International Journal of TROPICAL DISEASE & Health
4(12): 1287-1297, 2014
ISSN: 2278–1005

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Dietary Pattern and Antioxidants Levels in Patients with Simple Goiter and Thyroid Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Author KSA designed the study. Authors KSA, KAO, AAM and OO were involved in drawing up of the protocol, collection and analysis of specimen. Authors KSA, KAO and OO were involved in statistical analysis and drafting of the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2014/13218
Editor(s):
(1) Arun Kumar Nalla, College of Medicine, University of Illinois, Peoria, IL, USA.
Reviewers:
(1) Anonymous, Tufts Medical Center, USA.
(2) Anonymous, King Abdulaziz University, Saudi Arabia.
(3) Anonymous, National Research Centre, Egypt.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=673&id=19&aid=6465

Original Research Article

Received 8th August 2014
Accepted 25th September 2014
Published 10th October 2014

ABSTRACT

Background /Aims: Oxidative stress has been implicated in the pathogenesis of thyroid cancer and simple goiter among other diseases however; there has not been a direct comparison of the severity of the stress factor in these two conditions in relation to their dietary pattern in our environment.
Objective: This study assessed oxidative stress indices, antioxidant status and dietary pattern in thyroid cancer and simple goiter compared with the controls.

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Study Design: This is a case-control study.
Place and Duration of Study: Study groups were recruited from the Departments of Surgery and Nuclear medicine of University of Ilorin teaching hospital, Ilorin, Kwara State and University College Hospital, Ibadan, Oyo State respectively between March 2013 and September 2013.
Materials and Methodology: A total number of one hundred and five (105) age matched participants consisting of 88 females and 17 males were recruited for this study. They were divided into 3 groups; Group one 35 participants with thyroid cancer and group two, 35 participants with simple goiter and group three, 35 control participants. Plasma levels malondialdehyde (MDA), hydrogen peroxide (H_2O_2) and total plasma peroxide (TPP) were determined by colorimetric methods. Antioxidant status was determined by measuring total antioxidant potential (TAP), glutathione peroxidase (GPx), Superoxide dismutase (SOD), reduced glutathione (GSH), glutathione-s-transferase (GST) by colorimetric methods. Selenium (Se) was determined by atomic absorption spectrophotometry (AAS).Oxidative stress index (OSI) was measured and all values expressed as mean ± SD, while frequency of intake of various dietary sources of the participants were collated.
Results: TAP, SOD, GPx, GSH and GST (antioxidants) levels in group 1 (552.17±74.67; 1.30±0.32; 1.91±0.23; 4.47±0.59; 0.92±0.25; 1.28±0. 04 respectively) were significantly lower than group 3 (933.51±80.15; 2.85±0.39; 5.40±0.76; 8.34±1.12; 2.11±0.31). While the mean plasma levels of antioxidants in group 2 (704.74±62.22; 2.01±0.27; 4.62±0.89; 6.19± 0.56; 1.47± 0.14 and 1.40±0.04) were significantly higher than that of group 1. However, significant increase was observed in mean levels of oxidative stress markers; TPP, MDA, H_2O_2 and OSI, in group 1 (16.24±2.52, 13.88±2.95, 13.52±6.91 and 2.93±1.40 respectively) compared to group 3 (4.57±1.32, 3.22±1.20, 3.01±0.86 and 0.48±0.14). Oxidative stress markers in group 2 (9.79±1.40, 5.90±1.13, 3.81±1.40 and 1.62±0.23) were significantly lower than group 1. A p - value <0.05 was considered significant. Majority of the control participants consumed fruits and vegetables (sources of exogenous antioxidants) regularly more than the test groups
Conclusion: The study reported higher oxidative stress markers; oxidative stress index and lower antioxidant status in study subjects compared to controls .Oxidative stress appeared more marked in thyroid malignancy than the benign thyroid disease state. Adequate intake of fresh fruits and vegetables could be beneficial for thyroid cancer patients.

Keywords: Thyroid cancer; simple goiter; enzymatic antioxidant; oxidative stress index.

