

GLOBAL JOURNAL

OF MEDICAL RESEARCH: J

Dentistry & Otolaryngology

Long Non-Coding Ribonucleic Acids

Hypohidrotic Ectodermal Dysplasia (HED)

Highlights

A Real Compulsion of Hospital Linger

Comparitive Evaluation of Novel Desensitising

Discovering Thoughts, Inventing Future

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Perichondritis of the Pinna: A Real Compulsion of Hospital Linger

By Delwar AHM

Abstract- Background: Perichondritis of pinna is relentless, deadly cellulitis of the auricular cartilage, which may lead to necrosis. As a result, shrinkage and deformity of the pinna may occur. Different etiological factors, including self-trauma by high ear piercing for beauty and fashion, accident, assault, infections, progressive otitis externa, and allergy, are mentionable. **Methods:** It is a cohort retrospective study of 63 cases in the Department of Otolaryngology and Head-Neck Surgery, Cumilla Medical College, and Cumilla Medical Centre, Bangladesh, from 01 July 2016 to 31 June 2019.

Results: The incidence of perichondritis among ENT casualty was 0.86%. Off 63, the male was 33 (52.38%), and the female 30 (47.62%), children were 27 (42.86%), and adult 36 (57.14%), in which lowest age 02 years, highest 76, mean age 21.952, and the standard deviation 16.676, diabetic 08 (12.70%), smoker 09(14.29%), and all were unilateral.

Keywords: perichondritis, piercing, exploration, debridement, scooping, and curettage.

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Conclusion: Prevention and early treatment lowering the immensity of the disease.

Keywords: *perichondritis, piercing, exploration, debridement, scooping, and curettage.*

I. INTRODUCTION

The pinna projects at a variable angle as a fan-like formation from the side of the head and perform the collecting of sound. The unique pattern of it is comparable with fingerprint and can allow the identification of persons on the physiognomy of their auricles [1]. The body of the pinna is formed of a single piece of yellow elastic fibro-cartilage and is a continuous plate except for a narrow gap between the tragus and the helix. The cartilage of the auricle covers with perichondrium from which it derives its supply of nutrients, as cartilage itself is avascular. High ear piercing, accident or assault makes injury of the pinna, and stripping of perichondrium, which causes hematoma may lead to necrosis of cartilage with crumpled up 'boxer's ear, pugilistic or cauliflower ear [2]. The sequelae of inflammation of the pinna described by James W. Loock into four stages: 1. Erysipelas, 2. Cellulitis, 3. Perichondritis, 4. Chondritis [3]. Perichondritis is mainly traumatic, which includes lacerations of the pinna, surgery of external auditory canal, frost bite, insect bite, burns, infected hematoma Auris, incision, or aspiration for hematoma of the pinna, and in recent years high ear piercing for wearing fashionable ornaments [4]. In the process of perichondritis, various types of bacterial invasion occur. The most common organisms were *Pseudomonas aeruginosa* (69%) [5], Polymicrobial (22%), *Streptococcus* spp. (22%), *Staphylococcus aureus* (20%), and other Gram-negative organisms include *Proteus*, *Enterococcus*, and *Escherichia coli* [6], [7]. Body piercing is popular after 1990, which was done by well known singer Michael Jackson, Madonna, and so many Hollywood stars. The teenager and young adult following them piercing the Tongue, Lips, Eyebrows, Nose, Nipple, Umbilicus, and Genitalia [8], [9],[10]. Body piercing is one of the religious or rituals of mysticism to God in some countries of Asia and Latin America from teenager to adulthood. The procedure usually did by an untrained person; as a consequence, healing of the wound various from one month to one year [11]. The pathological process of perichondrium of pinna following hyperplasia of skin, thickened subcutaneous tissue, thickening of perichondrium by infiltration, and destruction of cartilage by phagocytes [12]. The classical presentation of the perichondrium of the pinna is severe earache, erysipelas, cellulitis, and auricular

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abscess, so diagnosis is clinical and special investigation aren't required routinely [3]. Some systemic disease related to perichondritis which includes Relapsing Perichondritis [13], non-Hodgkin lymphoma of pinna with or without immunodeficiency state [14], [15]. Different types of management options described by the surgeons depending on the staging of perichondritis. Stage of erysipelas and early cellulitis adequately managed by the use of a topical, and high doses of oral and parental antibiotics may halt the progression of disease due to *Pseudomonas aeruginosa* [16]. Some surgeons practiced minimum invasive procedures like aspiration of infected edematous fluid, syringing the cavity two to three times daily with streptomycin solution [17]. It is difficult to decide how much cartilage to excise, and frequent consecutive debridement to prevent the deformity of the pinna. Many surgeons suggested aggressive excision of

necrotic cartilage, including overlying skin and subcutaneous tissue [18] [19]. In severe cases, James W. Look, and Dowling et al. practiced total cordectomy via an incision in the helical margin, the ear splits in bivalve fashion, the necrotic cartilage removed, and a layer of fine mesh gauze placed between the flap and changed daily [3],[20]. Another group of surgeons applied fenestrated polyethylene tubes placed in subperiosteal tunnels on either side of the cartilage and aminoglycoside/cortisone solution used to irrigate these twice daily [21], [22]. Aggressive surgery, while it may, at times be necessary, may aggravate the ultimate deformity [3].

This study finds out the relative incidence, frequency, presentation, and complications of perichondritis of the pinna and the best management option for it.



Figure-1: Auricular abscess of the left ear.

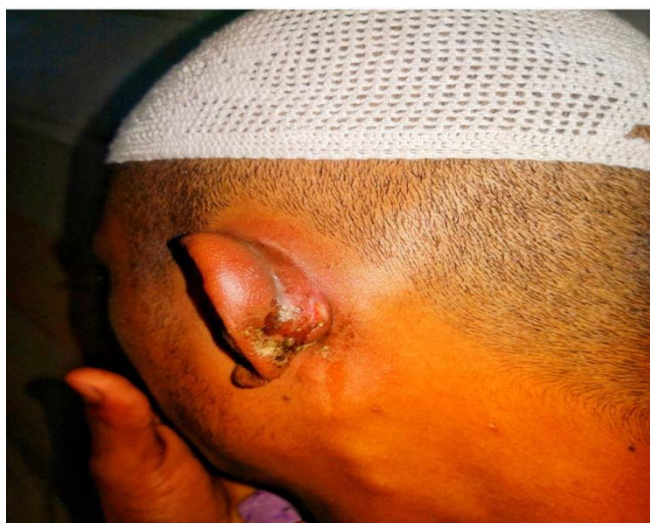


Figure-2: Perichondritis due to assault.

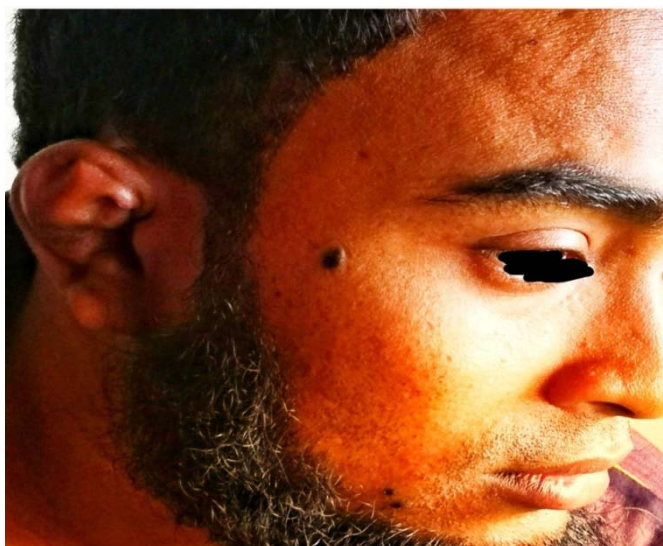


Figure-3: Auricular abscess due to blunt trauma.



Figure-4: Close view of the figure-3 case.

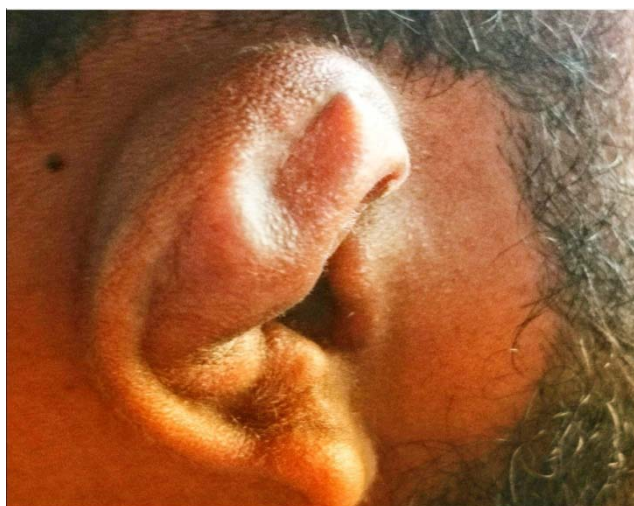


Figure-5: Auricular cellulitis with Hematoma.



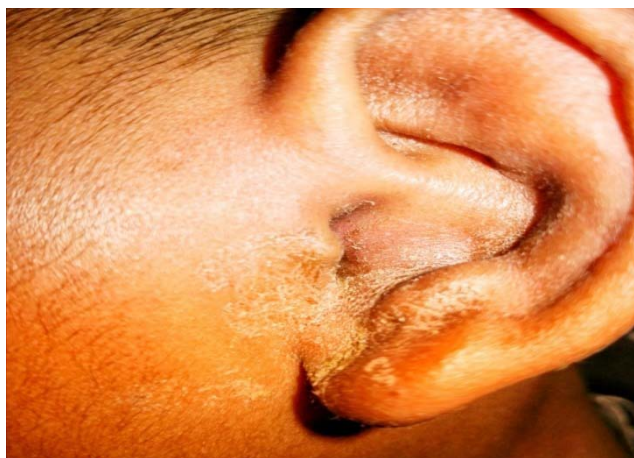


Figure-6: Cellulitis of pinna due to Furunculosis.



Figure-7: Post infective perichondritis including pos-auricular abscess of 03 years child.



Figure-8: Foreign body granuloma of the auricle with perichondritis of 02 years child.





Figure-9: Auricular sinus with perichondritis.



Figure-10: Perichondritis due to accident.



Figure-11: Helical incision along the margin of the helix of pinna.





Figure-12: Button placed medial and lateral side of bivalve pinna and fixed by thred 3/0 proline.



Figure-13: Fix the bivalve pinna of a teenage girl by button method.

II. METHODS AND MATERIALS

It is a cohort retrospective study of 63 cases in the two tertiary care Hospitals from 01 July to 31 June 2019. During three years period, ENT casualty patient was 7295. We divided the 63 patients into two categories depending on the James W. Cook's classification [3].

The category one patients produced mild to moderate symptoms like erysipelas, induration, and early cellulitis. They were twenty-seven and treated conservatively through out-patient department service. We discussed with the patient about the fatal out of the disease to maintain the proper treatment. We started parental intravenous combined systemic broad-spectrum like Injection Meropenem, Clindamycin, and Metronidazole to combat both aerobic and anaerobic bacteria especially *Pseudomonas aeruginosa*. We advised them to admit in the Upazilla Health Complex, which is the secondary care hospital, and near their homes to maintain the intravenous course properly for seven to ten days according to the condition of the

added pain killer, anti-ulcer, local drop, and ointment whichever were needed. Accordingly, they came to consult with us and exhibited 90% improvement. We converted the parental antibiotic into oral form like Tab Moxifloxacin (400mg), Cap Clindamycin (300mg), and Tab Metronidazole (400mg) for another ten days. They were disease-free since the last follow-up.

The rest 36 patients were category two, who produced symptoms auricular abscess, perichondritis, and chondritis. They need immediate surgical exploration and got admitted to the hospital. We started parental intravenous combined broad-spectrum systemic antibiotics without any delay like category one. We did incision and drainage 22 patients and regular surgical dressing with EUSOL pack (Edinburg solution of lime). We gave incision along the helical margin up to maximum fluctuate point and split the ear bivalve fashion. Through the splitting line, we placed the EUSOL pack and gave pressure bandage by maintaining the auricular shape. The 13 patients of category two need exploration, debridement, and extensive scooping and curettage. We gave helical incision from the upper

attachment of auricle up to the lobule (Figure-11) and split the ear bivalve fashion, debridement, scooping and curettage of all dead tissue and cartilage, and placing the EUSOL pack and regular dressing as before. We did the surgery of the children and uncooperative patients under general anesthesia and cooperative patients under local anesthesia when the infection was overcome and growing of granulation tissue, the bivalve ear attached by button method for ten to fourteen days (Figure-12, 13).

One patient did mastoidectomy operation. He cleared his ear by street ear cleaner like a hawker. Afterward he developed perichondritis with mastoiditis. Perichondritis treatment continued, but he complained the sever earache need narcotic analgesic. CT scan showed osteomyelitis change in the mastoid bone. After mastoidectomy, the patient cured of symptoms.

We followed-up the patient fifteen days interval for one month and the last follow-up after three months. We referred the major deformed patients to the Plastic and Reconstruction department for further consultation. The following data collected about the patient: Sex, age, laterality, personal history, presenting features, investigation, treatment, post-operative follow-up, complication, and hospital stay. Statistical software SAS used to calculate all data.

