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Comparative Analysis of Serum Zinc and Vitamin A in Patients with Head and Neck Squamous Cell Carcinoma and Healthy Individuals

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Authors' contributions

This work was carried out in collaboration between all authors. Author AD was involved in the study concept and design, data collection, analysis and interpretation, writing of manuscript and final draft approval. Author AJF was involved in the study design, data collection, manuscript writing and final draft approval. Author TNE was involved in the manuscript drafting and review for contribution to knowledge as well as the final draft approval. Author OGN was involved in the study concept and design, manuscript drafting and review for contribution to knowledge and correction as well as the final draft approval.

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ABSTRACT

Background: Deficiency of micro nutrients and trace elements has been associated with Head and Neck Squamous cell carcinomas (HNSCC). There is however a paucity of studies demonstrating this association in the West African sub-region.
Aim: To determine the serum level of zinc, vitamin A and nutritional status of HNSCC patients at the University College Hospital, Ibadan.
Methods: This was a case-control study of 65 consecutive patients with histological diagnosis of

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HNSCC. The controls were 65 healthy volunteers similar in age, sex and socioeconomic status. The participants' height, weight, mid upper arm and waist circumference were measured and, serum Zinc and Vitamin A (Retinol) levels were assayed. The data from cases were analysed and compared with the controls using statistical package for social sciences version 15 software. Significance was set at $p < 0.05$.

Results: The mean ages of cases and controls were 50.9±15.2 years and 49.49±16.35 years respectively. The commonest sites of HNSCC were the Nasopharynx and Sinonasal regions. Fifty five (84.6%) HNSCC patients presented with advanced form of the disease (stage III and IV). The mean body mass index of cases and controls was 22.66±4.70 and 23.14±3.8 respectively (p=0.524). The mean serum zinc level of the controls (113.63±6.04) was significantly higher than the cases (89.84±14.27) (p=0.000). The mean serum vitamin A (retinol) level of the controls (77.74 µg/dl±2.82) was significantly higher than the cases (61.34±5.89) (p=0.000).

Conclusion: There are more Head and Neck Squamous cell carcinoma patients with malnutrition than the healthy population. Although no abnormality of serum zinc and retinol was found in both groups, there is a trend of lower levels of these nutrients in the patients than healthy individuals.

Keywords: HNSCC; nutritional status; retinol; zinc.

1. INTRODUCTION

The incidence of head and neck cancers is increasing worldwide with 60% of new cases in the developing countries [1]. They are associated with high rates of mortality and morbidity [2,3]. About 300,000 individuals die from Head and Neck Cancers annually [4]. The disease impairs swallowing, speech, hearing or breathing depending on the affected anatomical location and these make their management more challenging. Poor nutrition from inadequate intake and metabolic effect of the tumour is seen in them.

Nutritional deficiencies, especially of trace elements and vitamins, are risk factors for the development of head and neck cancers [1,4]. The nutritional status of head and neck cancer patients is an important prognostic factor for survival and ability to tolerate treatment [6-8]. Aggressive nutritional intervention in head and neck cancer patients minimises weight loss, improves response to treatment and decreases treatment related toxicity [6]. Administration of supplemental micronutrients and trace elements to patients with pre-malignant oral cavity lesions has been shown to prevent malignant transformation [9] and also reduce the risk of developing head and neck cancers [10]. Vitamin A has been shown to be a chemoprevention agent in Head and neck cancers [11,12]. However, the role of vitamin A and Zinc in head and neck cancer patients has not been well investigated in the developing countries where there is a high burden of malnutrition.

Nigeria is a poor resource country in sub-Saharan Africa with a large number of the population suffering from malnutrition [13]. There are available studies on head and neck cancers in Nigeria but none on their association with nutritional status. This study therefore was designed to evaluate nutritional status, and assay the serum levels of Vitamin A and Zinc in patients with head and neck squamous cell carcinoma.