1. INTRODUCTION

Thyroid cancer is the most common endocrine malignancy with more deaths annually than other endocrine cancers combined [1,2,3]. Free radicals have been implicated in a wide variety of degenerative diseases including thyroid cancer. It is believed that oxidative stress plays a major role in the pathogenesis of thyroid cancer [4]. This may occur when the cellular antioxidant defense is unable to eliminate or detoxify the free radicals. The imbalance between the oxidant (free radicals) and antioxidant system in favour of oxidant generation has carcinogenic effect [5,6].

Thyroid hormones regulate oxidative metabolism and thus play an important role in production of free radical such as hydrogen peroxide [7,8,9]. Hydrogen peroxide is abundantly present in the thyroid gland as a substrate for the thyroperoxidase that catalyzes

iodine oxidation, binding to thyroglobulin and oxidative coupling of iodotyrosines into iodothyronine [7,8]. Therefore, reduced detoxification of hydrogen peroxide may lead to thyroid cell death. Thyroid hormones regulate the synthesis and degradation of antioxidants enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and non-enzymatic antioxidants such as vitamin E and C, uric acid, ferritin, transferring and ceruloplasmin [10,11]. Vitamin A, C and E have been proved to have antioxidant efficacy in-vivo. Many common foods are good sources of antioxidants. Spices, herbs, fibers and essential oils are plants rich in antioxidants properties. Fruits like oranges, guava, mango, grape juice; spices such as ginger, pepper, garlic, onion are also good sources of antioxidants [10].

This study assessed the degree of imbalance between the pro-oxidants and antioxidants in thyroid cancer and simple goiter in relation to their diet. The findings may help in understanding the role of diet in ameliorating oxidative stress and the development of thyroid cancer.

2. MATERIALS AND METHODS

Ethical approval was obtained from the University of Ibadan/University College Hospital (UI/UCH) and the University of Ilorin Teaching Hospital (UITH) ethical review committee respectively and written informed consent (attached to every questionnaire completed by each participant) was obtained from individual patients prior to recruitment into the study.

2.1 Study Design

A total of 105 participants matched by age and sex were recruited for this study from the thyroid clinics of the Nuclear Medicine of the University College Hospital (UCH), Ibadan and the thyroid clinics of Surgery department of the University of Ilorin Teaching, Ilorin (UITH) respectively between January, 2013 and February, 2014. All the study participants were examined and classified into 3 groups. Participants without any form of cancer or chronic illnesses constituted the controls (group1), participants with thyroid cancer constituted the second group while group 3 comprised of participants with simple goiter. Each group consisted of 35 participants. Their medical history and physical examination were documented. Diagnosis of simple goiter was by clinical examination, thyroid swelling and biochemical result of fT3, fT4 and TSH as well as thyroid ultrasound and fine needle aspiration cytology, while participants with thyroid cancer were diagnosed by thyroid swelling, thyroid ultrasound and histological diagnosis either by Fine Needle Aspiration Cytology (FNAC) or excision biopsy for confirmation. A structured questionnaire containing age, sex, educational qualification, diagnosis and treatment was administered to the participants as well as participants' dietary recall and the frequency of consumption of major food items.

Exclusion criteria included Individuals with other chronic illness or combination of any other forms of cancer. Participants on multivitamins or food supplements were also excluded from the study. Ethical approval and informed consent were obtained from UI/UCH and UITH ethical review committee respectively.

2.2 Blood Sample Collection

Five milliliters of venous blood was collected into lithium heparin anticoagulant bottles before commencement of clinical treatment. This was gently mixed to avoid coagulation and

heamolysis. The plasma samples were frozen at -20º until samples were analyzed. Sample collection covered a period of 12 weeks

2.3 Method of Analysis

Plasma antioxidants such as SOD, GPx, GSH, GST were measured based on standard colorimetric method respectively [12,13,14,15]. Total Antioxidant Potential (TAP) was measured by colorimetric method [16]. Total plasma peroxide (TPP), MDA and H_2O_2 levels were measured based on colorimetric method [17,18,19]. Selenium was determined by Atomic Absorption Spectrophotometry (AAS) with appropriate control [20]. The ratio of TPP level to TAP level was calculated as oxidative stress index (OSI).