III. RESULTS

The incidence of perichondritis of pinna, out of ENT casualty, was 0.86%. The etiological factors explored, post-traumatic was 18 (28.57%) in which high ear piercing 11 (17.46%), accident and assault 07(11.11%), furunculosis 12 (19.05%), post-infective 09 (14.29%), allergy due to hair color 06 (9.53%), Herpes

Zostus Oticus 04 (6.35%), Malignant otitis externa 03 (4.76%), post-operative 02 (3.17%), insect bite(honey bees) 02 (3.17%), burn 02 (3.17%), and unknown 05(7.94%). Of them, the female was 30 (47.62%), and the male 33(52.58%), children (according to UNICEF and WHO children age up to 18 years) were 27 (42.86%), and adult 36 (57.14%) in which lowest age 02 years, highest age 76, mean age 21.952, and the standard deviation 16.676, and all patients had a unilateral ear. Personal history revealed diabetic was 08 (12.70%), and non-diabetic 55 (87.30%), smoker 09 (14.29%), and non-smoker 54 (85.71%). Presenting features exhibited moderate to severe earache was 61 (96.83%), red, hotness, and stiffness of pinna 59 (93.65%), auricular abscess 36 (57.14%). Bacteriology showed Pseudomonas aeruginosa was 21 (58.33%), Staphylococcus aureus 15 (41.67%), Streptococcus pyogenes 13 (36.11%), and gram-negative Bacillus Proteus, Enterococcus faecalis, Escherichia coli 11(30.56%). Regarding the treatment of the patient, 27 (42.86%) treated by conservative medical through out-patient department service, and 36 (57.14%) surgical through indoor service in which incision and drainage did 22 (61.11%), exploration, debridement, scooping, and curettage of auricular cartilage 13 (36.11%), and mastoidectomy 01(2.78%). After four months of follow-up, complications revealed minor deformity was 15 (23.81%), major deformity 07 (11.11%), and rest 41 (65.08%) normal. The treatment response was variable depending on the condition of the patient and prolonged the hospital stay. 17 (42.22%) patients stayed in a hospital for up to two weeks, 06 (16.67%) patients three to four weeks, and rest 13 (36.11%) patients five weeks and above.

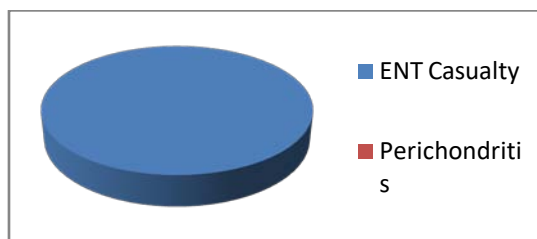


Chart-1: Incidence of perichondritis- n-7295; ENT casualty-7295: Perichondritis-63.

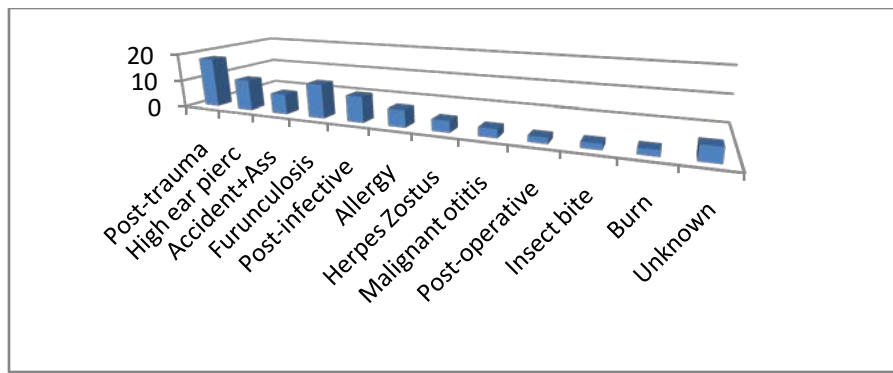


Figure-14: Etiological factor-n-63; 1.Post-trauma-18(A. High ear pierce-11, B-Accident & Assault-7).2.Furunculosis-12.3.Post-infective-9. 4. Allergy-6. 5. Herpes Zostus Oticus-4. 6. Malignant otitis externa-3. 7. Post-operative-2. 8. Insect bite-2. 9. Burn-2. 10. Unknown-5.

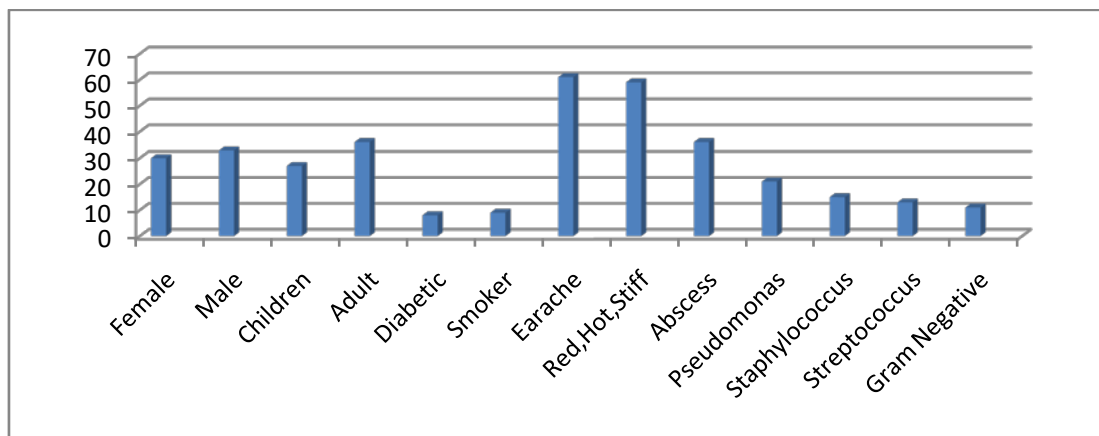


Figure-15: n-63; 1. Gender: Female-30: Male-33, 2. Age: Children-27: Adult-36, 3. Personal history: Diabetic-8: Smoker-9, 4. Presenting features: Earache-61: Red, Hot & Stiff pinna-59: Abscess-36, 5. Bacteriology: Pseudomonas-21: Staphylococcus-15: Streptococcus-13: Gram Negative-11.

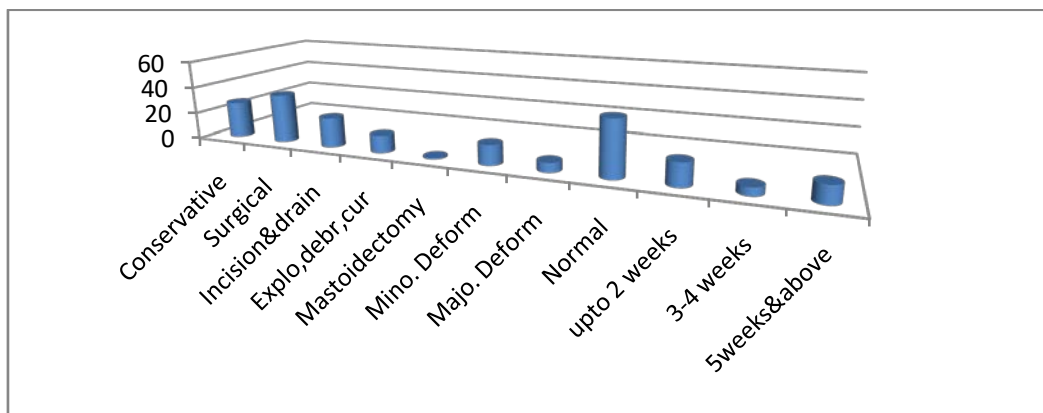


Figure-16: n-63; 1. Treatment: Conservative-27: Surgical-36: Incision & drainage-22: Exploration, Debridement, Scooping & Curettage-13: Mastoidectomy-1. 2. Complications: Minor Deformity-15: Major Deformity-7: Normal-41. 3. Hospital Stay: Upto2 weeks: 3-4 Weeks-6: 5 Weeks & above-13.

IV. DISCUSSION

Perichondritis of the pinna is a fatal infection and deformed the second identity of the body after fingerprint [1]. The incidence of perichondritis in the

present study, out of ENT casualty (7295) was 0.86%. There was no available data to compare it.

Regarding the etiology, post-traumatic was the common cause (28.57%) which included high ear piercing 11 (17.46%) usually found during Eid festival,

and accident and assaulted 07 (11.11%) supported by Cicchetti S et al. and Prasad HK study [23], [16]. Other factors were furunculosis 19.05%, post-infective 14.29%, allergy due to hair color 9.53%, Herpes zoster oticus 6.35%, malignant otitis externa 4.76%, post-operative, insect bite and burn all three were 3.17%, and unknown 7.94%, persistence with Hanif J, Prasad HK and Gautam D et al. series [4], [16], [24].

In gender epidemiology, males were 52.58%, and females 47.62%, almost equal in my work in opposition to Gautam D et al. series, revealed male 38 (76%), female 12 (24%), Prasad KC also exhibited male preponderance [24], [25]. It may be due to high ear piercing and furunculosis of external auditory canal patients; all or maximum were females in my paper.

Concerning the age, children were 42.86%, and adults 57.14% in the present study, against Gautam D et al. reported 76% was 30-50 years. Still, Fernandez ADP et al. series showed maximums were a teenager in favor of my observation [24], [26].

Personal history revealed diabetic was 12.70% and smoker 14.29% in my research causes delayed wound healing persistence with Fernandes LF work, recorded insulin depended on diabetic patient treated by hyperbaric oxygen after proper controlling of DM [27]. To control this type of fatal infection, the patient should stop smoking and diabetes should be normal through consultation with the Endocrinologist.

Presenting features exhibited earache was 96.83%, erythematous and indurated pinna 93.65%, and auricular abscess 57.14% in this paper, kept up by all others study like Prasad HK, Cicchetti C, Gautam D and Davis O et al. series [16], [23], [24], [28].

Culture and sensitivity report in my study, *Pseudomonas aeruginosa* was 58.33%, *Staphylococcus aureus* 41.67%, *Streptococcus pyogenes* 36.11%, and Gram-negative 30.56%, near to James W. Loock, Prasad HK and Gautam D papers [3], [16], [24]. James W. Loock showed *Pseudomonas aeruginosa* was 69%, Polymicrobial 22%, *Streptococcus* spp. 22%, and *Staphylococcus aureus* 20%. Prasad HK revealed *Pseudomonas* and *E Coli* were 50%, *Pseudomonas aeruginosa* 38%, *Pseudomonas* and *Staphylococcus* 07% and *Staphylococcus aureus* 05%. Gautam D exhibited *Pseudomonas aeruginosa* was 48%, *Staphylococcus* 20%, *Enterococcus faecalis* 10%, *Streptococcus* group A 06%, and Polymicrobial 08%. About bacteriology, Cossette JE, and Bergstrom L. observation also near to my report [29], [30].

Regarding treatment, we treated 42.86% patient conservative medical treatment supported by Prasad HK and Gautam D, though the number of patients fewer than me. They treated 19% and 24% patient accordingly conservative alone [16], [24]. Surgical treatment included incision and drainage was 61.11%, exploration, debridement, scooping and curettage 36.11%, and mastoidectomy 2.78% in this paper, near Prasad HK

percentage of the patient but the difference the method of surgery [16]. He presented incision and drainage was 31%, cartilage and wound debridement 31%, and mastoidectomy 07%. But my method of surgery kept up by James W. Loock, Dowling JA, Kent SE, and Widick MH et al. series [3], [20], [31], [32].

Post-operative follow-up presented minor deformity was 23.81%, extensive deformity 11.11%, and retain architecture 65.08% near to Gautam D et al. displayed partial deformity was 50%, total deformity 18%, and no deformity 32% [24]. Salem W and Scoog T et al. report also support our findings [33], [34].

Regarding hospital stay, conservatively treated 42.86% of patient received their treatment through out-patient department service. Surgically treated, 57.14% patients had got admitted to the hospital. Among them, 42.22% stayed in the hospital up to two weeks, 16.67% three to four weeks, and 36.11% five weeks and above-, consistent with Prasad HK, Gautam D, and Fernandez ADP works [16], [24], [26].

V. CONCLUSION

Perichondritis of the pinna is one of the dreadful diseases which can commonly strike teenagers, young, and diabetic persons. Teenagers and females are doing high ear piercing for wearing ornaments, which increases their fashion and smartness. It is necessary to develop their awareness to do high ear piercing a trained medical personnel. Development of realization about the ear infection and care to the people is essential through local health authority. Truculent surgical treatment without undue delay and the latest parental broad-spectrum antibiotic may restrain the disease and mitigate the hospital stay outstanding.

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Materials and Methods: The Diode Laser and three commercially available Desensitizers the Novamin^R group- (SHY-NMTM), Colgate Sensitive Pro-relief, Gluma were investigated in this study. 30 extracted mandibular molars were used (n=30). They were divided into 5 groups including the control group in which no treatment was done. Teeth were ground under water-cooled trimming wheel, to prepare flat dentin surfaces. The dentin surfaces were etched to remove any smear plugs and to mimic the open dentinal tubules of sensitive dentin using 0.5 M Ethylene Diamine Tetraacetic Acid (pH 7.4) for two minutes (applied with a micro brush) and then rinsed with an air-water syringe for 30 seconds.

Keywords: dentinal hypersensitivity; novamin; gluma; diode laser, pro-arginine; scanning electron microscope.

GJMR-J Classification: NLMC Code: WU 20.5



COMPARITIVE EVALUATION OF NOVEL DESENSITISING AGENTS ON DENTINAL TUBULE OCCLUSION A SCANNING ELECTRON MICROSCOPIC STUDY

Strictly as per the compliance and regulations of:



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Abstract- Aim: To comparatively evaluate the occlusion of dentinal tubules by four novel desensitizing agents for treatment of Dentinal Hypersensitivity.

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Results: Colgate Sensitive Pro-Relief and Gluma desensitizer produced a greater number of partially occluded tubules NovaMin[®] (SHY-NM[™]) and Laser Diode therapy produced a greater number of completely occluded tubules. The differences among all the groups were recorded as statistically significant ($P \leq 0.05$).

Conclusion: All materials were significantly effective in occluding dentinal tubules but, Laser diode therapy and Novamin[®] (SHY-NM[™]) containing dentifrice showed the best results for total occlusion of dentinal tubules.

Keywords: dentinal hypersensitivity; novamin; gluma; diode laser, pro-arginine; scanning electron microscope.