2. SUBJECTS AND METHODS

2.1 Study Design

This was a case control study of patients with histologically diagnosed head and neck Squamous cell carcinoma (HNSCC) from the Department of Otorhinolaryngology and Radiotherapy of the University College hospital, Ibadan, Nigeria from 2011 - 2013. The controls were healthy participants matched with the cases for age (+/- 2 years), sex, and socio-economic status. Their blood serum was assayed for micronutrient and Vitamin A at the Biochemical Laboratory of the International Institute for Tropical Agriculture, Ibadan, Nigeria. Ethical approval was obtained from University of Ibadan/University College Hospital, Ibadan Ethical Review Board. Informed consent was obtained from the participants before being enrolled in the study. Those receiving vitamin A or Zinc supplements, as well as those with dysphagia, malabsorption syndromes, and already on cancer treatment were excluded.

2.2 Data Collection Procedure

2.2.1 Questionnaire

Structured questionnaire was used to collect data on the participants' age, sex, occupation,

educational status, average income and clinical presentations. The patients were examined to identify and record the anatomical location of the primary tumour, presence of nodal and distant metastasis, and the disease stage. The socioeconomic status was estimated from the participants' level of education and occupation which was adapted from Hollingshead index of socioeconomic class [14].

2.2.2 Anthropometric measurement

This was determined using conventional methods [15-17] and includes weight (Kilograms), height (metres), Mid Upper Arm Circumference (MAC) and Waist Circumference (WAC). The Body Mass Index (BMI) in kg/m^2 was calculated. The values obtained (Kg/m^2) were recorded and categorized into underweight (< 18.5 kg/m^2), Adequate weight (18.5 to 24.9 kg/m^2) Overweight (25 to 29.9 kg/m^2), moderately obese (30 - 34.9 kg/m^2), severely obese (35 - 39.9 kg/m^2) and morbidly obese (> 40 kg/m^2) [15].

2.2.3 Biochemical assay

Approximately 10ml of fasted blood was obtained from each participant and assayed for vitamin A and Zinc. Their total serum protein and albumin were determined using the Bio-Rad protein assay based on the method of Bradford. The reference value for total serum protein was 6.0 - 8.0 g/dl and serum albumin was 3 – 5 g/dl. The low serum albumin level was then categorized into mild (2.7 - 3.4 g/dl), moderate (2.1 - 2.6 g/dl) and severe (< 2.1 g/dl) [18]. Serum retinol (Vitamin A) level was determined by High Pressure Liquid Chromatography manufactured by Polymer Laboratories Limited, Essex Road, Shropshire, United Kingdom. The reference value for serum retinol was 30 – 80 µg/dl [19]. Serum Zinc level was determined by Atomic Absorption Spectrophotometer (Buck Model 205). The reference value for serum Zinc was 70 to 120 µg/dl.

2.4 Data Analysis

Data obtained was recorded and analysed using the Statistical Package for Social Sciences version 15. The differences in socio-demographic characteristics between cancer cases and controls were compared using t-test for quantitative variables and chi square for qualitative variables. The difference in zinc and retinol levels between the groups was tested using t-test and Mann Whitney U test. The comparison of zinc and retinol levels at different stages of disease was done using Analysis of Variance (ANOVA) and/or Kruskal Wallis tests. Analysis of Covariance was used to adjust for differences in baseline characteristics in the comparison of zinc and retinol levels between cases and controls. The level of statistical significance was set at p value <0.05.

3. RESULTS

3.1 Socio-demographics

There were 65 HNSCC patients consisting of 39 (60%) males and 26 (40%) females with age ranging from 15-84 years, and mean age of 50.92±15.20. Similarly, there were 65 controls consisting of 36 (55.4%) males and 29 (44.6%) females with age ranging from 16 - 82 years, and mean age of 49.49±16.35. Thirty two (49.2%) HNSCC patients belonged to low socioeconomic class while 36.9% belonged to high socioeconomic class. The controls had similar socioeconomic class distribution (p=0.965).

3.2 Anatomical Sites of HNSCC

Nasopharyngeal and the sinonasal regions were the sites most frequently involved in this disease. They each constituted 29.2% of the cases seen. One (1.5%) patient had Squamous cell carcinoma of the right parotid gland. The distribution of the anatomical sites of this disease is shown in Table 1.

