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Adipocyte-fatty Acid Binding Protein is Associated with Clinical Stage and Inflammatory Markers in Head and Neck Cancer Patients

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Abstract **Background:** Head and neck carcinomas are the fifth most common cancer worldwide. Squamous cell carcinoma of the head and neck (HNSCC) is a highly heterogeneous tumor. Additional clinical and biological factors are needed to improve tumor diagnosis and to identify subsets of patients with unfavorable outcome. Several recent studies showed that cancer cells stimulate lipid metabolism during tumor progression. Studies have revealed the involvement of fatty acid binding proteins (FABPs) expression in the pathology of different diseases including malignant neoplasms. It has been suggested that the immune changes occurring in the tumour environment determine its aggressive behavior, these changes may affect the prognosis and treatment outcomes in patients with cancer. The tumor necrosis factor (TNF-α) is a proinflammatory cytokine that expressed in HNSCC has a possible role in cancer invasiveness and the risk of metastases. C-reactive protein (C-RP) is an acute-phase protein that increases in acute, chronic inflammations, infections and tissue damages. It has been suggested that C-RP also is elevated in cancers. **Objective:** The aim of this study was to determine whether the plasma levels of A-FABP are linked to head and neck cancer, inflammatory markers (TNF-α and C-RP) and tumor characteristics. **Subjects and Methods:** The present study was conducted on 50 healthy individuals and 50 newly diagnosed patients with histologically confirmed HNSCC that accepted to participate. Patients with distant metastases at time of diagnosis, hepatic insufficiency, active autoimmune or coexisting infectious disease were excluded. The study included HNSCC patients with tumours ranged from stage I-IVA (cT1-4a, N0-2, M0). Age, sex, date of diagnosis, tumor site, grade, TNM stage and treatment were recorded. **Results:** Statistical analysis of the results showed that the mean values of plasma A-FABP, TNF-α and C-RP in HNSCC patients before treatment were significantly higher than that in control group. The plasma levels of the three biomarkers were significantly decreased after treatment than their corresponding values before treatment and plasma C-RP levels became within the normal control values. The risk for head and neck cancer is significantly increased in higher plasma A-FABP group compared with lower levels group. A significant positive correlation was found between plasma A-FABP and both TNF-α and C-RP. There was also a significant correlation observed between plasma A-FABP levels and clinical stage. On the other hand, no correlation was found between plasma levels of TNF-α or C-RP and clinical stage. The three biomarkers were not correlated with other paramters like patient's age, sex, BMI or smoking status. **Conclusions:** The findings in the present study suggested elevated levels of A-FABP, TNF-α and CRP in HNSCC patients before treatment that significantly decreased after treatment. Higher plasma A-FABP is associated with clinical stage and risk of HNSCC.

Keywords: *Adipocyte-fatty acid binding protein, tumour necrosis factor-α, C-reactive protein, head and neck carcinoma*

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1. Introduction

Head and neck carcinomais are the fifth most common cancer worldwide. More than 95% of malignant head and neck tumours are squamous cell carcinomas, with many similar diagnostic and prognostic profiles. These tumours vary in clinical outcome and therapeutic characteristics depending on the topographic site of origin. [1]

The incidence of squamous cell carcinoma of the head and neck (HNSCC) has been increasing without typical risk factors although, are linked to certain lifestyle and environmental risk factors like tobacco and alcohol consumption. [2] The prognosis of HNSCC is still relatively poor and has shown only slow progress. Despite recent advances in tumor surgery and multimodal treatment regimens including new targeted therapies, the survival rate for HNSCC has not been improved. Additional clinical and biological factors are therefore needed to improve

tumor diagnosis, therapeutic interventions, and identify the subsets of patients with unfavorable outcome. [3]