I. INTRODUCTION

Dentinal Hypersensitivity (DH) is defined as one of the most painful and least predictably treated chronic conditions in dentistry.¹

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The nature of the exposed dentin is of relevance, as not all patients exhibiting dentin exposure will develop sensitivity. The number and diameter of dentinal tubules at the tooth surface is shown to be significantly increased in hypersensitive dentin.^{2,3} While the exact mechanism of dentinal hypersensitivity is still controversial, hydrodynamic theory is one of the most accepted hypothesis.⁴ The dentinal tubules, which are open and wide, contain a fluid. According to this theory, this fluid expands when exposed to heat and contracts when exposed to cold or touch. The contraction and expansion change the pressure in the fluid phase, which in turn activates mechanoreceptor nerves close to the pulp. When nerve receptors are activated, sodium ions enter the dentin and potassium exits. This ion exchange polarizes the nerves and causes pain.³ The concept of tubule occlusion as a method of dentin desensitization is a logical conclusion based on the hydrodynamic hypothesis.⁵

The two principal treatment options available are, preventing fluid flow, plugging the dentinal tubules, or desensitizing the nerve, making it less responsive to stimulation.⁶

In the last fifteen years, with the introduction of Lasers which gave further possibilities to DH therapy.^{7, 8-11}

It is now possible to show that the role of laser in DH therapy is twofold. The low-level power lasers also called "soft lasers," act directly on nerve transmission. The other, high-power lasers such as diode 980 nm and 808 nm, Nd: YAG 1064 nm, CO₂ 10600 nm, Er, Cr: YSGG 2780 nm, and Er: YAG 2940 nm act on DH by provoking a melting effect along with the crystallization of dentine inorganic component and also the coagulation of fluids into the dentinal tubules.¹² Among the "high power" devices, the diode lasers which are the most studied and also the ones that gave the best results in several clinical protocols even in very high-grade DH cases.

Gluma desensitizer, (Heraeus Kulzer GmbH, Wehrheim, Germany), is a combination product consisting of an aqueous solution of 35% hydroxyethyl methacrylate and 5% glutaraldehyde, that has been reported to have been an effective desensitizing agent. The glutaraldehyde intrinsically blocks dentinal tubules,

counteracting the hydrodynamic mechanism that leads to dentin hypersensitivity.¹³

A new product consisting of calcium sodium phosphosilicate NovaMin[®], (SHY-NM[™]), has now been introduced. NovaMin is the trade name that has been given to bioactive glass (e.g., Bioglass), that has been ground into a fine particulate with a median size of less than 20 microns. It reduces sensitivity by blocking open tubules and by supplying calcium (Ca²⁺) and phosphate (PO⁴³⁻) ions to form hydroxycarbonate apatite (HCA). It is composed of elements that are naturally occurring in the body and it reacts to form a mineral layer that is chemically and structurally very similar to natural tooth material.¹⁴

In 2009, Colgate-Palmolive company acquired the rights to the novel technology, now known as Pro-Argin technology, first introduced by Kleinberg et al in 2002. The pro-arginine therapy uses arginine, an amino acid, calcium carbonate a source of calcium and Bicarbonate a pH buffer.¹⁵

The main objective of this study was to evaluate and compare the occlusion of dentinal tubules for treatment of DH by four novel Desensitizing agents:

In-Office Treatment: Diode Laser (Zolar) and Gluma Desensitizer.

Patient Applied Products for Home Use: Novamin[®] containing Toothpaste (SHY-NM[™]) and Colgate Sensitive Pro-Relief Toothpaste.

II. MATERIALS AND METHODS

a) *Sample preparation:* Thirty freshly extracted mandibular molars were selected and stored in normal saline until use (n=30)

The teeth were cleaned of any gross debris. Tooth cuts were made with a carborundum disc attached to a cutting machine. The crown and the apical third of each tooth were removed, and the remaining teeth were sectioned to provide one to two dentin specimens each. Sectioned samples of 2-mm thickness were made. The dentin specimens were then placed for 30 seconds in an ultrasonic cleaner in distilled water, etched with 17% aq EDTA (Ethylene Diamine Tetra Acetic Acid) for 2 minutes to remove the smear layer and rinsed in distilled water. The control specimens were then dried, and the test specimens were treated as per the manufacturer's instructions with the desensitizing agents.

b) *Desensitising Agents:* 30 extracted mandibular molars were used. (n=30) They were divided into 5 groups including the control group in which no treatment was done. The Diode Laser and three commercially available desensitizers were investigated in this study.

Group 1: Diode laser (ZOLAR) at 980nm therapy was used on dentin discs, in a non-contact mode for 30 seconds.

Group 2: Novamin[®] containing toothpaste SHY-NM[™] is applied on the dentin discs for 30- 40 seconds using an applicator tip and air-dried.

Group 3: Gluma desensitizer (Heraeus Kulzer GmbH, Wehrheim, Germany) is applied on the dentin discs for 30-40 seconds using applicator tip and air-dried

Group 4: Pro-arginine group of toothpaste Colgate sensitive pro-relief is applied on the dentin discs and left for 30-40 seconds using applicator tip and air-dried.

c) *SEM Evaluation:* All specimens were dehydrated in graded acetone, sputter-coated with gold-palladium and critical point dried. The specimens were then examined under a scanning electron microscope (Zeiss Sigma VP, Zeiss, Oberkochen, Germany) at 20 kV acceleration voltage. Standardized images of the dentine discs were acquired at a specific magnification of 3000 \times . Twenty images were acquired per disc. and surface scans were made to study the covering of the discs. [Fig 1(a)(b)(c)(d)(e)]

d) *Quantitative Analysis of dentinal tubule occlusion:* The standardized SEM images in the form of microphotographs were imported into ImageJ software (NIH, USA) and converted into binary images. The black (open dentine tubules) and white (occluded dentine tubules and dentine) pixels were counted, and the numbers were transferred into a worksheet using Microsoft Excel.

III. RESULTS

The total number of tubules was counted from the various images captured by the SEM. Out of the total tubules, those that were completely occluded, partially occluded, and open tubules were counted. The ratio of completely occluded tubules to the total tubules as well as the ratio of partially occluded tubules to the total tubules were calculated. Nonparametric tests were done as the data obtained did not show a normal distribution. The data obtained was statistically analyzed using the Kruskal-Wallis test and Wilcoxon rank-sum test, through which comparison among the groups as well as an intergroup comparison was performed, respectively, and statistical significance was calculated (Table 1). The mean of the ratio of completely occluded tubules to total tubules and partially occluded to total tubules for each group were plotted (Figs.2 and 3). All of the statistical analyses were performed using IBM SPSS ver. 21 (IBM Co., Armonk, NY, USA).

After combining the mean values of occluded tubules/total number (partial and total) the more occluded tubules were seen in this order

Group 1>Group 2>Group 3> Group 4

IV. DISCUSSION

Dentin Hypersensitivity is defined as a pain arising from exposed dentin, typically in response to chemical, thermal, or osmotic stimuli, that can't be explained as arising from any other form of dental defect or pathology.¹⁶

SEM studies of hypersensitive dentin surfaces reveal that they need more patent tubules per unit area than nonsensitive dentin. Absi et al.¹⁷ and Yoshiyama et al.¹⁸ reported that most of the tubules were occluded in naturally desensitized dentin. Based on transmission electron microscopic studies, Yoshiyama et al.¹⁸ reported that tubular occlusions could be due to an extension of the intratubular dentin layer or deposition of substances in the tubules. It has been shown by Brannstrom in human studies that the patency of the dentinal tubules is a major characteristic of sensitive dentin. A significant direct correlation between the density of open dentinal tubules the intensity of pain responses induced from exposed cervical dentin surfaces has also been reported. The condition of dentin with either open or blocked tubules is decisive regarding the hydraulic conductance of dentin and thus stimulus-induced fluid flow in the dentinal tubules. Hence, blocking off the tubules should effectively abolish dentinal pain symptoms.¹⁹ Dentine tubule occlusion is achieved in two different ways, either by the deposition of an occluding layer on top of the dentin or by the introduction of occluding material into dentine tubules.

In the Morris et al.²⁰ study they highlighted a very powerful placebo effect inherent in clinical dentin sensitivity studies, particularly when dealing with small numbers of subjects and eligible teeth. Furthermore, the large standard deviations reported by Morris et al.²⁰ because of the highly subjective nature of pain and/or the variability of the individual pain response reported in dentin sensitivity studies, makes it extremely difficult to detect significant differences between groups without utilizing a large number of subjects. Thus, the in vitro examination of products using a reproducible model such as the dentin disc, can aid the understanding of the potential occluding, and thus desensitizing properties of possible desensitizing agents.²¹

Conventional therapies for the treatment of DH comprehend the topical use of desensitizing agents, either professionally or by using protein precipitants,²² tubule-occluding agents,^{23, 24} tubule sealants,²⁵ and, recently, lasers.²⁶

Several studies²⁷⁻²⁹ describe a synergistic action of lasers using desensitizing agents. The laser system can favor the permanence of the desensitizer for a longer time than when they are used alone. For this reason, if a laser device is employed additionally to a standard desensitizing agent, the latter remains above the tooth surface for 60 seconds before the irradiation.

Focusing on the effectiveness of only the diode laser, this was investigated by several authors. Matsumoto et al.³⁰ showed an 85% improvement in teeth treated with a laser; Aun et al.³¹ reported success in laser-irradiated teeth in 98% of their cases; Yamaguchi et al.³² noticed an effective improvement index of 60% within the group treated with laser compared to the 22.2% of the control non-lased group; Another study administered by Brugnera et al. showed the immediate analgesic effect using a diode laser.³³

Gluma desensitizer is a solution containing 5% glutaraldehyde and 35% hydroxyethyl methacrylate. Because glutaraldehyde is a biological fixative, it has been suggested that the dentinal tubules are occluded as an effect of reaction with plasma proteins from a dentinal fluid. Hydroxyethyl methacrylate is a hydrophilic monomer compound of dentin bonding agents with the ability to infiltrate into acid-etched and moist dental hard tissue.³⁴

NovaMin[®] (SHY-NM[™]) is a bioactive glass-ceramic material that falls into a class of newer materials that provide calcium and phosphate upon reaction. In the case of products with NovaMin, the active ingredient, calcium sodium phosphosilicate that reacts when exposed to aqueous media and provides calcium and phosphate ions that form a HydroxyCarbonate Apatite (HCA) with time.³⁵ The combination of the residual NovaMin particles and the HCA layer results in the physical occlusion of dentinal tubules, which will relieve hypersensitivity.³⁶

The results of the present study revealed that NovaMin-treated dentin specimens showed more complete tubule occlusion. This is in accordance with the findings of Litkowski¹⁴ and Du Min et al.³⁷ who found NovaMin to be a more effective desensitizer.

Pro-arginine, the effective components of this new technology are Arginine, an amino acid positively charged at physiologic pH (6.5-7.5), Bicarbonate, a pH buffer, and insoluble Calcium carbonate, a source of calcium. The arginine present in the products is obtained from vegetable sources. In 2009, Colgate-Palmolive launched Colgate Sensitive Pro-Relief in-office desensitizing paste.³⁹

When the desensitizing paste is applied to exposed dentin, Arginine (positively charged) and calcium carbonate, found in saliva naturally, work together to accelerate the natural mechanisms of occlusion by binding to the negatively charged dentine surface to deposit a dentin-like mineral, as a plug within the dentin tubules and a protective layer on the dentin surface. This consists of arginine, calcium carbonate, phosphate, and salivary glycoproteins. Freeze fracture images have shown that this plug reaches a depth of 2 μm into the tubule. It is effective in reducing dentin fluid flow thereby relieving hypersensitivity.³⁹

In the present study, we have shown that professionally applied dental (in-office) products containing Diode Laser (Zolar) and Gluma desensitizer are both capable of occluding the dentin tubules to varying degrees and may have the clinical potential to reduce dentin hypersensitivity.

In house application of dental products like Colgate Sensitive Pro-relief and Novamin (SHY-NM), also occluded dentinal tubules and reduced dentin hypersensitivity.

All the novel desensitizers occluded the tubules but Diode laser and NovaMin have shown superior results with respect to complete tubule occlusion on initial application. The results of the present study are limited to physical findings of the change in the dentinal tubules and do not present in vivo differences that may result from the physiological effect of these desensitizing agents. Differences between our results and those of other studies may be related to the dentin specimen utilized, etching process, time and mode of application of the desensitizing agent, or a combination of these variables. Further future clinical trials with larger sample size, comparison with positive controls and negative controls, different concentration should be taken under consideration to validate the result of this new product as an efficacious desensitizing agent. However, the results were consistent in demonstrating a significant effect in reducing the sensitivity with the desensitizing agents used.

V. CONCLUSION

In conclusion, NovaMin^R (SHY NMTM) and laser diode therapy showed a greater number of completely occluded tubules and Gluma desensitizer and Colgate sensitive Pro-relief produced a greater number of partially occluded tubules.

There was a statistically significant difference between the five groups when the ratio of complete and partial occlusion was calculated against the total number of tubules.

Hence, the Diode Laser application and NovaMin^R (SHY NMTM) application could be more effective in providing relief from dentinal hypersensitivity.

