” were also included in the moderate and hard PAs. In contrast, the study by Oyeyemi et al.[30], conducted at the University of Maiduguri, Borno state, northeastern Nigeria, sampled subjects (age = 36.2 ± 9.5 years, rage = 20-65 years, primarily males, and married) and had higher total PA than females— 4383.7 vs 3058.1 MET-Min week^{-1} respectively, and mean

rate pressure product, RPP = 9694.3±1195.94) from a different background— workplace (e.g., private establishments and university teaching hospital) and in Maiduguri city neighbourhoods, culturally adapted IPAQ-SF into the Hausa language. A pilot study was conducted on 7 (out of the 12 recruited) subjects who could speak/write in the Hausa and English languages using the prefinal final version, after which the final version was developed for collecting data. Additionally, similar to the study by Awotidebe et al.[31], some modifications were made after the pilot study of the Hausa version. For example, the phrase 'aikinkarfi'—meaning PA was misunderstood as being restless and replaced with, "motsajiki"—physical exercise, "tafiyadagawannanwurizuwawancan"—traveling from place to place by walking was replaced with "tafiya (tattaki) dagawannanwurizuwawancan"—"walking to move from place to place either for sports, leisure recreation or exercise".

The Yoruba IPAQ-SF by Awotidebe et al.[31] had good concurrent validity. For example, a significant correlation was found between vigorous PA in both the Yoruba and original English versions of the IPAQ-SF. Similar results were reported for the energy consumed in time spent sitting and total PA. However, there was a moderate correlation for energy consumed in walking and moderate activities between the original English and Yoruba versions. Additionally, in the female subjects, correlations were significantly greater than the in males for energy used in sitting times and other activities for both versions of the IPAQ-SF, which was inconsistent with the report of Oyeyemi et al.[30], which found no meaningful socioeconomic and gender variance. Similarly, the Hausa IPAQ-SF by Oyeyemi et al.[30] also had good concurrent validity ranging from moderate to high. For example, total PA from the original English version was significant/highly correlated with total PA in the Hausa version. Additionally, the time used in vigorous, walking, and moderate PA was significantly high and positively correlated with both versions of the IPAQ-SF. The time spent sitting on both versions of the IPAQ-SF (Hausa and English) was also significantly and positively linked. Additionally, in the study by Oyeyemi et al.[30], the "Bland–Altman plot" for the English and IPAQ-SF Hausa revealed a small mean variance that was not significant and with a wide range of 95% limits agreements. This finding was attributed to few subjects who reported moderate PA of more than 50 min/week. In contrast, the study of Awotidebe et al.[31] did not carry out this plot.

Additionally, while the study of Awotidebe et al.[31] carried out a discriminant and convergent validity (construct validity) and found a highly significant positive correlation between total PA and vigorous PA scores (good convergent validity) for the Yoruba version, the sitting time and total PA were not correlated (good discriminant validity). In contrast, the study of Oyeyemi et al.[30] assessed construct validity by correlating the scores accrued from RPP with the time spent sitting from the IPAQ-SF Hausa and found a weak positive significant correlation. A similar result was reported between time used in moderate PA and BMI however, time used in walking, vigorous PA, and total PA showed no relationship with BMI and RPP.

The Hausa IPAQ-SF by Oyeyemi et al. [30] showed an intraclass correlation (ICC) ranging from fair to good (substantial), with vigorous PA having the highest value and moderate PA having the lowest value. Additionally, the ICC scores for all items were significant and higher in males than in females (the ICC in women was lowest in moderate and highest in sitting activity). In contrast, the reliability (ICC value) of the Yoruba IPAQ by Awotidebe et al.[31] ranges from poor to modest— lowest for sitting and highest for vigorous PA. Additionally, the ICC value was fairly significant for all items in the Yoruba version; however, in the Hausa version, it was mostly substantial and modest. The findings for gender variance in the ICC value in the Yoruba version were consistent with those of Hausa—higher in males than females.

Meta-analysis of the data of the Hausa and Yoruba IPAQ-SF

We conducted a meta-analysis of the physical characteristics, sociodemographic variables and psychometric properties of the recruited studies. The mean age and BMI of the subjects (n = 453) were 29.3±6.255 years and 24.1±4.335 (kg/m^2)

respectively. There were more male subjects (*n* = 293) than female and singles (*n* = 375) than married (table 1 and Figure 2).

The correlation coefficient ranges from modest (*r* = 0.7185) to high (*r* = 0.8455), demonstrating good concurrent validity for the IPAQ-SF Yoruba/Hausa. These findings indicated that the total energy used in the total PA (MET-Min/week) in the IPAQ-SF Yoruba/Hausa was significant and highly (*r* = 0.839, p < 0.001) correlated with that of the original English version. Similar results were found in the moderate, vigorous, walking activities, and the time spent sitting. However, no meaningful gender variance was found, as presented in table 2.

Additionally, table 2 presents the results of the 1-week test-retest reliability (ICC), which generally ranged from 0.328-0.5815, highest for energy expended in vigorous PA and lowest for moderate PA. The coefficient of reliability for walking *ICC* = 0.469 (95% *CI* = 0.301-0.5715), vigorous *ICC* = 0.6205 (95% *CI* = 0.4825-0.7215), and total PA ICC = 0.481 (95% *CI* = 0.319-0.6115) were higher in males than in females. The time spent sitting showed the highest ICC in females (0.568, 95% *CI* = 0.357-0.729), while moderate activity showed the lowest score for reliability (*ICC* = 0.2275, 95% *CI* = -0.055-0.473).

In table 3, the concurrent validity Male (*p* = 0.012), reliability total (*p* = 0.026), reliability female (*p* = 0.018) was all significantly different in the Yoruba, Hausa, and meta-data, while the other variables were not significant (p> 0.05). The concurrent validity (*r* = 0.844) of subjects who were male in the Hausa was significantly (*p* = 0.022) higher than that in the Yoruba (*r* = 0.640) IPAQ-SF. Similar results were found in the reliability total and female (table 4). However, the concurrent validity total and female and the reliability were comparable in both Hausa and Yoruba IPAQ-SF table 4.

Discussion

A PA lifestyle is assumed to be uncultured by many individuals in Africa and globally, it requires self-discipline to keep, adhere to, and often habituated[6]. The African population is made of a diverse group of cultures and languages whose first language is not English, and to address the challenges with using the IPAQ-SF English, there is a need for cultural adaptation of the questionnaire. This will aid in strengthening efforts to encourage PA participation, advance research in PA, and curb NCDs in developing countries in Africa. This study systematically searched for literature on reliability, validation, and cultural adaptation of the IPAQ-SF into African languages to proffer probable reasons for differences between various versions. Additionally, we compared the validity and reliability of the different language versions of the IPAQ-SF in Africa.

We found two studies on the reliability, validation, and cultural adaptation of the IPAQ-SF in languages in Africa —birthing the Yoruba[31] and the Hausa[30] IPAQ-SF. Additionally, these studies were all conducted in the northern and southern parts of Nigeria; hence, it seems that only a few studies have culturally adapted the IPAQ-SF into languages in Africa; therefore, we recommend that more studies should be conducted in this regard. The two validated studies in Africa were similar for obvious reasons. First, they were Nigerian-based studies and followed the step-by-step systematic process of cross-cultural adaptation of questionnaires as prescribed by Beaton et al.[23]. Second, a pilot study was conducted before the main study and the recommendations from the pilot study were implemented. Third, the data collected during the main studies were cleaned in accordance with prescribed guidelines by the core group of the IPAQ found at http://www.ipaq.ki.se[32], and both studies found good concurrent validity for the IPAQ-SF, indicating that the questionnaire is a valid subjective instrument that can be used to measure PA with results similar to other subjective and objective measures of PA. These findings are consistent with the results of other validated studies on the IPAQ-SF in a diverse group of population alien to Africa, such as Greek, China, and Mexico[24-25, 26-27, 19, 35]. However, caution should be used when directly comparing the results of our included studies with those of the abovementioned studies, since most of these studies validated the IPAQ-SF by comparing it with common objective criterion

standards, such as accelerometers[17, 25, 35-36]. Fourth, both studies recruited subjects from a population made up of students.

In contrast, there were also some differences between the included studies. For example, the study of Oyeyemi et al.[30] assessed the Hausa IPAQ-SF construct validity by correlating the RPP scores (9694.3±1195.94, an index of cardiorespiratory fitness) with the energy consumed in sitting from the Hausa IPAQ-SF and found a weak significant positive correlation. The RPP was computed by multiplying the resting heart rate by the systolic blood pressure, and the result of the RPP was higher than that of a recent report by Ewah & Oyeyemi[37], which found the value to be 7790.18±1131.59 in physically active students. However, the study of Awotidebe et al.[31] assessed the construct validity by correlating the energy expended in total PA and vigorous PA on the Yoruba IPAQ-SF and found a highly significant positive correlation. Additionally, in the study of Oyeyemi et al.[30], the heteroscedasticity of the data was indicated by Bland–Altman analysis to describe the 95% limits of agreement between the Hausa IPAQ and retest English versions however, this analysis was not demonstrated by Awotidebe et al.[31].

Other obvious variances in our included studies have been discussed in the results section of this report. It appears that the study of Oyeyemi et al. [30] was more robust for the following reasons: conduction of additional analysis, collection of additional data (blood pressure, heart rate, socioeconomic status), and collection of data from a diverse population, which demonstrates the possibility of collecting data from a diverse segment of the population in the country. However, the strength of the study of Awotidebe et al.[31] lies in recruiting a modestly large sample of the study's population.

The results of the meta-analysis showed that the total score obtained from the concurrent validity in the male subject in the Hausa IPAQ-SF was significant and more than that of the Yoruba version. Similar results were found in the scores of the ICC total and female. This indicates that the IPAQ-SF Hausa's reliability and concurrent validity were better than those of the Yoruba version.

Limitations of the study

This study was limited by the small number of included studies that used a nonprobability sample to recruit subjects hence, the result should be interpreted with caution. For this same reason, we could not determine in detail the heterogeneity of the included studies. However, this is the first SR/MA on studies on the reliability, validation, and cultural adaptation of IPAQ-SF into languages in Africa.

Conclusion

Overall, we found a few studies that have successfully validated and cultural adapted the original English version of IPAQ-SF into the languages in African. Additionally, the results showed that both the Hausa and Yoruba IPAQ-SF have adequate ICC (test-retest reliability) and concurrent validity for assessing PA in a diverse inhabitant in Africa. We also found that the total score for the concurrent validity male, ICC total, and female were significant and higher in the Hausa IPAQ than in the Yoruba version. We recommend that the IPAQ-SF be culturally adapted to the following languages in Africa; Igbo, pidgin, Swahili, Ajagam, Boki, and Effik.

List of Abbreviation

SR/MA-systematic review and meta-analysis; PA-physical activity; BMI-body mass index; RPP-rate pressure product; NCD-noncommunicable disease; IPAQ-SF-international activity questionnaire short form; ICC-intraclass correlation coefficient, AMSTAR-assessment of multiple systematic reviews, PRISMA-Preferred Reporting Items for Systematic Review and Meta-analysis.

Declarations

Ethics approval and consent to participate

This was not applicable for this SR.

Consent for publication

Not Applicable.

Availability of materials and data

The data for this study can be obtained from the included studies.

Competing interests

All author herein states no conflict of interest.

Funding

The authors conducted this study without funding by any organization.

Authors contributions

The idea for conducting this systematic study was brought by PAE. PAE and ID searched the database, and IDW, PAA and PAE screened for eligibility. Preparation and writing of the manuscript were executed by all authors (PAE, IDW, PAA, FAD). All documented authors have read and therefore approved this manuscript for publication.

Acknowledgements

Not Applicable**.**

Table 1: Physical and sociodemographic characteristics of the subjects for the Yoruba/Hausa IPAQ-SF

Variables	**Yoruba (*n* = 351)**	**Hausa (*n* = 102)**	**Total (*n* = 453)**
Gender			
Female	114	46	160
Male	237	56	293
Marital status			
Married	5	69	74
Single	346	29	375
Variable	**Yoruba**	**Hausa**	**Combine mean**
Age (years)	22.4±3.01 (18-35)	36.2±9.5 (20-65)	29.3±6.255
Body mass index (kg/m^2)	24.3±4.37	23.9±4.3	24.1±4.335
Rat pressure product (RPP)		9694.3±1195.94	

kg/m^2 = kilogram per meter squared

Table 2 Reliability (ICC) and concurrent validity of the Hausa/Yoruba IPAQ-SF

Hausa- H (*n* = 102) plus Yoruba- Y (*n* = 351) IPAQ-SF H+Y/2	**Total (*n* = 453) *R***	**Female (*n* = 160) *r***	**Male (*n* = 293) *r***
VPA (Min week^{-1})	0.8105**	0.8875**	0.788**
MPA (Min week^{-1})	0.7185**	0.832**	0.705**
Walking (Min week^{-1})	0.7335**	0.8885**	0.6945**
TPA (MET-Min week^{-1})	0.8455**	0.9595**	0.791**
Time spent sitting (Min week^{-1})	0.839**	0.899**	0.7325**
Hausa- H (*n* = 102) plus Yoruba- Y (*n* = 240) IPAQ-SF H+Y/2	**Total (*n* = 342) ICC (95% CI)**	**Female (*n* = 102) ICC (95% CI)**	**Male (*n* = 240) ICC (95% CI)**
VPA (Min week-^{1})	0.5815 (0.4375-0.6855)	0.27 (-0.178-0.5805)	0.6205 (0.4825-0.7215)
MPA (Min week-^{1})	0.328 (0.164-0.472)	0.2275 (-0.055-0.473)	0.3185 (0.1005-0.505)
Walking (Min week-^{1})	0.4355 (0.291-0.5555)	0.2615 (-0.036-0.508)	0.469 (0.301-0.5715)
TPA (MET-Min week-^{1})	0.492 (0.365-0.599)	0.3645 (0.117-0.571)	0.481 (0.319-0.6115)
Time spent sitting (Min week-^{1})	0.3575 (0.2295-0.478)	0.568 (0.357-0.729)	0.242 (0.0445-0.413)

PA = Physical Activity, Min = Minute, MET = Metabolic Equivalent, *r* = correlation coefficient, **, p < 0.001, ICC = intraclass correlation coefficient, VPA = vigorous physical activity, TPA= total physical activity

Table 3: Comparison of concurrent validity and reliability of the Yoruba, Hausa and combined data of the IPAQ-SF

Variables	**F**	**p - value**
Concurrent validity total	3.544	0.062^{NS}
Concurrent validity female	3.243	0.075^{NS}
Concurrent validity male	6.576	0.012*
Reliability total	5.024	0.026*
Reliability female	5.739	0.018*
Reliability male	3.199	0.077^{NS}

Analysis of variance– ANOVA: * p<0.05 = significant, NS = not significant

Table 4: Comparison of concurrent validity and reliability of the Yoruba and Hausa IPAQ-SF

Variables	Yoruba	Hausa	T	P - value
CV total	0.723 ±0.111	0.856±0.054	-2.414	0.054^{NS}
CV Female	0.937 ±0.053	0.850±0 .062	2.381	0.045^{NS}
CV male	0.640 ±0.133	0.844±0.064	-3.099	0.022*
Reliability total	0.320 ±0.104	0.558±0.145	-2.986	0.020*
Reliability female	0.187 ±0.159	0.490 ± 0.126	-3.348	0.011*
Reliability male	0.296±0.126	0.556± 0.203	-2.432	0.047^{NS}

CV=concurrent validity, * p<0.05 = significant NS = not significant,

Table 5: The National Institutes of Health (NIH) quality assessment for the included studies

Studies	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	P
Awotidebe et al. 2021	**1**	**1**	**1**	**1**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**NA**	**1**	**11**
Oyeyemi et al. 2011	**1**	**1**	**1**	**1**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**NA**	**1**	**11**

Key:
Q = question,
P- Total score Assessment of the quality of the included studies by application of the NIH tool (Shea et al. 2017),
scoring – items scored 1 if yes, 0 if no, absent or not applicable.
The tool is composed of 14 closed questions, with possible answers: 1 = Yes, 0 = No, CD = cannot determine, NA = not applicable, and NR = not reported.

Figure 1: Flow chart

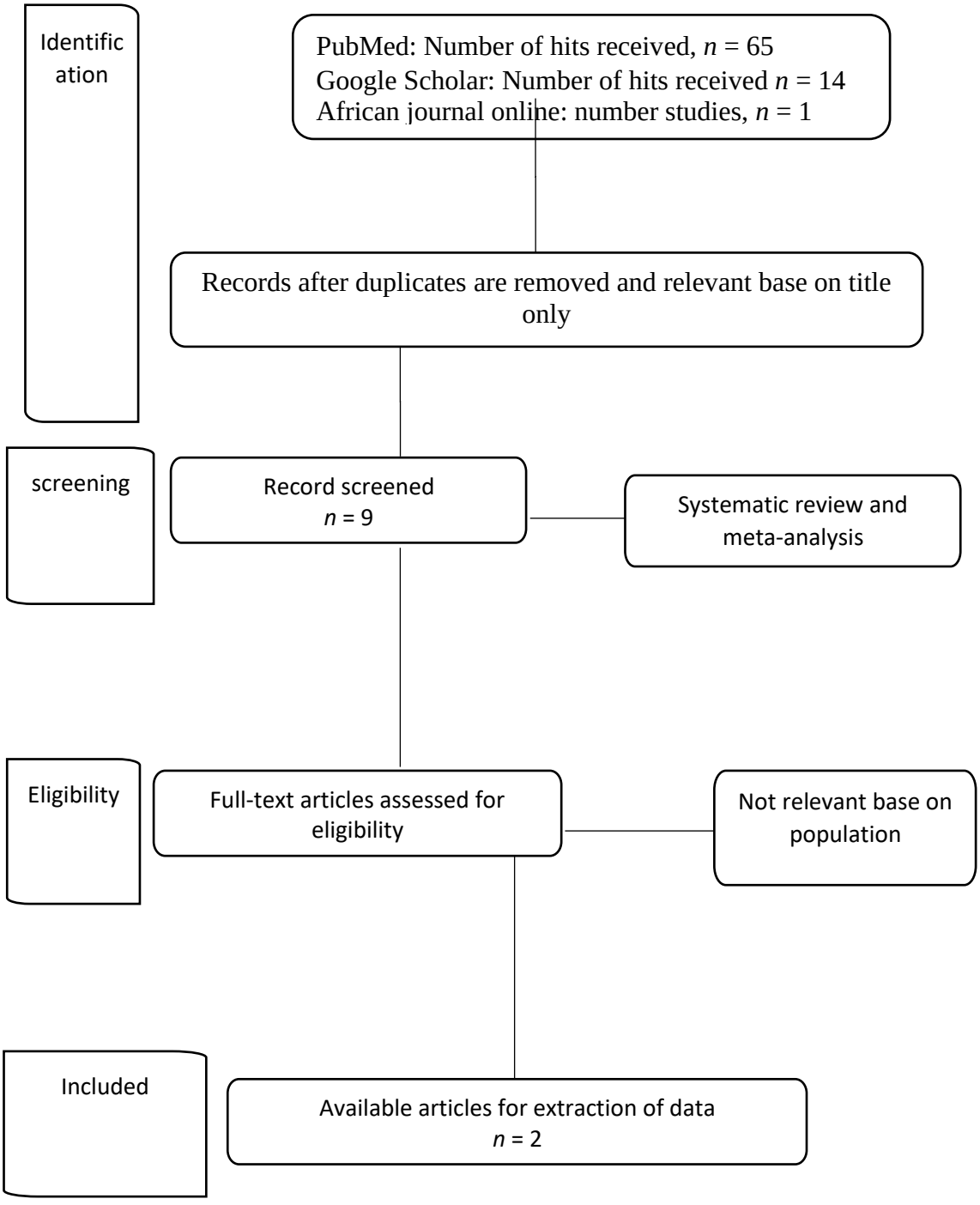
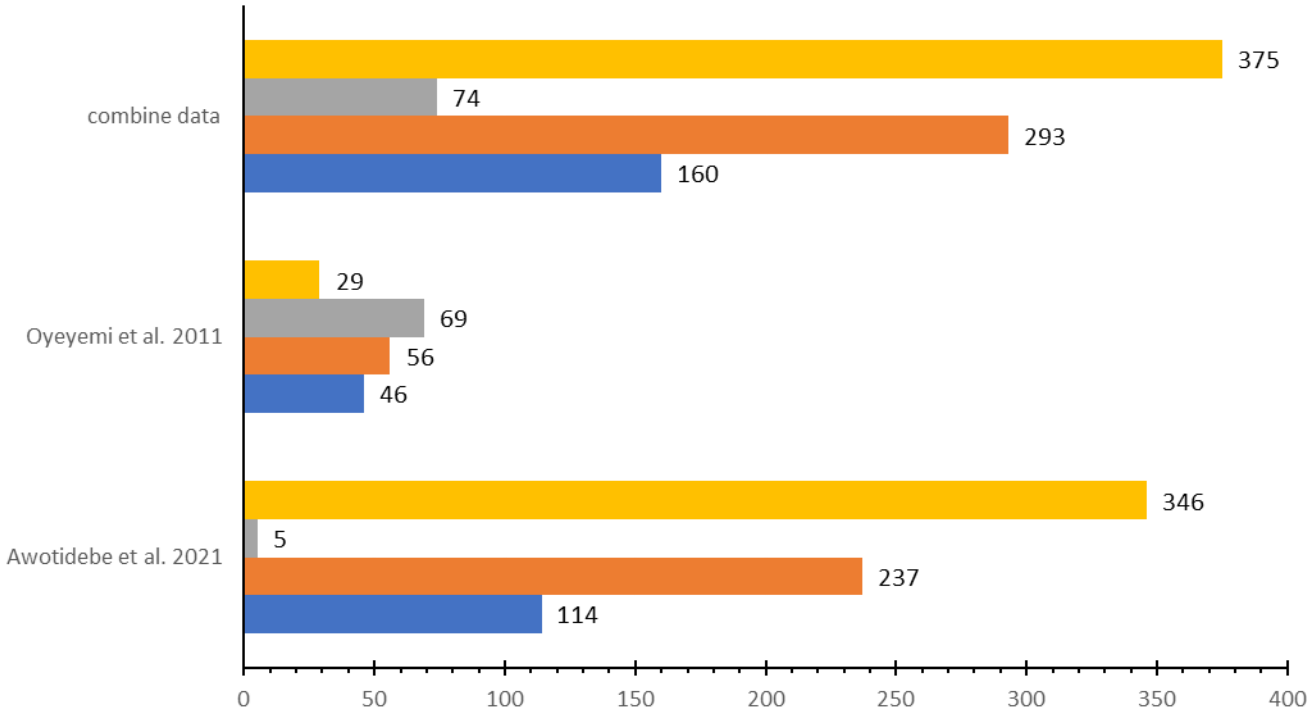