Several studies showed that carcinoma cells change the composition of lipid component in cell membranes. Moreover, cancer cells stimulate lipid metabolism during tumor progression. [4,5] Fatty acid-binding proteins (FABPs) are a family of proteins expressed in a tissue-specific manner, and are involved in transporting fatty acids to cellular compartments, modulating intracellular lipid metabolism, and regulating gene expression. FABPs facilitate the intracellular transport of long chain fatty acids which are required to serve as an energy source and metabolic signals in multiple intracellular processes like cell growth, survival and inflammatory responses. [6] These proteins act mainly through activation of enzymatic or transcriptional networks. The FABPs family consists of at least nine members that were originally identified in different human cells or tissue types, such as A-FABP in adipocytes and FABP5 in the epidermis. [7]

The adipocyte-fatty acid binding protein-4 (FABP-4) is the best characterized isoform among the entire FABPs family. It was originally identified in adipose tissues and mature adipocytes. FABP-4 plays an important role in biological processes, particularly in many aspects of metabolic syndrome beside its role in fatty acid transport. Studies have revealed the involvement of FABP expression in the pathology of different diseases including malignant neoplasms. [8,9]

Several studies have indicated the role of the immune system response in the course of cancer process. It has been suggested that the immune changes occurring in the tumour environment determine its aggressive behavior. [10,11] Thus, these changes may affect the prognosis and treatment outcomes in patients with cancer. [12]

The evidence for a role of tumour necrosis factor-alpha (TNF-α) as a proinflammatory cytokine in human cancer has been provided by several studies. [13,14] TNF-α plays an important role as a growth factor in certain tumour types thorough increasing concentrations of positive cell-cycle regulators and signaling pathways. TNF- α promotes also DNA damage and inhibits DNA repair. [14] The expression of TNF- α in squamous cell carcinoma of the head and neck has been suggested to have a possible role in cancer invasiveness and the risk of metastases. [15]

C-reactive protein (C-RP) is an acute-phase protein that increases in acute, chronic inflammations, infections and tissue damages. [16] It has been suggested that CRP also is elevated in cancers. [17]

The aim of this study was to determine whether the plasma levels of A-FABP are linked to head and neck cancer, inflammatory markers (TNF-α and C-RP) and tumor characteristics.

2. Subjects and Methods

This study was conducted on 50 healthy individuals and 50 newly diagnosed patients with histologically confirmed HNSCC that accepted to participate. Patients were presented to Future Hands Oncology Centre, Alexandria, Egypt. Patients with distant metastases at the time of diagnosis, hepatic insufficiency, active autoimmune or coexisting infectious disease were excluded. A written consent for participating in the study was taken according to the declaration of Helsinki.

The study included HNSCC patients with tumours ranged from stage I-IVA (cT1-4a, N0-2, M0). Clinical staging was defined by the seventh edition of the Cancer Staging Manual of the American Joint Committee on Cancer. [18] Patients were subjected to preoperative evaluation including history taking, clinical examination, fiberoptic endoscopy, fine needle aspiration (FNA) /core biopsy of any neck masses followed by further examination under anesthesia with additional biopsies if needed. Radiological investigations included computerized tomography (CT) or magnetic resonance imaging (MRI) of the head and neck, chest radiograph and liver ultrasound. Age, sex, date of diagnosis, tumor site, grade, TNM stage and treatment were recorded.

Treatment consisted of definitive radiotherapy for early stage tumors or chemoradiotherapy for advanced stage tumors. For advanced stage tumors (stage III and IVA), chemoradiotherapy consisted of external-beam radiotherapy (70-74 Gy) to the primary tumor and the positive lymph node area and (50-60 Gy) to the negative lymph node area (1.8-2 Gy/day 5 days weekly) combined with 3 cycles of cisplatin (100 mg/m^2) delivered on days 1, 22 and 43 followed by additional 3 cycles of cisplatin combined with continuous infusion of 5 flurouracil on day 1-4 every cycle. Radiotherapy was delivered to early stage disease for organ preservation; the dose range was (68.4–76 Gy).

2.1. Laboratory Investigations

A total of 5 ml fasting heparinized blood sample was obtained from healthy controls and HNSCC patients. Blood samples were collected from the patients at the time of diagnosis before any treatment and the second sample was collected at the end of the treatment course.

