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Quantitative Assessment of Serum Magnesium Levels in Head and Neck Cancer: A Tertiary Hospital Based Case Control Study

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background- Head and neck squamous cell carcinomas(HNSCC) are one of the most widespread malignancies worldwide. Trace elements such as magnesium are essential at cellular level, and it has been suggested that magnesium plays a role in carcinogenesis.
Methods- A hospital based case control study was conducted in a tertiary care medical college with an aim to determine the levels of serum magnesium in patients with head and neck cancer and to compare the levels of serum magnesium of head and neck cancer patients with healthy matched control group and derive significance if any.
Results- HNSCC was mainly found in males of age group 46 to 55 years. The mean serum Mg value of head and neck cancer patients was 0.71± 0.18 mmol/l while that seen in controls was 0.85± 0.09 mmol/l which was significantly lower($p<0.001$). Average serum magnesium levels in stages I, II, III and IV were 0.85, 0.849, 0.682 and 0.554 mmol/l respectively, and a statistically significant association was determined between the two.

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Conclusion- As the stage of cancer progressed, average magnesium levels decreased congruently, hence establishing that magnesium levels were undeniably correlated to onset as well as progression of HNC. These evidences could be utilized to identify role of magnesium asa potential prognostic biomarker to assess progression of disease or clinical response to various modes of therapy in head and neck cancer patients.

Keywords: Magnesium; cancer; head and neck; stage.

ABBREVIATIONS

HNSCC: Head and neck squamous cell carcinomas
HNC : Head and neck carcinoma
DNA : Deoxyribonucleic acid

1. BACKGROUND

Head and neck cancers(HNC) include malignancies arising from diverse sites in the upper aero-digestive tract. Indian subcontinent has one of the highest incidences of cancer in the head and neck region [1].The most common histologic type in head and neck cancers is squamous cell carcinoma, which occurs in the oral cavity, oropharynx, hypopharynx, and larynx. Therefore, the term "Head and Neck squamous cell carcinoma" (HNSCC) is frequently used to entail squamous cell carcinomas involving these anatomical sites [2].

Magnesium is a bivalent ion involved in several intricate biological reactions in the human body. Numerous different enzymes and ion transport mechanisms in body require magnesium. It is also involved in fatty acid and phospholipid metabolism which affects permeability and stability of cellular membranes [3]. Magnesium deficiency is believed to lead to certain changes in the DNA of cells leading to genetic alterations which could set stage for development of cancer. It is hence been suggested that magnesium deficiency leads to deterioration in physiological function of cells thereby setting stage for onset of cancer [4]. Whether magnesium deficiency can directly lead to cancers is still a matter of investigation.

Tumour cells involve multifarious neoplastic processes involving numerous sites with distinctive epidemiologic, pathologic, and treatment considerations. Head and neck cancer, as in other types of cancer, involves an interface between carcinogens and genes in a multistep manner that eventually leads to malignancy. Reactive oxygen species (ROS) has been associated with many ailments particularly those of chronic sequence including cancers [5,6]. The body is fortified with antioxidants, including the trace elements dependent enzymes namely superoxide dismutase, glutathione peroxidase, and catalase alongwith vitamins A, C, and E. Therefore trace elements such as magnesium are involved in countering the detrimental effects of reactive oxygen species, as they are persistently produced during metabolic processes [7,8]. The potential of an individual to counteract this state of oxidative stress is important, as a state of disequilibrium where the rate of generation of reactive oxygen species outweighs the individual's ability to remove them could lead to potential carcinogenic mutations [9].

There are many therapeutic options for cancers, however supportive management for a better quality of life should not be ignored. Role of various trace elements has been described effective as supportive therapy in some malignancies. Trace elements are likewise considered as pliable anticancer agents as they regulate diverse biological reactions at cellular level and researchers have observed association between trace elements and cancer mortality [10,11].

The prominence of nutrients in the etiopathogenesis of many cancers has recently gained widespread acceptance. Diets containing antioxidants such as carotenoids, vitamin C, and trace elements have been acknowledged to have a role in the prevention of the carcinogenesis in experimental animal model studies [12].

Trace elements have been evaluated in recent years to assess whether they have any modifying influence in the pathogenesis of cancers as they are imperative in the maintenance of DNA integrity, the results of such studies are although variable. Hence this study was undertaken to compare levels of serum magnesium in patients with head and neck squamous cell carcinoma and their matched controls, to determine association, if any, between them.