Figure 2: Gender and marital stutus of studies



	Awotidebe et al. 2021	Oyeyemi et al. 2011	combine data
single	346	29	375
married	5	69	74
male	237	56	293
female	114	46	160

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ANTIOXIDANT MICRONUTRIENTS AND PHENOL FRACTION OF *PIPER GUINEENSE* EXTRACT EXHIBITS DIFFERENTIAL CD68 CEREBELLAR EXPRESSION ON AZT INDUCED- NEUROINFLAMMATION.

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Abstract

Background of the study: Exposure to HAART regimen especially Azidothymidine (AZT) therapy has neurotoxic adverse effects like neuroinflammation.
Aim: We assessed the role of Phenol extract of *P. guineense* leaf and antioxidants on the Azidothymidine challenge.
Material and Methods: Thirty-six adult Wistar rats were randomized into nine groups of 4 rats each. Azidothymidine (AZT) was administered to all groups except the control which received 0.1mL saline. Others received 100 mg/kg of AZT for 8 days, 100 mg/kg of AZT+100 mg/kg of *P. guineense*, 100 mg/kg of AZT+ 200 mg/kg of *P. guineense*, 100 mg/kg of AZT + 400 mg/kg of *P. guineense,* 100 mg/kg of AZT+ Zinc, 100 mg/kg of AZT+ 3mg/kg of Melatonin, 100 mg/kg of AZT+ 1000mg/kg Cellgivity, and 100 mg/kg of AZT+ 50 mg/kg of Selenium for 14 days respectively.Cerebellar amoeboid microglia expression was by identified by CD68 marker.
Result: AZT induces reactive microgliosis, and the *P. guineense* extract exhibited dose-dependent pleiotropic microglia retraction. The antioxidants: Zinc, melatonin, selenium and cellgevity deferentially mitigate the AZT effect by providing neuroprotection.The high dose of *P. guineense*, selenium, and cellgevity had a pronounced reversal effect on the microglia.
Conclusion: The effective dose of phenol extract *p.guineense* was beneficial in halting the neuroinflammatory effect of AZT in the cerebellum.
Keywords: *Neuroinflammation, anti-retroviral, Antioxidants, Piper guineense, Microglia, Micronutrients*.

Introduction

In the nervous system, neuroinflammation is a maladaptive reaction to tissue damage that involves the recruitment of immune cells and mediators, which are frequently produced to spur on neuro-regeneration[1,2,3]. Neuroinflammation is an Azidothymidine (AZT) adverse side effect. AZT is a nucleoside reverse transcriptase inhibitor associated with the adverse phenomenon in the brain that contributes to neuronal and glial damage in the management of HIV[4]. People on AZT and living with HIV have been found to have a variety of the neuronal damage over time [4,5,6,7,8]. Prominent among the damages, cerebellar dysfunction is characterized by granules cell and primary cerebellar atrophy [5, 6,7,9]. The disruption of the granular cells indicates a pathological mechanism which in turn impacts altered Purkinje cell activity[5,6,7].

In addition, components of nutritional vulnerability are affected by the AZT regimen and other retroviral therapy. As a result, it has long been known that nutritional deficits has co-morbidity with a number of illnesses, including HIV/AIDS. Therefore, micronutrients and antioxidants supplementations may improve the course of disease and the effectiveness of treatment by addressing deficiencies and immune system stress. Furthermore, inadequate diet might lead to increased toxicity or reduce the effectiveness of medications[10,11,12,13]. Physiological changes brought on by drugs are linked to micronutrient deficits. Micronutrient supplements, on the other hand, can postpone the onset of AIDS and increase survival rates. They also provide a low-cost method of reducing the negative effects of medication and enhancing treatment results[11,12,13].

Antioxidants are compounds that prevent oxidation from occurring and protect the organism from the damaging effects of free radicals. In order to maintain homeostasis, it is essential for scavenging excess reactive oxygen species (ROS). The immune system is strengthened by optimizing the intake of antioxidants, minerals, and other bioactive food ingredients[14]. Antioxidants, which are found in vitamins, minerals, and enzymes, guard and restore cells against the harm caused by free radicals that target proteins, fats, and DNA[14].

In the form of glutathione peroxidase, selenium is an essential vitamin that may synthesis DNA, repair oxidative damage to DNA, alter cellular antioxidant defense, and promote leukocyte adhesion[12.] When taken as a supplement with HIV medication, selenium lowers the risk of brain damage via inhibiting inflammatory cytokines and glutathione peroxidase's antioxidant properties[12]. The antioxidant has shown promise in reducing platelet aggregation, lipid peroxidation, and microglial responses[15,16].

On the other hand, zinc functions as an immunological modulator, antioxidant, ant-viral, and anti-inflammatory agent and is crucial for cell-mediated immunity[17,18]. The enzymes that help the antioxidant defense system function well depend on zinc as a co-factor [17]. Neurons produce zinc in a number of situations where microglial activation is evident[18,19, 20].

In addition to its important role in the circadian cycle, melatonin is a neurohormone with a wide range of biological properties, including anti-inflammatory, anti-apoptotic, and antioxidant properties[21]. Microglia, neurons, and astrocytes are home to melatonin receptors, which can easily cross the blood-brain barrier (BBB)[22]. Melatonin has been shown to have a neuroprotective impact against disorders of the central nervous system[23,24]. By controlling inflammation, apoptosis, or autophagy following brain damage, it helps to preserve cell survival and homeostasis[23,24].

Cellgevity® is a dietary supplement that is classified as an antioxidant. It specifically enhances glutathione and contains riboceine

(D-ribose L-cysteine), which is its active ingredient. Other significant ingredients include alpha lipoic acid, selenomethionine, turmeric root extract, broccoli seed extract, resveratrol, aloe extract, vitamin C, grape seed extract, quercetin, milk thistle seed extract, curcumin, cordyceps, etc. Because glutathione (GSH) may scavenge reactive oxygen species, it provides protection against damage caused by oxidative stress[25]. Glutathione is necessary for immunological system function, tissue growth and repair, and the amelioration of neuropathological changes in the hippocampal region[26.]

Herbal plants continue to be a source of promising treatments for a variety of illnesses. Piper guineense is referred to locally as Ata Iyere in Yoruba and Uziza in Igbo, and is also known as African black pepper, Ashanti pepper, and Benin pepper[27,28]. It has long been used to treat infections, inflammation, and infertility. Pharmacologically, it possesses well-known anti-inflammatory and antioxidant qualities[27,29]. Flavonoids derived from P. guineense also prevent HIV replication[15].

On a more positive note, this study examined the potential of P. guineense (Uziza) and particular antioxidants in reducing alterations in microglia related to neuroinflammation caused by AZT.

Materials and Methods

Plant: *P.guineense*

The plant material was procured from Ogbete market in Enugu State, Nigeria. The plant was identified by a curator in the Department of Plant Science and Biotechnology of the University of Nigeria, Nsukka, Nigeria and its authentic name was confirmed on www.plantlist.org[30]. The *Piper guineense* (Uziza) leaves were carefully selected to remove leaves with pathological features to ensure disease free collection. The leaves were then washed with distilled water and air-dried for seven days at room temperature. Thereafter, the *P. guineense* leaves were pulverized into a fine powder, using a milling machine. The 500 g of the powder was soaked in 80% methanol and left for 48 hours with continuous stirring. 10% of N-hexene was then added to the filtrate, and left in the open air to dry up. The final extract was then kept in the refrigerator.

Estimation of Total Phenolic and flavonoid contents

The method of Kupina et al.[31] was adopted in the estimation of total phenol in the extract. The total phenolic content of dry extracts was performed with a Folin-Ciocaltaeu assay. 1 ml of sample (1 mg/mL) was mixed with 1 ml of Folin Ciocalteu's phenol reagent. After 5 minutes,10 ml of 7% sodium carbonate solution was added to the mixture followed by the addition of 13 ml of deionized distilled water and mixed thoroughly. The mixture was kept in the dark for 90 minutes at 23^0C, after which the absorbance was read at 760 nm. The total phenolic content was determined from the extrapolation of the calibration curve which was made by preparing a Gallic acid solution. The estimation of the phenolic compounds was carried out in triplicate. The TPC was expressed as milligrams of Gallic acid equivalents (GAE)/g of dried sample.

The content of flavonoids in plant extracts was determined using the spectrophotometric method adopted from Dirar et al[32]. In a 96-well plate, 25 µl of standard or sample solution was added followed by 75 µl of ethanol. Afterwards, 5 µl of $AlCl_3$ (10% prepared in methanol) and 140 µl distilled water were added to the mixture. The plate was shaken for 30 mins prior to the measurement of the absorbance at 420 nm. All samples and standards were measured against a blank prepared concomitantly with the exception of $AlCl_3$. The samples were prepared in triplicate for each analysis and the mean value of absorbance was obtained. Quercetin was used as a standard to construct the calibration curve. The TFC of the extract was determined using an equation obtained from the standard calibration curve and was expressed in terms

of Quercetin equivalent (mg of Quercetin/g of extract).

Drugs

Zinc and melatonin (Puritan Pride), and Cellgevity (Riboceine®) were purchased in bulk from a subsidiary of Max International, Selenium and AZT produced by (Aspen Pharmacare company in South Africa) was purchased from a registered pharmacy, Nigeria.

Animal Handling

Ethical approval was obtained from the Departmental of Ethics Committee on the Use of Laboratory Animals, Enugu State University of Science and Technology, Enugu State, Nigeria. All procedures were carried out following the National Academy of Science's Guide for Care and Use of laboratory animals[33]. Thirty-six (36) Wistar rats age 6-8 weeks, weighing 180-200 g were purchased from the animal husbandry of the College of Medicine, University of Nigeria, Enugu campus, Nigeria. The rats were acclimatized in the animal house of the College of Medicine, Parklane, ESUT for two weeks. The rats were housed in netted iron cages in groups of four, fed with the rat's chow (Growers mash, Nig, Ltd.), and provided water *ad libitum*. The laboratory conditions of temperature 32^0C, relative humidity of 60-70%, and 12hrs light-dark cycle were maintained. Thereafter, the animals were randomly divided into 9 groups of four animals each for the commencement of the study.

Experimental Design

Azidothymidine (AZT) was administered to all groups except the control which received 0.1mL saline. Others received 100 mg/kg of AZT for 8 days, 100 mg/kg of AZT+100 mg/kg of *P. guineense*, 100 mg/kg of AZT+ 200 mg/kg of *P. guineense*, 100 mg/kg of AZT + 400 mg/kg of *P. guineense*, 100 mg/kg of AZT+ Zinc, 100 mg/kg of AZT+ 3mg/kg of Melatonin, 100 mg/kg of AZT+ 1000mg/kg Cellgivity, and 100 mg/kg of AZT+ 50 mg/kg of Selenium for 14 days respectively.

Immunohistochemistry

For the analysis of phagocytic or amoeboid microglial morphology, the CD 68 anti-body marker for microglia was used. On the 15th day, all rats were anaesthetized with an overdose of thiopental sodium and transcardially perfused with 0.1 ml of phosphate-buffered saline (PBS, PH 7.4) at room temperature, followed by 4% paraformaldehyde. The brain was harvested and post-fixed in 10% neutral buffered formal saline for 72 hours: Thereafter, the cerebellum was dissected and manually processed for paraffin embedding. Paraffin-embedded blocks were sectioned at 10 µm thickness and further processed and deparaffinized. Immunoperoxidase was used to label CD68 antibodies for microglia. Endogenous peroxidase activity was blocked with pre-incubation in 0.3% H_2O_2. After washing, the sections were pre-incubated for 1 hour at room temperature in the appropriate normal serum before incubation in primary antibodies overnight at 4°C. The sections were then rinsed, incubated in secondary antibodies at 1:200 dilution for 2 hours at room temperature, and then reacted in Avidin-Biotin complex solution for 15 mins using 3-3-diaminobenzidine (DAB) as a chromogen. The sections were then mounted on slides, dried, dehydrated, cleared, and cover slipped. Thereafter, representative phtomicrographs of each group was captured using the Amscope 3.0 with a digital camera.

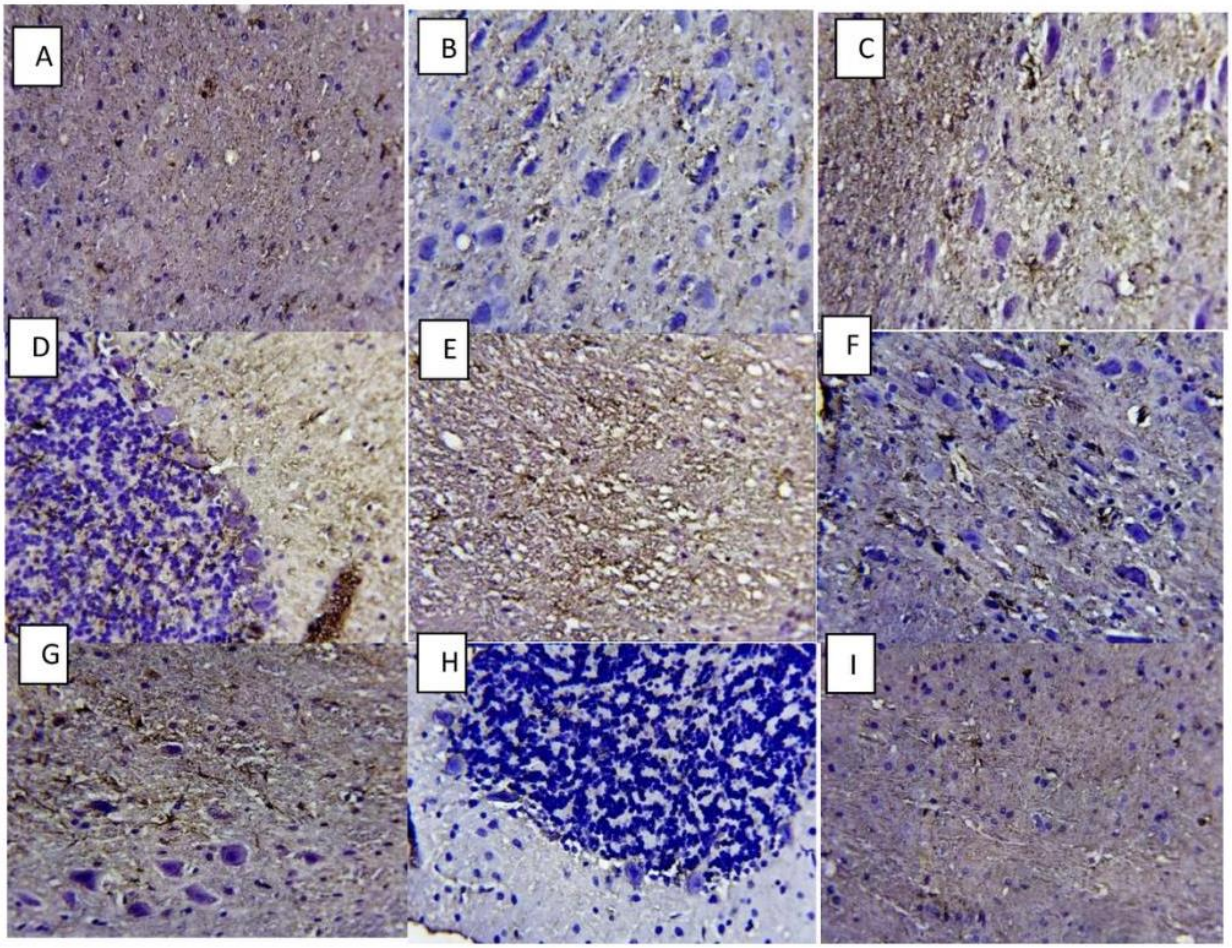

Figure I: CD68 immunostaining highlighted amoeboid microglia: A:normal saline, B :AZT only, C;AZT+100 mg/kg extract, D;AZT+200 mg/kg extract E;AZT+ 400 mg/kg extract, F; AZT+Zinc ,G: AZT +Melatonin, H: AZT + Cellgevity, H: AZT +Selenium. Anti-CD68. X 800.

Result and Discussion

Plant analysis revealed the concentration of total phenolic and flavonoid compounds as 31.99±4.21and 39.52±1.79 respectively. The CD68 is a granule protein and scavenger receptor found on macrophages. The macrophage of the brain is a microglial cell that plays a critical role in cross-talk responses during inflammation, hence its expression is associated with heightened neuroinflammation[34,35]. The over-activated microglial cells linked to neuroinflammation are a key indicator of neurological disorders. The over-activated microglia can disturb neuronal homoeostasis by releasing inflammatory mediators leading to neuronal

dysfunctions and death. Thus, inhibition of over-activated microglia might be an effective therapeutic approach for modulating neuroinflammation[34,35,36].