The plasma was separated within three hours and stored at −80 °C until analyzed. Plasma A-FABP levels were measured by enzyme linked immunosorbent assay according to the manufacturer's instructions (Aviscera Bioscience, USA). Plasma TNF-α levels were measured by radioimmunoassay according to the manufacturer's instructions (IBL, Germany). C-reactive protein levels were assessed by immunoturbidimetric test (HUMAN, Germany).

2.2. Statistical Analyses

Statistical analyses were conducted using the statistical software package SPSS version 17 (SPSS Inc., Chicago, IL, USA). Differences between groups were assessed by the Mann Whitney U test for nonparametric variables. Pearson's correlation coefficient was calculated to evaluate the association between relevant parameters. Statistical significance was set at $P \leq 0.05$. Multiple logistic regression analysis was used to assess the association between plasma biomarkers levels and head and neck cancer risk. The adjusted odds ratio (OR) and exact computation of 95% confidence intervals (95% CI) were calculated.

3. Results

3.1. Patients Clinical Characteristics

Clinical characteristics of the participants are summarized in Table 1. There was no significant difference

between the studied groups as regards age, sex, body mass index and smoking status.

Table 1. Participants clinical characteristics

	Head and neck cancer patients (n=50)	Controls (n=50)	P
Age (years)			
Mean ± S.D	56.08 ± 13.28	54.66 ± 12.48	0.563
Range	31– 74	34– 75	
<60	23 (46%)	22 (44%)	
≥60	27 (54%)	28 (56%)	
Sex			
Male	31 (62%)	29 (58%)	0.351
Female	19 (38%)	21 (42%)	
BMI (Kg/m^2)			
Mean ± S.D	27.1 ± 5.23	26.3 ± 4.35	0.629
Smoking			
Yes	29 (58%)	27 (54%)	0.251
No	21 (42%)	23 (46%)	
Clinical Stage			
I-II	21 (42%)	-	
III	19 (38%)		
IVA	10 (20%)		
Tumor site			
Oral cavity	17 (34%)	-	
Oropharynx	13 (26%)		
Hypopharynx	11 (22%)		
Larynx	9 (18%)		
Lymph node involvement			
N0-N1	30 (60%)		
N2	14 (28 %)		
N3	6 (12%)		
Treatment			
Chemoradiotherapy	35 (70%)	-	
Radiotherapy only	15 (30%)		

Abbreviations: BMI: body mass index, S.D: Standard deviation.

3.2. Plasma A-FABP, TNF-α and C-RP in Normal Control Subjects and HNSCC Patients

Comparison between the mean plasma levels of the three biomarkers (A-FABP, TNF-α and C-RP) were carried between control group and patient's groups either before or after treatment.

Table 2 showed that the mean values of plasma A-FABP (ng/ml) in HNSCC patients either before (88.25±17.71) or after (76.62±18.23) treatment were significantly higher than that in control group (4.65±2.80) (P<0.000 and P<0.000, respectively). A-FABP plasma levels were significantly decreased after treatment than its corresponding values before treatment (76.62±18.23 vs 88.25±17.71, P=0.015) (Figure 1).

Table 2. Plasma A-FABP, TNF-α and C-RP in normal control subjects and HNSCC patients

	Control group (n=50)	Head and neck cancer patients (n=50)	
		Before treatment	After treatment
A-FABP (ng/ml)			
Range Mean± SD	2-12 4.65±2.80	50-112 88.25±17.71	35-90 76.62±18.23
P1		0.000*	0.000*
P2			0.015*
TNF-α (pg/ml)			
Range Mean± SD	2-53 20.12±16.50	8-200 72.20±57.09	5-90 45.31±30.29
P1		0.000*	0.000*
P2			0.018*
C-RP (mg/L)			
Range Mean± SD	0-6 2.58±1.67	2-28 10.12±7.47	1-8 3.41±1.80
P1		0.000*	0.513
P2			0.000*

p_1: p value compared to normal control group.
p_2: p value compared to before treatment.
*: Statistically significant at $p \leq 0.05$.