Table 1. Anatomical sites of head and neck cancers

Sites	Frequency (N)	Percentage (%)
Nasopharynx	19	29.2
Sinonasal	19	29.2
Larynx	17	26.2
Parotid gland	1	1.5
Hypopharynx	2	3.1
Oropharynx	5	7.7
Middle ear	2	3.1
Total	65	100.0

Thirty six (55.4%) patients presented in Stage IV while only 2 (3.1%) patients presented in stage I. The distribution of the disease stage at presentation is shown in Table 2.

3.3 HNSCC and Nutritional Status

Sixteen (24.6%) HNSCC patients were underweight while 21 (32.3%) patients had

weight in excess of their height. This gives a total of 37(56.9%) patients with malnutrition. The control group had a higher number of participants with adequate weight for height (58.5%) and lower number of underweight participants (12.3%). However, the mean body mass index (BMI) of cases was 22.66±4.70 while that of the controls was 23.14±3.8 (p=0.524). The distribution of the weight classes of both groups is shown in Table 3.

There was also no significant difference in the Weight (p=0.691), Height (p=0.522), BMI (p=0.518), MAC (p=0.146) and WAC (p=0.062) among the different stages of the disease as shown in Table 4.

Similarly, there was no statistical difference in the total serum protein (p=0.224), serum albumin (p=0.797), serum zinc (p=0.949) and serum retinol (p=0.585) among the different stages of the disease as shown in Table 5.

Among the cases, only 2 (3.1%) patients with advanced nasopharyngeal cancer had low serum zinc level while the controls had normal values. The mean serum zinc level of the controls (113.63±6.04) was significantly higher than the cases (89.84±14.27) (p=0.000). There was a significant difference between the mean serum zinc level of cases and controls at different weight classes except in the obese as shown in Table 6.

The mean serum vitamin A (retinol) level of the controls (77.74 µg/dl±2.82) was significantly higher than the cases (61.34±5.89) (p=0.000). There was a significant difference between the mean serum retinol (vitamin A) of cases and controls at different weight classes except in the obese as shown in Table 7.

Table 2. Anatomical sites and disease stage at presentation

Site	I	II	III	IV	Total
Laryngeal tumour	1	0	9	7	17
Nasopharyngeal tumour	0	4	1	14	19
Sinonasal tumour	1	2	5	11	19
Parotid Squamous cell cancer	0	0	0	1	1
Hypopharyngeal tumour	0	1	0	1	2
Oropharyngeal tumour	0	1	2	2	5
Middle ear	0	0	2	0	2
Total N (%)	2 (3.1)	8 (12.3)	19 (29.2)	36 (55.4)	65 (100.0)

Table 3. BMI of the cases and the controls

Weight classes	Cases		Controls	
	N (%)	Range	Frequency	Range
Underweight	16 (24.6)	15.5 – 18.3	8 (12.3)	15.5 – 18.2
Normal	28 (43.1)	18.9 – 24.5	38 (58.5)	19.2 – 24.5
Overweight	17 (26.2)	25.0 – 29.8	17 (26.2)	25.0 – 29.4
Obese	4 (6.2)	30.9 – 38.6	2 (3.1)	31.6 – 36.7
Total	65 (100.0)		65 (100.0)	

Table 4. Relationship between tumour stages and Nutritional status using anthropometric measurements

	Stage I mean (SD)	Stage II mean (SD)	Stage III mean (SD)	Stage IV mean (SD)	p-value
Age (years)	58.00±7.07	52.50±20.83	59.21±12.22	45.81±13.79	0.013
Weight (kg)	71.50±12.02	68.13±9.70	62.61±12.04	63.90±15.35	0.691
Height (M)	1.63±0.02	1.70±0.84	1.67±0.10	1.69±0.09	0.522
BMI(kg/m^2)	27.13±5.28	23.58±3.46	22.36±3.12	22.37±5.55	0.518
MAC (cm)	32.50±2.12	28.50±3.85	26.53±3.27	27.09±4.00	0.146
WAC (cm)	99.50±14.85	83.25±7.70	79.00±8.73	80.12±11.52	0.062