In a recent review, the close relationship between neuroinflammation and neurodegeneration has been linked to the dysregulation of glial-neuronal communications[21]. Under physiological conditions, microglia appear resting and ramified with extending processes as they constantly sensor the brain environment for any change or pathology that can cause them to respond in a variety of different ways[34]. Cell morphology alone does not fully indicate microglial function but examining a range of microglial markers aids a better understanding of the behaviour of these cells. for instance, Cerebellar microglia are a unique population of immunologically responsive cells that are normally inactive in the absence of CNS pathology[5]. However, this cell becomes acutely sensitive to assault in the CNS and remains a vital participant in the process of the resolution. They regulate the survival of Purkinje and Granular cells during pathological events like exposure to alcohol, toxin, infection, and inflammation[37]. A previous study has highlighted the differential behaviour of cerebellar microglia, including differential expression, immunological gene, rapid turnover, and sensitivity to haemostatic disruption in disease and injury[37].

It is clear in this study, the reactivity of microglia is revealed by the CD68 marker. The AZT group revealed positive reactivity to the CD68 marker with prominent microglia cells. This implies that AZT neurotoxic adverse drug effects are immune-mediated leading to apoptosis of Purkinje and granular cells. Studies support the fact that AZT is not actively transported across the blood-brain barrier but high levels of AZT accumulate in the cerebrospinal fluid, and subsequently diffuse into the overlying parenchyma[4,37,38]. This might explain the mechanism of AZT-induced microglia response (microgliosis) observed in our study. Additionally, due to the close anatomical proximity of the neurogenic niches to the ventricular system, it collaborates with the hypothesize that diffusion from CSF exposes neurons to relevant levels of AZT that are sufficient to perturb normal cell functions including microglia[4]. The low dose of *P.guineense* exhibited similar features of microglia reactivity as the AZT group. Comparatively, the *P.guineense* phenol extract exerted a dose-dependent effect on the reactivity of microglia. These findings imply the withdrawal of microglia following the neuroinflammation induced by AZT. This affirms the anti-inflammatory properties of *P.guineense* previously reported[27].

The zinc and melatonin revealed positive immunoreactivity to the CD68 marker but activated microglia were less compared to the medium and high doses of the *P. guineense*, cellgevity, and selenium. Melatonin is a well-known neuroprotective and anti-inflammatory agent[24]. The anti-inflammatory and antioxidant effects of melatonin are intertwined[22]. Neuropathological conditions are accompanied by low-grade inflammation, blood-brain barrier impairment, and alteration of sleep which affects melatonin secretion[39]. The deviation in melatonin secretion response positively to exogenous melatonin. Hence, exogenous melatonin administration reduces the damaging effects of neuroinflammation in rodents[39,40]. It is not surprising that melatonin alleviates the effect of AZT on microglia expression.

Growing evidence supports the anti-inflammatory role of melatonin in acute and chronic inflammation processes[21,23]. The main mechanisms of action attributed to melatonin are free radical scavenging, endogenous antioxidant enzyme stimulation, and improved efficiency of other antioxidants [21,23]. Our finding likely supports the latter mechanism: that is the effect of melatonin was secondary to the enhancement of other endogenous antioxidant activities. Zinc is an essential

mineral in health that acts as a cofactor for the synthesis and transcription factor in a view to maintain the antioxidant defense[41,42]. It stabilizes the membrane, and inhibits the enzyme nicotinamide adenine dinucleotide phosphate oxidase and prevents apoptosis[12].

Zinc regulates gene expression through transcription factor activity and is responsible for the activity of dozens of key enzymes in neuronal metabolism[43]. However, our result implies Zinc showed a weak anti-inflammatory effect on microglia activation which collaborates with other report[11].

On the contrary, selenium showed a prominent effect comparable with the high dose of *P. guineense,* and cellgevity. The selenium effect was attributed to its neuroprotection capability afforded by modulation of Ca^{+2} influx into ion channels and anti-inflammatory by abrogating microglia invasion, especially via biosynthetic stimulation of antioxidative seleno-protein in the brain[44]. Cellgevity is a recent dietary supplement that enhances natural glutathione levels in the human body and targets the removal of damaging toxins from the body[45]. The major ingredients of cellgevity are the new nutritional compound known as Riboceine which enables the body to produce an optimal amount of glutathione[45]. The microglia scavenging effect of cellgevity due to the high level of glutathione, as a potent antioxidant suggests a modulatory interplay between the antioxidant and anti-inflammatory pathways. These findings implicate oxidative stress as a contributor to the underlying neurotoxicity and antioxidant provides an access point for adjunctive therapies to complement AZT therapy and reduce neuroinflammation.

Conclusion

P. guineense extract exhibited dose-dependent pleiotropic, anti-inflammatory and antioxidant effects. However, the zinc, melatonin , selenium, and cellgevity deferentially mitigate the neuroinflammatory effect of AZT by providing neuroprotection either via anti-inflammatory or antioxidant mechanisms. Although the high dose of *P. guineense*, selenium, and cellgevity had a more pronounced beneficial effect on the reversal of microgliosis. Hence, the effective dose of phenol extract of P. guineense should be considered in order to achieve the desired therapeutic outcome against neuroinflammatory effect of AZT in HIV patients.

Conflicts of Interest

The Authors declared that research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest

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Author Contributions:

FBE: Conception and design, perform the research, wrote the draft; EAE: gave conceptual advice, contributed to the discussion, reviewed, and edited the draft; OAE: analyzed the histology. All authors read and approved the manuscript.

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ESTABLISHMENT OF LOCAL DIAGNOSTIC REFERENCE LEVELS (LDRL) FOR ADULT CHEST COMPUTED TOMOGRAPHY EXAMINATION IN A SOUTH-EASTERN STATE OF NIGERIA.

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Abstract

Background: Diagnostic reference levels (DRLs) are indispensable tools and a sub-principle in optimization of radiation dose in the field of Radiography and radiological sciences. It is intended to identify and reduce unnecessary high ionizing radiation dose to patients during radiological examinations such as Chest Computed Tomography (CT) examination.
Objective: To determine local Chest Computed Tomography dose index ($CTDI_{vol}$) and Dose length product (DLP) in the selected CT centers, estimate the Effective dose (ED) for Chest CT examination and compare our results with both stated Nigerian national and international standards.
Materials and Methods: A total of 240 adult subjects referred for chest CT examination from the four considered CT radiodiagnostic centers were surveyed within a period of six months. Data were obtained from different models of CT scanners which included Toshiba Alexium, Brightspeed multidetector CT scanner and Siemens Somerton respectively. Radiation dose were generated from Computed Tomography Dose Index ($CTDI_{vol}$) and Dose Length Product (DLP) from where the effective dose (E) was calculated using the product of chest DLP and the normalized coefficient found in the European guideline. Data were analyzed using SPSS version 20 Chicago software. The mean values for each CT centre were calculated at 75th percentile of DLP and $CTDI_{vol}$ chosen as the basis for DRLs.
Results: The 75^{th} percentile of $CTDI_{vol}$ and DLP were 22 mGy and 800 mGy.cm. The effective dose was 13. 6mSv.
Conclusion: Radiation dose variations across the four CT centres surveyed have revealed the need for urgent dose optimization to narrow down centre-specific and composite DRL values to national and international best practice.
Key Words: Computed Tomography, Diagnostic Reference levels, Dose Optimization, Effective dose.

Introduction

Computed Tomography (CT) examination has globally contributed to more than 63% of ionizing radiation from total medical exposures[1]. In some developed countries such as the United States of America (USA), CT scans constitute only 12% of all radiological investigations which however account for about 50% of the collective radiation dose to the population from medical radiation procedures [2]. The USA effective radiation dose have so far declined by 20% due to increased awareness, regular retraining and education of staff, periodic radiation dose optimization, production of advanced machines with high sensitive detector technology and improved operator performance[2]. It is estimated that over 400 million CT procedures are performed globally with an average frequency of 55 per 1000 (5.5%) subjects [1]. Patient dose variation were reported between interdepartmental and intradepartmental levels [3]. According to researches, more than one percent of patients receives an effective dose of more than 100.0mSv after 5.0 years; and malignant tumors incidence from CT treatments will likely approach two percent [4,5]. Consequently, it became imperative strike a balance by ensuring that radiation dose is well optimized and image quality maintained. The principle of optimization expects that the likelihood of incurring radiation exposures, the number of people exposed and the magnitude of their individual exposure should all be kept as low as reasonably achievable (ALARA principle)[6]. Optimization of patient dose in CT requires the application of examination-specific scan protocols tailored to patient age, size, region of body and clinical indication in order to ensure that the dose to each patient is as low as reasonably achievable (practicable) for the clinical purpose of the CT examination[7]. Currently, the number of chest CT examinations is on the increase due to technological advancement which allow scanning of large area including the radiosensitive organs such as the mammary gland [8].

Establishment of diagnostic reference levels (DRLs) was first proposed by the International Commission on Radiation protection in 1996 [9] and saddled with the responsibility of optimizing radiation dose to patients during radiographic procedure and to minimize dose variations within and among healthcare facilities [10,11]. It is simply an essential control mechanism used to shield patients from unnecessary radiation exposure[12.] The dosimetric parameters recommended for monitoring the DRL in CT examination are weighted Computed Tomography Dose Index ($CTDI_{vol}$) and Dose Length Product (DLP), displayed on the CT scanner console at the end of each scan which are measures in 16 and 32cm diameter acrylic phantoms [10]. $CTDI_{vol}$ is a standardized measurement of the radiation output of a CT scanner and fixed. It is independent of the size of patient and scan length. It therefore allows for comparison between other scanners and scan protocols [13]. Also, the DLP is the product of $CTDI_{vol}$ and the scan length, used to quantify the radiation dose received by a patient and therefore a direct estimate of radiation dose received by a patient [10]. DRLs are usually calculated by collection of patient dose data at the 75th percentile point of the dose spread or reported median [10] of $CTDI_{vol}$ and DLP from a survey conducted across a

broad user base [14,10]. Because 25% of the population will exceed the DRLs, it should be regarded as an indicator rather than an overexposure of radiation dose. DRLs can be established at local, hospital or center based [14].

The International Atomic Energy Agency (IAEA) mandated every country to establish a radiation regulatory body for radiation protection. Consequently, Nigerian Nuclear Regulatory Authority (NNRA) and National Institute for Radiation Protection and Research (NIRPR) in 1996 and 2005 respectively were established by Act 19 of 1995. These two bodies are responsible for research, regulation and training of Radiation Protection Personnels in Nigeria as well as establishment of national, regional and local diagnostic reference levels. DRLs should be reviewed frequently to guarantee that patient doses are optimized within a justified levels preferably on annual bases [10]. In Anambra state, there is paucity local data base for Chest DRLs and thus there is need for its determination. This study was therefore aimed at determining the local diagnostic reference levels for Chest computed tomography examination in a South-Eastern state of Nigeria.

Materials and Methods.

A retrospective cross-sectional study was conducted in four CT centers in Anambra state, Nigeria for a period of six months. A total of 240 subjects aged from 18 years and above were purposively surveyed. For establishment of Diagnostic Reference levels (DRLs) and in several reviewed literatures, a minimum of 10 subjects for each body region were considered significant [15,16, 17]. Among the CT centres considered for this study, two were Mission-owned hospitals, one was private-owned while one was government-owned hospital. They were coded as A,B,C and D and had different installed models of CT scanners which included Toshiba Alexium, Brightspeed multidetector CT scanner and Siemens Somerton. These centres were selected because they were functional, fully licensed, undergo regular calibration and are authorized to administer ionizing radiation by the Nigerian nuclear Regulatory Authority (NNRA) as at the time of study. Ethical consideration was obtained from the Ministry of Health Anambra state (MH/Awk/M/132/413) and informed consent form the hospitals/ centres under study. Data collection plan was adopted from the International Atomic Energy Survey form which has the following sections: Subject demographic information, Scan parameters and Dosimetric quantities/parameters were collected with the assistance of the CT Radiographers in charge of each of the four centres surveyed. SPSS version 20.0 Chicago was used for data analysis. Statistical significance level among CT centres surveyed were considered at 0.05. Data were calculated to generate the mean values and standard deviation for each CT centre with 75th percentile (third quintile) of DLP and $CTDI_{vol}$ chosen as the basis for establishing local DRLs. Results from this present study were compared with other similar studies both locally and abroad.

.The following steps were taken to determine the local diagnostic reference levels (DRLs) for chest CT examination in this study:

Stage 1

The mean values were used to summarize all the data. This was achieved by adding all the values of $CTDI_{vol}$ and DLP obtained from different centres and dividing the sum by the number of subjects. Comparism of the mean $CTDI_{vol}$ & DLP values for chest CT examination from one center to another were carried to determine whether there was dose variation among the respective CT centres.

Stage 2

The 75^{th} percentile values of the mean $CTDI_{vol}$ and DLP were obtained and used to determine the local Diagnostic Reference Levels. The 75^{th} percentile (third quartile) value was chosen as an appropriate investigation level on the grounds that if 75% of CT units can operate satisfactorily below this dose level, the remaining 25% sho uld to be made aware of their potential less th an optimal performance. The values obtained were compared with other similar studies to ascertain the level of conformance of current practices in Anambra state.

Stage 3

Effective dose for chest C.T examination in Anambra state was calculated by multiplying the composite 75^{th} percentile of the DLP values for chest C.T scans by the normalized coefficient found in the European guideline ($0.017\ mSv.mGy^{-}1$) for chest CT [9].

Stage 4

The dosimetric parameter ($CTDI_{vol}$ and DLP) values and age were correlated to ascertain if there was any statistical significance.

Results

Table 1: Age, Gender and Number of Subjects

As shown in Table 1, two hundred and forty (240) subjects which were made up of one hundred and twenty-one (50.4 %) male and one hundred and nineteen (49.6 %) female were surveyed in the study. Their ages ranged between 18 – 80 years.

CT Centres	Frequency		Total	Range (Age)	Mean ± SD (Age)
	Male	Female			
Centre A	30	30	60	18 - 80	51 ± 16.4
Centre B	33	27	60	18 - 79	45 ± 16.3
Centre C	31	29	60	19 - 80	54 ± 16.2
Centre D	27	33	60	25 - 79	50 ± 14.3
Composite values.	121	119	240	18 - 80	50 ± 16.1

Table 2: Range and mean of the computed tomography dose index (CTDI).
Table 2 shows the range and mean of the CTDI. Chest had a CTDI ranging from 4.5– 139.0 mGy and mean value of 17.6 ±14.8 mGy.

Variables	**Chest** (mGy)	
	Range	Mean
Centre A	7.0 – 38.0	17.8 ± 8.0
Centre B	4.5 – 34.0	13.8 ± 8.5
Centre C	5.3 – 139.0	23.3 ± 25.0
Centre D	11 – 41.0	22.4 ± 8.2
Composite values	4.5 – 139.0	17.6 ± 14.8

Table 3: Range and Mean of the Dose Length Product (DLP).
Shown in Table 3 is the composite and centre-specific range and mean of the DLP.
Centre A had DLP of 562.7 ± 137.8 mGy-cm while centre B had the highest of 928.5 ± 257.2mGy-cm.

Variables	**Chest DLP (mGy-cm)**	
	Range	Mean
Centre A	288 - 816	562.7 ± 137.8
Centre B	214 -1580	928.5 ± 257.2
Centre C	203 - 966	659.3 ± 183.7
Centre D	441 - 900	657 ± 125.0
Composite values.	203 -1580	714.3 ± 327.5

Table 4: The 75th percentile of the $CTDI_{vol}$.
Table 4 shows the specific 75^{th} percentile of the $CTDI_{vol}$. The 75^{th} percentile of the $CTDI_{vol}$ ranged between 19.0 – 27.6 mGy and composite 75^{th} percentile was 22 mGy.

Variables	**Chest**	
	Mean	75^{th} percentile
Centre A	17.8 ± 8.0	23.5
Centre B	13.8 ± 8.5	19.0
Centre C	23.3 ± 25.0	24.3
Centre D	22.4 ± 8.2	27.6
Composite values.	17.6 ± 14.8	22.0

Table 5: The 75th percentile of the DLP.

Table 5 shows the 75th percentile of the DLP. The centre with the least and highest values were A (672.7 mGy-cm) and D (823.3 mGy-cm) respectively. Composite DLP was 800 mGy-cm

Variables	**Chest (mGy-cm)**	
	Mean	75th percentile
Centre A	562.7 ± 137.8	672.7
Centre B	928.5 ± 257.2	823.3
Centre C	659.3 ± 183.7	802.0
Centre D	657 ± 125.0	741.4
Composite value	714.3 ± 327.5	800.0

Table 6: The 75th percentile of the CTDI$_{vol}$ and DLP according to gender

Table 6 gives the 75th percentile of the CTDI$_{vol}$ and DLP in both gender. The composite CTDI$_{vol}$ recorded a higher value in female (25.0 mGy) than male (24.0 mGy). For the DLP in female values (747.0 mGy-cm) were higher than male (740.0mGy-cm).

Variables	**CTDI(mGy**	**DLP (mGy)**	**CTDI(mGy**	**DLP (mGy)**
	MALE	FEMALE	MALE	FEMALE
Centre A	21.0	26.5	684.0	675.0
Centre B	18.0	23.6	936.4	823.2
Centre C	24.0	25.0	800.0	864.0
Centre D	30,3	26.3	718.0	743.0
Composite value	24.0	25.0	740.0	747.0

Table 7: Effective dose values for chest C.T in Anambra state.

Table 7 gives the effective dose for chest CT scans in Anambra state. This was calculated by multiplying the composite 75th percentile of the DLP values for C.T scans by the normalized coefficient found in the European guideline (0.017 mSv.mGy^{-}1) for chest CT (European Commission, 1999 and Nwodo et al., 2018). The effective dose value for chest CT was therefore 13.6 mSv for Anambra state.

BODY REGION	Chest
DLP	800 mGy.cm
Effective Dose	13.6 mSv

Table 8: Comparison of present work with similar publications.

A comparison of the present with other similar publications were shown in Table 7 below. From this work, the $CTDI_{vol}$ for chest (22 mGy) fall apparently within the range found in the literature (10 – 22 mGy). However, the DLP for chest (800 mGy-cm) was higher than the values from the literature (390 – 735 mGy-cm).

Research Study	Location	Chest	
		CTDI (mGy)	DLP(mGy-cm)
Present study, 2023	Anambra (Local)	22	800.0
Diana et al., 2017	Egypt (Local)	22	420
Kam et al., 2020	Australia (Local)	10	390
Saravanakumar, 2014	India (Local)	12	456
Marema et al., 2023	Addis Ababa (Local)	13	635
Muhammad et al., 2016	Ilorin (Local)	10	407
Ernest et al., 2018	Nigeria (National)	17	735

Table 9: Correlation of anthropometric variables with $CTDI_{vol}$ and DLP

Correlation of age with the CTDI and DLP is given in Table 9. Age correlates poorly with the CTDI and DLP. The p-values > 0.05 indicating that the correlations are also statistically not significant.

Variables				
		CTDI	**DLP**	**REMARK**
Age	**R**	-0.024	0.000	Poor correlation
	P	0.792	0.998	Not significant

Discussion

Local diagnostic reference level for chest CT examination for a South-Eastern state of Nigeria was determined using weighted Computed Tomography Dose Index ($CTDI_{vol}$) and Dose Length Product (DLP) at the 75th percentile point of the dose spread or reported median

Four CT centres were purposively selected for the study with a total sample size of 240 adult subjects retrospectively surveyed. They were gender-divided into 121 (50.4%) male and 190 (49.6%) female subjects with age bracket that ranged from18-80 years.

In 2017, the ICRP acknowledged two major principles of radiation protection in clinical and medical applications which include justification of imaging procedures and

optimization of radiation exposure during radiological procedures. Justification of imaging procedures and practices indicates that the procedure is necessary and that the overall subjects benefits outweighs the potential risks. Also, optimization refers to keeping radiation dose as low as reasonably achievable, economic and societal factors being taken into consideration without undermining the diagnostic aim [17].