1. Total Plasma Peroxide (TPP) levels were determined using the ferrous oxidation (FOX2) method (Miyazawa, 1989) with minor modifications [17]. The FOX2 system is based on oxidation of ferrous ion (Fe^{2+}) to ferric ion (Fe^{3+}) by various types peroxides contained within the plasma samples to produce a coloured ferric-xylenol orange complex whose absorbance can be measured
2. Malondialdehyde (MDA) [18] Lipid peroxidation was determined by measuring the thiobarbituric acid reactive substances (TBARS) produced during lipid peroxidation. Malondialdehyde react with 2-thiobarturic acid (TBA) in acidic pH to form a pink complex at was measured spectrophotometrically at 532nm.
3. Hydrogen peroxide (H_2O_2).This is based on coupled oxidation. Catalase or peroxidase combines with hydrogen peroxide as it is liberated, and the complex thus formed then brings about the oxidation of substances such as nitrite, ethanol, cytochrome C or manganese ions in the presence of p-cresol. The extent of these oxidations is measured spectrophotometrically [19].
4. The total antioxidant potential (TAP) is equivalent to the total antioxidant capacity (TAC) described by [20] as the sum of all known endogenous and exogenous antioxidants in a medium. Measurement of the total antioxidant activity was carried out by using the ferric reducing antioxidant power (FRAP) assay of Benzie and Strain (1999). At low pH, ferric tripyridyl triazine (Fe III TPTZ) complex reduced to ferrous form, an intense blue colour which was measured at 593nm.
5. Glutathione peroxidise was determined Rotruck et al method [13].
6. Super oxide dismutase activity was determined by the method of Misra and Fridovich [12]
7. Glutathione-S-transferase activity was determined according to Habig et al. [21]. The principle is based on the fact that known glutathione-S-transferase demonstrate a relatively high activity with 1-chloro-2, 4,-dinitrobenzene as the second substrate, consequently, the conventional assay for glutathione-S-transferase activity utilizes 1-chloro2, 4,- dinitrobenzene as substrate. The absorption increase at the new wavelength of 340nm provides a direct measurement of enzymatic reaction.
8. The method of Beutler et al. [22] will be followed in estimating the level of reduced glutathione (GSH). The reduced form of glutathione comprises in most instances the bulk of cellular non-protein sulfhydryl groups. This method is therefore based upon the development of a relatively stable (yellow) colour when 5', 5'-dithiobis-(2-nitrobenzoic acid) (Ellman's reagent) is added to sulfhydryl compounds. The chromophoric product resulting from the reaction of Ellman reagent with the reduced glutathione, 2- nitro-5-thiobenzoic acid possesses a molar absorption at 412nm.
9. Selenium was determined by atomic spectrophotometry (AAS) [23].

2.4 Statistical Analysis

Statistically analysis was performed using SPSS software version 17.0. All data were expressed as mean ±SD (standard deviation). ANOVA was also used to compare the 3 groups (thyroid cancer, simple goiter and control) while Post Hoc test was used to compare the difference between the means of the participant's groups. The Pearson's correlation was used to determine the relationship between the oxidative stress index (OSI) and other biochemical parameters. Data were analyzed at 95% confidence interval and *p*-values 0.05 were considered statistically significant.

3. RESULTS

A total of 105 participants were recruited. The anthropometric data of the participants showed no significant differences among the three groups (P<0.05) (Table 1).

Consumption of carbohydrate, animal protein, smoked food and sea foods was similar among the three groups. Larger percentages of the control participants consumed fruits and vegetables (sources of exogenous antioxidants) regularly more than the test groups (Table 2).

Table 1. Anthropometric indices in thyroid cancer, simple goiter and control participants

Variables	Thyroid cancer n=35	Simple goiter n=35	Control n=35	F-value	p-value
Age (years)	41.83±6.11	41.97±6.14	44.51±7.12	1.908	0.15
Weight (Kg)	64.40±4.29	65.03±3.88	64.11±4.57	0.422	0.66
Height (M)	1.60±0.03	1.60±0.05	1.59±0.03	1.230	0.30
BMI (kg/m^2)	25.33±1.93	25.54±1.59	25.53±2.09	0 .142	0.86
Systolic BP (mmHg)	136.97±7.55	134.29±9.67	120.41±4.24	29.206	0.30
Diastolic BP (mmHg)	80.49±5.99	76.14±4.75	74.26±3. 25	0 .843	0.43
Males	6(17.1%)	5(14.3%)	6(17.1%)		
Females	29 (82.9%)	30(85.7%)	29(82.9%)		