Table 5. Nutritional status and disease stage using biochemical parameters

	Stage I mean (SD)	Stage II mean (SD)	Stage III mean (SD)	Stage IV mean (SD)	p-value
Serum protein g/dl	8.05±0.49	7.8±0.31	7.28±0.73	7.25±0.87	0.224
Serum albumin g/dl	3.75±0.78	3.96±0.43	3.84±0.49	3.73±0.64	0.797
Serum Zinc µg/dl	95.74±23.07	90.28±12.05	89.51±15.83	89.59±14.05	0.949
Serum retinol µg/dl	62.70±13.12	59.69±1.79	59.92±6.49	62.25±5.66	0.585

Table 6. Difference in the mean serum zinc levels between cases and controls of different nutritional status

Weight classes	Serum zinc level of cases (µg/dl)	Serum zinc level of controls (µg/dl)	Level of significance (p<0.05; 96% CI)
Underweight	82.42±17.19	116.63±4.03	0.000
Adequate	89.98±12.86	112.98±6.54	0.000
Overweight	92.16±9.73	113.21±5.67	0.000
Obese	108.66±8.93	117.73±1.76	0.250

Table 7. Differences in the mean of serum vitamin A levels between cases and controls of different nutritional classes

Weight classes	Serum retinol of cases (µg/dl)	Serum retinol of controls (µg/dl)	Level of significance (p<0.05; 96% CI)
Underweight	62.33±6.95	79.06±0.87	0.000
Adequate	59.55±5.27	77.83±2.69	0.000
Overweight	61.49±4.54	76.67±3.54	0.000
Obese	68.69±5.14	79.41±0.21	0.050

4. DISCUSSION

The observed similarity in the socioeconomic status of patients with head and neck cancers and those of healthy participants in this present study is an indication that head and neck cancer affects people of all classes in the society. Generally, it is believed that people in the upper socio-economic classes are more literate, have healthier lifestyles behaviour than people in lower classes [20]. Studies from Canada, Scotland and Denmark have shown that socioeconomically disadvantaged people have higher incidence rates of head and neck cancers [21-23]. This present study also agrees with this finding as about 49% of the participants with HNSCC belong to the low socioeconomic class.

The commonest sites involved by HNSCC were the Nasopharynx, Sinonasal region and larynx, this agrees with findings from previously similar studies [24-28]. Majority of the patients (84.6%) presented in advanced disease stage and this is in consonance with previous reports by Otoh et al. [29] and Amusa et al. [30]. The late disease stage presentation of these patients could be attributed to the religious and socio-cultural beliefs and practices of the people in this environment [31,32]. Other contributing factors to late presentation include ignorance, local taboo, poverty and poor recognition of the disease condition by primary health providers [30,33]. Udosen et al. [34] found societal beliefs and misconception to be responsible for patronage of alternative medical practitioners even by highly educated and enlightened patients in Calabar [34].

Anthropometric measurements are reliable parameters for assessing nutritional status of patients with HNSCC [35]. In this study, 24.6% HNSCC patients were underweight which is similar to the reported 20-30% of HNSCC patients with undernourishment in other similar studies [36,37]. Poor nutrition has been demonstrated to have adverse effects on patients' tolerance to therapy, treatment outcome and prognosis of the disease [37,38]. Initiation of nutritional intervention before commencement of chemo-radiotherapy has been shown to improve treatment outcome as well as reduce the period of hospital stay [39]. Obesity, seen in 6.2% of HNSCC patients in this study, has been implicated to be a predisposing factor to cancers [37]. Paradoxically, a study had reported a higher survival rate in HNSCC patients who were

smokers with BMI above 25 kg/m^2 than those with lower BMI [40]. The study postulated that body size may modify the risks associated with tobacco smoking and alcohol consumption [41].