Diagnostic reference level is a tool to ensure that procedures are optimized and remain optimized by continuous improvement of procedures and evaluation of performance of examination[8]

From our study, the 75th percentile of the $CTDI_{vol}$ and DLP for chest CT were 22 mGy and 800 mGy.cm respectively. These values were higher than the values published for adult chest in Australia by approximately 55% for CTDIvol (10 mGy) / approximately 51% for DLP (390 mGy·cm). The values were also higher when compared to the published values for adults in the India by approximately 46% for $CTDI_{vol}$ (12mGy) / approximately 43% for DLP (456mGy·cm) for chest. In Egypt, our result was similar for $CTDI_{vol}$ (22mGy) and approximately higher 48% for DLP (420mGy·cm). In Addis Ababa, Ethiopia when compared to our study, we recorded higher values by approximately 41% for $CTDI_{vol}$ (13mGy) and approximately 21% for DLP (635mGy·cm). In Nigeria, after five years of national dose survey, our local DRL finding were still higher by approximately 49% for $CTDI_{vol}$ (17mGy) and approximately 49% for DLP (735mGy·cm) Similarly in Ilorin, Nigeria, our values were also higher by approximately 49% for $CTDI_{vol}$ (10mGy) and approximately 49% for DLP (407mGy·cm) [18,15, 19, 20, 21, 22].

These dose variations generated could be as a result of inter-departmental and intra-departmental protocols and technical factors. It can also be attributed to inadequate staff training, variation in patients build up and equipment variation used in different CT centers in Onitsha.

Also our study recorded values lower than those generated in Ibadan, western Nigeria by approximately 3.1% for CTDIvol (22mGy)/approximately 32.7% for DLP (800mGy.cm).

There was obvious radiation dose variation for same chest computed Tomography examination among different CT centres. These variations may be due to CT user's variation in selection of parameters which include kVp, mAs, pitch, patients BMI, quality control practice and manufacturer-specific variations in design of CT equipment used by different facilities.

In other to ascertain the level of compliance of current practices in Anambra state and similar research findings in the literature, further analysis were made.

From our findings, the $CTDI_{vol}$ (22 mGy) fall within the range found in the reviewed literature (10–22 mGy) However, the DLP (800 mGy-cm) was higher than the values found the reviewed literature (390 – 735 mGy-cm) [18,15, 19, 20]. This finding calls for dose audit and optimization in Anambra as well as other State in Nigerian due to high percentage variation between the national dose reference level and our finding.

Comparison between results obtained from different CT centres surveyed in Anambra state and our proposed local DRLs showed remarkable variation across. It was observed that almost 50% of C.T centres surveyed exceeded the DLP set for the local

DRL. Also, 75 % of chest values exceeded the $CTDI_{vol}$ proposed for Anambra state. These observations indicate that there is urgent need for dose audit and optimization in Anambra state, Nigeria.

DLP was converted to effective dose using a normalized coefficient found in the European guideline (0.017 mSv.mGy^{-}1) for chest CT. The mean effective dose values for chest C.T was 13.6 mSv per scan. This value was higher than value obtained in Egypt (7.14 mSv), Australia (6.63mSv), India (7.75 mSv), Addis Ababa, Ethiopia (10.73 mSv), Ilorin, Nigeria (6.92mSv) and Nigerian National reference level (12.50 mSv) [18, 15, 19, 20].

This indicates urgent need for dose audit and optimization through adjustment of CT. Parameters/ technique and quality assurance.

Age of subject's anthropometric parameter had weak negative correlation with CTDIvol for chest ($r = -0.024$, $p= 0.792$) at p-values > 0.05 level of significance.

Subject's age also showed weak positive correlation with DLP ($r = 0.012$, $p = 0.998$) at p-values > 0.05 level of significance. These indicated that there was no correlations between subject's age and DRLs for Chest Computed tomography examination and statistically insignificant.

Limitations of the study

Data were collected from four C.T centers only due to equipment breakdown in some centres while some centers were not fully licensed and therefore not legally authorized to administer ionizing radiation by the Nigerian nuclear Regulatory Authority (NNRA) as at the time of this research. Weight and height of subjects were not captured by the CT radiographers on their archives, thus, limiting anthropometric statistical correlations with dose. The proposed LDRL is only applicable to the centres that participated in the study.

Conclusion

Local Diagnostic Reference Levels (LDRL) for chest CT scan in Anambra state have been established which were significantly higher than most published results from other countries as well as National and states in Nigeria. From our study, only a few CT center met up with the international recommended reference levels and best of practice.

In spite of the established national reference levels, values from most CT centers in our study were significantly high and were not observing proper dose optimization.

Recommendation

We recommend regular staff retraining, seminars and workshop for CT radiographers on dose optimization and audit in Anambra state on regular bases.

All CT centres/facilities in Anambra state should consider the proposed DRLs as a reference data when conducting their regular audit of as least every three years and imbibe on proper adjustment of their CT dose parameters as well as quality control practice to ameliorate unjustified high radiation dose exposure to the patients.

Disclosures of conflict of interest

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SYSTEMATIC REVIEW ON EPIDEMIOLOGICAL STUDIES OF SCHISTOSOMIASIS IN SOKOTO STATE, NIGERIA

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Abstract

Background of the study: Schistosomiasis has been as one of the dangerous neglected tropical diseases that cause huge socioeconomic health problems in many parts of Nigeria including Sokoto State. However, there is a dearth of information on the disease distribution, intensity and risk factors associated with the illness in the state.
Aim of the Study: The present study was conducted to systematically review the prevalence, intensity and risk factors causing schistosomiasis infection in Sokoto state, Nigeria.
Methodology: Information from more than five hundred (500) research articles at ResearchGate, ScienceDirect, PubMed, Google Scholar and World Health Organization (WHO) were gathered. However, only manuscripts that were found with relevant information needed for the sake of the present research were highly considered, articles that contained information on the prevalence, intensity, or risk factors associated with the schistosomiasis were given much emphasis, only articles in which at least their abstract was written in English language were considered.
Results: Results from the available article showed that; the overall schistosomiasis infection rate across the state ranged from 2.9% to 61.8, and the overall intensity of the disease in the state was between 499.0 to 1.75. Identified risk factors in the State were: occupation, education, age group, personal habits socioeconomic status, personal hygiene and residence location.
Conclusion: It was concluded that there is a high prevalence and intensity of schistosomiasis in Sokoto state, Nigeria as a result of many risk factors such as environmental, socioeconomic and demographic.
Recommendation: It was recommended that further research should focus on investigating the antigenic factors responsible for the persistence of the parasite in the state to allow for best preventive and control measures.
Keyword: *distribution, intensity, factors, schistosomiasis, Sokoto state*

Introduction

Schistosomiasis is a Neglected Tropical Disease (NTD) caused by trematode worms which belong to the genus "Schistosoma"[1]. The six species of schistosomes which have been discovered to be medically important to humans include *Schistosoma haematobium* which is responsible for Urinary schistosomiasis, *S. mansoni, S. mecongi, S. japonicum, S. guineensis* and *S. interclatum* are responsible for intestinal schistosomiasis[2].

Schistosomiasis is one of the 20 illnesses classified as one of the NTDs which have been documented in 78 nations[3]. World Health Organisation (WHO) estimates, around 290.8 million persons need care in 2018[4]. *S. haematobium,* which causes urinary schistosomiasis, is widespread in sub-Saharan Africa, the condition requires annual treatment for an estimated 30 million Nigerians[5]. Infection with the parasite occurs when an infected individual passes urine contaminated with eggs of the parasites in a freshwater body, the egg hatch into miracidia which penetrate the snail body which belongs to the genus *Biomphlaria* or *Bulinus.* When the miracidia undergo a certain developmental stage, infective stage (cercaria) are discharged from freshwater snails, the infectious larvae pierce the skin of any human or mammalian body that comes into touch with the water[6]. The adult worms live inside the blood vessels of the human host[7].

Urinary schistosomiasis is the most pathological form of schistosomiasis that causes blood in the urine, pain when urinating, and, in more severe cases, also causes fibrosis of the bladder and ureter, kidney damage, and bladder cancer[8]. Men who have genital forms may experience testicular pain and blood in their sperm[9]. Women who have had eggs placed in their cervix and lower female genital tract develop intravaginal lesions, which cause genital itchiness, pain, bleeding, and dyspareunia. Additionally, eggs that lodge in the fallopian tubes and uterus might cause infertility[10].

Since schistosomiasis is primarily thought of as a disease in rural areas where people depend on natural freshwater bodies for daily activities, research and control efforts have been concentrated in such areas[11]. However, schistosomiasis centres have been appearing and even growing in urban and peri-urban areas during the past few decades due to rapid migration from rural to urban settlements[12]. Nigeria has a significant number of cases of urinary schistosomiasis and young people, who will be tomorrow's leaders, suffer the brunt of the cost because they are the most vulnerable group in endemic countries[13]. Subsequently, various activities that children engage in such as swimming, fishing, irrigation farming, passing through contaminated water and passing urine and faeces into the freshwater body are factors associated with the transmission of the disease[14].

Although there is no up-to-date estimate for the disease in Nigeria, earlier estimates which indicated that, there were approximately 25 million infected and 101 million at risk of infection have been documented in Nigeria. The majority of infection is either caused by *S. haematobium* (Urinary Schistosomes) or by *S. mansoni* (intestinal Schistosomes)[15]. It was reported that the urine form of the disease (*S. haematobium*) had more prevalence and intensity in the country than the intestinal form (*S. mansoni*)[12]. The main risk factor for infection is contact with river water that is

thought to be infected with cercariae[16]. The distribution of schistosomiasis prevalence, the severity of infection, morbidity, and death are all influenced by a variety of environmental factors[17]. The degree of transmission and severity of infection, which might differ amongst groups, are determined by patterns of contact with the infected water. Sometimes, in particular, irrigation farming and water development plans are linked to schistosomiasis[18].

Schistosomiasis typically affects the poor, who lack access to basic care and preventative measures while living in conditions that facilitate transmission[12]. The disease is widespread in many parts of Nigeria, including Sokoto State. Despite the widespread occurrence and its intensity in the state, there is no documented review search indicating the distribution and intensity of *S. haematobium* infection among the people of the state. Hence a systematic review was conducted across the state to find out the distribution and infection rate as well as the intensity of the disease among the people of the state. It is hoped that the present review will serve as the baseline data for determining the other factors associated with schistosomiasis and for providing the best way to prevent and control the disease in the state and other parts of the country.

Methodology

Standard for Eligibility

All research articles examining the prevalence, and intensity of human schistosomiasis in Sokoto were considered and reviewed, overall prevalence and intensity of schistosomiasis were recorded from each location. There was no discrimination regarding, age, gender, occupations, of the participants while conducting the review. Studies examining non-human *Schistosoma* infection in animals other than snails were not included in the search. This study looked at Sokoto State inhabitants contracting an infection while visiting rural areas as tourists.

Search Engines and Information Sources

ScienceDirect, PubMed, Google Scholar, Research Gate, Academia and WHO database were used in organizing the systematic literature review with the aid of computer-assisted literature search. The first review was started in July 2021 and then updated in October 2022, Schistosomes, Sokoto, prevalence, intensity, distribution, and risk factors were keywords used as search terms, no additional selection was undertaken. The individual study's methodologic quality was not evaluated. There was no distinction established between the various schistosomiasis types. All available records were evaluated for eligibility for the review, to get the clearest picture possible of the research done on schistosomiasis distribution among the Sokoto people in general. The deadline fell on January 2023.

Studying Choice

The present review search only took into account research articles for which either a complete paper or the abstract was available, articles written in a language other than English were considered as long as the abstract was written in the English language, therefore, only data with the abstract written in the English language were included; no data were taken from any non-English content. Any paper underlying data quality was not included. Studies that had no information regarding a peer review procedure in progress were also included.

Items of Data

For the present review, information on the frequency and severity of *Schistosoma* infection in humans was considered, the location and the year of the data collection were also noted when available, the majority of studies were cross-sectional, and information given in the articles on infection over time was retrieved and reported on in the review to establish a knowledge of how Sokoto schistosomiasis has altered in that specific context over time. In each setting in Sokoto, data on factors recognised or deemed relevant for promoting the spread of *Schistosoma* infections were also logged.

Bias Risk in Individual and Systematic Studies

To avoid biases in the present review, the methodological excellence of the various studies was not considered, because the possibility of biased papers being included may have grown as a result, a large number of papers were included, though, as the aim of the study was to evaluate whether there was evidence of schistosomiasis in Sokoto state completely. Performing high-quality prevalence surveys will allow for more precise prevalence estimates if there is evidence of schistosomiasis in the state. The review contains a bias toward works published in English because only works having English-language abstracts or those that were available in English were included.

Results and Discussion

Distribution of Schistosomiasis Across the Sokoto State

The distribution of schistosomiasis around Sokoto state local government areas was illustrated in Table 1, it was observed that infection with schistosome changes from year to year, and also increases in some parts of the state, The Majority of the conducted research on schistosomiasis in the state were concentrated on the infection among the schools' children precisely primary school children. Scanty research on *S. mansoni* identified very low infection.

Riverine areas of Sokoto South and Kware were observed to be more prevalent (61.8%) with the disease while, while the lowest infection rate of 21.3% was reported among the primary school children of the Silame local government area of the state. Although previous findings on schistosomiasis showed a scanty focus on *S. mansoni,* 2.92% of the riverine pupils were reported to be infected with the parasites. According to previous reports, the intensity was reported to be heavier among the people residing at Goronyo Dam settlements (499.0 egg/10 ml of a urine sample) also, there was a lighter intensity of 12.05 egg/ 10ml of urine and 1.75 egg/50g of stool sample among the primary school pupils of Wamakko.

Schistosomiasis in Sokoto State was found to be more prevalent when compared with numerous epidemiological studies on schistosomiasis carried out in various parts of Nigeria: In Minjibir Local Government Area of Kano State, the prevalence and intensity of urinary schistosomiasis among primary school students revealed that 44.2% of students were afflicted[50]. In Ogbadibo Local Government Area, Benue State, the prevalence of urinary schistosomiasis showed that 46.6% of people were infected[51]. Furthermore, a study of urinary schistosomiasis in some areas around the Gusau Dam Site in Zamfara State revealed that 47% of those surveyed were infected[52]. according to another research on the frequency of *S. haematobium* infection among primary school students in Keffi Town, Keffi Local Government Area,

Nasarawa State, 30.5% of the students were infected[54], 12.9% of children in selected Minna, Niger state schools tested positive for urinary schistosomiasis[55], 19.0% of people in central Ebonyi State tested positive for Schistosoma haematobium infections, according to another study[56]. Salwa *et al.* [57], in the study of the prevalence and risk factors of schistosomiasis among Hausa communities in Kano State, reported 17.8% infection. Additionally, among junior high school students in two local government areas near Zobe Dam in Katsina State, the prevalence and intensity of genito-urinary schistosomiasis and associated risk factors revealed that 22.7% of the students were found to be infected [58]. However, the infection was found to be lower than the 74.0% of those examined in the Abarma district of the Gusau Local Government Area of Zamfara State[53].

Risk Factors Associated with *Schistosoma* Infection in Sokoto

i. Occupational Activities

Any work, deal, advisory services, or other work or service activity, whether for pay or not, whether regular, part-time, irregular, temporary, or permanent. In Sokoto State, occupational activities responsible for contracting schistosomiasis include, farming, hauling water, fishing, washing inside irrigation canals, car washing, and gathering sand from lakes, rivers and dams [33].

The state economy is partially or highly dependent on the people living around riverine areas who use fishing as their occupation, fishing activity results in higher infection with schistosomiasis because fishing with or without boats results in varying degrees of water interaction [34].

People who move from endemic areas to non-endemic areas where the snail intermediate host is present in the water body may spread the disease to regions where it had previously been absent through their occupational and recreational activities that involve coming into contact with water contaminated with cercariae from the intermediate host snails [35].

ii. Education

Educational awareness on the Schistosoma parasites, mode of transmission of the infective stage, life cycle pattern, clinical manifestations and pathogenic effects of the parasites, method of prevention, control, eradication and elimination were inadequate among the people in the state, therefore many people were predisposed to the infection with the parasite [36].

In addition, the majority of the community members living around riverine communities in Sokoto state were not going for formal education, they rather go for irrigation farming, fishing activities and other activities related to freshwater bodies than for formal education, that why susceptibility rate is high in the state[37].

Although the majority of the research articles conducted in Sokoto concentrated on school-age children precisely primary school students, many students were reported positive because no teaching subject emphasised teaching the students the impact of neglected tropical diseases like schistosomiasis and others, the disease became more prevalent throughout the state [38]

iii. Socio Economic Status

The term "socioeconomic status" in this context refers to a person's or a group's place on the socioeconomic hierarchy. This position is based on a variety of social and

economic factors, including income, the level and type of education, the type and prestige of occupation, the location of the home, in certain communities, segments of society, ethnic origin or religious background [29]

Statistical analysis showed that Sokoto state is one of the Nigerian states that has a higher number of people that are said to be at the lower class of socioeconomic status and also residing very close to the freshwater body, as a result, these people have multiple occupations that are link with fresh water body, for example, an individual may engage him/herself as an irrigation labourer, fisher, nomadic, and washing cars, for him/her to get food for survival [39].

Similarly, many people are substantial farmers, and they cannot afford modern farming techniques due to lack of money and other means that will prevent them from direct contact with water bodies infested with cercaria [40], it was also observed that many people from riverine areas of Sokoto, doesn't have money to purchase Molluscicides that will kill the intermediate host which generally harbour the infective stage of the parasites[22]

Due to the poorness of the people living around the riverine areas of Sokoto, it was reported that many people were urinating and defecating in and around the freshwater body because they don't have toilet facilities in their residences, hence a large number of Schistosoma eggs are deposited directly or directly into the water body [28].

iv. Age Group

Findings from previous research indicated that children and youths are the most susceptible group for *Schistosoma* infection in most areas of Sokoto state because the majority of these age groups engaged themselves with activities that predisposed them to water bodies infested with the parasite infective stage [31].

For example, there is clear evidence that the majority of the children in riverine communities were not going to formal school, instead, their parents preferred Almajiri school because Almajiri school give the children more ability to help their parents with other activities that are related with rivers and lakes contact (such as fishing, watering animals, irrigation etc) than the formal school[41], as a result of that, there is higher contact with cercaria in the freshwater body[22].

Additionally, children have weaker immune systems than the other group, hence whenever there is cercaria penetration into their body through the skin, the developmental stage of the parasites may withstand antigen-antibody fight inside the body system of the children and heavier infection could result in many pathogenicity and clinical manifestations [42].

Also, youths living around riverine areas of Sokoto State have the habits of swimming, laundering, washing cars watering animals, and many other activities that are linked with water contact in the areas, hence the higher infection rate among the age group [43].

v. Residence Location

Residence refers to a house or home that was or is utilized as the primary place of living. It can refer to a house for a single person or a family, an apartment, or a refuge that is used as a shelter. It could be a group of dwelling homes created to help children or people with long-term impairments for nursing and is such a place where elderly people who need help are cared for.

The location of the houses is one of the factors that cause the high distribution of schistosomiasis in the state. This is because

people with residences very close to the rivers and lakes are more highly infected than those that are not close to them [44]. This could be due to their habit of depending on the water bodies for many activities and also frequently passing into the water body on their way of going to neighbouring towns, villages or the main city of Sokoto state [45].

Due to the nearness of the residents to the water bodies in the state, many people can visit the lakes and rivers for swimming, washing, watering, and fetching water for domestic uses, also Some children make a habit of playing inside the water body day and night [46.]

vi. Personal Habit

Habit is a pattern of conduct that is routinely practised and often happens unconsciously. It is a slightly set style of thinking, feeling, or doing that was learned by prior mental repetition. Habitual behaviour frequently goes unnoticed by those who engage in it since it is unnecessary to conduct self-analysis when performing everyday chores [47].

Because the behavioural patterns that humans repeat become imprinted in neural pathways, old habits are difficult to break and new habits to form, but it is possible to form new habits through repetition. The relationship between the context and the action gradually strengthens when behaviours are repeated in the same environment [30].

