REVIEW ARTICLE

Implication of Salivary Chemerin in Diagnosis of Oral Squamous Cell Carcinoma - A Review

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ABSTRACT

The development of salivary biomarkers of oral squamous cell carcinoma (OSCC) is the area of great interest and research. OSCC is ranked as, the sixth most common cancer worldwide. Most often, its symptoms are not evident during the initial stages or even absent until the cancer has metastasized. If detected early, the rate of cure may be as high as 50%. Hence, there is a dire need to develop diagnostic tools, which may help in early detection and differentiation between high-risk individuals, oral pre-malignant lesions and OSCC. Recently, increased levels of salivary biomarker Chemerin have been shown to be associated with malignant tumors. Since, the validity of any biomarker is the most challenging task for the researcher therefore, there is still debate going about its circulating effects on OSCC growth, whether high levels of Chemerin may act as a valuable biomarker for OSCC. The information was extracted from search engines including Medline, Google Scholar and PubMed through different research papers from 2000-2020. The review emphasized the need to conduct further studies on the significance of Chemerin. Very few studies have shared the association between Chemerin and detection of oral cancer. However, this relationship is strong enough to claim Chemerin as an important diagnostic marker during diagnosis of oral cancer.

Keywords: Chemerin; Oral Squamous Cell Carcinoma; Biomarker; Neoplasm Metastasis; Proteins.

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INTRODUCTION

Globally, oral cancer is the sixth most common carcinoma and potentially fatal disease. Worldwide the incidence ratio in Female: Male is 2.6:5.3 and mortality rate is same for both gender i.e. 1.2 respectively¹. The annual incidence rate of oral cancer is around 27500 two hundred and seventy five thousand that is 90% among other cancer². The survival rate of oral cancer is quite low and is considered a major threat to health care system.³ The incidence and mortality rates widely depend upon the geographical variation. The highest incidence rates of oral cancer have been reported among developing nations such as India and Pakistan.³

Boscolo-Rizzo et al. has provided an estimate of 833,000 new cases of squamous cell carcinoma of

head and neck in 2020 in western countries⁴. Squamous cell carcinoma is the most commonly occurring cancer among all subtypes of oral cancers. In Pakistan, it is second most commonly occurring cancer⁵. As per gender stratification, it is ranked as first highly prevalent cancer among Pakistani males⁶. Oral cancer occurs primarily due to neglected oral hygiene along with consumption of tobacco and alcohol that is made up of different carcinogens and has deleterious effects on oral mucosa leading to cancerous transformation. The debilitating disease accounts for sixty to eighty percent survival rate in stage 1 and 2, which implies early detection and the need for treatment⁷.

Oral cancer initiates as silent epithelial dysplasia in histopathological findings, which is not apparent clinically. The silent transformation of epithelium

progresses to advance stages until symptoms are apparent⁸. Within 30 years, twenty percent of the tumor transformation becomes malignant⁸. Oral cancer always carries a risk of transformation into severe dysplasia. However, prediction of severe transformation is still yet to be studied. Therefore, definitive diagnostic approach such as biopsy of the lesion is helpful in early screening but is not useful in predicting future severity of the lesion. Moreover, it is invasive, expensive, and time-consuming screening tool. Hence, there is utmost need to detect cost effective and quicker screening methods where laboratory techniques can be used to meet the requirement of diagnosing oral cancer at much early stage of development⁹.

DISCUSSION

Oral squamous cell carcinoma is commonly diagnosed at advanced stage leading to only 10 percent survival rates¹⁰. The gold standard for diagnosis of staging of tumor is TNM system (tumor (T), nodes (N), and metastases (M)). However, it is still an unreliable predictor¹⁰. With advances in oral sciences, number of biomarkers has been established in diagnosing oral cancer. Among all the biomarkers, the role of chemerin is least discussed in diagnosing oral cancer. Serum chemerin is studied whereas salivary chemerin is yet to be studied in detail¹¹.