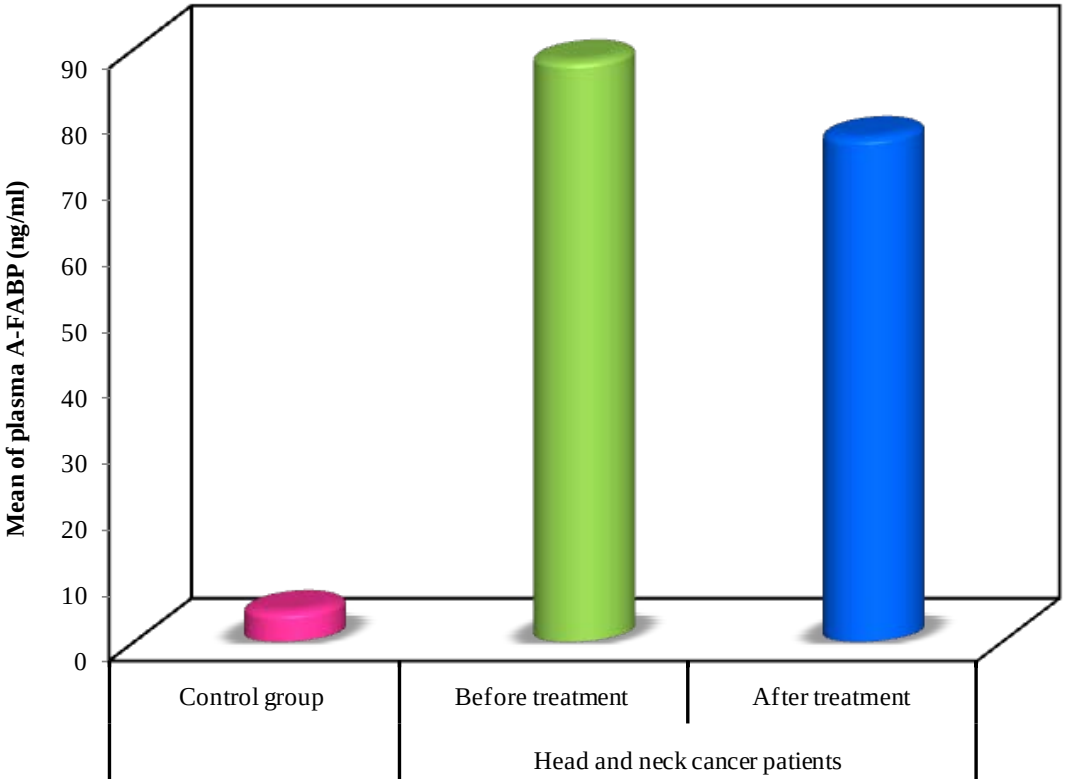

Figure 1. The mean values of plasma A-FABP (ng/ml) in normal control subjects and HNSSC patients

Concerning plasma TNF-α (pg/ml), it was significantly increased in cancer patients either before (72.20±57.09) or after (45.31±30.29) treatment as compared to healthy controls (20.12±16.50) (P<0.000 and P<0.000, respectively). After treatment plasma TNF-α significantly decreased than its corresponding values before treatment (45.31±30.29 vs 72.20±57.09, P=0.018) (Figure 2).