People of Sokoto state who are living around the riverine area are well equipped with a personal habit of river visits frequently, some visit rivers for tourism, fishing, swimming, loundering, playing, passing, and many other purposes, that is the reason why they were exposed to the infested water environment[48].

Additionally, a large number of male and female children and young adults who are parasite-infected and do not receive treatment exhibit the behaviour of urinating or defecating within bodies of water. This leads to an increase in the parasite population in the water and increases the risk of reinfection[49].

Furthermore, Numerous villagers in the Sokoto State exhibit the behaviour of refusing to take synthetic medications when given to them, and they avoid going to hospitals when they suffer from symptoms of schistosomiasis, such as bloody stool, difficulty urinating, difficulty urinating, and haematuria. As a result, the parasite greatly increased the morbidity rate among the state's residents[27].

Advantages and Disadvantages of the Present Review

In terms of schistosomiasis in Sokoto, the current literature review aimed to offer an overview of the earlier studies and surveys conducted up till 2023. This review can provide a more thorough summary than would otherwise be feasible by including works for which only the abstract was accessible. The same holds for the search period, which was extended back several decades to better comprehend how things have changed through time.

By finding and including additional studies by using the papers given as references in the studies found by the web search, the scope of the review may have been improved. It is also possible that some studies were overlooked because they did not include the terms Schistosomiasis, Prevalence, Distribution, Intensity, or Sokoto in the title, abstract, or keywords but did discuss the variations in schistosomiasis in the text. Even though the chosen keywords made an effort to avoid this, the issue might not completely be solved.

The review probably lacks several papers because publications in languages other than English were not included. Lastly, since documents with only abstracts were included, it was impossible to judge the calibre of the methodology used and the resulting data that were published. Therefore, it is important to exercise caution when concluding the provided data.

Advantages and Disadvantages of the Reviewed Articles

Published manuscripts used for the present review were concentrated on prevalence, intensity, and risk factors associated with schistosomiasis in some selected areas in the state. Much attention was on finding the prevalence among the children (particularly primary school pupils). Numerous demographic, social, and behavioural aspects were examined as potential risk factors for schistosomiasis, with a large portion of the study focusing solely on riverine locations. Filtration techniques were also widely utilised to measure the parasites' intensity under a microscope.

The reviewed articles also provide much information on *S. haematobium* which is the most dangerous species globally causing urinary Bilharziasis, while few studies on *S. mansoni* were availably documented across the state

On the other hand, there is a dearth of research information about the disease from the people living in urban areas of the state even though people from urban migrate to other parts of the state by passing through the freshwater body contaminated with the snail intermediate host

Similarly, other age groups especially youths and old ages could be more obtained visiting rivers and lakes for fishing, washing clothes, bathing, irrigation farming, swimming, passing through, watering animals, fetching water for domestic use, and many other purposes than primary school children, however, previous documented articles across the state had inadequate information on schistosomiasis infection rate and intensity of youths and old age groups

Additionally, identified factors (demographic, socioeconomic, and behavioural) could not be the only factors responsible for the diseases in the state, since there is reoccurrence and persistent of the diseases, other factors such as resistant antigens, and resistant genes, which could result in parasite resistant even after taking treatment were not considered in the available documents

The majority of the previous study emphasised sensitivity identifications of the parasite (microscopy), specific methods such as molecular and immunological methods were inadequately deployed in epidemiological studies of schistosomiasis across the state.

Table 1: Distribution and Intensity of Schistosomiasis Across the Sokoto State

S/N	Study Area/ Location/LGA(s)	Population composition	Sample size	Prevalence (%)	Intensity	Reference
1	Goronyo	Children and adults	500	52.0 infected with *S. haematobium*	91.7	[19]
2	Settlement of Goronyo Dam	Children and adults	400	32.3 infected with *S. haematobium*	499.0	[20]
3	Wamakko Town	Children and adult	300	38.3 infected with *S. haematobium*	134.0	[21]
4	Riverine areas of Sokoto	School children	375	60.8 infected with *S. haematobium* while 2.92 infected with *S. mansoni*)	43.85 for *S. haematobium*) And 1.75 for *S. mansoni*	[22]
5	Sokoto Metropolis and Hamma Ali District of Wurno	School children	375	60.8 infected with *S. haematobium*	43.85	[23]
6	Sokoto South and Kware	Primary school pupils	375	61.8 infected with *S. haematobium*	41.85	[24]
7	Wamakko	Primary School Children	50	60 infected with *S. haematobium*	NILL	[25]
8	Wamakko	Primary school pupils	400	48.0 infected with *S. haematobium*	12.02	[26]
9	Kware and Sokoto South	School children	375	60.8 infected with *S. haematobium*	43.87	[27]
10	Riverine Areas of Wamakko	School Children	400	32.8 infected with *S. haematobium*	NIPA	[28]
11	Kware	Children	206	17.8 infected with *S. haematobium*	NIPA	[29]
12	Goronyo and Taloka Communities	Children and adolescents	300	37.0 infected with *S. haematobium*	NIPA	[30]
13	Salame	Primary school children	188	21.3 infected with *S. haematobium*	22.10	[31]
14	Wamakko	Primary School children	100	12.5 infected with *S. haematobium*	NIPA	[32]

Key: NIPA= Not in the published article

Conclusion

From the present review it was observed that schistosomiasis is present in Sokoto State with higher intensity, the prevalence of the parasite ranged from 60.8 to 2.92% while intensity was reported to be between 499.0 to 1.75 egg/10ml of the sample. Risk factors associated with the infection of the parasite in the state were; occupational activities, level of education, personnel habit, personal hygiene, residence location, age group and socioeconomic status

Recommendations

There should be more research from other parts of the state especially in urban areas because infection may be prevalent among the traveller and if not investigated the urban people could serve as a source of retransmitting the disease in riverine communities after treatment, prevention and control of the disease in the areas, hence could result in persistent, and resistant of the parasite throughout the state

Molecular and immunological techniques should be used in the feature research for the diagnosis of the Schistosoma infection since the use of these techniques in the study area was inadequate, despite they being more reliable, because they provide specific information on the parasites

There should be more emphasis on the detection of the resistant antigens of the parasites in the areas of Sokoto State because they could be among the factors that cause persistent parasite infection among the individuals in the state.

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Conflict of Interest

The authors declared no conflict of interest.

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PATTERN AND PREVALENCE OF WORK-RELATED MUSCULOSKELETAL DISORDERS AND ITS ASSOCIATION WITH QUALITY OF SLEEP AMONG FOOD VENDORS IN OGBOMOSHO, NIGERIA

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Abstract

Background: Food vendors are at risk of musculoskeletal disorders due to the awkward postures they attain while cooking and serving the food. The pain that results from musculoskeletal disorders could impact their sleep.

Objective: This study investigated the prevalence of work-related musculoskeletal disorders (WMSDs) on food vendors' sleep quality.

Method: This cross-sectional study was conducted on food vendors in selected food outlets in Ogbomosho, Nigeria. Data was collected on participants' socio-demographics, prevalence of work-related musculoskeletal disorders using the Nordic Musculoskeletal Questionnaire and quality of sleep using the Pittsburgh

Sleep Quality Index. Descriptive statistics and Chi-square were used to analyze the data. The alpha level was set at $p \leq 0.05$.

Result: There were 82 participants [19 males (23.2%) and 63 females (76.8%)]. The mean age was 31.5±9.592 years. The average number of weekly working hours for participants was 69.95±17.318 hours. The majority of the participants (83%) reported having pain in one or more parts of the body in the last 12 months, with the low back (53.7%) and knees (51.2%) reported as the most affected regions. There was a significant association between WMSDs and participants' sleep quality ($p = 0.003$). Also, there was a significant association between sleep quality and the number of participants' work hours ($p = 0.025$).

Conclusion: The study revealed a high prevalence of WMSDs among food vendors in Ogbomosho which was significantly associated with quality of sleep. Hence, proper education and awareness programmes on WMSDs and their prevention should be done for food vendors.

Keywords: work-related, musculoskeletal disorders, food vendors, sleep quality

Introduction

Work-related musculoskeletal disorders (WMSDs) refer to a gamut of inflammatory and degenerative disorders initiated or aggravated largely by the performance of work or associated work settings.[1] According to the National Institute for Occupational Safety and Health, previous injuries, physical condition, genetics, lifestyle, and poor diet are factors that contribute to musculoskeletal symptoms. Work-related musculoskeletal disorders are observed at workplaces where there is a discrepancy between the physical capacity of the human body and the physical requirements of the job.[2]

Food vendors are individuals or businesses that sell food or food-related products to the public[3]. They may be exposed to work-related musculoskeletal disorders due to repetitive movements, awkward postures, and duration spent in these postures. Anecdotal reports reveal that some of the awkward postures that food vendors assume include bending over the payment counters, food display shelves and even in the kitchen while cooking. They have been said to remain on their feet for long periods with little to no breaks, which may be a risk factor for musculoskeletal discomfort and in the long run result in musculoskeletal disorders that may affect their sleep quality.

Quality of sleep is a multidimensional construct that encompasses aspects such as sleep duration, sleep continuity, sleep architecture and

subjective satisfaction with sleep.[4] It encompasses the degree to which a person's sleep is restful, rejuvenating, and interruption-free.[5] The rejuvenation provided by sleep is vital for the body systems as well as our ability to think clearly, learn new information, and manage our emotions.[6] People who are sleep deprived are also more likely to make errors and omissions.[7] Saghir et al.[8] submitted that working while sleep-deprived can leave people feeling more irritable, angry, and vulnerable to stress. Different researchers have described the mechanism through which WMSDs affect sleep quality. The prevailing scientific view on the association of pain (a major symptom of WMSDs) and sleep is that they are reciprocally related [9] implying that the presence of pain can precipitate acute sleep disturbances and the presence of sleep disturbances can predispose to more pain and dysfunction even in the cause of instrumental activity of daily living which is summarily describe as work-related musculoskeletal disorders. Also, Inflammatory-mediators released during WMSDs may cause depression and anxiety which then impairs sleep[10].

Food vending practice has different models in the typical Nigerian metropolis of which Ogbomosho City is a unique example. Two models are commonly practised, and this involves formal and informal ready-to-eat models. [3] The uniqueness of the food vending model practised may alter the pattern of WMSD preponderance and sleep disturbance that is prevalent in this Nigerian city. Although the literature on work-related musculoskeletal disorders among food factory workers is available, none exists with a focus on food vendors' musculoskeletal health and sleep quality. Hence, this study investigated the association between WMSDs and the quality of sleep of food vendors in Ogbomosho, Nigeria.

Materials and Methods

Design

A cross-sectional survey design was utilized in this study.

Population

The participants in the study were food vendors in Ogbomosho, Nigeria. Those who have been involved in the occupation for at least 12 months were included. While food vendors who have pre-existing, musculoskeletal disorders were excluded from the survey.

Sample size determination and selection

Nine food outlets were initially purposively selected to be involved in this study out of the identified 52 food outlets in the Ogbomosho metropolis. Food vendors in these 9 food outlets were then approached to participate in this study based on consecutive sampling techniques. The sample size was determined using Slovin's[11] formula given as $n = N / (1 + ne^2)$, where n= sample size to be recruited, N= Total population size, and e=

margin of error which is approximately 5%. A minimum sample size of 80 was estimated.

Measurements

A self-reported questionnaire was used to obtain socio-demographic data on age, gender, job position, years of experience, working hours per week, weight and height of the participants. The weight and height of each participant were measured by the first author using a standardized weighing scale and stadiometer respectively. The body mass index (BMI) was thereafter calculated. The Nordic Musculoskeletal Questionnaire (NMQ) was used to investigate the presence of musculoskeletal disorders in the body and their effects on activities of daily living, and the Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality.

Procedure/survey Administration

An informed consent stating the rationale for the study as well as an assurance of confidentiality and anonymity was sought and obtained from participants before involving them in the research. The questionnaire was interviewer-administered to each participant by the data collector. Ethical approval was sought and obtained from the Bowen University Teaching Hospital Health Research and Ethics Committee (BUTH-HREC) with approval number BUTH/REC-861.

Data Analysis

Descriptive statistics of mean, frequency, standard deviation, bar charts, pie chart, tables, and figures were used to summarize the sociodemographic data and data on Work-related Musculoskeletal Disorders and Sleep Quality of Participants. The chi-square test was used to determine the association between Work-related Musculoskeletal Disorders and Sleep Quality, selected sociodemographic variables and each of Work-related Musculoskeletal Disorders and Sleep Quality. All statistical analyses were carried out using Statistical Package for Social Sciences (SPSS) version 21.0. The alpha level was set at 0.05 ($p \leq 0.05$).

Results

Eighty-two food vendors participated in the study and there was a hundred percent response rate. Figure 1 shows the sociodemographic data of the participants. Most of the participants were female (76.8%) and within the age group of 19–35 years (68.3%). A large proportion of the participants had less than three years of experience (97.6%). Of the total participants, more than half (73.2%) worked overtime. The mean height of the participants was 1.64±0.07m (1.51 – 1.80 m) and the mean weight was 63.46±14.25 kg (45.00 – 140.00kg). The mean BMI was 23.78±5.30 kg/m^2 (17.00 – 54.00 kg/m^2). The study showed that pain at the low back was the most prevalent work-related musculoskeletal disorder in the last 12 months among the participants (53.7%), followed closely by pain in the knees (51.2%) (Fig. 2).

Overall, 82.9% of the participants had a musculoskeletal disorder during the last 12 months (Fig. 2). Furthermore, 47.6% of the participants reported to have very good subjective sleep quality, 13.4% used sleep medication once or twice a week and 51.2% of the participants had acute sleep disturbance (Table 1). The Chi-square test showed that there was a significant association between the WMSDs and the quality of sleep of participants (p=0.003) (Table 2). Also, WMSDs were significantly associated with the age of the participants (p=0.031) but gender (p=0.080), years of experience (p=0.450) and work hours (0.098) were not. Moreover, a significant association was found between the quality of sleep and the number of work hours (p=0.025) of the participants (Table 2).

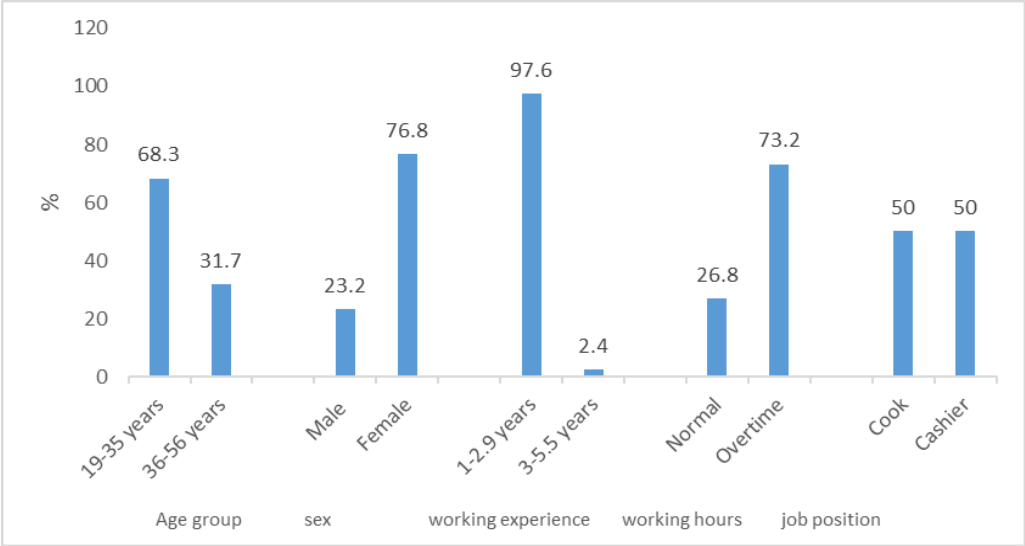

Figure 1: Sociodemographic variables of the Respondents

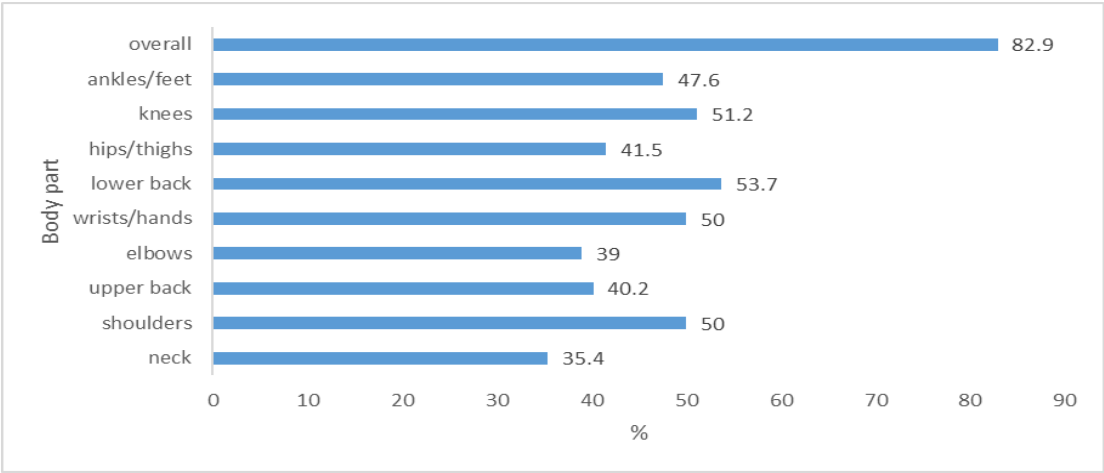

Figure 2: 12-month prevalence of work-related musculoskeletal disorders

Table 1: Components of sleep quality

Components of sleep quality	Characteristics	Frequency (N)	(%)
Subjective sleep quality	Very good	39	47.6
	Fairly good	38	46.3
	Fairly bad	5	6.1
Sleep latency	0	18	22.0
	1	32	39.0
	2	26	37.1
	3	6	7.3
Sleep duration	0	19	23.2
	1	22	26.8
	2	28	34.1
	3	13	15.9
Habitual sleep efficiency	0	49	59.8
	1	19	23.2
	2	12	14.6
	3	2	2.4
Sleep disturbance	Not during the past month	5	6.1
	Less than once a week	66	80.5
	Once or twice a week	11	13.4
	Not during the past month	64	78.0
Use of sleep medication	Less than once a week	6	7.3
	Once or twice a week	11	13.4
	Three or more times a week	1	1.2
Daytime dysfunction	Not during the past month	39	47.6
	Less than once a week	36	43.9
	Once or twice a week	5	6.1
	Three or more times a week	2	2.4
Sleep disturbance of participants	Reduced sleep disturbance	40	48.8
	Acute sleep disturbance	42	51.2

Table 2: Association among Work-related musculoskeletal disorders, sociodemographic variables, and quality of sleep of participants.

Variable	Quality of sleep		χ^2	Df	p-value
	Reduced sleep disturbance	Acute sleep disturbance			
WMSDs					
Present	28	40	9.217	1	0.003*
Absent	12	2			
Age (years)					
19-35	28	28	0.105	1	0.815
36-56	12	14			
Gender					
Male	9	10	0.020	1	1.000
Female	31	32			
Year of experience					
0-2.9	38	42	2.006	1	0.228
3-5.5	2	0			
Work hours					
0-56	6	16	5.567	1	0.025*
57-105	34	26			
Job position					
Cook	18	23	0.781	1	0.508
Cashier	22	19			

*****Significant at $p \leq 0.05$

Discussion

Food vendors are predisposed to work-related musculoskeletal disorders due to the strenuous activities carried out in awkward positions during the cooking and sales of food. These disorders may disrupt the quality of sleep achieved by the vendors. This study investigated the impact of work-related musculoskeletal disorders (WMSDs) on the quality of sleep of eighty-two (82) food vendors in Ogbomosho, Nigeria.