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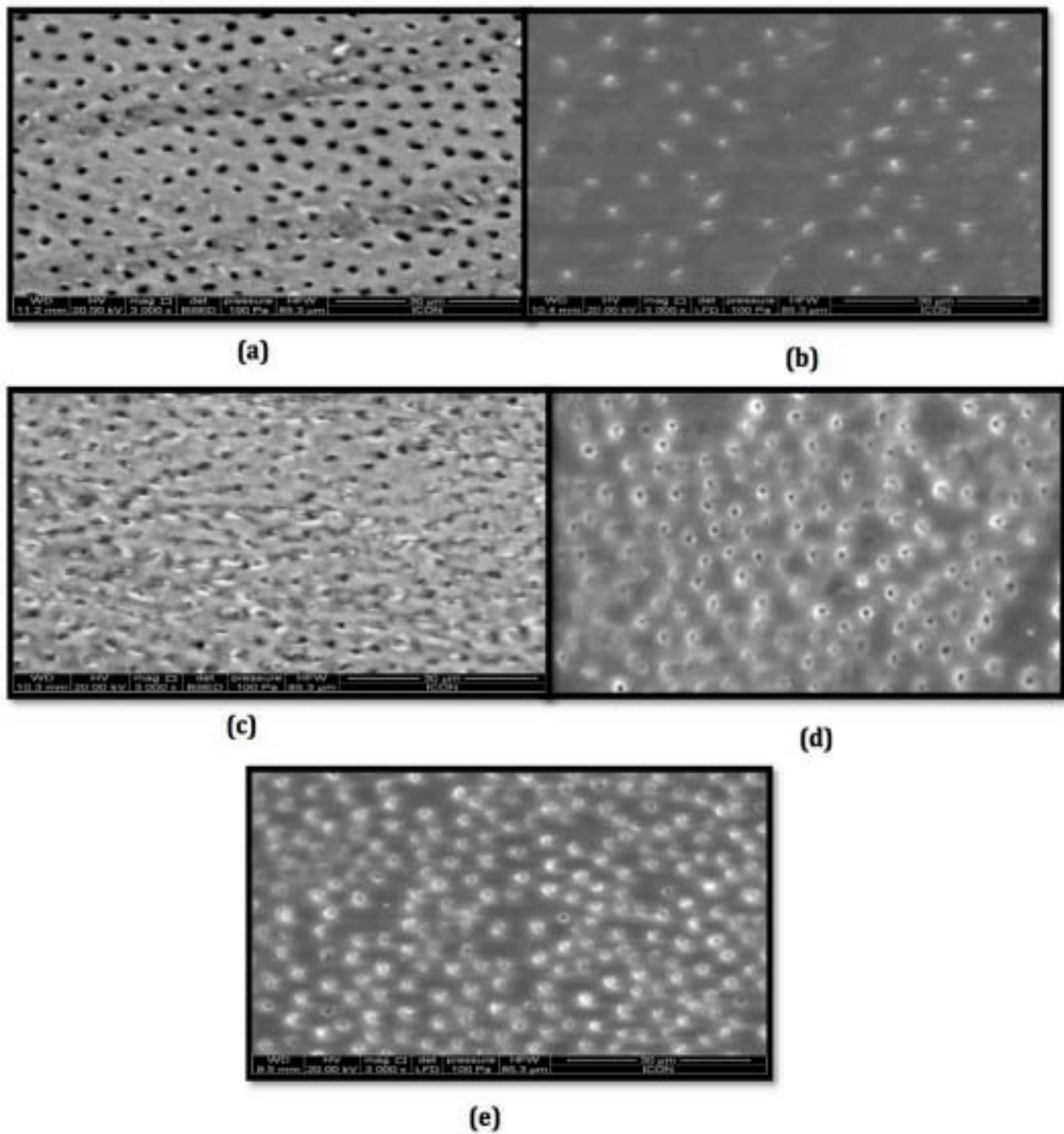


Figure 1(a) to (e): Representative image of dentinal tubule occlusion following the use of four desensitizing agents. (a) Control group (b) Laser group (c) Novamin group (d) Gluma desensitizer (e) Colgate Sensitive Pro-relief



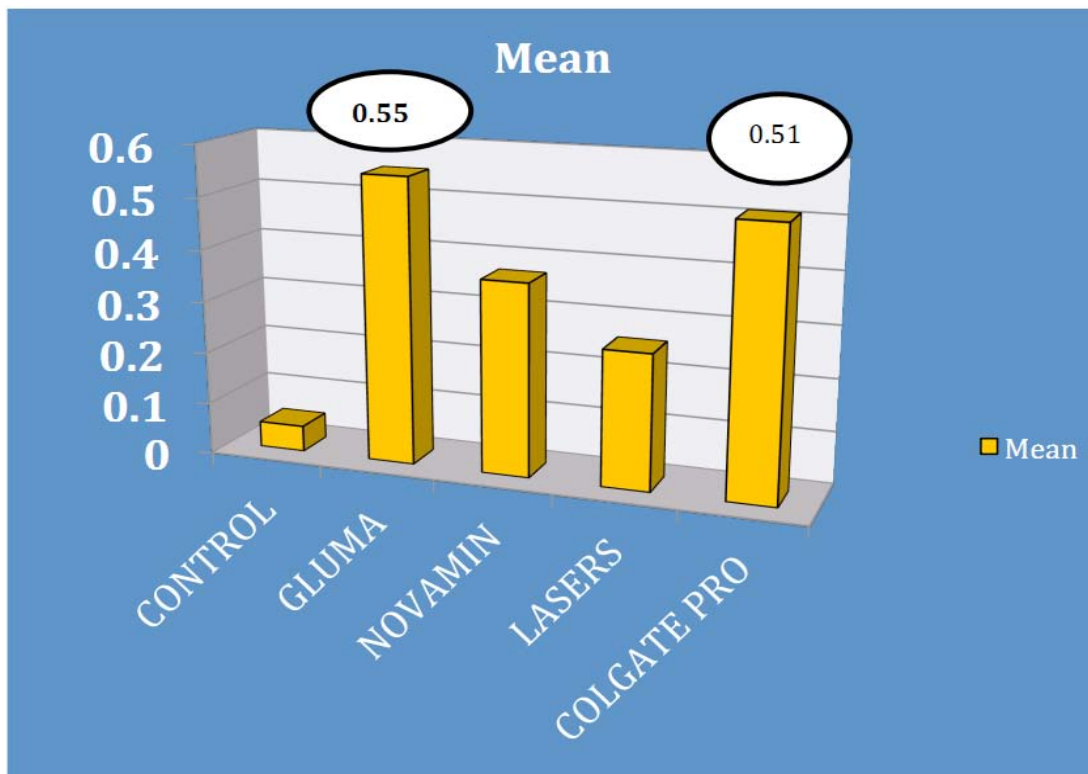


Figure 2: Graphical Representation of Partially Occluded Tubules of all study groups.

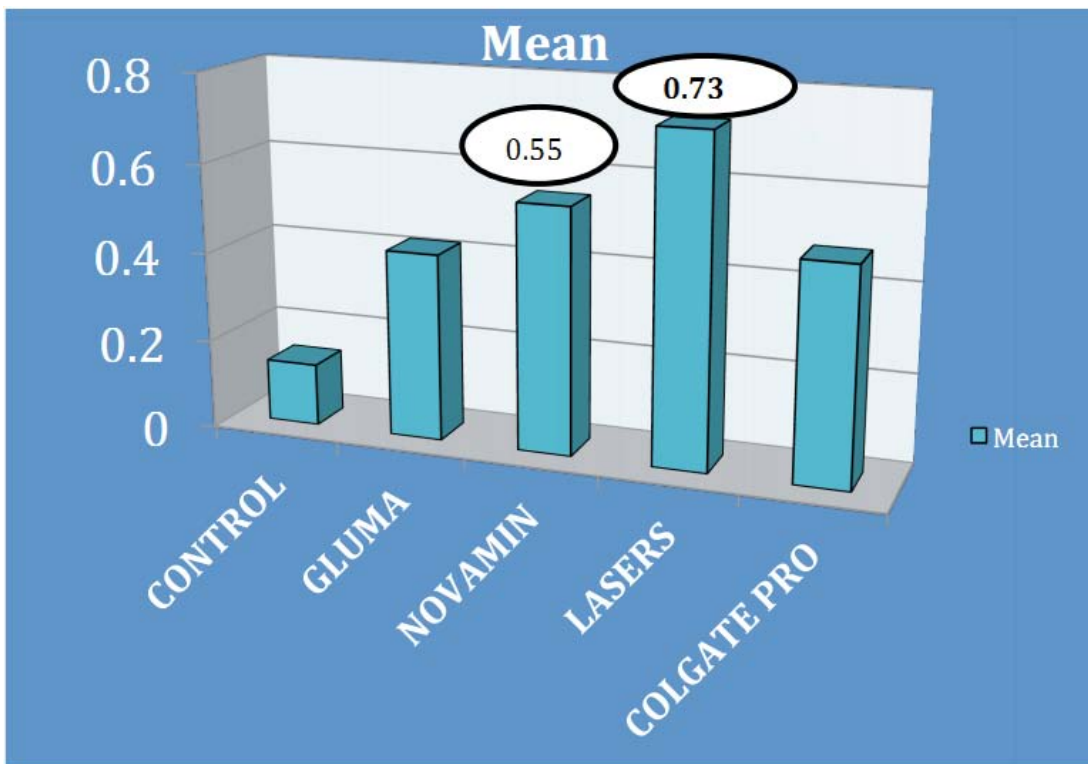


Figure 3: Graphical Representation of Totally Occluded Tubules of all study groups.

Table 1: Descriptive Statistical data of Partially and Totally Occluded scores of the study Groups.

		PARTIALLY OCCLUDED		TOTALLY OCCLUDED	
		Mean	SD	Mean	SD
Groups	CONTROL	.05	.01	.14	.01
	GLUMA	.55	.03	.42	.01
	NOVAMIN	.37	.01	.55	.02
	LASERS	.26	.02	.73	.02
	COLGATE PRO SENSITIVE	.51	.01	.48	.01





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Literature Review: Oral Rehabilitation in Patients Up To 16 Years Old with Hypohidrotic Ectodermal Dysplasia (HED)

By Carneiro CS, Mello LS, Brooks JS, Posch AT & Reis KR

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Abstract- Hypohidrotic Ectodermal Dysplasia (HED) is part of a heterogeneous group of inherited diseases that affect the structures derived from the ectodermal tissue. Among the common oral manifestations, hypodontia is observed, generating the need for prosthetic rehabilitation. The objective of this paper is to present the main difficulties in the oral rehabilitation of patients with HED in the age group 0 from to 16 years old. A bibliographic search was done using articles published between 2004 and 2019 in the Pubmed database, using the MeSH terms Hypohidrotic Ectodermal Dysplasia AND Dental Rehabilitation. There were 26 articles available for download, reporting a total of 46 patients. The main limiting factors found in these patients are: hyposalivation, atrophic alveolar ridge, decreased vertical dimension of occlusion and varying levels of hypodontia. The constant bone growth of child and adolescent patients also limits the prosthetic rehabilitation options and decreases the fit index of the confectioned prostheses. In addition, psychological and social factors should be considered, as it is necessary to promote a treatment in which the young patient is able to adapt and maintain it.

Keywords: *hypohidrotic, ectodermal, dysplasia, dental, rehabilitation.*

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Carneiro CS^α, Mello LS^σ, Brooks JS^ρ, Posch AT^ω & Reis KR[✱]

Abstract- Hypohidrotic Ectodermal Dysplasia (HED) is part of a heterogeneous group of inherited diseases that affect the structures derived from the ectodermal tissue. Among the common oral manifestations, hypodontia is observed, generating the need for prosthetic rehabilitation. The objective of this paper is to present the main difficulties in the oral rehabilitation of patients with HED in the age group 0 from to 16 years old. A bibliographic search was done using articles published between 2004 and 2019 in the Pubmed database, using the MeSH terms Hypohidrotic Ectodermal Dysplasia AND Dental Rehabilitation. There were 26 articles available for download, reporting a total of 46 patients. The main limiting factors found in these patients are: hyposalivation, atrophic alveolar ridge, decreased vertical dimension of occlusion and varying levels of hypodontia. The constant bone growth of child and adolescent patients also limits the prosthetic rehabilitation options and decreases the fit index of the confectioned prostheses. In addition, psychological and social factors should be considered, as it is necessary to promote a treatment in which the young patient is able to adapt and maintain it. It is important that the professional knows how to recognize the clinical characteristics of HED and understands the limiting factors in the prosthetic rehabilitation of the individual, so that the final result of treatment is successful. Therefore, it is necessary that the dentist has knowledge about the characteristics of the disease and knows how to perform procedures for an effective oral rehabilitation of these individuals.

Keywords: hypohidrotic, ectodermal, dysplasia, dental, rehabilitation.

I. INTRODUCTION

Hypohidrotic Ectodermal Dysplasia (HED) is included in a large and heterogeneous group of hereditary diseases that affect the ectodermal tissue, affecting 1 in every 100,000 births. It is a X-linked pattern disease and also recessive, being more common in males, not presenting a complete phenotype when present in females.

Hypodontia, hypotrichosis and hypohidrosis form a classic triad of characteristics of HED, which are manifested in clinical signs such as the dry aspect of the skin, the presence of thinning hair, absence of primary teeth and permanent dental germs. In addition, there is

a typical facial concavity, the prominence of the frontal region of the face, the presence of the saddle nose, and thick and everted lips. As a result of the absence of dental elements, there is an underdevelopment of the gnathic bones, resulting in a decrease in the vertical dimension of the face, as well as a projection of the chin, giving the patients an aged appearance. Among the oral manifestations of this dysplasia, in addition to hypodontia, there is the presence of conoid teeth and hyposalivation, which can generate the clinical condition of xerostomia. It is important that the dentist knows how to identify these characteristics and that the oral rehabilitation of this patient is performed early, in order to reduce its impacts on masticatory function, speech and esthetics.

II. LITERATURE REVIEW

HED is a syndrome with signs and symptoms that can be seen since the individual's birth, such as the presence of dry mucous membranes and the absence of sweat glands, while others develop as the child grows. In the first months it is possible to observe the non-eruption of some dental elements and after the first year, facial characteristics become more evident.

Multidisciplinary monitoring of patients with HED is fundamental to their quality of life, even though it is an irreversible condition, it is possible to mitigate the effects of their signs and symptoms. When performing routine consultations from early childhood (0 to 5 years old), the dentist is able to identify the main oral manifestations and plan an appropriate conduct, according to the patient's needs. In this phase, it is already possible to observe absences and or changes in the shape of dental elements that can directly interfere in the development of speech, food and even in the social relationship during the beginning of the school phase.

The case reports found in the literature described oral rehabilitation as an option to reestablish the esthetics and function of the stomatognathic system, assisting in the musculoskeletal development of patients with HED. The different techniques analyzed varied according to the previous planning carried out in each clinical case. From the earliest age (3 years) to the later reported rehabilitation (16 years) it was seen that when

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reestablishing the patient's oral function, the impacts of HED manifestations were minimized. There was less bone resorption from the alveolar crest, with lesser changes in the vertical dimension of occlusion and a lesser tendency to develop Angle class III malocclusion.