Significance of Saliva during Carcinogenesis

There is no satisfactory knowledge about specific biomarkers that raises malignant potential in the oral cavity. There is prime need to detect tumor inducing biomarkers that could help in early detection of oral cancer in order to gain full advantage from the treatment¹². Saliva consists of various and numerous biomarkers. It can help in the diagnosis and prognosis of oral cancer. It is an inexpensive, quick, easy and non-invasive technique used to diagnose oral cancer in comparison to serum¹³. Saliva has variety of functions such as lubrication, digestion, protection against different microbes, remineralization and taste sensation¹⁴. Salivary secretions are a mixture of different gland secretions. It comprises of secretions from major salivary glands, minor salivary glands, gingival crevicular fluid, oral, nasal, pharyngeal mucosal secretions, oral desquamated epithelium, blood and external sources like drugs and food¹⁵. Thus, the composition of saliva consists of water, organic and inorganic components.

It has been proposed that salivary analysis is an effective diagnostic modality for diagnosing oral cancer because of direct contact with the lesion in the oral cavity. Moreover, it serves as convenient, cost-effective and affordable screening method for high risk individuals for early detection of oral cancer⁹. The diagnostic accuracy of salivary

biomarkers concerning diagnosis, prognosis and monitoring of disease is very high. In comparison with other body fluids, saliva is composed of very fewer inhibiting agents, which makes it a simple diagnostic tool. Saliva is mainly made up of proteins and polypeptides. Albumin, lactoferrin, α -amylase, cystatins, proline, statherin, lysozymes and chemerin are abundantly found in saliva. It is also made up of DNA, mRNA which are regarded as biomarkers that play significant role in chromosomal translation^{16,17}.

The ability of saliva to respond to cancerous formation is already programmed. Multiple authors have found high levels of salivary constituents among different cancers. Streckfus and Dubinsky found first salivary biomarker in breast carcinoma which has elevated levels of CA15-3¹⁸. Schapher et al. found high levels of salivary leptin in salivary gland cancers¹⁹. Chen et al. found increased levels of salivary CA125 in ovarian cancer²⁰. Wu et al. found salivary proteomes in gastric cancer patients²¹. Therefore, Nagler stated that salivary analysis is an effective way of detecting cancerous transformation and identifying high risk patients⁹. In oral cancer, use of salivary biomarkers and proteomic analysis play an integral part in comprehending head and neck carcinomas²².

Salivary Biomarkers in Detection of Oral Squamous Cell Carcinoma

There are numerous biomarkers in saliva, researchers have found numerous biomarkers among different cancers and studied them in great depth. In a systematic review of different salivary bio markers, Kaur et al. stated different salivary biomarkers such as Annexin 1, peroxiredoxin 2, keratin 10 (CK10), Interleukin 8, Tetranectin protein, TNF α , Interleukin 6, DUSP1, HA3, OAZ1, S100P, DUSP1, HA3, OAZ1, S100P, Interleukin-1B beta, Cancer antigen 125,50, CEA, Metalloproteinase (MMP1, MMP-10, MMP-12, MMP-3), Chemerin and MMP-9, Cystatin SA-1, Transferrin, ALDH (aldehyde dehydrogenase), Adenosine deaminase (ADA) ECAD, TMEFF2, MGMT, RNA, SAT, OAZ1, H3F3A, MicroRNA 125a, Micro-200, MiR-31, lncRNA, Cortisol, Nicotinamide, Telomerase, DUSP1, GADD45B, RGS2, S100P, Actin and myosin, mRNAs²³. These biomarkers are crucial for diagnosis of oral squamous cell carcinoma (OSCC)²³. The development of cancer occurs by degrading of extracellular matrix and basement membrane along with angiogenesis. This process is regulated by numerous factors. Angiogenesis takes place during transformation from mild to severe epithelial dysplasia regulated by variety of angiogenic factors. One factor is chemerin that regulates the entire angiogenetic process during carcinogenesis²⁴. Previous studies have demonstrated that chemerin act as a pro-angiogenic molecule. It promotes angiogenesis *in vitro* as well as *in vivo*²⁵.