The results of the study revealed that the food vendors are within the age range of 19 and 56 years, with an average age of 31.5±9.6. This is similar to the results of a study conducted by Afolaranmi et al.[12] in north-central Nigeria. It is not surprising because this is the age group that makes up the workforce of a country. Furthermore, it was observed that a large proportion of the participants were female. This is consistent with studies conducted in different parts of Nigeria,[12–15] which show that females dominate the food vending workforce. This is due to sociocultural factors, which expose females to cooking and food matters and encourage the training of females to perform household activities such as cooking and cleaning at an early age.

The 12-month prevalence of musculoskeletal disorders in at least one body region among food vendors in Ogbomosho was 82.9%, indicating that 8 out of every 10 food vendors presented with pain within the last year. This is similar to the findings of a study conducted in Ethiopia, where the prevalence of musculoskeletal disorders among participants within the 12 months prior to the study was 81.5%.[16] This shows the high propensity of food vendors to acquire musculoskeletal disorders. The high prevalence of musculoskeletal disorders among food vendors can be attributed to their activities and the demands of their work.

Furthermore, this study indicates that the lower back (53.7%) and the knees (51.2%) were the most affected anatomical regions. This is slightly less than the value reported by Jayaraman et al.[17] (56% for the lower back). This pattern is expected of food vendors because they are exposed to heavy lifting, repetitive movements and awkward postures. Muscle fatigue and pain develop due to the exposure they receive from repetitive tasks, uncomfortable posture, and long hours

of work. Working in an abnormal posture can cause injury and damage to body tissue from the overstretching of ligaments, muscles, and tendons.[18]

Also, it was observed that the majority of the participants had acute sleep disturbances, but a higher percentage recorded their subjective sleep quality to be very good, implying that despite the sleep disturbances, their quality of sleep was very good. This contradicts the findings of the study done by Saah and Amu,[19] where the majority of restaurant workers reported poor sleep quality using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. The perception of a good quality of sleep that contradicts an overall estimate of acute sleep disturbance as reported in this present study could mean that participants were unable to give an accurate, objective report on their quality of sleep. Moreover, it could be that, over time, they have employed various coping mechanisms, so they slept well regardless of the disturbance(s).

The prevalence of musculoskeletal (MSK) disorders was significantly associated with participants' quality of sleep. The association between specific MSK disorders, such as low back pain, and sleep quality has been established in various studies among different populations.[20–23] However, studies on the relationship between MSK disorders and sleep quality among food vendors are sparse. A plausible explanation for the significant association is that the pain, discomfort, and unrest from musculoskeletal disorders can cause sleep disturbances, further affecting the quality of sleep.[22–24]

This present study shows a significant association between WMSDs and the age of the participants. This is in line with Ahmed et al.[25] who revealed that age is significantly associated with WMSDs, and this could be due to disc degeneration as people grow older. This study reported that there was no significant association between WMSDs and the job positions of participants, which is in contrast with Jayaraman et al,[17] who reported that there was a higher prevalence of musculoskeletal disorders among the cooks and chefs than the waiters and cashiers. A possible reason for the contrast is the difference in the location of the study. This research involved food vendors who majorly use informal food vending practice models whereby there is no strict job description differences between cooks

and cashiers. The cooks and the cashier do the same jobs specifications even though their job titles are different.

There was a significant association between the quality of sleep and the working hours of food vendors. This is supported by the submission and trend in previous studies by Saah and Amu,[19] Lajoie et al.,[26] Dhande and Sharma,[27] that long hours and shift work predispose waiters working in upscale restaurants to poor sleep quality.

Conclusion

There was a high prevalence of WMSDs among food vendors in Ogbomosho, Oyo State. The prevalence of WMSDs was significantly associated with the quality of sleep and age of the food vendors. The most prevalent WMSD body sites were the low back and knees. More than half of the food vendors had acute sleep disturbances. Therefore, it is recommended that adequate awareness, sensitization, and education be done on proper ergonomic practices among food vendors. Also, there should be adequate rest periods in between shifts. Food vendors should have a regulatory body that can provide the means to proper education, awareness, and interventions such as regularly inviting health care professionals, especially Physiotherapists, to transfer appropriate knowledge and teach musculoskeletal disorder prevention techniques.

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RISK PROFILE, KNOWLEDGE OF FALL AND PRACTICE OF SAFE BEHAVIOUR AMONG COMMUNITY-DWELLING ADULTS IN KANO METROPOLIS, NIGERIA

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Abstract

Background: People who grow older may increasingly be at risk for fall and are susceptible to injuries from fall. Fall-related injuries are associated with serious psychological and behavioural consequences including fear of recurrent fall and isolation. It is doubtful if knowledge of fall will be associated with the fall risk profile and safe behavioural practices among elderly.
Objective: The objective of this study is to determine if there is any association between knowledge of fall, fall risk profile and safe behaviour among community dwelling adults in Kano metropolis.
Methods: A cross-sectional survey of community-dwelling adults (n= 287) was carried out using Fall Knowledge Assessment Questionnaire, Desmond Fall Risk Questionnaire and Fall Behaviour Scale for the Older Persons. A snow balling sampling technique was used to recruit volunteers regardless of their education, gender, socio-economic status and irrespective of walking with aid or not.
Results: The results of this study showed that there was a weak significant correlation between the knowledge of fall and fall risk ($r = -0.219$, $p < 0.05$) and no significant correlation was observed between knowledge of fall and behaviour ($r = 0.030$, $p < 0.05$) and behaviour and fall risk ($r = 0.090$, $p < 0.05$).
Conclusion: From the outcome of this study**,** it was concluded that there was a reciprocal relationship between knowledge of fall and fall risk among this cohort of elderly participants in Kano metropolis.
Keywords: *Risk profile, Knowledge, Behaviour, Fall, Community-dwelling adults*

Introduction

Falls and fall-related injuries constitute an important public health concern[1]. Each year, one in three community-dwelling older adults (65 year or above) sustain a fall[2]. Fall is a sudden, unintentional change in position causing an individual to land at lower level, on an object, the floor, or the ground, other than as consequences of sudden onset of paralysis, epileptic seizure or overwhelming external force[3]. About 20%-30% of fall results in serious injuries, and injuries care is costly[4].

Population ageing and the increased tendency to fall with age, present a major challenge to health care providers and health system as well as for older people and their caregivers[5]. Older people make up a large and increasing percentage of the population of countries worldwide[6]. As people grow older they are increasingly at risk for fall and are susceptible to injuries from fall[6, 7]. Falls are also associated with serious social and psychological consequences as people lose confidence in functional activities and become isolated and may therefore face restrictions in their activities[8].

Evidence of falls in older adults in low and middle income countries is sparse, and there is a lack of standardized terminology and definition. Methodological and sampling differences make it difficult to generalize across diverse settings and populations[9]. A review of studies for falls has shown annual fall rates for older adults of between 14 and 51 % among Indians[10]. Studies in China, Hong Kong, Macao, Singapore and Taiwan[11] reported annual rates of falls for adults aged 60 years and over of between 14.7 and 34 %. In Nigeria, a study conducted on fall incidence in a population of elderly persons in Nigeria showed that, of the 2,096 persons who responded to the question on fall, 23% reported having had a fall in the previous 12 months with females (24%) were more likely than males (17.9%) to have experience a fall[12].

Falls occur because of various complicated interactions rather than one factor, and are divided into internal and external risk factors[13]. The risk factors most commonly seen in hospital patients are previous falls, muscle weakness or difficulty in mobility, dementia, delirium, continence problems or urinary frequency, medication that increases the risk of falls, and orthostatic hypotension[14]. Others include increasing age, gender, medication use and predisposing medical conditions including Parkinson's disease, osteoporosis and vision problem etc[15, 16]. The spectrum of clinical processes of identifying individuals at risk or increased risk of falls involve risk profiling

For the risk profiling, various fall predisposing factors should be comprehensively assessed[17]. When screening an elderly population, it is not necessarily the case to determine a clear relationship between the incidence of falls and associated risk factors[18]. Indeed, the score of a questionnaire, which comprehensively assess fall-risk factors, does not always accurately predict when fall will occur in the future[19]. Therefore, knowledge of fall and fall demographics is important for self-prevention, and for health professionals to formulate falls prevention and target those at highest risk [20].

Effective self-prevention is achieved by behavioural adjustment to fall predisposing factors[21]. Behaviour has been operationally defined as something that people "do or refrain from doing, although not always consciously or voluntarily" and relates to overt behaviour patterns, actions, and habits[22]. This working definition also includes "mental events and feeling states that are 'observed' or measured indirectly" which promote safety and alleviate risks of falling in elderly[22].

At the moment, we do receive recurrent complains of fall among our elder patients. These cases of fall and its devastating consequences are increasingly becoming a burden on elderly and their support network. Although our routine elderly care is now refocusing towards prevention and interventions of fall. However, for successful fall prevention and intervention programs, the need for assessing risk profile, knowledge of fall; and fall behaviour among elderly is eminent. Therefore, this study is an attempt at assessing the risk profile, knowledge of fall and safe behaviour among community-dwelling adults in Nigeria.

Materials And Methods

The research design of this study was a cross-sectional survey of risk profile, knowledge of fall and safe behaviour among community-dwelling adults in Kano. A snow balling sampling technique was used to recruit volunteers regardless of their education, gender, socio-economic status and irrespective of walking with aid or not. Participants were recruited in spite of their medical (e.g. hypertension, diabetes, heart disease, etc) or orthopedics conditions (e.g. spondylosis, lower limb fractures, lumbosacral/ back pain, etc). Only participants that were conscious and oriented in time, place and people were included in this study. Participants with mental impairment, hearing impairment, visual impairment, inability to answer or provide respond to the items on the questionnaire were excluded from the participation. Ethical approval for the study was sought from the Ethical Committee of Kano State Ministry of Health.

The sample size of this study was arrived at using sample size proportion of Bekibele and Gureje (2010) as proposed by survey general formula:

$N = (Z)^2.P\ (1-P)/d^2$ Where N= Sample size

Z= 95% Confidence interval

P= 0.23 (Proportion of the participants)

d = 0.05 (worst case scenario)

$N= (1.96)^2 \times 0.23(1-0.23)/(0.05)^2$

$= 0.6803/0.0025$

$= 272$

But, 10% of 272 were added up to accommodate for non-response rate

$10/100 \times 272= 27$

27+272=299. Therefore, the sample size was approximately 300.

Fall Knowledge Assessment Questionnaire with 6-items, Desmond Fall Risk Questionnaire with 15-items of binary scale, Fall Behaviour Scale for the Older Persons with 30-items and a socio-demographic sheet of 9-items were administered by the researcher. The 6-items binary subscale Fall Knowledge Questionnaire was developed by the researcher, and was not tested for

validity and reliability. The Desmond Fall Risk Questionnaire was adopted for the study; this questionnaire has universal applicability on fall risk screening, 0.98 content validity and test-re-test reliability of 0.88[23]. The Fall Behavioural Scale for the Older Person was also adopted for this study. This questionnaire is a 30-item Likert scale that has an internal consistency of 0.84 using Cronbach alpha and content validity index of 0.94[24, 25].

The socio-demographic information of the study participants includes age, weight, height and BMI. Weight was measured with the aid of Mechanical Bathroom Weighing Scale (LCNZ0011). This was measured to the nearest 0.1 kg, with the participant wearing light clothes and without shoes. The reading of the scale was recorded while the participants were on the scale and repeated measure was taken to minimize error. The height was measured with the aid of 60"/150cm Sewing Tape Measure (HTS103D3). The height was measured to the nearest 0.1cm and was performed by standing the participants on a flat wall, with feet together with heels, back and shoulder straight and touching the wall. The top of the participants head was used as reference. This was marked and measured from the ground level repeatedly in order to minimize error.

The knowledge component of the data collection sheet composed of 6-items of binary scale. It was coded as zero (for "no" response) and one (for "yes" response). The maximum score of knowledge was six while the minimum was zero. Participants were categorized as either having poor knowledge (a score of 0-3) or a good knowledge (a score of 4-6). The risk profile component composed of 15-items of binary scale. It was also coded as zero (for "no" response) and one (for "yes" response). The maximum score of this component was fifteen while the minimum was zero. Participants were categorized into high risk (a score of 0-7) and low risk (a score of 8-15) respectively.

Furthermore, the safe behaviour practice component of the data collection sheet has 30-items on a 4-points Likert scale. This was coded as one (for "never" response), two (for "sometimes" response), three (for "often" response) and four (for "always: response) respectively. The maximum score of this component was one hundred and twenty while the minimum was thirty. Participants were categorized as having a bad behaviour (a score of 30-79) and good behaviour (a score of 80-120) respectively. The questionnaires administration and the anthropometric measurements were carried out by MK. These questionnaires were written in English and were not translated into any other language before administration.

The participants were approached in their communities (home, religious centers, rest points, social gathering centers, etc) based on the requirements of snow balling using a consensual procedure. This procedure entails explaining the study's focus to the participants, assurance of the utmost confidentiality of the participants' information, respects for their consents, freedom of voluntary participation and withdrawal from the study at any point in time. It also includes educating the

participants on the study, advising participants on risk prevention associated with the study and allowing freedom of asking question for possible clarification. Data were collected from participants who declared their consent and were able to understand and respond to the English version of the questionnaire. There were no personal identifiers or contact details that are linked the questionnaire, personal information of the participants were not disclosed and were used for research purpose only. The participants were given two weeks to complete the questionnaire after which the questionnaires were retrieved by MK from the participants.

Descriptive statistics in the form of frequency distribution table was used to describe the socio-demographic characteristics of the participants. Chi-square statistics was used to determine the proportional differences of fall risk levels, knowledge levels and behaviour categories among the male and female participants. Spearman's rho correlation was used to determine the relationship between knowledge of fall and fall risk, knowledge of fall and behaviour and behaviour and fall risk among the participants. All statistical analyses were performed using SPSS version 20. Alpha value was set at 0.05

Results

This survey was carried out to determine the association between the knowledge of fall, fall risk profile and safe behavioural practices of elderly in Kano metropolis, Nigeria. Three hundred questionnaires were administered to these community-dwelling adults who declared their voluntary consents for the study. Out of the 300 questionnaires, only 287 were retrieved from the participants after two weeks of administration with a response rate of 95.66%. The mean age of the participants was 70.32 ± 8.48 years (Table 1); among which male participants were 204 (71.1%) while 83 (28.9%) were the female folk(Table 2).

Results show that there was good knowledge of fall in male (55.88%) and female (63.86%) participants, a low fall risk profile among male (82.84%) and female (91.57%) participants and a good behavioural in the male (66.6%) and female (27.2%) participants respectively (Table 2). There was a statistically significant weak negative correlation between knowledge of fall and fall risk ($r = -0.219$, $p < 0.05$), there was no statistically significant correlation between knowledge of fall and behaviour ($r = 0.030$, $p < 0.05$) and between behaviour and fall risk ($r = 0.090$, $p < 0.05$) as shown in Table 3.

Table 1: Socio-demographic Characteristics of the Participants

Dependent variables	M ± SD (n = 287)
Age (years)	70.32±8.48
Weight (kg)	54.71±8.06
Height (m)	1.62±0.80
BMI (kg/m^2)	21.02±4.25

BMI= Body mass index,
n = sample size

Table 2: Difference in Knowledge levels, Fall Risk and Behaviour by Gender

Variables	**Gender**		**X^2**	**P-value**
	Male n = 204	**Female n = 83**		
Knowledge category				
Poor	90 (44.12%)	30 (36.14%)	1.54	0.001
Good	114 (55.88%)	53 (63.86%)		
Risk category				
Low	169 (82.84%)	76 (91.57%)	0.281	0.002
High	35 (17.16%)	7 (08.43%)		
Behaviour category				
Bad	13 (4.5%)	5 (1.7%)	0.012	0.000
Good	191 (66.6%)	78 (27.2%)		

Significance level set at $p<0.05$

Table 3: Association between Fall Risk, Knowledge and Behavior among the participants

	Correlation coefficient (r)			
	Risk (p-value)	Knowledge (p-value)	Behavior (p-value)	N
Risk	1.000 (0.000)	- 0.219** (0.000)	0.030 (0.609)	287
Knowledge	-0.219** (0.000)	1.000 (0.609)	0.030 (0.609)	287
Behavior	0.090 (0.126)	0.030 (0.609)	1.000 (0.126)	287

** Significance level set at $p<0.05$

Discussion

This cross-sectional survey was carried out to determine if there is association between knowledge of fall, fall risk and safe behavioural practice among community dwelling adults in Kano metropolis, Nigeria. The adults sampled in this study were mostly male (71.1%), this outcomes differs from what was obtained in a study that found higher female respondents (67.9%) than their male folk[26]. The reason for this variation was that, this present study was conducted among community-dwelling adults while the previous study included elderly participants from community and elderly home which may results in enrolling more female[26].

Majority of the participants in this study reported having good knowledge of fall with 55.88% score among male and 63.86 score in female. This is higher than a previous study that found less than one-half (38%) of elderly reported feeling "very knowledgeable" about fall and its associated risks in Indonesian elderly[27]. The knowledge of fall among community dwelling adults in Kano seems good, as compared to their counterparts in Indonesia. An optimistic attitude in believing that awareness and knowledge regarding fall and fall prevention among elderly remains poor was not supported in this study as good knowledge of fall was found among the participants[28]. Notwithstanding, knowledge of fall was shown to be a strong preventive factor against episodic falls and recurrent falls, our finding corroborates the importance and the need for health care professionals to explain and make an elderly persons understand more about fall to minimize the associated risks.

This study revealed two category of fall risk profile, these were high risk (17.16% male and 8.43 female) and low risk category (82.84% male and 91.57% female). Majority of the participants have low risk profile and good behaviour towards fall (93.63% male and 93.98% female). This may be as a result of cultural and social prejudice around them. The fall risk profile proved to be low and the behavioural attributes were good. This is explaining that shifting in one affects the other. In essence, change in behaviour either ways affects the risk and susceptibility of fall and/or recurrent episodes same way. Therefore, safety among the community-dwelling adults is basically determined by behavioural adjustments. The correlation between the fall risk and behaviour was found to be insignificant. This implies that

the behaviour does not influence the risk of fall among community-dwelling adults. The likely reason to that is because; both the behavioural attributes and fall risk profile are moderately favourable, therefore none can influence the other but any shift or adjustment in any leads to significant effect.

According to the global report of the World Health Organization in 2010 on fall prevention in old age, behavioural determinants refer to human actions, emotions, or daily choices potentially modifiable through strategic interventions. So, discussing these preventive behaviours practiced by the community-dwelling adults may guide us on predicting their susceptibility to fall. It helps in ascertaining their fall risk profile and knowing how much they contribute to preventive and autonomous attitudes among themselves. These behavioural components have psychosocial domains that explore the risk profile and as such the behavioural determinants predict fall susceptibility.

In this study we found that there was a weak negative and statistically significant relationship between knowledge of fall and fall risk among the participants. This outcome corroborate with a similar finding that reported that majority of the elderly population in the city of Juiz de Fora, displayed little knowledge on falls and were exposed to a variety of daily risk factors[29]. This reciprocal relationship implies that as the knowledge of fall increases, the risk of having a fall or a recurrent fall episode reduces. Base on the relationship between knowledge and risk of fall, clinicians may deduce how adequate awareness campaign on fall can reduce serious health concern and psychological problems in older people.

The study contributed to the body of research that examines risk profile, knowledge of fall and safe behavioural practice in community dwelling adults in Kano metropolis, Nigeria. For clinicians involved in adults care, fall prevention needs to be a key public health priority because of the devastating consequences caused by fall and to achieve this goal, there is need for considering the clients knowledge, risk profile and behavioural domains. Clinicians require expertise in knowledge assessment, effective fall risk profiling and reliable behaviour appraisal for designing fall prevention interventions for elderly within their particular risks and abilities. Therefore, healthcare professionals in the areas of elderly care must be familiar with behavioural and risk constraints of their elderly patients while choosing appropriate fall prevention programs and for effective referrals.