Currently, the development of materials and techniques in Dentistry offers a variety of prosthetic rehabilitation options. However, removable prosthetic devices are still the most indicated in cases of early manifestation of HED (Table 1), as they are easy to make options, have a satisfactory cost-benefit ratio and are easy to replace during peak periods of bone growth in child and adolescent patients. The limitations found to rehabilitate these patients with conventional removable prostheses are largely associated with the difficulty in fitting for their use¹⁵, the presence of hyposalivation^{19,16} due to changes in the exocrine glandular pattern, causing discomfort and lack of adhesion of the prosthesis to the oral mucosa. The set of limitations linked to continuous bone growth in this age group, leads to the need for frequent replacement of these prostheses.^{2,6,11,16,18.}

Most of the patients in the analyzed studies had conoid teeth during primary dentition. The pointed shape of these elements gives the smile a vampiric appearance, and re-anatomization with light polymerizable composite resin was the most used option for these cases. Esthetic procedures like these, require a thorough restoration technique, generally requiring a longer clinical time. In these cases, the patient's age and his / her degree of collaboration are the main limiting factors found, and are not directly related to specific manifestations of HED. A study presented the making of crowns in the CAD / CAM system as an alternative to ensure the proper anatomy for conoid teeth, which overcomes the disadvantages of direct composites, avoiding the adverse effects resulting from polymerization, such as contraction.¹⁰

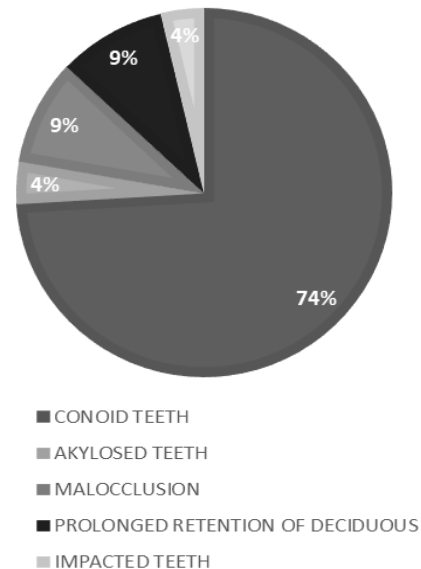
After the eruption of the first permanent tooth, the phase that begins on average at 6 years old, the individual begins to have a mixed dentition, that is, he has permanent and deciduous teeth in his oral cavity. In patients with HED, this fact will depend on the existence of permanent dental germs, and in most cases due to hypodontia or anodontia they are absent. Thus, there is a prolonged retention of primary teeth^{6,10,17,22,25}, which should exfoliate naturally, allowing the eruption of permanent teeth. In some prosthetic rehabilitation, extraction of these retained elements is necessary, as it is considered as a limitation by some reported cases, since this step may involve a more invasive surgical procedure, as these dental remnants may be ankylosed. Due to the limitations in retention and stability of conventional removable prostheses, it is possible to use the remaining teeth in order to guarantee these properties, an alternative mentioned were the prostheses

known as overdentures^{2,7,11,17,20,26}. The prosthetic device is stabilized by a fitting system, which can be made on remaining teeth or on intraosseous implants. Tooth supported overdentures can be made if the dental element has sufficient bone insertion to guarantee the support of the prosthesis. Its greatest disadvantage is the need for invasive dental preparations and elective endodontic treatment in child and adolescent patients.

Overdentures when retained by intraosseous implants require prior surgery to install them. The preservation of alveolar bone is its greatest advantage in relation to conventional prostheses, a subject that was widely discussed in the Delphi International Consensus²⁴. Different types of implants with varying sizes and shapes can be used for oral rehabilitation, mini implants were alternatives reported in some clinical cases, as they guarantee the same advantages as the conventional implant, presenting less amplitude, being less invasive and therefore more suitable for child and adolescent patients^{4,17}.

According to Schnabl (2018), orthodontics can be considered a good option to redistribute toothless spaces and modify alveolar and maxillomandibular growth, through functional devices. Of the clinical reports analyzed, 83% included orthodontic treatment as a phase of oral rehabilitation, some of them used maxillary expanders associated with removable dental prostheses¹⁴. (Graph 2)

The fit for the use of these devices by the patient and the greater accumulation of bacterial plaque may be limitations of this treatment, requiring more effective oral hygiene and greater effort for its continuous use.



Graph 1: Analysis of oral characteristics

Table 1: Relationship between the types of prosthetic devices used in oral rehabilitation and the patient's teething stage. Primary Dentition (0-5 years). Mixed dentition (5-11 years). Permanent dentition (6-12 years).

PROSTHETIC REHABILITATION	PRIMARY DENTITION	MIXED DENTITION	PERMANENT DENTITION
TOOTH SUPPORTED OVERDENTURE		4	3
REMOVABLE PROTHESIS	2	4	2
REMOVABLE PARTIAL PROTHESIS	3	8	1
FIXED PROTHESIS WITH NANCE	1		
RP WITH EXPANSION SCREW		9	8
CAD/CAM RESTORATION		1	
MINI IMPLANTES		1	1
ORTHODONTIC TREATMENT		4	1
COMPOSITE RESTORATION		3	2
FIXED PROTHESIS		1	1
IMPLANTS WITH MANDIBLE		1	1

III. DISCUSSION

Among the main characteristics of HED, the one that most interferes in the oral rehabilitation of these patients, consists of the underdevelopment of the mandible and maxilla bones (Graph 3), resulting in the difficulty of guaranteeing retention and stability of the prostheses. This is due to congenital hypodontia seen in individuals with the disease. The difficulties encountered in the management of these patients are similar to those of an elderly edentulous patient (Table 2), but in child and adolescent patients there is the challenge of reconciling rehabilitation treatment with the continuous development of craniofacial bones, making it difficult to carry out long-term treatment, and leading to need for regular adjustments.^{2,6,11,16,18.}

Retention of removable prosthetic devices is one of the essential biomechanical principles to ensure stability in the oral cavity. It is facilitated by the presence of a film of saliva capable of creating a surface tension, between the mucosa and the base of the prosthesis, keeping it in position. Patients with HED can report dry mouth, most often caused by hyposalivation^{2,4,16,19,20,25,} and consequently may compromise retention in cases where there is the use of removable prosthetic devices.

In relation to maxillomandibular occlusion, a greater tendency is observed for these patients to present Angle class malocclusion^{24,15,11,9,19.} This factor is a challenge in prosthetic rehabilitation, since surgeries capable of reversing this condition are generally invasive and are not indicated for patients in the analyzed age group.

When making dental prostheses, the step of impression of the bone edge and dental structures is of paramount importance to reproduce plaster casts with intraoral references. The difficulty in selecting appropriate impression trays for the patients' anatomy, and finding stock teeth with ideal size and shape, has

been reported in the literature as one of the factors that could limit prosthetic rehabilitation. However, it can be considered that they are more associated with the early age of rehabilitated individuals, than with HED itself.

Family support for the patient's rehabilitation treatment is an indispensable factor for their success. The lack of good oral hygiene and encouragement of the use of prosthetic and orthodontic devices were seen as limitations during oral rehabilitation. In individuals at an early age, especially, the role of family members is of utmost importance both in helping to insert and remove the prosthesis properly, as well as in cleaning and encouraging its continued use.

Intraosseous implants have been described by some researchers as a treatment option for growing patients due to physiological bone conservation. The recommendation is that the patient has completed his bone growth phase, which can be observed through radiographic examinations of the hand and wrist. However, in children with conditions such as HED, the alveolar bone does not develop in the region of congenital tooth absence. According to the Delphi Consensus (Klineberg et al, 2013), it is possible to install implants before the pubertal growth spurt, in cases of severe anodontia and oligodontia, as long as there are no adjunct teeth.^{12,13}

Implants in the maxilla region are contraindicated for these patients, as they grow through sutures, and there is no safe area for placement. Although there are reports of implants placed in this region, clinical or experimental data, especially in the long term, are insufficient to support this indication.^{12,13} On the other hand, they can be placed in the anterior region of the mandible when clinically justified, from 7 to 8 years old (Klineberg et al, 2013). The mandibular posterior region should be avoided until the end of childhood, due to its anteroposterior, transversal and vertical growth. In this area, bone growth can generate

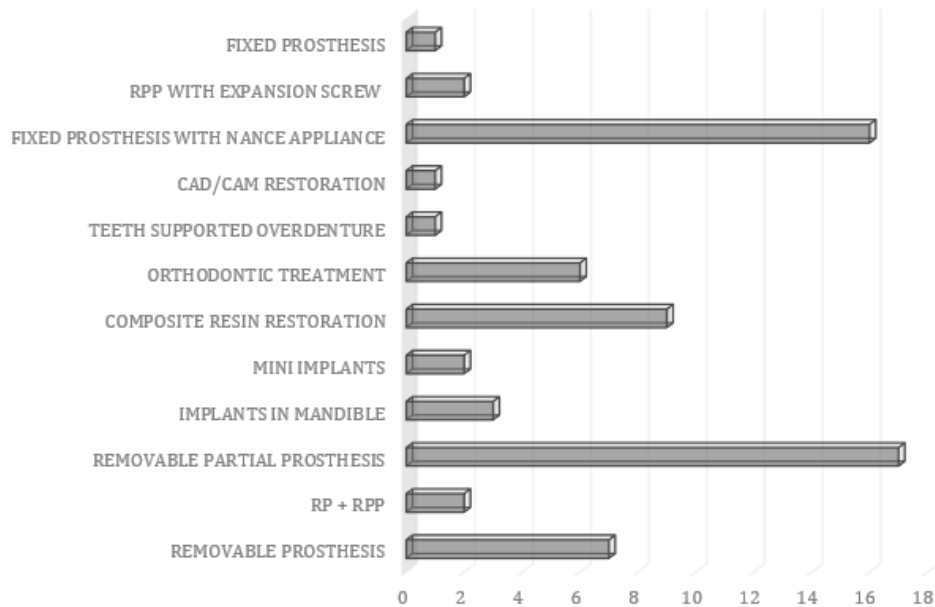
infra-occlusion and multidimensional dislocation of the implants.

In contrast to natural teeth, implants do not allow the compensatory movements that are provided by the periodontal ligament. They behave like ankylosed teeth, and can prevent bone growth around them.^{12,13} Thus, rehabilitation with implant-supported prostheses can impair the continuous growth of the mandible and

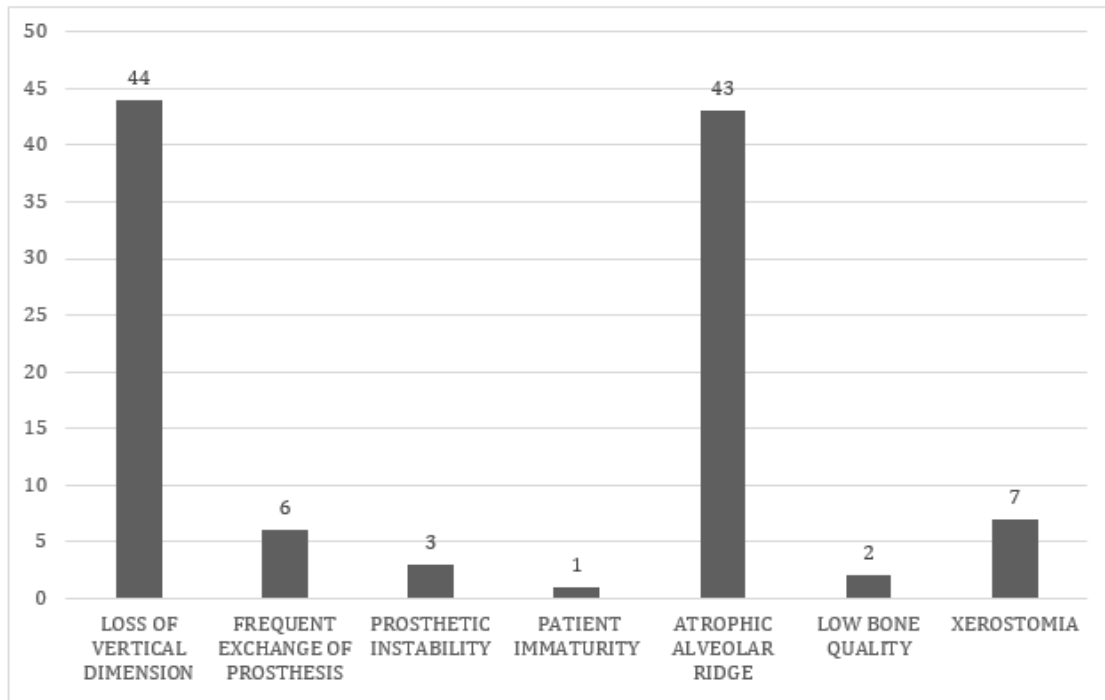
maxilla in child and adolescent patients, as they are in the bone development phase. According to the literature, the installation of intraosseous implants is preferable in patients with complete anodontia, as they do not present dental germs susceptible to eruption, and consequently bone growth occurs on a smaller scale, decreasing the chances of unwanted movements in the regions of the implants.

Table 2: Relationship between the limiting factors in the prosthetic rehabilitation and the patient's teething stage. Primary Dentition (0-5 years). Mixed dentition (5-11 years). Permanent dentition (+12 years).

LIMITING FACTORS IN THE PROSTHETIC REHABILITATION	PRIMARY DENTITION	MIXED DENTITION	PERMANENTE DENTITION
LOSS OF VERTICAL DIMENSION	6	24	15
FREQUENT EXCHANGE OF PROSTHESIS	2	4	
PROSTHETIC INSTABILITY	1	1	
PATIENT IMMATURITY	1		
ATROPHIC ALVEOLAR RIDGE	6	22	15
LOW BONE QUALITY		1	1
XEROSTOMIA	1	4	1



Graph 2: Types of prosthetic rehabilitation. RP: Removable Prosthesis. RPP: Removable Partial Prosthesis.



Graph 3: Limiting factors in the prosthetic rehabilitation.

IV. CONCLUSION

Through this literature review, it can be concluded that the underdevelopment of gnathic bones is the greatest limitation for the oral rehabilitation of patients with HED, hindering the retention and stability of prosthetic devices. As a first treatment option, as it is a less invasive technique, the use of conventional prosthesis should be considered, especially in patients at an early age. The use of intraosseous implants is preferably indicated after bone maturity and in cases of severe anodontia, due to bone growth on a smaller scale. Mini-implants can be considered effective and less invasive options when compared to conventional ones. The other reported rehabilitation options can be indicated according to the needs of each clinical case.

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Oral Health Condition in Patients with Chronic Renal Failure under Hemodialys Treatment

By Marco Xavier Vizuete Bolaños, Marina Antonia Dona Vidale,
Diana Patricia Gordon Navarrete, David Andrés Sempertegui Jácome,
Miguel Ángel Sosa Carrero & Christian Andrés Singo Salazar

Abstract- Chronic renal failure is a disease considered as a catastrophic disease; moreover, it is among the first 50 leading causes of death in Latin America. This disease presents several manifestations at the oral cavity with a big dental importance because they can affect the oral health of patients with chronic renal insufficiency. The objective of this study was to determine the frequency of oral, dental and periodontal manifestations in patients with chronic renal insufficiency treated with hemodialysis, who are attended at the "NEFROLOGY" center through a cross-sectional study of 62 patients who approved the inclusion criteria. A direct clinical observation of oral manifestations, periodontal examination, and epidemiological indices of oral morbidity (CPO, Oral Hygiene of Greene-Vermillion and O'Leary's dentobacterial plate) were performed. The results were obtained using the χ^2 test $p < 0.05$. The main oral manifestation was mucosal pallor, severe periodontitis was the main diagnosis found periodontally and 57 patients presented tooth loss along with a high index of dentobacterial plaque accumulation.