In this study, 57% of HNSCC patients have abnormal weight (underweight, overweight and obese) as against 41.5% healthy controls. This is an indication that a significant percentage of the study population has malnutrition but more among the HNSCC patients. Malnutrition has been reported to be a frequent complication in cancer patients, decreases patient's ability to manage treatment and negatively affect treatment outcome [42,43]. Inadequate intake from dysphagia or odynophagia and increased metabolism due to cancer growth may be responsible.

There was an observed reduction in the BMI, MAC and WAC of the HNSCC patients with advancing disease stage, the difference was not significant. Although, the mean serum total protein, albumin, zinc and retinol were within the normal limit at all the disease stages, there was an observed insignificant (statistical) reduction in the level of these parameters with advancing disease stages. This may be because the tumour also makes use of these nutrients for their growth. The patients in advanced disease stage have been reported to be more malnourished when compared with those with early disease stage.[44] The serum levels of both zinc and retinol were significantly higher in the controls than the HNSCC patients except in those who were obese. Previous similar studies have also reported significant difference between the serum retinol of patients with HNSCC and healthy participants [45-47]. Obese patients with HNSCC are more likely to become malnourished due to misidentification or a delay in nutritional support [37].

Zinc is an essential micronutrient with antioxidant and anti-inflammatory properties. Its deficiency is prevalent in developing countries, associated with cell mediated immune disorders and pivotal in the development of HNSCC [48]. Its deficiency promotes oxidative stress and chronic inflammation in cancers. Prasad et al. reported that zinc status correlated with frequency of hospital admissions and infections in head and neck cancer patients [48]. Tumour size and overall stage of HNSCC have also been shown to correlate significantly with zinc status whereas no correlation was seen with Prognostic Nutritional Index, alcohol intake and smoking [49]. This present study did not find any significant difference in the level of serum zinc across the cancer disease stages. Driscoll et al. reported that zinc deficiency could potentiate the induction and progress of lingual and oesophageal tumours in P53 deficient mice [50]. Direct connection between zinc deficiency and development of oesophageal cancer was demonstrated in high oesophageal carcinoma areas in China [51]. None of the HNSCC patients in this present study had oesophageal cancer.

Vitamin A and its metabolites has been shown to enhance immunity by potentiating antibody responses to T cell-dependent antigens, increase lymphocyte proliferation, responses to antigens and mitogens, inhibit apoptosis and restore the integrity and function of mucosal surfaces [52]. Dennert et al. have also demonstrated that retinoic acid can induce cell-mediated cytotoxicity (CMC) to allogenic tumour cells by at least tenfold in low doses (5-300 ug) in mice [53]. In humans, low serum retinol levels have been reportedly associated with increased risk of HNSCC and development of a second primary tumour [54]. Kapil et al. [46] discovered that the mean serum vitamin A levels were significantly lower in laryngeal cancer patients as compared to the controls in a hospital based case- control study. Another similar study in India reported a strong association of these micronutrients (vitamins A, C and zinc levels) with laryngeal cancer [46].

Serum zinc is a better prognostic indicator than serum protein and albumin levels in HNSCC patients [8] It has been postulated that the reduced intake of food due to lack of appetite and aversion for some types of food by HNSCC patients might be responsible for the low level of serum nutritional parameters [55]. This study did not investigate the type of diet the patients were taking before this evaluation. A limitation of this study is that the premorbid nutritional status and serum vitamin A and Zinc levels of these patients with HNSCC are unknown. Therefore it cannot be established that these relatively low levels when compared with healthy controls are associated with an increased risk of developing these tumours in these patients.

5. CONCLUSION

There are more HNSCC patients with malnutrition than the healthy population. Although no abnormality of serum zinc and retinol was found in both groups, the levels of

this micronutrient and vitamin have been demonstrated to be significantly lower in patients with HNSCC when compared with controls. With consideration of these relatively low levels and the impact of these nutrients on overall immunity and prognosis of these patients, it is recommended that early and aggressive nutritional intervention and supplementation of these micronutrients is necessary to improve the outcome of this disease.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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