Limitations of the study

Limitations of this study include; (1) Results from this study may not generalize to all elders in Kano metropolis due to the restrictive nature of snow balling sampling technique. (2) Older adults sample included community dwelling adults and excluded residents of elderly home facilities. (3) The study was a descriptive survey using questionnaires; therefore, the information concerning the knowledge, risk exposure and behaviour may differ from the reality due to recall bias.

Conclusion

It is therefore concluded that, there was low fall risk profile, good knowledge of fall and safer behaviour and among the study

participants. Thus, the risk of fall is influenced by knowledge of fall among these community-dwelling adults. Therefore, for effective fall prevention and community reintegration of elderly with previous fall episodes, clinicians may focus on risks profiling, behavioural modifications and fall education.

Recommendations

Therefore, it is recommended that other studies may be necessary to examine the knowledge, intrinsic and extrinsic risk factors and safety behaviours using scientific methods to analyze the participants' abode and to include both family members and care givers in the subsequent evaluations for their life style and habits and to establish relationship accordingly.

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SOCIAL DETERMINANTS OF OBESITY IN THE UNITED KINGDOM: A SYSTEMATIC REVIEW OF THE LITERATURE

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Abstract

Background: Obesity is a global public health problem. The increasing prevalence arise from complex and multifaceted determinants that relate to individual lifestyles, choices people make and the influence of social circumstances of the wider society in which they live. There is a worldwide phenomenon that obesity follows a social gradient that makes it possible for higher obesity risk to reflect lower level of socioeconomic profile (SEP) or socioeconomic status (SES). The levels of SEP or SES define the conditions of daily living which, are in turn shaped by the broader political, economic, social and cultural environment.
Aim: The aim of this study was to conduct a systematic review of published literature over a timeframe of 2000 to 2018 on lifestyle factors, economic conditions, environmental and socio–cultural issues as they constitute social determinants of obesity in the UK.
Methods: Based on the modified PRISMA protocol, a literature search was conducted for the social determinants of obesity in the UK across four generalisable themes or search areas: living environment, behaviour/psychology, biology/physiology and economic drivers of food production and consumption. The systematic review identified published works done in the UK from 2000 to 2018 using ten databases. Only studies characterised by empirical evaluations of causality of obesity predicated on four generalisable themes and which, met the inclusion criteria were considered in this review.
Results: A total of 14 articles met the inclusion criteria and were reviewed in this study. The majority of the determinants related to living environment and economic drivers for food production and consumption, rather than behaviour/psychology or biology/physiology. This review found living environment and economic drivers for food production and consumption to be demonstrably having the most influence on obesity as a public health problem in the UK.

Conclusion: The living environment and economic drivers for food production and consumption were the two key determinants of obesity in the UK as shown in this review. Many limitations are noteworthy and should be considered when interpreting the findings highlighted here. Future studies on causalities of obesity would benefit from pursuing two vital paths of inquiry recommended in this review.

Key words: *obesity, social determinants, epidemiology*

Introduction

Obesity is most commonly determined with body mass index, a simple index of weight–for–height commonly used to categorise whether an individual is underweight, healthy, overweight or obese, and is defined as the weight in kilograms divided by the square of height in metres (kg/m^2). The World Health Organisation (WHO) describe these categories using cut–off points that indicate an individual with a basal metabolic index (BMI) between 25 and 30 is considered to be 'overweight' whilst a BMI >30 is defined as 'obese'.[1-3]

A startling development about prevalence of obesity in the UK is the variations in the regional distribution. The trends over time in England indicated that adult obesity increased from 15% in 1993 to 28% in 2019 while the proportion of adults who were either overweight or obese increased from 53% to 64% for the same period.[4,5] Obesity rose from 10% in children aged 4–5 years, and rising to 23% by age 10–11 for the period between 2006 and 2022. Childhood obesity is more likely due to widening gap in poverty and deprivation.[4]

A study by National Child Measurement Programme 2021/2022 showed that 12.1% and 10.1% of children aged 4–5 years were overweight and obese respectively. These percentages were higher among children aged 10–11 years, with 23.4% being obese and 14.3% overweight.[6] The likelihood of overweight or obese based on BMI above normal is higher in men (69%) than in women (59%), and higher (>70%) in adults aged 45–75 years relative to other age groups, with adults aged 16–24 years least likely to be overweight or obese to underscore dissimilarities in age and sex considerations.[5]

Demographic characteristics of overweight and obesity prevalence is important. Data on inequalities showed marked variations in percentage of either overweight or obesity between social groups.[7] Overweight or obesity is 14% higher in most deprived areas compared to least deprived areas. Similarly, overweight and obesity is 12% higher among people with disability than those without.[4] Excessive weight gain is highest in the black (72%) and lowest in the Chinese (37%) ethnic population, and rates of excessive weight gain in people without qualifications are 12% higher than those with at least level 4 qualifications or higher.[4]

Prevalence of overweight or obesity also differ among local authorities in England.[7] Data from Public Health England Active Life Survey in 2021/2022 showed that

Sandwell Local Authority at 14.9% and Richmond–Upon–Thames Local Authority at 5.4% recorded the highest and lowest percentages of overweight or obese children aged 4–5 years respectively. Similarly, Sandwell Local Authority at 34% and Surrey Local Authority at 12.4% recorded the highest and lowest percentages of overweight or obese children aged 10–11 years respectively.[6] Among adults, Thurrock Local Authority recorded the highest percentage (76.3%) of overweight or obesity while Islington Local Authority recorded the lowest percentage (44%) of overweight or obesity.[7]

Data from Scottish Health Survey in 2021 showed that 36% of adults were overweight, 31% were obese while 33% were neither overweight nor obese. Of these, more men (69%) than women (31%) were overweight, but more women (65%) than men (35%) were obese.[8] More than 70% of adults aged >55 years were overweight or obese to further underscore the importance of apparent differences in age and sex distribution.[8] Obesity prevalence in Scottish children varies with age and household socioeconomic status (SES) with obesity commonest in children living in households with lower incomes. Obesity in children aged 2–6, 7–11 and 12–15 were 20%, 22% and 12% respectively. The likelihood of obesity however, was higher in boys than in girls (20% versus 16%).[8]

The National Survey for Wales in 2021/2022 reported higher prevalence of obesity in women (26%) than in men (23%), and a higher proportion of overweight in men (67%) compared to women (58%). Obesity was highest in people aged 45–64 years (29%) and lowest in those aged 16–24 and >75 years (16%). Overweight and obesity in Wales is influenced by inequalities in health and geographical location.[9] Data from Child Measurement Programme for Wales for 2018/2019 showed higher prevalence of overweight (14.4%) than obesity (12.6%) in children aged 4–5 years. There were only small dissimilarities between obesity rates for boys and girls. Childhood obesity rate was almost twice as high (15.3%) in most deprived areas of Merthyr Tydfil as those in least deprived areas of Monmouthshire and Vale of Glamorgan (8.3%).[9] There were only small dissimilarities between obesity rates for boys and girls.

Data from Heath Survey Northern Ireland in 2019/2020 showed highest obesity rates among ages 65–74, with a rising trend from 23% in 2010/2011 to 27% in 2019/2020.[10] More adults were overweight (38%) than obese (27%), and of these, more men (71%) than women (60%) were overweight or obese. However, twice more women (48%) than men (24%) said they were trying to lose weight through healthy diet, exercise or bariatric surgery for those with a BMI above 40 and 35–40 if health problems such as diabetes or heart diseases exist.[11] Obesity rates were 7% and 4% in children aged 2–10 and 11–15 respectively in Northern Ireland in 2019/2020. However, the survey's small sample size made it difficult to subject the data to meaningful and robust comparisons over time between different age groups in the children population.[10]

The foregoing data therefore indicate that obesity rate in the UK is subject to regional variations in age, gender, trends over time and other inequalities related to deprivation, disability, ethnicity and

education.[4] A comprehensive understanding of these factors is vitally important to help guide assessment of obesity risks and rising prevalence in the UK. This systematic review (SR) is therefore aimed at summarizing the rising impact of lifestyle factors, economic conditions, environmental and socio–cultural issues as they constitute social determinants of obesity in the UK.

Methods

Search strategy

The purpose of search strategy was to find published works in healthcare and management journals based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta–Analyses (PRISMA) framework[12] incorporating summarised revisions formulated according to Quality of Reporting of Meta–Analyses (QUORUM) guidelines.[13] The rationale of PRISMA framework was predicated on the need to ensure comprehensive database search for social determinants of obesity within the targeted UK population.

Three search steps were involved in the search strategy.

1. Identification: Wide search groups were used to include analysis of text words in journal titles and abstracts of index terms in published works. Ten bibliographic databases were searched, namely:

- PubMed,
- Education Resources Information Center (ERIC),
- Excerpta Medica Database (EMBASE),
- Medical Literature Analysis and Retrieval System Online (MEDLINE),
- National Institute for Health and Care Excellence (NICE),
- Cumulative Index to Nursing and Allied Health Literature (CINAHL),
- Health Management Information Consortium (HMIC),
- Database of Abstracts of Literature in the field of Psychology (PsychINFO), and
- ProQuest Theses and Dissertations.

Thereafter COCHRANE Central Trials Register was searched to identify qualitative reports of SR on obesity. This completed the search at this stage.

2. Screening: Identified keywords and index terms such as overweight, obesity, lifestyle, determinants, economic, environment, social, cultural, behavioural, psychological, biology and physiology were used to search the databases in step 1. To ensure a comprehensive report, keywords were searched to identify SR (e.g., "systematic" or "review") that specifically discussed the social determinants of obesity among UK population. Therefore, search was refined to combine keywords like "obesity", "social determinants" and "United Kingdom".

3. Eligibility: Reference lists from both selected citations and bibliographies of major reports and relevant guidelines were identified and checked for inclusion or exclusion according to review criteria discussed in the next section. Details of PRISMA flow chart protocol[12] of search strategy, study selection and review criteria are contained in figure 1.

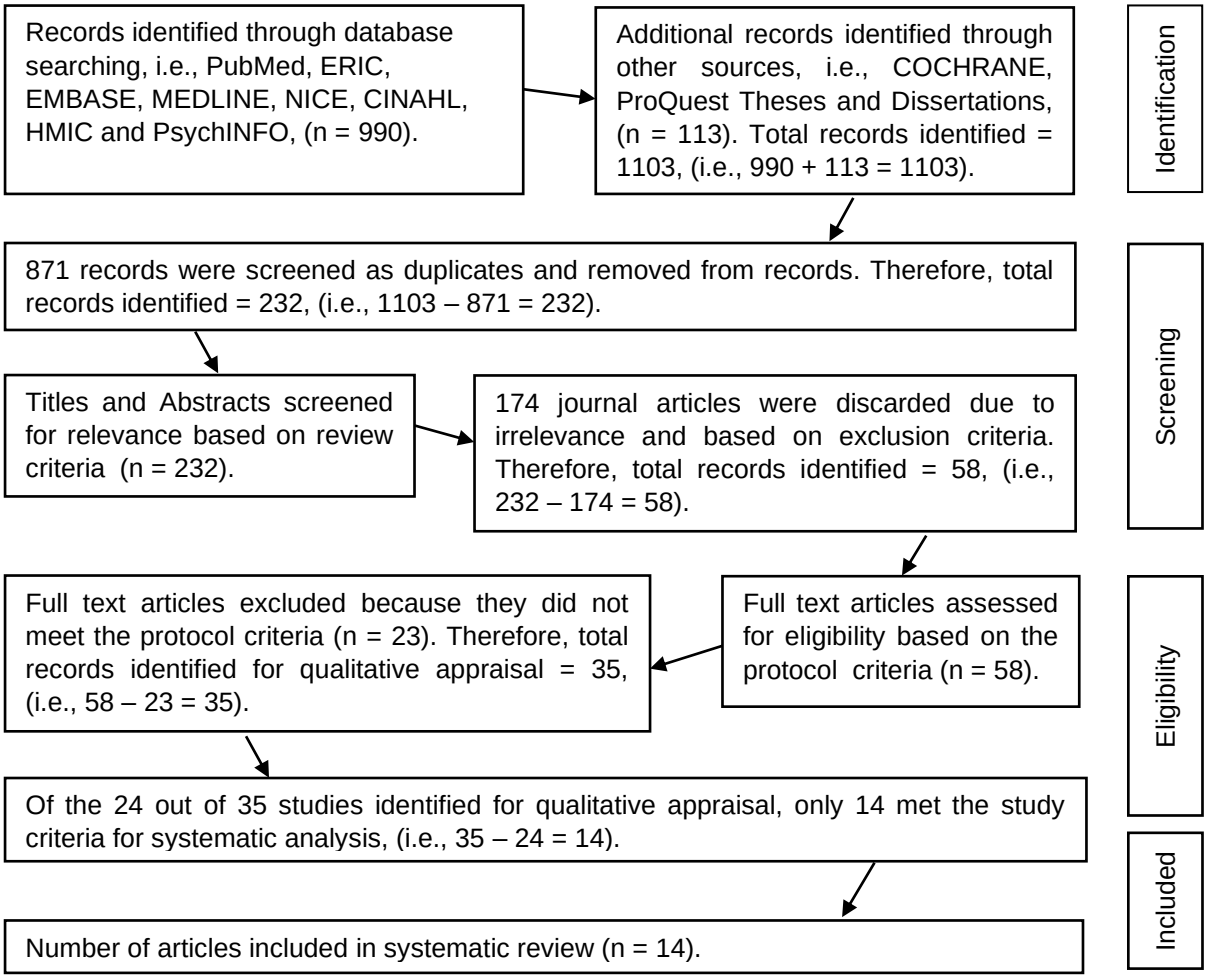
Review criteria

Increasing obesity prevalence among UK population presents a key challenge to

public health. The Foresight Study[14] projects more than half of UK population could become obese by 2050. This has significant economic implication on the National Health Service (NHS), wider cost to business and society.[15]

It is not that the present UK population are more gluttonous, have reduced willpower and dissimilar genetic constitution compared to previous generations[14]. Societal transformations since the last 50 years have brought changes to work patterns, access to recreational facilities, food production and sales. The tendency for the UK population to be obese has increased with devastating consequences on quality of life, leading to upsurge in prevalence of cancer, diabetes and cardiovascular diseases.[15]

Furthermore, the pace of technological advancement has outstripped human evolution to ensure that contemporary lifestyle favour obese predisposition inevitably. These considerations and other issues bordering on socioeconomic disadvantages loaded against some vulnerable ethnic minorities have conspired to push obesity as a 'normal condition' among UK population.[15]


Records identified through database searching, i.e., PubMed, ERIC, EMBASE, MEDLINE, NICE, CINAHL, HMIC and PsychINFO, (n = 990).
Additional records identified through other sources, i.e., COCHRANE, ProQuest Theses and Dissertations, (n = 113). Total records identified = 1103, (i.e., 990 + 113 = 1103).
Identification
871 records were screened as duplicates and removed from records. Therefore, total records identified = 232, (i.e., 1103 – 871 = 232).
Titles and Abstracts screened for relevance based on review criteria (n = 232).
174 journal articles were discarded due to irrelevance and based on exclusion criteria. Therefore, total records identified = 58, (i.e., 232 – 174 = 58).
Screening
Full text articles excluded because they did not meet the protocol criteria (n = 23). Therefore, total records identified for qualitative appraisal = 35, (i.e., 58 – 23 = 35).
Full text articles assessed for eligibility based on the protocol criteria (n = 58).
Eligibility
Of the 24 out of 35 studies identified for qualitative appraisal, only 14 met the study criteria for systematic analysis, (i.e., 35 – 24 = 14).
Number of articles included in systematic review (n = 14).
Included

Based on the importance of the Foresight Study,[14] it is justifiable that a review which will elicit government intervention strategies to address the need to halt the rising prevalence of obesity in relation to economic costs[15] and associated health risks[16] must be anchored on review criteria, search strategy, selection process, quality assessment and data extraction that not only targets the UK population but most importantly, defines the inclusion criteria to incorporate studies done in the English language, among UK population, from 2000 to 2018, in local health authority (LHA) and primary care or community healthcare setting. Studies not undertaken in the English language, outside the UK population, before 2000 and after 2018, and in other settings outside the LHA and primary healthcare environments were excluded from the study.

Selection of studies

Following completion of searches, the results were then assembled in the citation manager for sifting. Duplicate results were removed. Selected abstracts were re–screened for compliance with inclusion criteria. Those marked for exclusion were carefully re–screened according to exclusion criteria. Full text versions of all selected articles were then put together for the next stage of data extraction.

The fact that abstracts were not selected in a stratified random manner meant that critical studies were not missed as this would have knocked the credibility of the selection process. Also, the non–randomised selection process widened the scope of the themes that emerged. Therefore, it was justifiable that data collected in this way would address the objectives of this study and any focused question arising therefrom.

Data extraction

Data were extracted using standardised qualitative data extraction technique[17]. Thereafter, the data extraction table were reviewed. Data were extracted from the published works in the 10 databases that were relevant to the objectives of the systematic review using a data extraction form in Microsoft Excel. Information extracted from each journal article include details of the authors, sample size, study design and environment, originating country, objectives of study, age, gender and ethnic background of the study population, data collection method and findings. These are set out as the data extraction tables 1 and 2.

Assessment of quality

The quality of papers included in the review was assessed for procedural validity according to standardised guidelines contained in the Joanna Briggs Institute (JBI) critical appraisal checklist for qualitative research based on the JBI System for Unified Management, Assessment and Review of Information (SUMARI).[18,19]

Majority of the journal articles identified related to the diagnosis, prognosis and management of obesity in the country of origin and setting where the studies were undertaken, and were therefore excluded. Further screening to remove duplicates and review the articles and abstracts for relevance sieved the list down to 14 articles that met the inclusion criteria (figure 1). The articles were procedurally varied to capture the 4 search areas of Behaviour/Psychology,

Biology/Physiology, Living Environment, and Economic drivers for food production

and consumption. Due to predicted variety of the types of articles and small sample size, formal grading of studies was not undertaken. Rather, efforts were made to identify major themes and outcomes of the studies. Common themes were identified and collated, and any inconsistencies were discussed and reconciled[20]. A library staff played the role of an independent reviewer in this study.

Data analysis methods

Thematic analysis (TA) is the method of data analysis chosen for this study. TA was chosen because it affords the researcher the opportunity to be engrossed in the dataset in a manner that facilitates recognition and correct interpretation of themes generated from the dataset.[21] Further justification derives from the TA being able to foster order, structure and meaning to the dataset irrespective of the size or diversity. Conducting a TA involves a six–phase framework that include familiarisation with the dataset, generation of initial codes, searching for themes, reviewing themes, defining themes and writing–up the exercise.[20]

Essentially, relevant information about individual theme of interest was abstracted from each paper included in the review. This information were summarised in a tabular form to reflect the scope of literature review. Thereafter, the findings were imported into the tables to represent information regarding each study paper.

However, the TA as applied in this study is limited by the extent to which an individual's perspectives could favourably compare with those of others, coupled with the intrinsic doubt and bias about justifying 'common themes' as belonging to a specific category of dataset.[21] To overcome this limitation, an attempt was made to avoid formulating themes around questions thrown up by the dataset which, have the potential to overlap. Rather, themes were allowed to emerge naturally from the dataset.

Results

Search results

Steps were taken to identify articles for inclusion based on the modified PRISMA flow chart protocol shown in figure 1. In step 1, a total of 1103 papers were identified through the bibliographic database search and other sources.

In step 2, 871 of these papers were excluded because they were duplicates, with 232 papers qualifying for hand review screening of the titles and abstracts for relevance based on review criteria explained under the method section. This led to 164 journal articles being discarded based on the exclusion criteria.

After steps 1 and 2, 58 full text articles were considered for eligibility based on the protocol criteria. Following eligibility assessment, 23 full text articles were excluded because they did not meet the protocol criteria, leaving 35 full text articles to be considered for inclusion.

Next, 21 full text articles were excluded because they were not empirically based, did not use primary care settings as the units of analysis and did not examine the social determinants of obesity as the primary aim/objective of the study. A total of 14 remaining studies were included in this review.