2. METHODS

A hospital based case control study was conducted in ENT department of a tertiary care medical college. The authors aimed to determine the levels of serum magnesium in patients with head and neck cancer and to compare the levels of serum magnesium of head and neck cancer patients with healthy matched control group and derive significance if any.

Fifty patients of head and neck squamous cell carcinoma along with same number of age and gender matched healthy controls were enrolled in the present study. The controls were neither on any kind of supplements, medications nor did they have any addictions to tobacco or alcohol.Histopathologically proven squamous cell carcinoma cases were included in case group. Subjects with history of other systemic illness, long term drug intake and concurrent malignancies were excluded from the study. Ethical clearance for the study was obtained from the institutional ethical committee. After complete history and clinical examination, the patients were subjected to investigations following informed consent. For serum Magnesium [Mg] estimation, 5 ml blood was drawn from a vein and collected in an airtight vial tube attached to needle. Blood was sent for biochemical examination, where serum was obtained after centrifuging the sample and then assayed by Xylitol Blue method . The same procedure was done on 50 age and gender matched healthy controls. In normal healthy adults total serum magnesium ranges between 0.85 to 1.10 mmol/L.

The collected data were entered in Microsoft Excel spread sheet. All statistical calculations were done using SPSS (Statistical Package for the Social Sciences) version 21 (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows. Comparative evaluation was done using student 't' test with Pearson correlation. P value <0.05 was considered statistically significant.

3. RESULTS

Head and neck squamous cell carcinoma was mainly found in males, comprising 88% of the study group. Patients in the ages ranging from 46 to 55 years contributed mainly tothe cancer group followed by age group of 56 to 65 years (Fig. 1). Head and neck cancer was mainly seen in larynx(46%) with supraglottis being the most common subsite involved (Fig. 2). Upon staging of the head and neck cancer patients as per American joint committee on cancer 8thedition, 6 patients were found to have to have stage I, 10 patients had stage II, 27 patients had stage III while 7 patients had stage IV cancer.

The mean serum Mg value of head and neck cancer patients was 0.71± 0.18 mmol/l which was significantly lower($p<0.001$) than that seen in controls(0.85± 0.09 mmol/l). (Table 1)

In this study, it was found that of all patients of head and neck cancer, serum magnesium level of 80%were below the normal range while serum magnesium levels of 14% patients were within normal range .However, three of the patients had serum magnesium above normal range levels (6%).Amongst the seven patients who had magnesium levels within normal limits, four patients had serum magnesium level in range of 0.86- 0.97mmol/l (lower range of normal) while remaining three had levels between 0.98-1.09mmol/l (Table 2).

Average serum magnesium levels in stages I, II, III and IV were 0.85, 0.849, 0.682 and 0.554 mmol/l respectively (Fig. 3). It could be inferred from these findings that magnesium levels were inversely related to stage of cancer i.e as the stage of cancer advanced, magnesium levels decreased.

On further evaluation with respect to staging of cancer and magnesium levels it was found that 57.5% of hypomagnesemic patients had stage III cancer while 17.5% had stage IV cancer. Hence a large proportion of hypomagnesemic patients had advanced cancers. (Fig. 4) It was also observed as shown in table 3, that 66.7% of stage I, 60% of stage II, 85.2% and as much as 100% of stage IV patients had low serum magnesium levels. Moreover, a significant correlation between serum magnesium level and stages of cancer was found, with p value of 0.024 at 5% level of significance (Table 3).