3.1 Oxidative Stress Markers

The mean plasma levels of oxidative stress markers differed significantly between the study participants and the controls. The mean plasma levels of MDA (µmol/L), H_2O_2 (µmoles) and TPP (µmolH_2O_2/L) in group 1 (thyroid cancer group) were significantly higher than group 3 (controls) (13.88±2.95, 13.52±6.91; 16.24±2.52) vs (3.22±1.20; 3.01±0.86; 4.57±1.32) respectively (Table 3). While, the mean plasma levels of MDA, H_2O_2, TPP in group 2 (simple goiter) were also significantly lower than group 1 (5.90±1.13; 3.81±1.40; 9.79±1.40) vs. (13.88±2.95, 13.52±6.91; 16.24±2.52) respectively. The mean plasma levels of oxidative stress markers were significantly higher in group 2 compared with group 3.

3.2 Antioxidants

The mean plasma levels of total antioxidant potential (TAP), superoxide dismutase (SOD), glutathione peroxides (GPx), reduced glutathione (GSH), glutathione-s-transferase (GST) in group 1 were significantly lower than group 3 (552.17±74.67; 1.30±0.32; 1.91±0.23;

4.47±0.59; 0.92±0.25; 1.28±0.04) vs. (933.51±80.15; 2.85±0.39; 5.40±0.76; 8.34±1.12; 2.11±0.31) respectively (Table 3). Meanwhile, the mean plasma levels of TAP, SOD, GPx, GSH, GST in group 2 were significantly higher than that of group 1 (704.74±62.22; 2.01±0.27; 4.62±0.89; 6.19± 0.56; 1.47± 0.14; 1.40± 0.04) vs. (552.17±74.67; 1.30±0.32; 1.91±0.23; 4.47±0.59; 0.92±0.25; 1.28±0.04) respectively. The mean plasma levels of TAP, SOD, GPx, GSH, GST were significantly lower in group 2 than that of controls (group 1).

Table 2. Percentage frequency of diet style in the test and control groups

Variables	Frequency of intake	Thyroid cancer (%) n=35	Simple goiter (%) n=35	Control (%) n=35
Carbohydrate	Regular	86	83	84
	Not regular	14	17	16
Protein (Animals)	Regular	82	76	71
	Not regular	18	24	29
(Plants)	Regular	44	62	70
	Not regular	56	38	30
Smoked food	Regular	77	74	66
	Not regular	23	26	34
Sea foods	Regular	62	66	69
	Not regular	38	34	31
Fruits/Vegetables	Regular	59	63	70
	Not regular	41	37	30

Table 3. M**ean values of biochemical parameters in the study participants**

	Thyroid cancer	Simple goiter	Controls	F-value	P-value
MDA	13.88±2.95[a,b]	5.90±1.13[a]	3.22±1.20	283.25	0.00*
H_2O_2	13.52±6.91[a,b]	3.81±1.40[a]	3.01±0.86	220.51	0.00*
TPP	16.24±2.52[a,b]	9.79±1.40[a]	4.57±1.32	356.82	0.00*
TAP	552.17±74.67[a,b]	704.74±62.22[a]	933.51±80.15	243.72	0.00*
SOD	1.30±0.32[a,b]	2.01±0.27[a]	2.85±0.39	193.56	0.00*
GPX	1.91±0.23[a,b]	4.62±0.89[a]	5.40±0.76	247.48	0.00*
GSH	4.47±0.59[a,b]	6.19±0.56[a]	8.34±1.12	206.30	0.00*
GST	0.92±0.25[a,b]	1.47±0.14[a]	2.11±0.31	199.59	0.00*
Se	1.28±0.04[a,b]	1.40±0.04[a]	1.60±0.05	450.20	0.00*
OSI	2.93±1.40[a,b]	1.62±0.23[a]	0.48±0.14	348.75	0.00*

** Statistically significant at p< 0.05 (2-tailed), [a] Value significantly different (p<0.05) from control value (Post hoc test), [b] Value significantly different (p<0.05) from simple goiter value (post hoc test)*

3.3 Selenium

The mean plasma selenium in the thyroid cancer group (group 1) was significantly lower compared with the control group (3). (1.28±0.04 vs 1.60±0.05) While, the mean plasma selenium in group 2 (1.40±0.04) was significantly higher than group 1. The selenium level in group 2 was lower compared to that of controls (group 3) (Table 3).