Study findings

Of the 14 studies reviewed as shown in table 1, findings from four (28.6%) studies demonstrated that eating

behaviour/psychology (i.e., people's motivation for decisions and choices, food intake, energy expenditure and activity behaviours) contributes to the rising prevalence of obesity in the UK.

One (7.1%) study that focused on biology/physiology and the impact of early life and growth patterns (i.e., genetic constitution, homeostatic mechanism of energy balance, basal metabolic rate (BMR), adiposity rebound and critical role of the leptin hormone)) showed that obesity can be transmitted over generations via both genetic and non–genetic pathways.

Five (35.7%) studies that focused on the living environment (i.e., access to technology, opportunities for recreational activity, and access to, and availability of food and drinks) demonstrated that limited access to outdoor space for physical activities are associated with high risks of obesity to health and wellbeing and its prevalence.

Four (28.6%) studies that focused on the economic drivers of food production and consumption (i.e., cost of food and drinks, food marketing, feeding patterns and purchasing capacity, and effects of working practices) showed a strong association between low socioeconomic position (SEP) measured by income gradient and the associated health risks to obesity across all age groups in the UK.

Furthermore, a majority of the studies (n = 12, 85.7%) were found in the EMBASE and HMIC databases, while 2 (14.3%) were found in the CINAHL database. It, therefore, follows that the studies contained in the other 7 bibliographic databases were excluded from the study based on the established criteria.

The information presented in table 2 summarizes the study characteristics (i.e., aim/objective, study design, setting, study population and demographics, data collection and findings) of the 14 studies included in the review. In all, 11 (78.6%) studies did not state the ethnic background of their subjects, while 3 (21.4%) indicated theirs as Black, Chinese, South Asian, non–South Asian and White British. Ethnic background is important since the prevalence of obesity varies across different ethnicities among the UK population. Across 13 (92.9%) studies, variations in the study population ranged from 35 to 1,001,096 subjects with an average of 89,944 subjects. Only in 1 (7.1%) study that used the UK Observational Data Model was the size of the study participant not stated.

Of the 13 studies that stated their method of data collection, 6 (46.1%) used questionnaire, 2 (15.4%) used data from The UK Millennium Cohort Study, 2 (15.4%) used Geographic Information System (GIS), 1 (7.7%) used Accelerometry, 1 (7.7%) used Peer–reviewed Literature and 1 (7.7%) used the BMI scale. Age is a key demographic index of obesity study and in 6 (42.9%) studies, this was shown to vary from 4 to 73 years while 8 (57.1%) studies did not state the age of their subjects. However, these subjects were reported as adults in 6 (75%) studies, adolescents in 1 (12.5%) and children in 1 (12.5%) study each.

Table 1- Studies of behaviour/psychology, biology/physiology, living environment and economic drivers for food production and consumption including grey literature searches in the bibliographic databases and article selection

Search Area	Title of Journal Article	Author (s)	Journal/ Volume/ Page(s)/ [Year Published]	Database
Behaviour/ Psychology	Maternal eating behaviour differs between ethnic groups: considerations for research and practice.	Ref. 22	*Maternal and Child Nutrition*, 14 (4): e12630, [2018].	EMBASE
	Sociodemographic, lifestyle and behavioural factors associated with consumption of sweetened beverages among adults in Cambridgeshire, UK: The Fenland Study	Ref. 23	*Public Health Nutrition*, 4 (15): 2766 – 2777, [2017].	EMBASE
	Food outlet availability, deprivation and obesity in a multi-ethnic sample of pregnant women in Bradford, UK.	Ref. 24	*Social Science and Medicine*, 75 (6): 1048 – 1056, [2012].	HMIC
	A health assessment tool for multiple risk factors for obesity: results from a pilot study with UK adults.	Ref. 25	*Patient Education & Counselling*, 62 (1): 79 - 88, [2006].	CINAHL
Biology/ Physiology	A Mathematical Model for Predicting Obesity Transmission with Both Genetic and Nongenetic Heredity.	Ref. 26	*Obesity*, 26 (5): 927 – 933; [2018].	EMBASE
Living Environment	The impact of greenspace and condition of the neighbourhood on child overweight.	Ref. 27	*European Journal of Public Health*; 28 (1): 88 – 94, [2018]	EMBASE
	Physical activity in older age: perspectives for healthy ageing and frailty.	Ref. 28	*Biogerontology*, 17 (3): 567 – 580; [2016]	EMBASE
	Understanding the relationship between food environments, deprivation and childhood overweight and obesity: evidence from a cross sectional England-wide study.	Ref. 29	*Health Place*, 27: 68 – 76, [2014].	HMIC
	Perceptions of the environment, physical activity, and obesity.	Ref. 30	*Social Science and Medicine*; 63 (11): 2835 – 2846 [2006].	HMIC
	Effect of socioeconomic status on objectively measured physical activity.	Ref. 31	*Archives of Disease in Childhood*, 91 (1): 35 – 38, [2006].	CINAHL
Economic drivers for	Poverty, weight status, and dietary intake among UK adolescents.	Ref. 32	*International Journal of Environmental Research and Public Health*, 15 (6): pii: E1224 [2018].	EMBASE
	Unevenly distributed: a systematic review of the health	Ref. 33	*BMC Public Health*, 12(18):doi: 10.1186/ 1471	HMIC

food production and consumption	literature about socioeconomic inequalities in adult obesity in the United Kingdom.		– 2458–12–18 [2012].	
	Childhood obesity and overweight prevalence trends in England: evidence for growing socioeconomic disparities.	Ref. 34	*International Journal of Obesity (London)*, 34 (1): 41 – 47,[2010].	HMIC
	Adult socioeconomic, educational, social, and psychological outcomes of childhood obesity : a national birth cohort study.	Ref. 35	*British Medical Journal*, 330 (7504): 1354 – 1357, [2005].	HMIC

Table 2- A summary of the characteristics of selected studies on social determinants of obesity in the UK population. The common demographics (i.e., age, gender, ethnic background and location) are representative of the diverse study population that reflect dissimilar aims/objectives, study design and setting, data collection and findings

Journal Article	**Study Aim / Objective**	**Study Population**	**Ethnic Background**	**Gender/Age of Study Participants**	**Data Collection Method**	**Finding (s)**
Maternal eating behaviour differs between ethnic groups: considerations for research and practice.	Explore how maternal eating behaviour may differ between UK ethnic groups.	660	Chinese, Black, South Asian and White British.	Female / Not Stated	Survey Questionnaire	Maternal eating behaviour may therefore be a contributor to higher levels of overweight among South Asian and Black children living in the UK.
Poverty, weight status, and dietary intake among UK adolescents	(1) Determine if income gradient to obesity exists in UK adolescents, (2) Examine associations between poverty, weight status, and dietary intake among adolescents.	10,736	Not Stated	Male and Female / Not Stated	Wave Six of The UK Millennium Cohort Study	There is a strong income gradient to overweight and obesity among UK adolescents
The impact of green space and condition of the neighbourhood on child overweight.	Assess the influence of the green space, access to garden and neighbourhood condition on being obese.	6,467	Not Stated	Male and Female / Not Stated	The UK Millennium Cohort Study	This study suggests that limits on access to outdoor space are associated with future childhood overweight/ obesity.
A mathematical model for predicting obesity transmission with both genetic and	Examine the contribution of genetic and nongenetic effects to	Not Stated	Not Stated	Not Stated	UK Observational Data Model	The proposed "first approximatio n" model

nongenetic heredity.	assess their influence on obesity prevalence.					captured the complex interactions between the genetic and nongenetic effects on obesity.
Sociodemographic, lifestyle and behavioural factors associated with consumption of sugar-sweetened beverages (SSB) among adults in Cambridgeshire, UK	Identify socio-demographic, lifestyle and behavioural determinants of SSB and artificially sweetened beverages (ASB) among adults in Cambridgeshire, UK.	9,991	Not Stated	Male and Female / 30 – 64 years	Food Frequency Questionnaire.	Frequent consumers of SSB and ASB differ by several socio-demographic characteristics. But increased BMI, younger age & unhealthy eating behaviours are common to both groups.
Physical activity in older age: perspectives for healthy ageing and frailty.	Examine how regular physical activity helps in reducing obesity risks in older people.	92,000	Not Stated	Male and Female / Not Stated	Survey Questionnaire	Obesity risk is reduced by regular low intensity walking and more vigorous sports and resistance exercises.
Understanding the relationship between food environments, deprivation and childhood overweight and obesity.	Assess the positive association between density of unhealthy food outlets and the prevalence of obesity in children.	1,001,096	Not Stated	Male and Female / 4 – 5 and 10 – 11 years.	Geographic Information Systems (GIS)	Associations between obesity and deprivation do not appear strongly due to local food environment characteristics.

Journal Article	Study Aim / Objective	Study Population	Ethnic Background	Gender/Age of Study Participants	Data Collection Method	Finding (s)
Food outlet availability, deprivation and obesity in a multi-ethnic sample of pregnant women in Bradford, UK.	Explore the association between food outlet location, deprivation, ethnicity and weight status.	1,198	South Asian, non–South Asian.	Female / Not Stated	Geographic Information Systems (GIS)	Stronger association exist between area level deprivation and fast–food density than with area level deprivation and obesity.
Unevenly distributed: a systematic review of the health literature about socioeconomic inequalities in adult obesity in the UK.	To summarise important differences in the prevalence and determinants of obesity by different indicators of SEP in the UK.	35	Not Stated	Male and Female / Not Stated.	Peer–reviewed literature	Socioeconomic indicators of low SEP were generally inversely associated with adult obesity risk in the UK
Childhood obesity and overweight prevalence trends in England: evidence for growing socioeconomic disparities.	To update the prevalence trends among school-age children and assess the changing socioeconomic gradient.	15, 271	White British	Male and Female / 5 – 10 years	BMI and SEP score as a composite score based on income and social class.	There is an urgent need to reduce socioeconomic disparities in childhood overweight and obesity.
Perceptions of the environment, physical activity, and obesity.	Examine (1) the association of environment with obesity (2) whether physical activity mediates association between	14,836	Not Stated.	Male and Female/ Not Stated.	Survey Questionnaire	The results show that certain aspects of the environment may contribute to the risk of obesity and poor health.

	environment and obesity.					
Adult socioeconomic, educational, social, and psychological outcomes of childhood obesity.	To assess adult socioeconomic, educational, social, and psychological outcomes of childhood obesity.	16,567	Not Stated.	Male and Female / 10 – 30 years	Self–Report Questionnaire	Obesity limited to childhood has little impact on adult outcomes.
A health assessment tool for multiple risk factors for obesity: results from a pilot study with UK adults.	Pilot a measure of multiple risk factors for obesity, designed to assess their relative importance at individual and population levels.	80	Not Stated.	Male and Female / 19 – 73 years.	Self–Report Questionnaire	Strong associations exist between BMI and attitudes, emotions and social influences on eating and activity behaviours.
Effect of SES on objectively measured physical activity.	Examine if habitual physical activity and/or sedentary behaviour are associated with SES in young Scottish children.	339	Not Stated.	Male and Female / 4 – 6 years.	Accelerometric measurement of physical activity and sedentary behaviour.	Low SES in young Scottish children is not associated with lower habitual physical activity or higher engagement in sedentary behaviour.

Discussion

The implications of appraising the social determinants of obesity as a function of the disparities in the socioeconomic indicators pertaining to low SEP or SES, and as a growing problem of public health among the UK population is considerable. Indices of SEP predict obesity in women more than in men.[33] Furthermore, socioeconomic indices of SEP such as 'occupational social class of the head–of–household at birth and during childhood, earlier adulthood occupational social class, contemporaneous occupational social class, educational attainment, and area–level deprivation' bear inverse relationship to adult obesity risk.

Health risk factors in childhood that may predict obesity in adulthood have been evaluated to include birth weight, parental fatness and dietary habit alongside other behavioural factors.[36] There is increased risk of childhood obesity progressing into adulthood among offspring of obese parent(s). But what remains unknown is the relative contribution of genes and hereditary lifestyle factors from obese parent(s) to a child. Whilst no clear association appear to exist between childhood SES and obesity, however, a strong relationship between low childhood SES and obesity in adulthood exist[36]. What this portends is an enormous cost implication to public health finance regardless of the intervention measures being applied.[15]

Main finding of this study

This review underscores the influence of lifestyle choices, economic conditions, environmental factors and social issues in relation to obesity risks and prevalence in the UK population. The study analysis further demonstrated the degree of dissimilarities in respect of the intervention strategies suggested in the works of different researchers examined in this review.

The results, together with verifiable trends and socio–demographic elements that are fundamental to misunderstanding body weight considerations in obese adults, demonstrate evidence that the rising trend in under–estimation of obesity status among the UK population is probably the result of normalizing obesity.[15] This observation draws from the stereotypic narrative that is predicated on generalised depiction of a critical public health issue as a 'new normal' within the UK population.[16] What this portends is the necessity for obesity intervention strategies to incorporate the diverse socio–demographic attributes that are connected to under–estimation of body weight status.

Majority of the social determinants of obesity among the UK population are related to the living environment and economic drivers for food production and consumption.[37] These assessments found that limited access to outdoor space for physical activity and the unequal distribution of opportunities resulting in growing socioeconomic disparities largely constitute the vital causal factors of obesity.[27–31] Some of these limitations exacerbate the risk of developing obesity alongside cardiovascular diseases.[26] Lack of greenspace and access to recreational facilities restrict the opportunity to engage in regular physical exercises ranging from low intensity walking to more vigorous sports and resistance activities.[27–31]

Cost–effectiveness of inadequate recreational facilities, poor work environment and poor housing facilities are diverse elements of environmental

factors that predispose to physical inactivity. While frequent physical exercise helps to improve mental and physical health and wellbeing including reversing some effects of obesity particularly in adults, there is evidence that predominantly sedentary lifestyle accounts for increasing prevalence of adult obesity.[23] Notwithstanding the widely acknowledged benefits of access to outdoor space for physical activity, the overwhelming majority of adult UK population still fall short of the minimum level of physical activities needed to maintain healthy living and reduce the incidence of obesity.

The fact that local authorities are statutorily responsible for providing green space, access to garden and neighbourhood conditions, meant that their involvement in mitigating the disease burden of obesity is vital.[38] The challenge of stimulating frequent physical activity across all population groups is enormous and noteworthy. However, the benefits that accrue from intensified awareness of engaging in physical exercise to reduce the health risks associated with adverse events of obesity is worthwhile. Local authorities could undertake as part of informed public health initiatives, to encourage the elderly particularly the relatively healthy elderly and those with physical frailty to increase their participation in physical activities.

Evaluation of the economic drivers for food production and consumption in relation to poverty, deprivation, inequality, inequity, unemployment and low income, was an objective of this review. Socioeconomic disparities in obesity and related health risks factors are increasing among UK population. There is increased likelihood of obesity for adolescents living in poverty and multiple deprivation.[32–35] Meagre household income and poverty accounted for the strong income gradient to obesity that exist among the adolescent UK population. This is further accentuated by concomitant consumption of cheap and nutritionally deficient diets of fast foods and sweetened drinks with less recurrent consumption of fruits and vegetables.[22–25] Urgent intervention strategies needed to reduce adolescent obesity must target the reduction of indices of deprivations and inequalities in household SES via more employment opportunities and higher wage structure to alleviate poverty.

The adult population has not fared better either. Available evidence showed that adult obesity is largely a function of poverty and deprivation, and an outcome of poor household income and unemployment in childhood.[35] Initiatives to reduce the socioeconomic burden of obesity within adult population have always focused on measures aimed at preventing the incidence of childhood obesity. However, the impact of childhood obesity on adult outcomes has not been fully elucidated given the paucity of UK–wide representative data.[35]

Overall, it can be speculated that through a combination of poverty, deprivation, inequalities, inequities and differential health behaviours, increased prevalence of adult obesity may probably be explained by multifaceted and hard–to–measure interaction of health determinants operating at disparate levels throughout the life course.[33] But whether poverty, deprivation and low income constitute the determinants of adult obesity beyond the UK setting, to inform public health initiatives for reducing obesity is still debatable.

This review demonstrates that the number of UK–based, primary care studies on the social determinants of obesity around generalisable themes of living environment, behaviour/psychology, biology/physiology and economic drivers of food production and consumption within a timeframe of 2000 to 2018 is incredibly small. Further studies specific to the themes evaluated in this review that will target the health risks of obesity and increasing prevalence are needed.[36,38]

Whilst this review supports the opinion that evaluation studies on causality of obesity is better undertaken within LHA for reasons of cost–effectiveness and availability of primary care data, there is however, as much dissimilarities in outcomes as there are studies. More studies may not necessarily improve statistical reinforcement for reliability of study outcomes in an ethnically diverse population like the UK. There is, however, the need for studies undertaken in hospitals/acute care settings, screening programmes and tertiary environments to provide outcomes for robust comparative analysis with those of LHA, primary care and community healthcare centres.

Extensive studies that would emphasise ethnic diversities, gender disparities and regional variations in the prevalence of obesity across the UK population may help to situate the public health burden of obesity in its proper perspective. When there are adequate studies available to conduct SR on the assortment of settings, widespread recommendations for prompt interventions can be made with greater confidence. However, the contradictory views of different studies on the social determinants of obesity is underscored by overlapping outcomes of generalisable themes in this study. This observation was lacking in previous studies.

Although White and colleagues[38] argued that preventative public health intervention strategies for obesity are generally cost–effective notwithstanding the further studies that could justify the continuing increase in public health funding, El–Sayed and colleagues[33] advocated a strong reliance on the measures of SEP as being more predictive of obesity on gender basis. The fact that this review evaluated the social determinants of obesity in the UK on broad generalisable themes to support broad harmonisation of outcomes should count as a strength, and an addition to existing knowledge on the topic.

Limitations of this study

Some limitations of this review need to be considered when interpreting the findings. Firstly, the inclusion criteria limited the studies reviewed to those undertaken in LHA, primary care settings and community healthcare practices. It is possible that this scope of the review could introduce bias in the conclusions reached. Though the inclusion criteria is comparatively permissive and comprised many studies that involved largest obesity surveys in the UK,[36] the findings reported here may not precisely reflect contemporary knowledge of social determinants of obesity in the UK.

Secondly, there was uncertainty about COCHRANE database as a search strategy. It is probable that some studies on causality of obesity in the UK population may have been missed in the findings. However, the identification of records during step 1 of the search strategy was meticulously done to reduce this probability. Much interest was therefore

focused on finding published works in both healthcare and management journals. A broader search on Google Scholar may have provided scholarly articles on recent reviews on the health risks of obesity and its prevalence.[39]

Thirdly, the breadth of the findings may be limited by the considerable overlap of the surveys conducted in the studies reviewed. This, nonetheless, is an inevitable constraint forced on this review by the studies themselves.

Fourthly, the fact that the findings reflected TA of this review meant that the conclusions may have been influenced by the generalisable themes.

Fifthly, this review was limited to studies on the social determinants of obesity in the UK population. This would therefore render it inapt to generalise the findings outside the UK context.

Conclusion

This SR of literature from 2000 to 2018 showed substantial disparities in the social determinants of obesity among the UK population. Most of the determinants focused on the four generalisable themes of economic drivers for food production and consumption, living environment, behaviour/psychology and biology/physiology, with economic drivers for food production and consumption, and living environment demonstrably having the most influence on obesity as a public health problem in the UK.

Conversely, several factors limit an understanding of causality of obesity risks and rising prevalence in the UK. A careful consideration of these limitations relative to an understanding of the causality factors will necessitate an inquiry along two pathways: One, the theory and investigation of future studies on causality factors would benefit from composite and multisystem methods that encompass the significant influence of SEP at different levels of personal, family and community, on the health risks of obesity and its prevalence. Two, future reviews would be enriched by assessing the social determinants of obesity based on disparate ethnic milieu of the UK population. As this review suggests, the interplay of SEP and ethnic background may have significant influence on obesity.

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