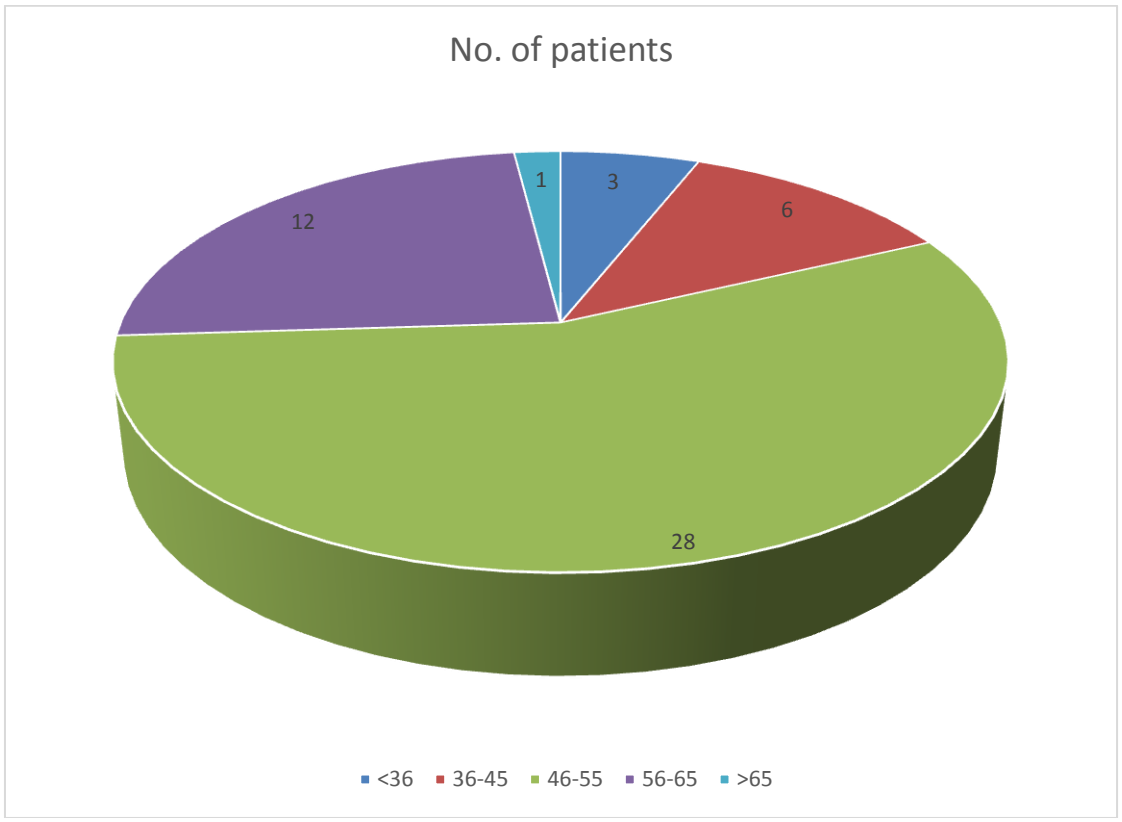

Fig. 1. Pie chart depicting age distribution in cancer group

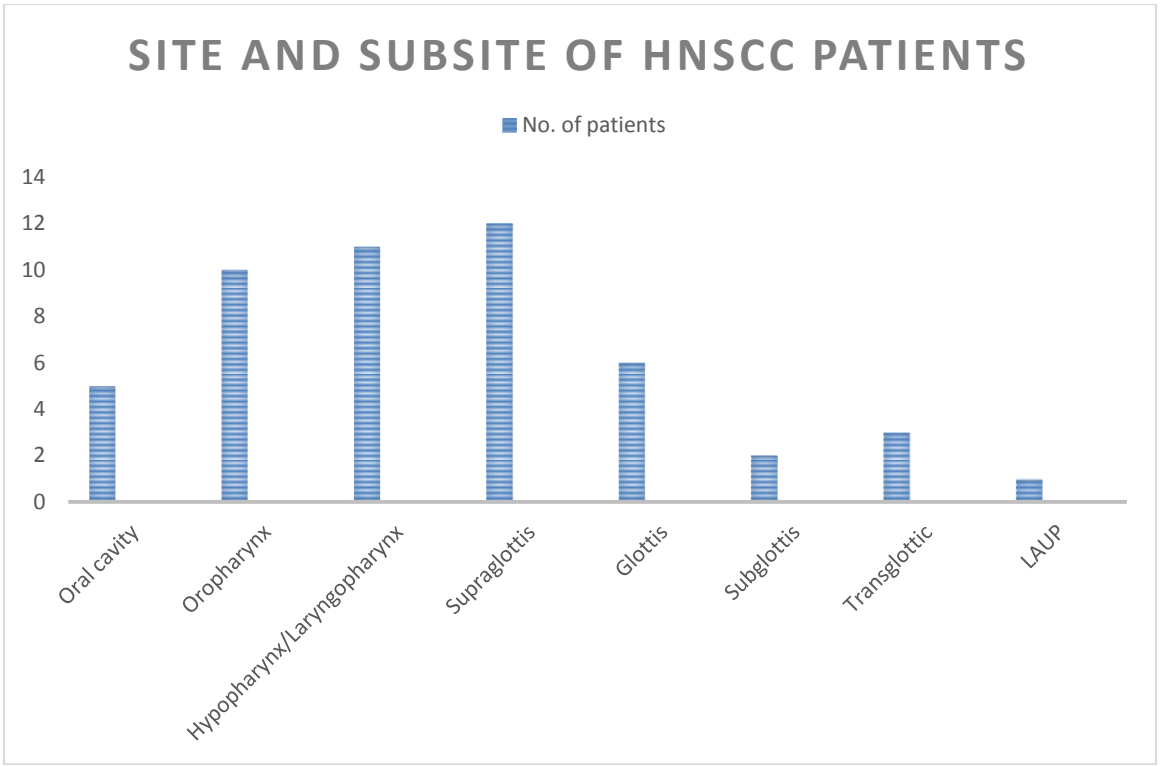

Fig. 2. Bar diagramdepictingsite and subsite involved in head and neck cancer

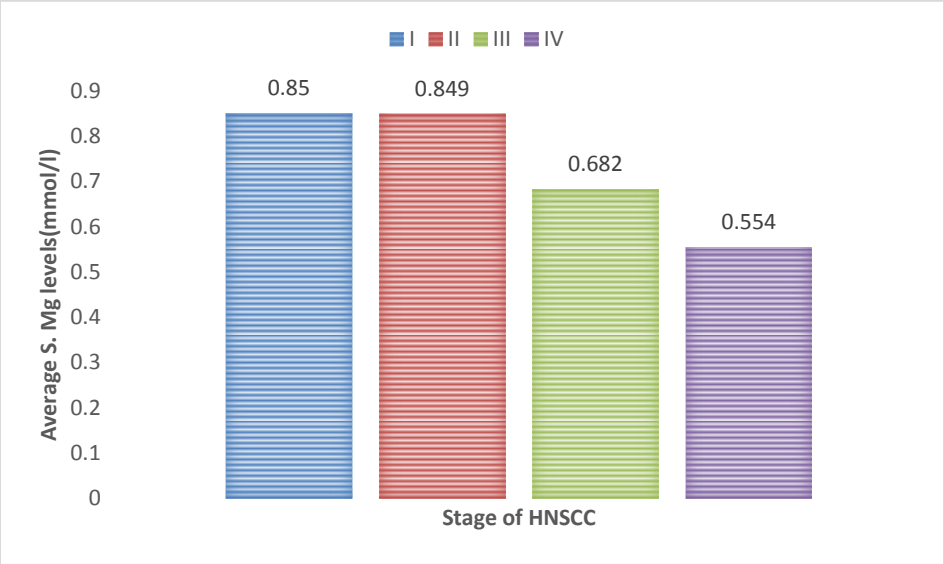