3.4 Oxidative Stress Index (OSI)

The mean plasma OSI in group 1 was significantly higher compared to that of group 2(2.93±1.40) vs. (1.62±0.23). The OSI level in group 2 was also significantly lower than

group 1 but was significantly higher that the control (group 3) (0.48±0.14) (Table 3) respectively.

The correlation studies showed a strong positive significant association between OSI and oxidative markers TPP, MDA and H_2O_2 in thyroid cancer participants. Also there was a negative significant association between OSI and TAP; SOD GST in thyroid cancer group Table 4.

Table 4. Correlation studies between oxidative stress index (OSI) and biochemical parameters in the study participants

	Group 1 (Thyroid cancer) n=35	Group 2 (Simple goiter) n=35	Group 3 (Control) n=35
MDA (µmol/L)	r = 0.554*	r = 0.192	r = -0.345*
	p = 0 .00	*p* = 0.27	*p* = 0.04
H_2O_2 (µmoles)	r = -0.420*	r = 0.099	r = -0.187
	p = 0.012	p= 0.57	*p* = 0 .28
TPP (µmolH2O2/L)	r = 0.775*	r = 0.844*	r = -0.898*
	p = 0 .00	*p* = 0.00	*p* = 0.00
TAP	r = -0.762*	r = -0.610*	r = -0.139
	p = 0.00	*p* = 0.00	*p* = 0.43
SOD	r = -0.375*	r = 0.842	r = -0.190
	p = 0 .03	*p* = 0.64	*p* = 0.27
GPx	r = -0.074	r = -0.051	r = -0.017
	p = 0.69	*p* = 0.75	*p* = 0 .93
GSH	r = 0.277	r = 0.009	r = -0.271
	p = 0.11	*p* = 0.96	*p* = 0.12
GST	r = -0.368*	r = 0.245	r = 0.370*
	p = 0.03	*p* = 0 .16	*p* = 0 .03
Se	r= -0.401	r = -0.149	r = 0.012
	p= 0.17	p = 0 .39	p= 0.95

** Correlation is significant at the 0.05 level*

There was also a positive significant association between OSI and TPP in simple goiter group and GST in the controls respectively.

TAP in the simple goiter group, MDA, and TPP in controls showed negative significant association with OSI (Table 4).

4. DISCUSSION

An imbalance between the oxidant and antioxidant system has been reported to play a major role in development of thyroid cancer and simple goiter [6]. The observed higher levels of pro-oxidants and lower levels of antioxidants in thyroid cancer participants compared with the controls supports the reported imbalance between the oxidants and antioxidant defense system.

Observed increases in the level of hydrogen peroxide (H_2O_2) a pro-oxidant generated in the synthesis of thyroxine by the thyroglobulin-iodine-tyrosine complex in the thyroid gland may be the basis of the free radical generation as earlier reported by other authors [6,24].

In this study, there were significantly increased levels of total plasma peroxide (TPP), malondialdehyde (MDA) and hydrogen peroxide (H_2O_2) in thyroid cancer subjects and to a lesser extent in patients simple goiter compared with the controls. TPP is a measure of increased ROS in the test group. This further confirms the increase in generation of free radicals which appears to be progressive or worsened in the thyroid cancer group. It has also been registered that as age increases the risk of development of thyroid cancer increases [25]. This may not be unexpected from increase in the duration of exposure to environmental factors and toxic chemicals as reported by Jemal et al. [26].

Significantly decreased levels of antioxidants (superoxide dismutase, glutathione peroxidase, reduced glutathione, glutathione-s-transferase) were observed in thyroid cancer and simple goiter subjects when compared with controls. The significant decrease observed in the test group could be due to their involvement in scavenging free radicals generated in thyroid gland. Several authors [6,27] have reported a significant correlation between antioxidant enzymes and oxidants in patients with thyroid cancer and simple goiter. Therefore as the oxidant level increases, the antioxidants level decreases in thyroid cancer and simple goiter patients. It was suggested that a decrease in total antioxidant potential (TAP) of the body may increase the oxidative damage in the tissue including the thyroid gland.