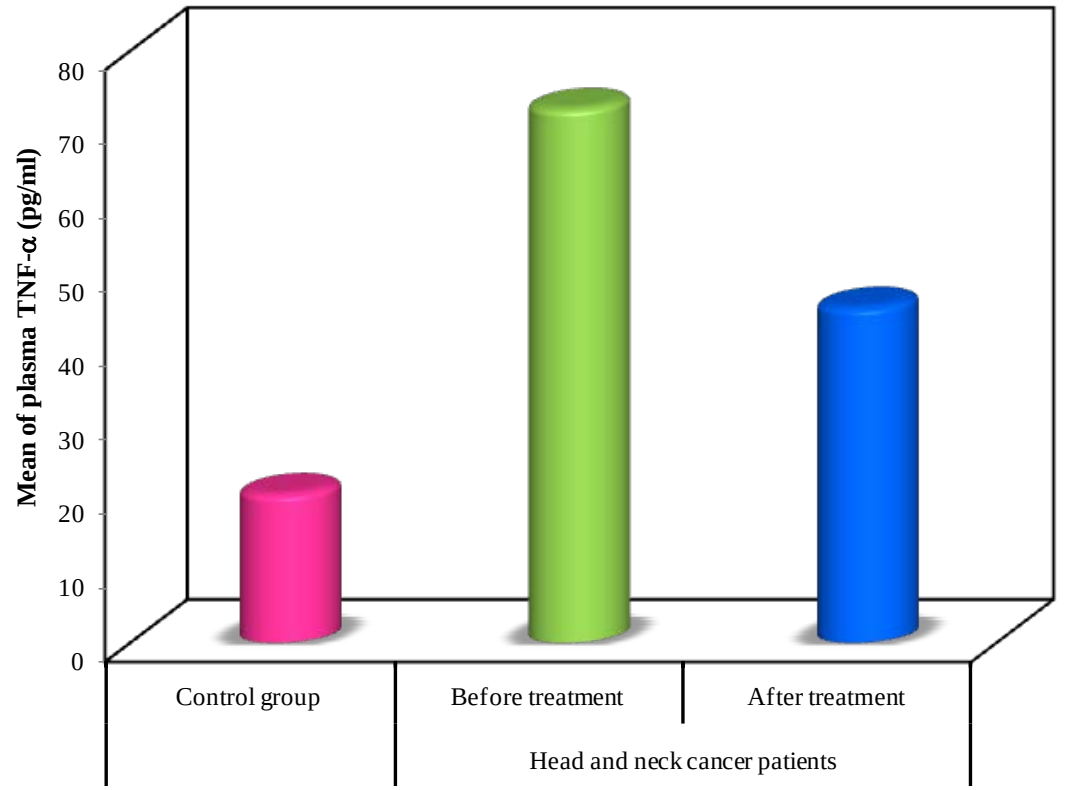

Figure 2. The mean values of plasma TNF-α (pg/ml) in normal control subjects and HNSSC patients

With respect to C-RP (mg/L), its values were significantly higher in plasma of cancer patients before treatment than in healthy control group (10.12±7.47 vs 2.58±1.67, P<0.000). After treatment plasma C-RP levels significantly decreased than its corresponding values before treatment (3.41±1.80 vs 10.12±7.47, P<0.000) and

became within the normal control values (3.41±1.80 vs 2.58±1.67, P=0.513) (Figure 3).