Keywords: chronic renal insufficiency, hemodialysis, oral manifestations.

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Oral Health Condition in Patients with Chronic Renal Failure under Hemodialysis Treatment

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Resumen Y Palabras Claves- La insuficiencia renal crónica es una enfermedad considerada como una enfermedad catastrófica y se encuentra entre las primeras 50 principales causas de muerte en América Latina. Esta enfermedad presenta varias manifestaciones en la cavidad oral de gran importancia odontológica, ya que pueden repercutir en la salud bucal de los pacientes con insuficiencia renal crónica. El objetivo de este estudio fue determinar la frecuencia de manifestaciones bucales, dentales y periodontales en pacientes con insuficiencia renal crónica bajo tratamiento con hemodiálisis, atendidos en el centro "NEFROLOGY", mediante un estudio transversal realizado en 62 pacientes que cumplieron los criterios de inclusión. Se realizó una observación clínica directa de manifestaciones bucales, examen periodontal e índices de epidemiológicos de morbilidad bucal (CPO, Higiene Oral de Greene-Vermillion y Placa dentobacteriana de O'Leary). Los resultados obtenidos fueron mediante la prueba de χ^2 $p < 0.05$. La principal manifestación bucal fue la palidez de mucosa, la periodontitis severa fue el principal diagnóstico hallado periodontalmente y 57 pacientes presentaron pérdidas de piezas dentales junto con alto índice de acumulación de placa dentobacteriana.

Palabras Claves: insuficiencia renal crónica, hemodiálisis, manifestaciones orales.

Abstract- Chronic renal failure is a disease considered as a catastrophic disease; moreover, it is among the first 50 leading causes of death in Latin America. This disease presents several manifestations at the oral cavity with a big dental importance because they can affect the oral health of patients with chronic renal insufficiency. The objective of this study was to determine the frequency of oral, dental and periodontal manifestations in patients with chronic renal insufficiency treated with hemodialysis, who are attended at the "NEFROLOGY" center through a cross-sectional study of 62 patients who approved the inclusion criteria. A direct clinical observation of oral manifestations, periodontal examination, and epidemiological indices of oral morbidity (CPO, Oral Hygiene of Greene-Vermillion and O'Leary's

dentobacterial plate) were performed. The results were obtained using the χ^2 test $p < 0.05$. The main oral manifestation was mucosal pallor, severe periodontitis was the main diagnosis found periodontally and 57 patients presented tooth loss along with a high index of dentobacterial plaque accumulation.

Keywords: chronic renal insufficiency, hemodialysis, oral manifestations.

Abreviaturas, Siglas y Unidades: IRC= Insuficiencia Renal Crónica, IRA= Insuficiencia Renal Aguda, Ca= calcio, CPO= Cariados/Perdidos/Obturados, IHO= Índice de Higiene Oral, IPDB= Índice de placa Dentobacteriana, IC= Índice de Calculo, %= porcentaje

I. INTRODUCCIÓN

Los riñones son los encargados de cumplir importantes funciones en el cuerpo humano como regular el volumen de líquido corporal, equilibrar las concentraciones ácidas y alcalinas del plasma sanguíneo, la eliminación de sustancias nitrogenadas a través de la orina y la producción de eritropoyetina, hidroxicolecalciferol <<vitamina D>> y renina.¹ La disminución de las funciones renales por deterioro o destrucción irreversible de las nefronas <<unidades funcionales del riñón>>, ya sea esta de evolución lenta o progresiva se denomina Insuficiencia Renal; dando como resultado una acumulación elevada de productos nitrogenados como la urea, creatinina y otros productos de excreción en la sangre; dando como resultado en general trastornos metabólicos y alteraciones óseo mineral.²

De acuerdo a la velocidad de deterioro de las nefronas y la disminución del filtrado glomerular, la insuficiencia renal se divide en:

- Insuficiencia Renal Aguda (IRA) que se caracteriza por una disminución en la tasa de filtración glomerular rápida que puede variar desde semanas hasta horas; esto con lleva a una rápida concentración en sangre de productos de desecho del organismo como urea y creatinina.³
- Insuficiencia Renal Crónica (IRC) que se caracteriza por ser un daño renal lento, progresivo e irreversible secundario a diferentes etiologías. Tiene un inicio asintomático y compensatorio hasta que finalmente la tasa de filtrado glomerular disminuye casi en su totalidad y la depuración sanguínea se debe realizar

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Co-autor $\¥$: Concepción, diseño, análisis y la interpretación de los datos sobre Índice de Higiene Oral de Greene y Vermillion.

Co-autor \S : Concepción, diseño, análisis y la interpretación de los datos sobre Índice de placa de O'Leary.

mediante medios externos <<hemodiálisis o diálisis peritoneal>> o trasplante renal.³

La IRC presenta manifestaciones sistémicas:

- Cardiovasculares: siendo la hipertensión arterial la manifestación más hallada; además se puede presentar en el paciente insuficiencia cardíaca congestiva debido a la retención de sodio y agua.⁴
- Oseas: debido a la menor producción de vitamina D activa por parte del riñón y por lo tanto una menor absorción de Ca a nivel del intestino, lo cual disminuye la concentración de Ca sérico y obliga a una reabsorción ósea con el fin de mantener niveles de Ca normales.⁵
- Hematopoyéticas: causados por la disminución en la síntesis de eritropoyetina y dando origen a una anemia de tipo normocrómica y normocítica.⁴
- Hematológicas: por la acumulación sérica de compuestos nitrogenados y acidificación del pH, alteran la adhesión y agregación de las plaquetas causando alteraciones en la hemostasia y coagulación.¹
- Inmunológicas: una concentración elevada de urea, anula la respuesta de linfocitos y altera la función de los granulocitos junto con reducción de la inmunidad celular.^{1,4}
- Dermatológicas: siendo la palidez en piel y mucosas las manifestaciones clínica más frecuente ocasionadas por la anemia.⁶

Las manifestaciones bucales son inespecíficas pero entre las más frecuentes se encuentran:

- Xerostomía: dada principalmente por la restricción de líquidos, efectos secundarios de la farmacoterapia <<antihipertensivos>> y respiración bucal secundaria a problemas de perfusión pulmonar.⁷
- Palidez de mucosas: debido a disminución de eritrocitos por falta de eritropoyetina, hemorragias, menor vida de los eritrocitos y disminución en el aporte de oxígeno hacia los tejidos y por lo tanto dando una coloración parda a los tejidos.¹
- Petequias y Equimosis: los problemas hemorrágicos que se presentan en la IRC dan también lugar a la formación de equimosis y petequias ya sea en la dermis o en la mucosa, causados por el deterioro de la hemostasia y coagulación sanguínea.⁸
- Estomatitis urémica: son úlceras bucales causadas por la acumulación sérica de urea y dando lugar a una uremia, produciendo así heridas tanto a nivel de piel como en mucosas.⁹
- Enfermedad periodontal: la reabsorción ósea causada por la disminución de vitamina D junto con una mala higiene, acumulación de biofilm y cálculo

dental, son factores que además de producir inflamación gingival y periodontitis; aceleran la destrucción del hueso alveolar más rápido que en pacientes únicamente con enfermedad periodontal.¹⁰

Los niveles bajos de Ca sérico provocan una producción excesiva de hormona paratiroidea, lo cual produce una mayor movilización de Ca desde los huesos hasta la circulación sanguínea provocando así descalcificaciones y fragilidad ósea.³

La mayoría del tratamiento general abarcara el cambio estricto de la dieta del paciente, al restringir en gran parte la ingesta de líquidos, sodio y potasio; así como un control en la ingesta proteica excesiva.¹¹ Las enfermedades sistémicas acompañantes como diabetes, hipertensión, entre otras deberán ser corregidas o controladas.¹² La hemodiálisis se debe realizar cada 2 o 3 días por un tiempo aproximado de 3 a 4 horas por sesión a través de una máquina dializadora con un filtro artificial y con el objetivo de suplir la función excretora del riñón.¹³

En América Latina, durante el año 2014 la IRC ocupaba el puesto número 20 entre las 50 principales causas de muerte, con un número de *fallecidos de 27.838*. Del cual el 48.7% eran mujeres y 51.3% eran hombres.¹⁴

Al ser una enfermedad en crecimiento, el presente artículo es de un estudio transversal en el que se valoró la salud bucal de pacientes con IRC utilizando índices de morbilidad bucal, periodontograma y registro de signos en la mucosa bucal, para de esta forma el profesional de salud odontológica pueda identificar de mejor manera los signos y síntomas que pueden presentarse en esta enfermedad y así poder tener una visión más clara del proceso salud-enfermedad que genera la IRC a nivel odontológico.

II. MATERIAL Y MÉTODOS

a) Selección de Pacientes

Se seleccionaron 62 pacientes de sexo femenino y masculino, que tienen IRC y reciben tratamiento de hemodiálisis, mayores de 17 años de edad. Se seleccionó esta edad debido a que los pacientes debían legalmente ser mayores de edad <<18 años de edad>>, de acuerdo con la ley vigente del Ecuador. Los pacientes aceptados en el estudio fueron aquellos mayores de 17 años de edad y que presentaban piezas dentales tanto en el maxilar como en la mandíbula. Los pacientes excluidos del estudio fueron aquellos que presentaban ausencia total de piezas dentales, antecedentes psiquiátricos, limitada apertura bucal y menores de 18 años. Los pacientes fueron atendidos en el centro de diálisis "NEFROLOGY". Todos los pacientes fueron previamente explicados acerca del estudio y firmaron una carta de consentimiento informado.

b) *Diseño del Estudio*

Se inició con la recolección de datos sociodemográficos <<edad, sexo>> y de datos médicos <<tiempo en meses que lleva el paciente realizándose hemodiálisis>> de los pacientes a través de las historias clínicas de cada paciente, las cuales fueron autorizadas por cada participante en el estudio y fueron protegidos mediante codificación individual y única. Luego se realizó una inspección de la cavidad bucal con el objetivo de encontrar a nivel de las distintas partes que conforman la cavidad bucal, las manifestaciones bucales más usuales encontradas en pacientes con IRC. A continuación, se ejecutó el índice CPO de Klein y Palmer con el cual se contabilizó el número de piezas dentales permanentes que se encontraban cariadas, perdidas y obturadas. Junto con un periodontograma se continuó con el examen gingival para evaluar el estado periodontal en que se encontraba cada paciente. Seguidamente se entregó a cada uno de ellos una pastilla reveladora de

placacombacteriana para de este modo evaluar la calidad de cepillado dental al realizar el índice de O'Leary y por último, se evaluó la acumulación de placa bacteriana y cálculo dental por superficie dental, para valorar de este modo la calidad de higiene oral de cada paciente mediante el uso del índice de Greene y Vermillion.

III. MEDICIONES CLÍNICAS

a) *Manifestaciones Bucles*

Se realizó una observación meticulosa de cada región de la cavidad bucal, utilizando un espejo bucal plano N#5 y una gasa, siguiendo el siguiente orden: labios, carrillos, paladar duro/blando, oro-faringe, lengua, piso de boca y encías.¹⁵ Con el objetivo de encontrar manifestaciones bucales usuales en pacientes con IRC como: palidez de mucosa, petequias, equimosis, agrandamiento gingival y estomatitis urémica (Figura 1).¹

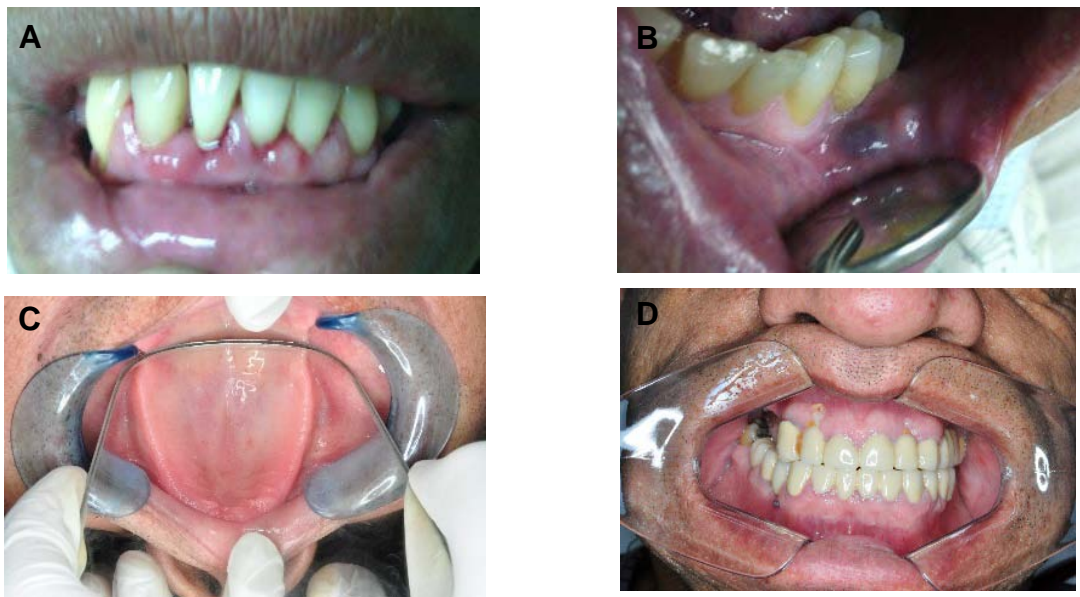


Figura 1: Manifestaciones bucales encontradas en pacientes con IRC. A) Agrandamiento gingival. B) Equimosis en labio inferior. C) Petequias en paladar. D) Palidez de mucosa en encía.

b) *Índice CPO de Klein y Palmer*

Usando un espejo bucal plano #5 y un explorador #5, se empieza por el 2^{do} molar superior derecho hasta su homólogo del lado izquierdo, prosiguiendo el examen con el 2^{do} molar inferior izquierdo hasta finalizar en el 2^{do} molar inferior

derecho.¹⁷ Finalmente, contabilizó el número de piezas dentales que han tenido alguna experiencia con caries, por lo que se obtiene las piezas dentales tanto: cariadas, perdidas y obturadas; siguiendo los parámetros establecidos para levantar el índice (Figura 2).