Fig. 3. Bar diagram depicting average serum Magnesium levels in various stages of head and neck cancer

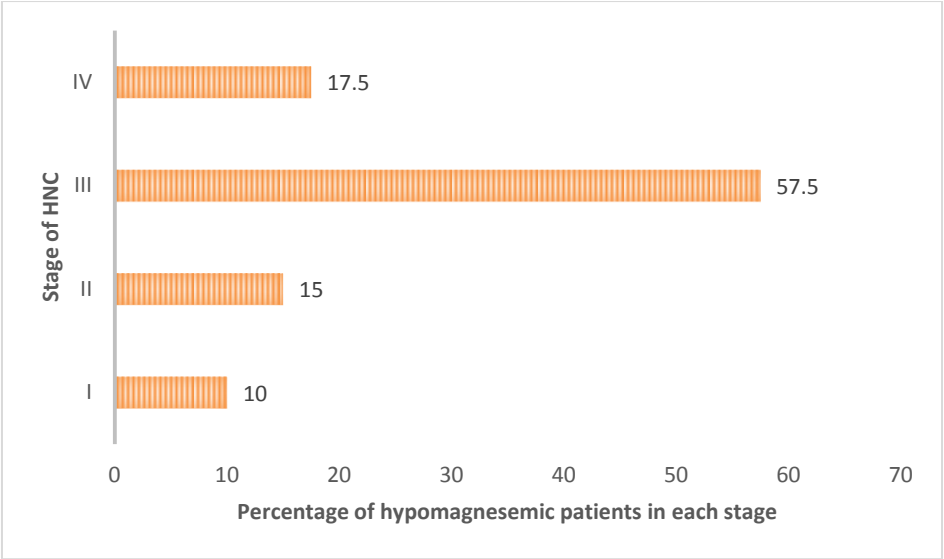

Fig. 4. Bar diagram depicting HNC stage distribution amongst hypomagnesemic cases