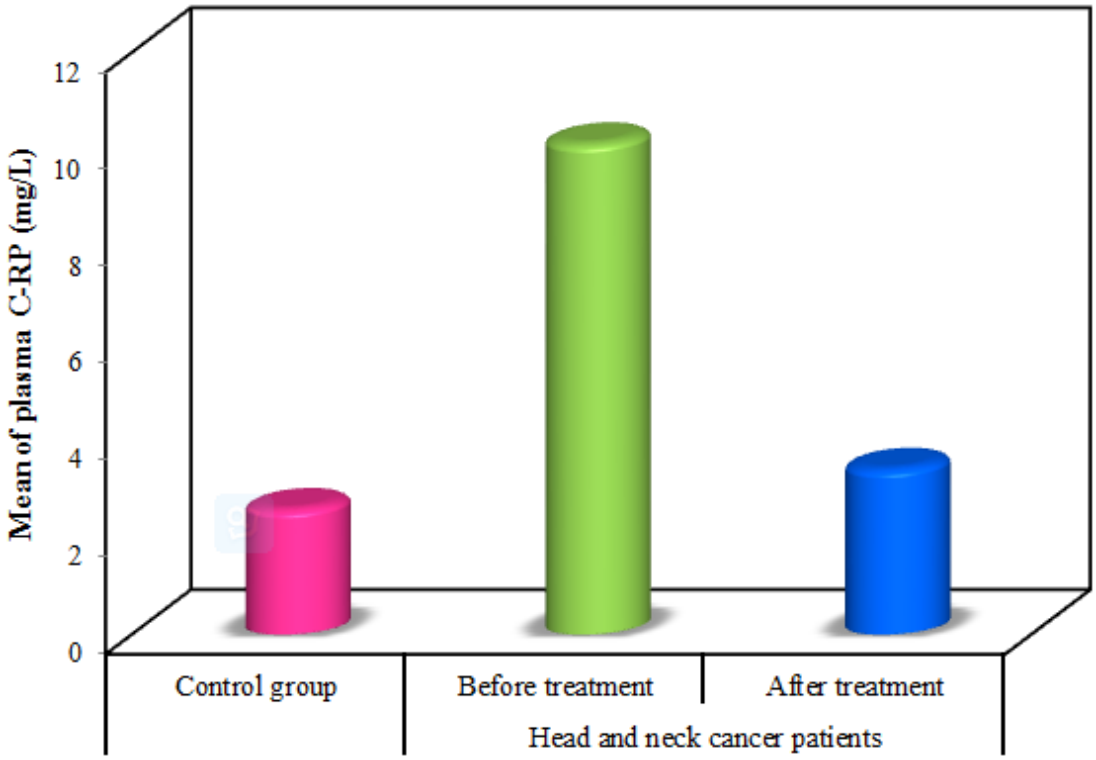

Figure 3. The mean values of plasma C-RP (mg/dl) in normal control subjects and HNSSC patients

3.3. Plasma A-FABP, TNF-α and C-RP and Head and Neck Cancer Risk

Logistic regression model was performed to evaluate the impact of plasma biomarkers on head and neck cancer risk. The models were adjusted to age, sex, BMI and smoking status. The estimated odds ratios are shown in Table 3 with 95% confidence interval (CI) and P values. The analyses showed that the risk for head and neck cancer was significantly increased in higher plasma A-FABP group with an odd ratio of 3.615 (P=0.004) compared with lower plasma group. Elevation of plasma TNF-α and C-RP levels did not significantly change the risk of head and neck cancer.

Table 3. Analysis of multiple logistic regression for the risk of head and neck cancer according to plasma A-FABP, TNF-α and C-RP levels

	OR	95%CI		P
		Lower	Upper	
A-FABP	3.615*	1.023	7.501	0.004*
TNF-α	0.937	0.880	1.501	0.062
C-RP	0.794	0.569	1.107	0.173

OR: odd ratio.CI: confidence interval.
*: Statistically significant at $p \leq 0.05$.

3.4. Correlation between Studied Parameters and Clinical Characteristics of the Disease

As shown in Table 4 a significant positive correlation was found between plasma A-FABP (P<0.000) and both plasma TNF-α (P<0.000) and plasma C-RP (P=0.000). There was also a significant correlation observed between plasma A-FABP levels and clinical stage. Moreover plasma A-FABP is highly increased in stage III and IVA in comparison to stage I and II (P=0.001) (Table 5). On the other hand, no correlation was found between plasma A-FABP and other parameters like patient's age (P=0.383), sex (P=0.548), smoking status (P=0.210) or BMI (P=0.461).

TNF-α was significantly correlated with plasma C-RP (P<0.000) while it was not correlated with patient's age (P=0.973), sex (P=0.152), BMI (P=0.463), smoking status (P=0.228) or clinical stage (P=0.183).

There was no correlation observed between plasma C-RP and patient's age (P=0.895), sex (P=0.745), BMI (P=0.323), smoking status (P=0.778) or clinical stage (P=0.257).