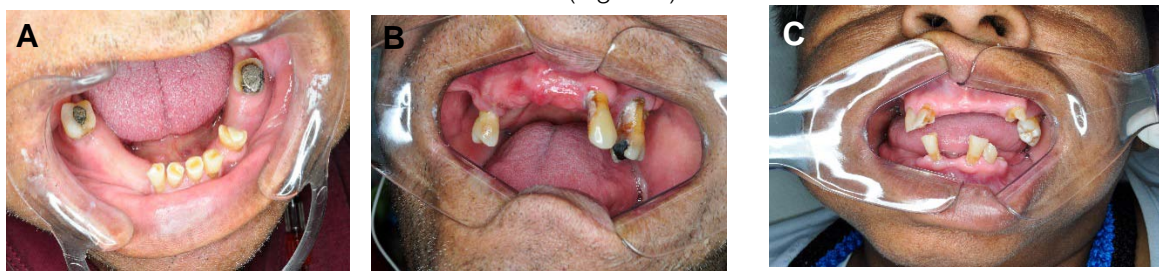


Figura 2: A) B) y C) Piezas dentales Cariadas, Perdidas y Obturadas

c) *Periodontograma*

Utilizando un espejo bucal plano #5, una sonda periodontal (PCP116 Satin Steel, Hu-Friedy) y una sonda de Nabers (P2N6 Satin Steel, Hu-Friedy) se procedió a realizar el examen periodontal e iniciando por la pieza 17 hasta 27 y del 37 al 47 tanto por

vestibular como palatino/lingual. Para un correcto diagnostico se examinó: margen gingival, profundidad de sondaje, nivel de inserción, línea mucogingival, movilidad dental y presencia de furca, para así lograr un adecuado diagnostico periodontal y siguiendo los parámetros establecidos para realizarlo (Figura 3).¹⁸

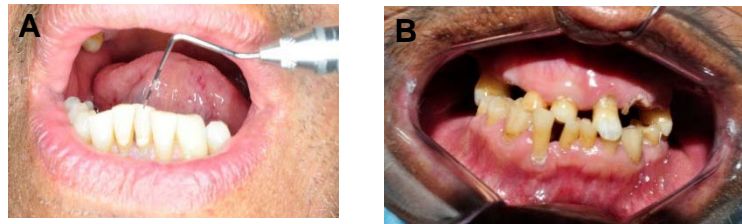


Figura 3: Evaluación periodontal. A) Uso de la sonda periodontal Hu-friedy. B) Alteración gingival.

d) *Índice de placa de O'Leary*

Se le entrego a cada paciente una pastilla reveladora de placa utilizando pastillas reveladoras de placa (Viarden), la cual se indicó masticar la pastilla y mezclarla con la saliva de su boca, luego agitarla la saliva por todas las áreas de la boca durante unos 30 segundos y al final escupir. Seguido de esto y con la ayuda de un espejo bucal plano N#5, se recorre y examina todas las superficies dentarias excepto las

superficies oclusales e incisales, con el objetivo de contabilizar el porcentaje de superficies dentarias en donde se ha impregnado el colorante de la pastilla. El examen se inició por la arcada superior desde el molar más distal hasta el molar del lado contrario para luego seguir con el segmento inferior y realizando el mismo procedimiento de acuerdo a los parámetro establecidos para levantar este índice (Figura 4).¹⁶

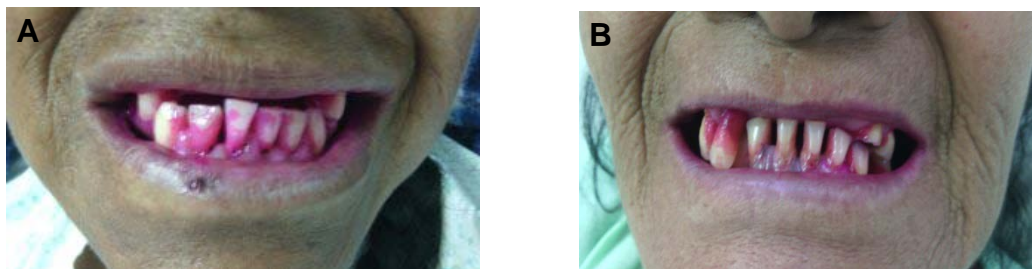


Figura 4: Índice de O'Leary. A) pigmentación de la arcada inferior. B) pigmentación superior e inferior.

e) *Índice de Higiene Oral de Greene y Vermillion*

El IHO está conformado por la valoración de dos componentes: IPDB y el IC a su vez cada uno de estos índices está basado en doce valoraciones clínicas codificadas numéricamente, las cuales representan la cantidad de placa y/o cálculo presente en las superficies bucales y linguales. La valoración se hizo por seis sextantes en total <<3 superiores y 3 inferiores>>.¹⁶

poniendo atención a la cantidad de placa que es barrida durante el recorrido, tomando en cuenta el nivel hasta donde se ha desarrollado se indicara la gravedad de la pieza. Para la valoración del IC, se realizó colocando suavemente el explorador dental en el surco gingival distal y dirigiéndolo subgingivalmente desde el área de contacto distal, al área de contacto mesial. Durante la exploración se tomó en cuenta la condición más desfavorable observada en todas las superficies de los dientes que integran el sextante en cuestión (Figura 5).¹⁶

Para el IPDB se colocó el explorador de forma paralela a la superficie dentaria, llevando acabo un desplazamiento de una cara proximal a la otra y

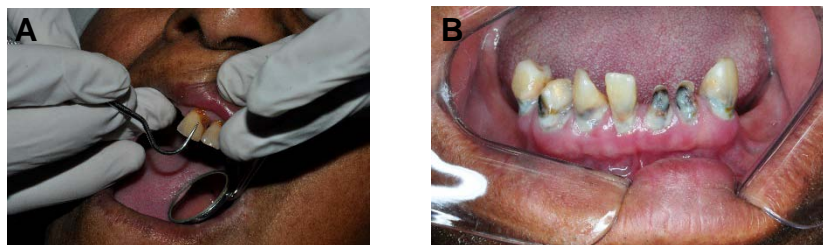


Figura 5: IHO. A) Levantamiento del índice IHO B) Acumulación de placa bacteriana en piezas dentales inferiores.

IV. ÉTICA

El estudio fue analizado en sus fundamentos metodológicos, bioéticos y jurídicos, por lo cual fue aprobado por el Subcomité de Ética de Investigación en Seres Humanos de la Universidad Central del Ecuador.

V. ANÁLISIS ESTADÍSTICO

Los datos obtenidos de las distintas evaluaciones realizadas, se analizaron mediante estadística descriptiva y tomando en cuenta tanto las variables independientes <<manifestaciones bucales, Índice CPO, Periodontograma, Índice de O'Leary y

IHO>> como dependiente<<tiempo de hemodiálisis>>se realizó la prueba χ^2 de Pearson.

VI. RESULTADOS

De los 62 pacientes incluidos en el estudio, 34 fueron de sexo femenino y 28 de sexo masculino. Fueron agrupados por edad, 4 pacientes de 18 a 33 años, 8 pacientes de 34 a 49 años, 31 pacientes de 50 a 66 años y 19 pacientes de 67 o mas años (Figura 6). Se agruparon por tiempo de hemodiálisis que llevan los pacientes, 19 pacientes de 1 a 36 meses, 18 pacientes de 37 a 60 meses y 25 pacientes de 61 a 84 meses (Figura 7).

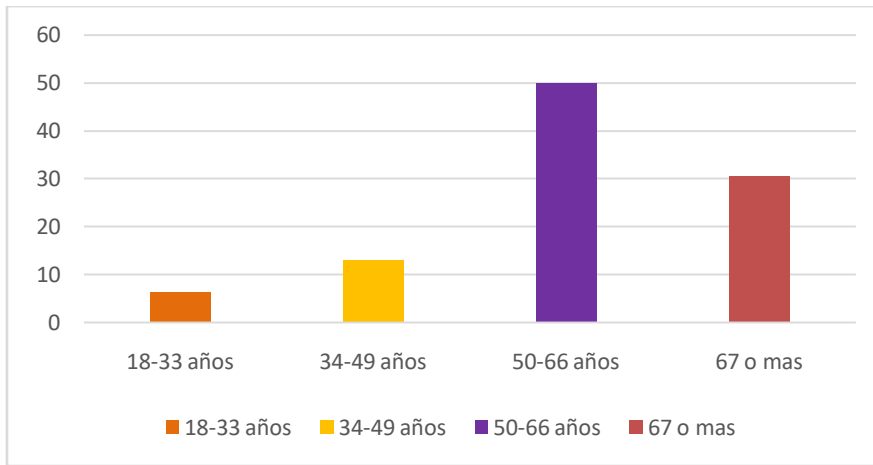


Figura 6: Porcentaje de casos por edad del paciente.

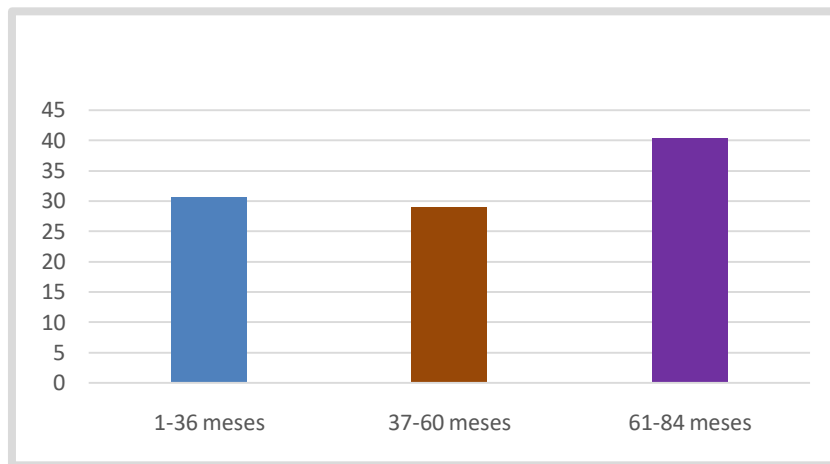


Figura 7: Porcentaje de casos por tiempo de hemodiálisis

De los 62 pacientes, 4 no presentaron manifestaciones bucales en la cavidad bucal y 59 si presentaron. La palidez de mucosa fue la que presento mayor numero de casos registrados; se localizo a nivel labios de 18 pacientes, carrillos de 22 pacientes, paladar de 41 pacientes y en encías de 33 pacientes. Las petequias fueron la segunda manifestación con mayor registro de casos en la cavidad bucal a

excepción de encia. La equimosis se presento mas casos a nivel de lengua de 15 pacientes y piso de boca de 11 pacientes (Figura 8).

Las manifestaciones bucales en paladar presentó una relación significativa $p=0,00154$ con el tiempo de hemodiálisis que llevan realizándose los pacientes.

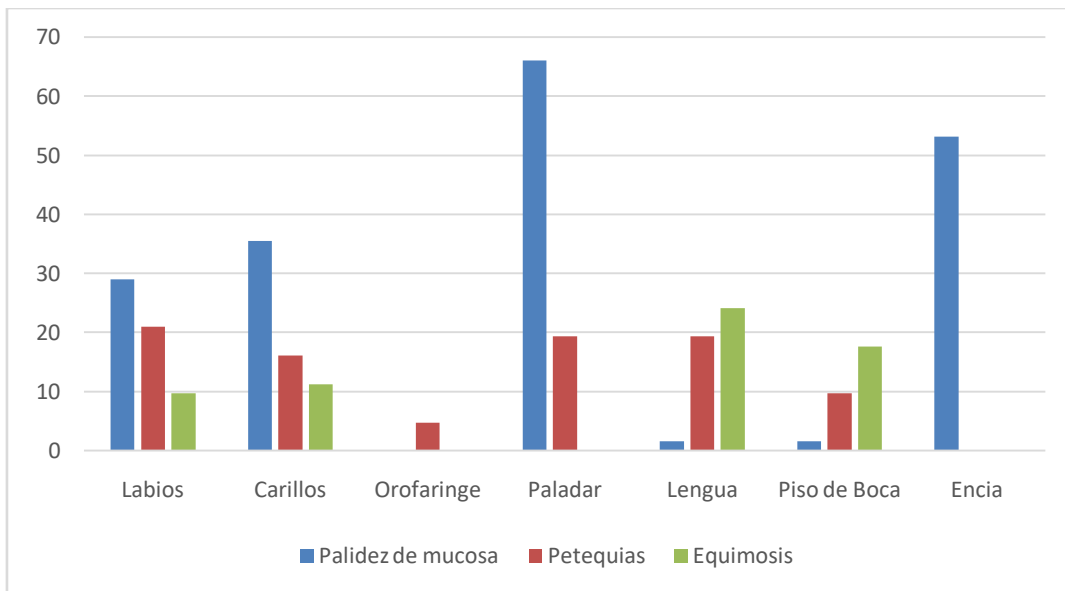


Figura 8: Porcentaje de casos por manifestaciones bucales

En el Índice CPO de Klein y Palmer, 35 pacientes presentaron de 1-5 piezas dentales con caries y 7 pacientes presentaron de 6-10 piezas cariadas. De los 69 pacientes, 38 tenían de 1-10 piezas dentales obturadas y 5 pacientes de 11-20. Los pacientes presentaron un alto número de piezas

dentales perdidas, siendo 1-10 piezas dentales perdidas la categoría con mayor número de casos registrados (Cuadro 1). Existe relación significativa $p=0.00154$, entre el Índice CPO y el tiempo de hemodiálisis.

Cuadro 1: Piezas dentales perdidas

Piezas Perdidas	Frecuencia	Porcentaje (%)
Ninguna pieza perdida	5	8.1
1-10 piezas perdidas	25	40.3
11-20 piezas perdidas	19	30.5
21-27 piezas perdidas	13	21.10

El cuadro muestra el número de piezas dentales perdidas de acuerdo al rango de gravedad, los cuales indican un gran número de piezas perdidas por lo pacientes.