Table 1. Mean distribution of serum magnesium levels in controls and cases

Group	N	Mean ± Std. Deviation*
Serum Mg control	50	0.8519 ± 0.09300
Serum Mg cases	50	0.7104 ± 0.17884

p- value 0.001, highly significant

Table 2. Serum magnesium levels in HNSCC cases vs controls

Serum Mg levels (mmol/l)		Cases		Controls
≤0.85		40		29
0.86-1.09	0.86-0.97	7	4	20
	0.98-1.09		3	
≥1.10		3		1

p- value 0.017, significant

Table 3. Magnesium levels in various stages of head and neck cancer

Stage Mg (mmol/l)	Stage I N (%)	Stage II N (%)	Stage III N (%)	Stage IV N (%)
<0.85	4 (66.7)	6 (60)	23 (85.2)	7 (100)
0.86-1.09	0 (0)	3 (30)	4 (14.8)	0 (0)
>1.10	2 (33.3)	1 (10)	0 (0)	0 (0)

p- value is 0.024 , significant

4. DISCUSSION

Trace metals are important in the sustenance of several enzymatic reactions responsible for maintaining the integrity of DNA(deoxyribonucleic acid). Some of the proposed mechanisms include- antioxidant potential of trace element dependent enzyme system, effects on immune response and DNA repair system and apoptosis of the malignant cells [10]. Magnesium cations are one of the most pivotal of these trace elements and several biological mechanisms have been postulated regarding its mechanism of action in initiation of malignant process. Magnesium ions are known to bind to DNA, thereby reducing their negative charge density thus helping in stabilizing DNA. Additionally, these ions also plays a vital role in cell cycle as well as in immunocompetence as it is a constituent of several enzymes involved in cell cycle [13].

Evaluation of trace elements such as magnesium has been pursued, however studies indicate ambiguity till date [3,14-16]. More comprehensive analysis of cancer patients so as to examine and corroborate relationship between magnesium and carcinogenesis has been recommended [16].

Recently, studies evaluating the mechanisms underlying variations of magnesium levels in cancer patients bring to fore the fact that alterations in magnesium could be attributed not only to the disease initiation but also due to the process itself, and the treatment modalities being followed [16]. Thus, the current study was pertinent as it not only enabled the comparison of serum magnesium levels in cancer patients vis a vis controls but also the magnesium levels in various stages of cancer.

A major proportion of our study group were males and more than half of them were in the age group of 46 to 55 years. HNC has been seen more frequently amongst males in numerous studies [17-19]. However, the relatively younger age group contributing to a large chunk than before is alarming as it indicates a trend towards early onset of HNC [17,18]. This could be attributed to practice of consuming known carcinogenic substances such as tobacco and alcohol, which is rampant and acceptable in the community including amongst young males of this geographic area. This furthermore stresses upon the need of special focus on the pathogenesis of this grave disease as more and more addictions are increasingly being witnessed in the younger population.

Larynx was the most common site involved in the study population, with supraglottis contributing mainly amongst subsites. Similar site distribution has been quoted by other researchers too [13,18,19]. Regarding stage at presentation of patient, AJCC stage III was encountered most frequently in the study group patients followed by stage II. Stage at presentation has been variable from early to advanced in different studies, [18-20] which could be due to several reasons such as population demographics, to location and level of the catering medical institution.

In the current study, mean serum magnesium levels in healthy control group was 0.85mmol/l whilst that in HNSCC group was 0.71mmol/l, this difference was statistically significant (table 1). Micke et al compared magnesium levels in HNSCC and tonsillectomy(control) patients. They reported mean levels of 0.78mmol/l in tumour group and 0.86mmol/l in control group which was almost comparable to our study [19]. Similarly hypomagnesemia in cancer patients has also been reported by certain other researchers [13,20-22]. Hypomagnesemia was reported in as high as 80% of cancer patients included in the current study(Table 2). In concurrence, Micke et al. [19] also reported low magnesium levels in 78% of the HNSCC patients included in their study. This was consistent with other investigators who suggested lower serum magnesium concentrations in HNSCC patients [5,20,23]. It can hence be inferred that low magnesium levels are certainly seen in HNC patients. However, point of contention being

whether it is a cause or a consequence of malignant process and needed further prodding.