Chemerin – As a Diagnostic and Prognostic Salivary Biomarker

In recent decade, oral science have become advanced in the biomarker field²⁶. A significant progression in the investigation of salivary biomarkers in diagnosing oral cancer is under process as it is crucial scientific research topic²⁷. In light of the presence of Chemerin, an exceptionally explicit and crucial marker, saliva can be utilized as an analytic tool for an early diagnosis of Oral Squamous Cell Carcinoma (OSCC)²⁸. Chemerin is present in human body in almost negligible amount²⁹. It was also found in healthy patients during salivary analysis in the concentration of 1.3 ± 0.5 ng/mg³⁰. Chemerin is found in human plasma in the form of pro-chemerin, which is an inactive form, and it is activated by extracellular proteases. It is widely found in macrophages, monocytes, natural killer cells, dendritic cells, adipocytes, endothelium, fibroblast and keratinocytes. Chemerin is 18 to 48 kDa chemokine like receptor 1 protein (CMKLR1), known as chemerin receptor (ChemR23) was first cloned in 1996 and categorized as G protein coupled receptor (GPCR). It was discovered as retinoid gene (tazarotene) in skin and was called tazarotene induced gene 2 (TIG2). It serves as a chemotactic protein³¹. The receptor ChemR23 is also reported to have been expressed on vascular endothelial cells and its expression is up regulated by the release of pro-inflammatory cytokines³². The other two receptors of Chemerin include G protein-coupled receptor 1 (GPR1) and C-C chemokine like-receptor 2 (CCRL2), but the receptor ChemR23 is of great importance as mentioned in this article further.

Once Chemerin is activated further cleavage converts the active Chemerin to its isoforms and much shorter inactive proteins in humans, it is converted to three active products i.e. Chemerin156, Chemerin157 and Chemerin158, all of these isoforms have been detected in biological fluids³³. Among all of the isoforms known, chem157S appears to be the most effective isoform of chemerin in terms of triggering chemotaxis of several types of immune cells that play an important role

during the process of inflammation³⁴. During 19th century, German Pathologist Virchow suggested the association between inflammation and cancer. Literature suggest that long term inflammation promotes carcinogenesis³⁵. In a study performed in 2018, possible mechanisms by which Chemerin can induce carcinogenesis via the process of angiogenesis were examined and the effects of Chemerin on human-umbilical vein endothelium cells were explored²⁵. It was concluded that chemerin stimulated the differentiation of human umbilical vein endothelium cells into capillary like structures and promoted the proliferation of these cells²⁵. The mechanism behind this is that it induces the phosphorylation of extracellular signal-regulated kinase (ERK) in human-umbilical vein endothelium cells and also promotes angiogenesis via the p42/44 and Akt pathway²⁵.

Role of Chemerin in Different Types of Cancers

Literature shows that chemerin plays an important role in development and advancement of cancer³⁶⁻³⁹. It is involved in development of various forms of cancer via different signaling pathways such as Wnt/ β -catenin, RhoA/ROCK/MAP, and PI3K/AKT³⁹. Chua et al. suggested that Chemerin is mediated by tumor necrosis factor alpha, which increases the angiogenesis via ERK signaling pathway leading to carcinogenesis⁴⁰. Recent studies have found a vital role of Chemerin in cancer development, as it was found either in a reduced or an upregulated manner. Thus, Chemerin has both effects i.e., the tumor-promotion and suppression. Binding of chemerin to GPR1 or CMKLR1 causes the activation of β -arrestin 1 and 2. Effects of this binding is opposite in pathogenesis of cancer, depending on the tumor microenvironment. Since β -arrestin 1 has tumor-promoting effects, β -arrestin 2 has been reported to have inhibitory effects on cancer growth and angiogenesis. Binding of Chemerin to GPR1 only causes weaker signaling internalization, while the activation of CMKLR1 results in stronger mobilization of calcium and phosphorylation of ERK1/2 pathway³⁴. The mechanism of action of Chemerin is explained in the diagram (Figure 1).

Figure 1: Role of Chemerin during tumorigenesis.