Table 4. Correlation between the studied parameters and clinicopathological characteristics of the disease

	A-FABP		TNF-α		C-RP	
	r_s	P	r_s	P	r_s	P
Age	0.187	0.383	0.007	0.973	0.028	0.895
Sex	0.129	0.548	0.301	0.152	0.070	0.745
Clinical Stage	0.699	0.000*	0.150	0.183	0.241	0.257
BMI	0.193	0.461	0.157	0.463	0.211	0.323
Smoking status	0.266	0.210	0.256	0.228	0.016	0.778
C-RP	0.446	0.000*	0.401	0.001*	-	
TNF-α	0.548	0.000*	-		0.401	0.001*

*: Statistically significant at $p \leq 0.05$.
r: Pearson's coefficient.

Table 5. Association of plasma A-FABP with different clinical stages

Clinical stage	Plasma A-FABP Mean±S.D	P Value
I-II (n=19)	70.9±16.15	0.001*
III-IVA (n=31)	95.84±10.31	

*: Statistically significant at $p \leq 0.05$.

4. Discussion

The current study revealed that plasma A-FABP in HNSCC patients either before or after treatment was significantly higher than that in healthy controls. A-FABP plasma levels were significantly decreased after treatment than its corresponding values before treatment. Moreover, plasma A-FABP was positively correlated with clinical stage of the disease and risk of HNSCC. Suggesting enhanced energy production by A-FABP may result in the rapid proliferation of carcinoma cells and tumor expansion.

Lee et al [21] studied A-FABP using an immuno-histochemical approach. He found a significant higher expression of A-FABP protein in the tumor area of tongue SCC than in the non-tumor area in the same tissue samples. They stated that the expression of A-FABP in tumors may affect SCC cell growth. Moreover, Ohyama et al [22] stated that A-FABP expression was identified in almost all the tongue carcinomas examined and undetected in the normal epithelium. These studies agree with our finding.

Concerning A-FABP plasma levels and the risk of head and neck cancer, to our knowledge, to date, no published data are available concerning A-FABP plasma levels and the risk of head and neck cancer and therefore our results stand out as unique. Our result is supported by Hancke et al [23] study who found that serum levels of A-FABP were significantly higher in breast cancer patients than in controls and high A-FABP serum levels were associated with breast cancer risk, and adverse tumor characteristics.

Carcinoma cells change the lipid composition of cell membranes and stimulate lipid metabolism during tumor progression. [5] Fatty acid-binding proteins (FABPs) are the lipid chaperones that transport long chain fatty-acids (LCFAs) to specific cell compartments, such as lipid droplets for storage; the endoplasmic reticulum for signaling, trafficking and membrane synthesis, mitochondria or peroxisomes for oxidation, cytosoles or other enzymes for activity regulation, the nucleus for gene transcription, or even outside of the cells in order to signal in an autocrine or paracrine manner. [24]

Among the FABPs, A-FABP is highly expressed in adipocytes, macrophages and dendritic cells and affects these cells in various manners. [8] In cancer cells, A-FABP transports energy by carrying fatty acids, encouraging metastasis and tumor cell growth. [25] Yet, A-FABP performs other roles in tumor growth, through its various functions. A-FABP is known to mediate transcription of peroxisome proliferator-activated receptor γ (PPARγ) that plays key roles in squamous cell carcinomas growth. [26] A-FABP expression has been reported in various types of tumors [25,27] and found to be involved in carcinoma progression. [28]

Regarding the correlation between A-FABP and the inflammatory markers, our study showed significant positive correlation between plasma A-FABP and plasma TNF-α and C-RP.

A-FABP is an adipokine highly expressed in adipocytes, making up about 1% of all soluble proteins in adipose tissue. Interestingly, A-FABP is also expressed in macrophages. Moreover, macrophages are the major producers of TNF-α, reflecting a possible link between cancer - related inflammation and increased A-FABP secretion. [29]

Cancer-related inflammation is considered the "seventh hallmark of cancer"; numerous studies demonstrate that tumors develop and progress within inflammatory diseases. Infiltration of immune cells facilitates tumor development through the production of factors that promote carcinogenesis and by enabling tumors to evade the host immune response. Small molecules including cytokines, chemokines, and growth factors play key roles in both inflammation and cancer by promoting proliferation, angiogenesis, and carcinogenesis and by recruiting immune cells. [29]

In the current study, plasma TNF-α and C-RP levels before treatment were significantly increased in cancer patients as compared to healthy controls and their levels significantly decreased after treatment. There was a significant positive correlation between plasma TNF-α and C-RP levels.