In the current study, hypomagnesemia was seen in 66.7% of stage I, 60% of stage II, 85.2% of stage III and all patients of stage IV disease and these findings were also statistically significant (Table 3). The average serum magnesium levels were negatively related to the stage of HNC, while in stage I it was 0.85 mmol/l a sequential decrease was seen upto 0.554 mmol/l in stage IV congruently (Fig. 4). Very few studies could be found corelating stage of HNC with serum magnesium levels. Taysi et al also determined low serum magnesium levels in all stages of laryngeal cancer cases, however contrarily this decrease was found to be statistically insignificant in their research [13]. If low magnesium levels were to play a role only in onset of cancer, its levels would be comparable in early as well as late stages of HNC. However this wasn't what was observed in the current study, rather a steady decline in magnesium levels were seen as the stage of cancer progressed. This could help us weigh in the fact that magnesium levels were definitely related to progression of HNC as well and low magnesium levels could be subsequent to disease process rather than only being an aetiological factor.

Studies propose variable mechanisms responsible, Castiglioni et al. [20] reported that cancer cells have increased affinity for magnesium which is accumulated in high concentration intracellularly. This could be due to overexpression of magnesium transporters or its impaired extrusion. Magnesium is also associated with enzyme complexes of glycolysis pathway which is preferentially used by neoplastic cells causing its utilization and accounting for low serum magnesium.

Hypomagnesemia in cancer are also ascribed to reduced oral intake, intracellular shift of magnesium, gastrointestinal and renal losses. Shift of magnesium cations intracellularly occurs due to stimulation of beta adrenergic receptors in cancer. This in conjunction with reduced dietary intake owing to nausea, vomiting and diarrhoea causing gastrointestinal loss may collectively cause reduced serum magnesium levels in cancer [16]. Moreover, renal losses are also seen with chemotherapeutic and other pharmacological agents associated with treatment of cancer.

The lack of follow up of levels of magnesium levels was the limitation of this study and it could have helped predict the outcome better. However as in the current study, the aim was to evaluate and compare magnesium levels in controls vis a vis HNSCC patients, hence levels were evaluated specifically before treatment initiation. Moreover, long term follow up could also bring up confounding factors such as dietary and medicine induced associations which could bring up false results. Hence, it is prudent to undertake further research in this wide field and evaluate serial levels of trace elments such as magnesium with respect to cancer.

To summarize, serum magnesium was clearly associated with HNC. Additionally, a significant association between low magnesium levels and stage of cancer was determined. While certain researcher suggest low magnesium to be an aetiological factor for cancers [20], others suggest it to be a consequence of neoplastic process. Moreover, as an advanced HNC stage was encountered, average serum magnesium levels decreased in a parallel manner which supported the school of thought associating decreasing magnesium levels owing to malignant process [16]. The role of magnesium in cancer can hence not be undermined, several studies reaffirm the role of magnesium and certain other nutritional elements in cancer. A study by Leone et al furthermore even suggested that serum magnesium levels are decreased in cancer and also add to an increased mortality risk [24].

5. CONCLUSIONS

Vastly varied amount of information displaying different outcomes of magnesium levels in head and neck cancer patients indicate that there is undoubtedly disordered magnesium metabolism in cancer patients and in most of the cases it is hypomagnesemia. The present study also substantiates it by establishing the mean serum magnesium value of head and neck cancer patients as 0.71± 0.18 mmol/l which was significantly lower($p<0.001$) than that seen in controls(0.85± 0.09 mmol/l). The study was extended further to find out the correlation between magnesium levels and stages of cancer. As the stage of cancer progressed, average magnesium levels decreased congruently and a statistically significant association was determined between the two. Hence establishing that magnesium levels were undeniably correlated to onset as well as progression of HNC. As a future direction, evaluation of magnesium levels in premalignant conditions could be undertaken and followed up

to reasserting its role in carcinogenesis. This could help establish a potential preventive/ therapeutic role or used as a prognostic biomarker to assess progression of disease or clinical response to various modes of therapy in head and neck cancer patients .

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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