The significant decrease in TAP in the thyroid cancer and simple goiter compared with controls confirmed the reduced plasma antioxidant defense system. Similar findings by [4,28,29] confirmed the significant difference between the total antioxidant status of thyroid cancer patients and controls. Hence the progression of oxidative stress contributes to the development of thyroid cancer in the absence of adequate consumption of antioxidant vitamins and failure of the endogenous antioxidants to detoxify the free radicals.

The effect of dietary antioxidants on the overall antioxidant status of test groups (thyroid cancer and simple goiter) was evaluated in this study. More than 70% of the thyroid cancer participants consumed food rich in carbohydrate, animal proteins and smoked foods as against the controls who regularly took more of the plant proteins and less of the smoked food. About 59% of thyroid cancer participants ingest fruits and vegetables regularly as against 70% of the controls that consumed fruits and vegetables more than four days in a week. Therefore, dietary antioxidants seem to be associated with an improved antioxidant status in our study, this finding has been earlier reported [30].

Diet is one of the lifestyle factors that influence the risk of developing cancer. The foods that we eat affect the risk of developing certain types of cancer; diet high in energy, fat and low in fruits, vegetables and fibers are more likely to influence cancer development [31]. There is convincing evidence that smoked foods and meat cooked at high temperature increase the risk of developing cancer. Smoking is a known source of food contamination caused by carcinogenic polycyclic aromatic hydrocarbons while meat cooked at high temperature contains heterocyclic amines (HCA) also a carcinogenic compound [31]. Studies indicate a correlation between the increase occurrence of cancer and the frequent intake of smoked foods [32]. Smoked foods absorb large amount of tars that arise from incomplete combustion of wood or charcoal fire which are known to contain numerous carcinogens [33].

Plants based diet (fresh fruits, legumes and vegetables) contain many beneficial nutrients such as vitamins, minerals, antioxidants, phytochemicals and fiber which may reduce risk of developing cancer [33]. Carotenoids present in significant amounts in fruits, as well as vitamin E in oil are probably responsible for protection against cancer [34]. Lycopene is a

potent antioxidant found in tomatoes, watermelon and strawberries that may lower the risk of cancer development [35]. On the other, fatty red meats, processed meats, processed foods that are low in fiber, antioxidants, phytochemicals, heavily salted and pickled foods may increase risk of cancer development [36]. Therefore, these dietary antioxidants may increase the level of antioxidant defense system. A low fat, high fiber diet is recommended with plenty of fresh fruits and vegetables that are rich in vitamins A, B, C, D, E and trace elements such as zinc, selenium can help to reduce the risk of complication [37]. The effect of free radicals generated in these subjects (thyroid cancer & simple goiter) could or possibly be ameliorated by dietary antioxidants thereby reducing the risk of oxidative stress.

Significant decreased level of selenium was observed in thyroid cancer and simple goiter subjects compared with the control. Selenium is an essential trace element for the biosynthesis and function of selenocystiene-containing selenoproteins implicated in thyroid hormone metabolism and thyroid gland function. However, generation of hydrogen peroxide and oxidative damage are decreased by selenoenzyme systems in the thyrocytes involved in regulating hormone synthesis. Low selenium levels and lower selenoenzyme activity levels have been documented in thyroid cancer and simple goiter [35].

5. CONCLUSION

The findings in this study support the hypothesis that oxidative stress contributes to the development of thyroid cancer and simple goiter in our environment. The study has established the fact that inadequate level of antioxidants (both endogenous and exogenous) as well as selenium could be associated with the development of thyroid cancer and simple goiter. Diets including fruits and vegetables which contain vitamins could increase dietary antioxidant status and mitigate the harmful effect of increased oxidative stress in the thyroid gland.

CONSENT

All authors declare that informed consent was obtained from the participants for publication.

ETHICAL APPROVAL

All authors declare that all experiments have been examined and approved by the appropriate ethics committee.

ACKNOWLEDGEMENTS

The authors appreciate the collective efforts and cooperation of Resident Doctors in Nuclear Medicine Department especially Drs Ayeni A.O and Lawal I.O in recruitment of participants.

COMPETING INTEREST

Authors have declared that no competing interests exist.

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