Few researchers have claimed that the higher levels of Chemerin is very helpful in diagnosing active carcinogenesis in the oral cavity as well as other parts of body^{41,42}. Multiple authors have studied the levels of Chemerin in different types of cancer. Wang et al. found out that serum Chemerin was elevated in gastric cancer⁴³. Erdogan et al. found its increased levels in colorectal carcinoma⁴⁴. Chemerin levels are extraordinarily high in solid tumors like breast, colon and rectum cancer^{45,46}. Increased levels are likewise found in glioblastoma, squamous cell carcinoma of the throat, neuroblastoma and mesothelioma⁴⁷. Due to angiogenesis, small blood vessels are formed as Chemerin has a similar role as VEGF pathway²⁵. Research shows that the secretion of chemerin by adipocytes or tumors that are in close contact may have auto or paracrine effects that are not quite the same as the hormonal influence of Chemerin that is executed by serum. It has been found to invigorate angiogenesis, consequently, another conceivable mechanism is the connection between tumor cell Chemerin and ChemR23 receptor, that is exposed on endothelial cells resulting in an improved angiogenesis³³.

Role of Chemerin in Oral Squamous Cell Carcinoma
During tumorigenesis, Chemerin induces proliferation and morphogenesis of endothelium activating

angiogenic pathway leading to angiogenesis in cancerous cells. Wang et al. conducted a study recruiting patients having tongue cancer and found out that mRNA expression of Chemerin was elevated in tongue cancer specimens⁴⁸. The amplification of its expression is associated with poor differentiation of tumor, high staging, and lymph node metastasis. According to the literature, it is stated that Chemerin can be used as an independent method for diagnosing cancer. Moreover, high levels of Chemerin are associated with low survival rates. Hence, it is not only diagnostic but also a prognostic biomarker during carcinogenesis⁴⁹. According to literature search only three studies have been conducted on clinical significance of Chemerin levels present in oral cancer (Table 1). The first study was conducted in the year 2016 by Ghallab et al. They found elevated levels of salivary and serum Chemerin in oral squamous cell carcinoma patients and concluded that it can be used as diagnostic approach for oral cancer. The study compared experiment group with healthy individuals and showed that serum and salivary Chemerin was highly overexpressed in oral cancer patients as compare to healthy controls. Hence, the study concluded that salivary Chemerin had hundred percent sensitivity and specificity in diagnosing oral squamous cell carcinoma⁵⁰.

Table 1: Studies reporting the salivary chemerin levels in diagnosis of oral squamous cell carcinoma.

Author and Year	Study and Method	Study Design	Outcomes
Ghallab et al. 2016	Serum and Salivary levels of Chemerin were detected in oral squamous cell carcinoma via enzyme-linked immunosorbent assays.	Clinical trial	Serum and salivary levels of Chemerin were significantly higher than control group. Receiver operating characteristic (ROC) analysis showed 100% sensitivity and 100% specificity in detecting early-stage oral cancer.
Lu et al. 2019	Role of Chemerin was investigated in oral cancer patient via western blot assay, and Polymerase chain reaction (PCR).	Case-control study	Serum Chemerin was elevated as compare to healthy controls. High serum chemerin was linked with tumor progression and lymph node metastasis. Chemerin promotes carcinogenesis.
Shree et al. 2019	A systemic review was conducted identifying Role of saliva in oral cancer.	Systematic review	Chemerin was regarded as novel biomarker in early diagnosis of oral cancer patients.

There is vast amount of literature available on several biomarkers present in saliva. However, till now the novel inflammatory biomarker Chemerin is the least studied biomarker and very little research has been done regarding the clinical significance of Chemerin. The developing field of salivary biomarkers has incredible possibilities to demonstrate its clinical importance to battle oral malignant growth. Thus, we recommend more randomized control trials in this context.

CONCLUSION

Oral malignancy has risen as a disturbing medical issue with expanding incidence and death rates all over the world. Hence, early screening and diagnosis is of most extreme significance, which could decrease mortality. Delicate and explicit biomarkers present in saliva in order to diagnose oral disease are best screening methods for high-risk patients. In contrast to other diseases, oral cancer is situated in oral cavity with an immediate saliva contact making it an appealing option in contrast to serum and tissue testing. Subsequently, salivary biomarkers, a non-obtrusive option in contrast to serum and tissue-based biomarkers might be a successful methodology for early detection of oral cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

SMM had done the literature search and written the complete manuscript. MH critically reviewed the

paper while SM gave the concept and design of the review study. MAS had summarized the content and proofread it.

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