In line with our results, Peter et al, found that the level of C-RP in HNSCC patients was elevated as compared to controls. [30] Similar to our study, Andersson et al, showed a significant difference between the mean values of the C-RP level in patient plasma compared with the level in controls plasma. Plasma TNF-α in the patients were also significantly higher than plasma levels of controls. [31] In contrast to the present study, Brailo et al, [32] found no significant difference in the levels of TNF-α in the serum and saliva of oral cancer patients compared with controls.

A study by Green et al [33] revealed that TNF-α was detected in only less than 50% of the serum samples of HNSCC patients pre- and post-treatment and in contrast to the current study, no significant differences in the detected levels of TNF-α were observed between the pre and post-treatment samples.

Cytokines have a substantial role in the oncogenesis and pathology of squamous cell carcinoma of the head and neck. [15] The importance of TNF-α as a proinflammatory cytokine, in human cancer had been confirmed by several studies. [13,14] TNF-α acts as a growth factor in certain tumour types through increasing concentrations of positive cell-cycle regulators and components of growth-factor receptor signaling pathways such as RAS or c-MYC. TNF-α promotes DNA damage, inhibits DNA repair and promotes angiogenesis. [14]

Serum C-RP is a sensitive marker of inflammation that is elevated in response to tissue damage or infection and has been shown to be a prognostic factor in oral squamous cell carcinoma. [34] The association between C-RP and chronic inflammation may lead to excessive cell proliferation and subsequent accumulation of DNA damage. [35] Host immune system responds to tumor growth via elevated levels of inflammatory cytokines, which may further increase C-RP levels. [36] C-RP and proinflammatory cytokines are present at increased levels in various malignancies. In Oliveira KG et al study, [37] an association between elevated serum C-RP and TNF- α has been demonstrated in head and neck cancer patients which agreed with the current study.

In our study, upon correlation of plasma TNF-α and C-RP levels and patients' characteristics, we found both biomarkers not associated with tumour characteristics or head and neck cancer risk.

Several studies have found a relation between higher C-RP level and worse overall outcome in patients with

HNSCC. [35,38] In a study conducted by Khandavilli et al, [38] C-RP was found to be an independent prognostic indicator in oral squamous cell carcinoma and in accordance with our study, serum C-RP level was not associated with tumour stage. Andersson et al, [31] also agreed with us and reported no association between the plasma level of C-RP and TNF-α and the tumor location or tumor TNM stage.

In contrast to our findings Chen et al, [39] demonstrated that elevated pretreatment C-RP level acts as a predictor of clinical stage. They stated that the C-RP was associated with a high metabolic rate as well as the proliferative activity. Therefore, elevated levels of C-RP have the potential to serve as biomarker for the prediction of tumor aggressiveness in cases of pharyngolaryngeal cancer.

5. Conclusions

- The mean values of plasma A-FABP, TNF-α and C-RP were highly elevated in HNSCC patients than in the control group.
- A significant positive correlation was found between only A-FABP levels and clinical stage while, neither plasma TNF-α nor C-RP correlated with the clinical stage.
- The risk for head and neck cancer was significantly increased in higher plasma A-FABP group when compared with lower plasma levels group.

6. Recommendations

- Further analysis of these biomarkers may provide information about the pathophysiologic mechanisms of HNSCC, facilitate early diagnosis, and serve as a marker of response for novel therapeutic strategies. More investigations on larger sample size are recommended with study the association of these biomarkers and the survival data.

Conflicts of Interest

We declare that we have no conflict of interest that could be perceived as prejudicing the impartiality of the study.

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All authors have contributed significantly to this work.

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