En el examen periodontal, 49 pacientes presentaron periodontitis severa, 5 presentaron periodontitis moderada y 1 paciente presentó periodontitis leve, teniendo una relación significativa $p=0,0079$ con el tiempo de hemodiálisis del paciente (Figura 9). De acuerdo con la clasificación de movilidad dental de Miller, la movilidad dental de tipo I y II presentaron mayor número de casos registrados (Cuadro 2).

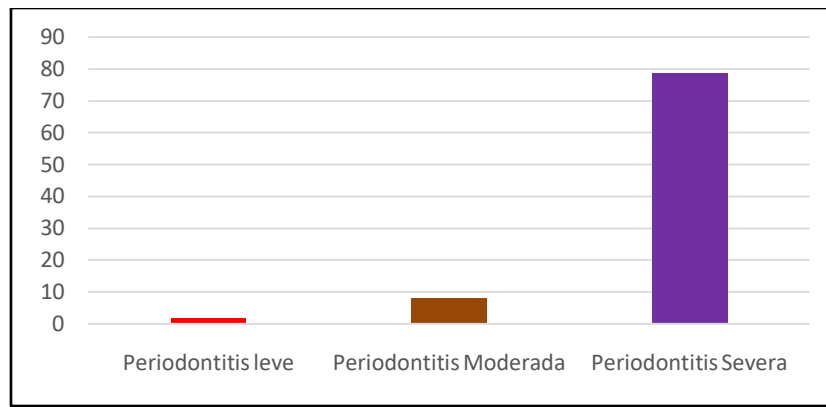


Figura 9: Porcentaje de casos de enfermedad periodontal

Cuadro 2: Movilidad Dental

Tipo de Movilidad según Miller	Frecuencia	Porcentaje (%)
Grado I	39	62.9
Grado II	15	24.20
Grado III	7	11.30

El cuadro muestra el número de piezas dentales que presentaron grado de movilidad según Miller.

En el índice de O’Leary, 61 pacientes presentaron una técnica de cepillado deficiente y 1 paciente presento un cepillado cuestionable. Sin embargo en el IHO de Greene y Vermillion, 37 pacientes

presentaron un condición de higiene oral buena y 25 pacientes como regular, ya que no presentaron altos índices de amulucacion de placa dentobacteriana y cálculo dental durante la investigación. (Cuadro 3).

Cuadro 3: IHO

Condición	Índice de Placa (%)	Índice de Cálculo (%)	Índice de Higiene Oral (%)
Bueno	21	100	59.7
Regular	64.5	0	40.3
Deficiente	14.5	0	0

El cuadro muestra los resultados encontrados en el IHO en porcentajes

VII. DISCUSIÓN

Mantener una adecuada salud dental como periodontal es indispensable para una adecuada salud bucal, con el fin de evitar procesos infecciones localizados a nivel bucal que pueden ser desencadenantes de futuras complicaciones sistémicas en pacientes vulnerables como los son los que tienen Insuficiencia Renal Crónica. Un indicador epidemiológico es un parámetro de comparación que permite evaluar la situación de salud a nivel poblacional y/o individual. En cambio, un índice epidemiológico es una unidad de medida que permite cualificar y/o cuantificar un evento epidemiológico. Los índices CPO, IHO, O’Leary junto con el examen periodontal y examen clínico de manifestaciones bucales nos permitieron conocer la realidad en cuanto a la salud oral de pacientes con IRC atendidos en el centro “NEFROLOGY”.

En nuestro estudio se incluyeron 62 pacientes diagnosticados con IRC de sexo masculino yfemenino,

además se dividieron por edad, en grupos comprendidos entre 18 a 33 años, 34 a 49 años, 50 a 66 años y 67 o mas años, donde se consideró a todos como población de estudio debido a que se estableció como objetivo el conocer el estado de salud bucal de todos los pacientes del centro “NEFROLOGY”. Los resultados de este estudio fueron valorados mediante observación directa para las manifestaciones bucales, uso de índices epidemiológicos <<CPO, HIO, O’Leary>> y periodontograma para evaluar la salud bucal de la población de estudio.

Nuestro estudio encontró relación significativa $p < 0.05$ entre el tiempo de hemodialis que ha recibido el paciente con: manifestaciones bucales en paladar, Índice CPO y enfermedad periodontal; lo que nos indica que los pacientes que han tenido mayor tiempo realizándose hemodialis tienen mayor probabilidad de tener manifestaciones a nivel del paladar, más piezas perdidas y tener procesos infecciosos a nivel periodontal.

Cobos et al¹⁹ argumentaron investigaciones realizadas por Boyce, M Path et al en 1986, indicando en sus hallazgos que pacientes con insuficiencia renal crónica existe una mayor movilidad dental, el cual relacionan a la desmineralización ósea que tiene el paciente debido a la disminución de calcio sérico. En nuestro estudio podemos corroborar lo antes mencionado, ya que nuestros pacientes también presentaron movilidads dentales y una relación directa con la enfermedad periodontal/tiempo de hemodiálisis concluyendo así en una pérdida de hueso alveolar.

Cobos et al¹⁹ describen un estudio de KHO S et al en 1999 en donde evaluaron la prevalencia de manifestaciones orales en 82 pacientes con insuficiencia renal crónica donde encontraron como signos principales a petequias y equimosis. En nuestro estudio el principal signo bucal fue la palidez de mucosa seguidos de petequias y equimosis.

Scannapieco et al²⁰ comenta acerca del estudio de Davidovich et al en 2005, donde indico que los grupos con insuficiencia renal tenían mayor inflamación gingival, profundidad de sondaje y elevada pérdida de inserción periodontal. En esta investigación sucede de la misma manera, ya que los resultados indicaron presencia de periodontitis y elevada pérdida de inserción periodontal.

Lecca et al²¹ en un estudio realizado en 119 pacientes con insuficiencia renal crónica indica que se encontró que el 80,7% presentó cálculo dental. Por el contrario en nuestra investigación los resultados de IC señalaron una condición buena y poca cantidad de cálculo dental acumulado.

Cobos et al¹⁸ resaltan un estudio realizado por Hamissi J, Porsamimi J et al en 2009 donde realizaron un estudio con 180 pacientes en Irán, donde la población tuvo un índice de placa bacteriana elevado, lo cual contrasta con los resultados del estudio donde los pacientes presentaron una buena condición en el IHO a pesar de tener una deficiencia en el cepillado dental.

VIII. CONCLUSIONES

El estudio demostró que los pacientes con Insuficiencia Renal Crónica bajo tratamiento con hemodiálisis presentaron un serio deterioro en su salud bucal. La palidez de mucosa, petequias y equimosis fueron los principales signos clínicos encontrados, siendo estos una señal clara de problemas tanto de coagulación como de aporte sanguíneo tisular; por lo que se debe tomar siempre en cuenta todas las medidas posibles durante intervenciones dentales invasivas o con probabilidad de sangrado. Los pacientes presentaron gran cantidad de piezas dentales perdidas que dan como resultado una alteración grave del plano oclusal, dimensiones verticales asimétricas, problemas durante la masticación de alimentos y en la

seguridad emocional del paciente. La periodontitis severa fue la principal enfermedad periodontal diagnosticada y por lo tanto focos infecciosos localizados con posibilidad de diseminación sistémica. También encontramos pérdida de hueso alveolar atribuida a niveles de Ca sérico bajos y niveles altos de hormona paratiroidea generando reabsorción ósea y al mismo tiempo movilidad dental, por lo que el tratamiento y mantención de la salud periodontal por parte del Periodoncista debe ser exigido para estos pacientes. Aunque la no se presencié grandes cantidades de biofilm en piezas dentales durante el Índice de Higiene Oral, la técnica de cepillado de los pacientes fue deficiente por lo que se debe buscar mejorar la técnica de cepillado y evitar futuras acumulaciones de biofilm en piezas dentales con complicaciones dentales y gingivales a largo plazo.

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Eminence Grise of the Genome: Long Non-Coding Ribonucleic Acids in Oral Squamous Cell Carcinomas

By Dr. Reshma Venugopal, Dr. Radhika Manoj Bavle,
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Abstract- Non-coding ribonucleic acids (ncRNAs) are a class of RNA molecules that are transcribed but not translated into proteins, but they affect various cellular processes. Around 60% of genes in humans do not code proteins but regulate target gene expression. Presently, a lot of research is carried out on ncRNA involvement in oral squamous cell carcinoma (OSCC) and its precursor lesions termed as oral potentially malignant disorders (OPMDs). They are broadly classified as small ncRNAs (sncRNA) and long ncRNAs (lncRNA). sncRNAs are extensively studied, whereas the divulgence of lncRNAs in OSCCs needs more revelation, hence reviewed in the present article. lncRNAs have a base pair length of more than 200, can form complex structures and influence the gene expression in a multifaceted pattern that attracts interest.

Keywords: oral squamous cell carcinoma, potentially malignant disorders, non-coding RNAs, long non-coding RNAs, competing endogenous RNA.

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Eminence Grise of the Genome: Long Non-Coding Ribonucleic Acids in Oral Squamous Cell Carcinomas

Dr. Reshma Venugopal ^α, Dr. Radhika Manoj Bavle ^σ, Dr. Sudhakara Muniswamappa ^ρ
& Dr. Soumya Makarla ^ω

Abstract- Non-coding ribonucleic acids (ncRNAs) are a class of RNA molecules that are transcribed but not translated into proteins, but they affect various cellular processes. Around 60% of genes in humans do not code proteins but regulate target gene expression. Presently, a lot of research is carried out on ncRNA involvement in oral squamous cell carcinoma (OSCC) and its precursor lesions termed as oral potentially malignant disorders (OPMDs). They are broadly classified as small ncRNAs (sncRNA) and long ncRNAs (lncRNA). sncRNAs are extensively studied, whereas the divulgence of lncRNAs in OSCCs needs more revelation, hence reviewed in the present article. lncRNAs have a base pair length of more than 200, can form complex structures and influence the gene expression in a multifaceted pattern that attracts interest.

Keywords: oral squamous cell carcinoma, potentially malignant disorders, non-coding RNAs, long non-coding RNAs, competing endogenous RNA.

I. INTRODUCTION

Oral Squamous cell carcinoma (OSCC) is a heterogenous malignancy which results in decreased survival rates due to local recurrence and lymph node metastases [1]. Various other cancers like lymphomas and certain sarcomas possess relatable gene alterations for which effective target drug therapies are developed, but due to complex genomic and epigenomic changes and interactions in OSCC, use of an effective chemotherapeutic agent is still a challenge. Recent research has now focused on epigenomic modifications that effect the gene expression rather than gene mutations to understand these complex mechanisms [2,3,4]. In context to this, non-coding ribonucleic acids (ncRNAs, previously considered as "junk or transcriptional noises") that are transcripts not translated to proteins but are potential effectors of target gene expression have gained additional interest [5,6].

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Statistics of Ensemble 1 show that around 34% of the human genome are protein-coding genes. Among which 66% of genes encode ribonucleic acids (RNAs) that are not translated into proteins [5,6]. The Encyclopedia of DNA Elements Consortium (ENCODE) revealed that humans have 60554 genes out of which 19815 are protein-coding genes, and the rest represents ncRNAs that regulate gene expression involved in vital physiological and pathological processes [4,7].

They are grouped as house-keeping ncRNAs and regulatory ncRNAs. The house-keeping RNAs include ribosomal [rRNAs], transfer RNAs [tRNAs], small nuclear RNAs [snRNAs] and small nucleolar RNAs [snoRNAs]. The regulatory ncRNAs are divided into: a) Short ncRNAs: size < 200 base pairs (bp); b) Long nc 25 RNAs (lncRNA): size > 200 bp; c) Pseudogenes; d) Circular RNAs; e) Intronic RNAs [7,5,6].

The small ncRNAs include small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), micro RNAs (mi RNAs) and transcription initiator RNAs (tiRNAs) [5,3].

There are about 16,000 lncRNA genes that encode 28,000 lncRNAs. Five types of lncRNA are identified based on the position of DNA protein-coding strands [Figure 1a] from which they are synthesized.

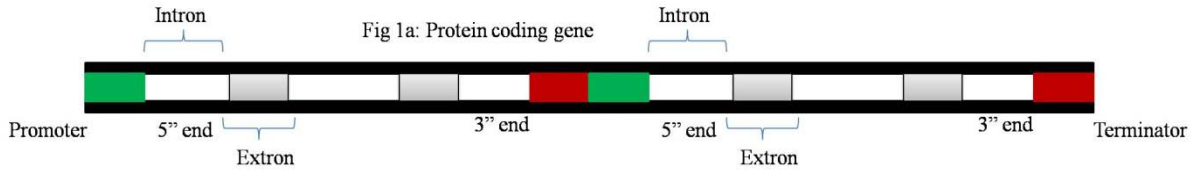


Figure 1a: Protein coding gene

They are grouped as: a) *sense lncRNAs*: overlap the nearest protein-coding genes on the same strand; b) *antisense lncRNAs*: located across the exons of protein-coding genes from the opposite strand [Figure 1b];

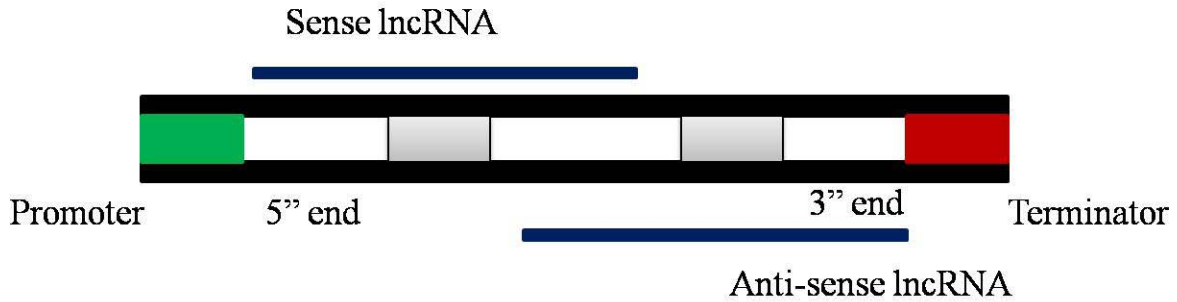


Figure 1b: Sense lncRNA on same strand overlapping the protein coding gene and antisense lncRNA on the opposite strand of protein coding gene

c) *Bidirectional lncRNAs*: transcribed on the opposite strand within 1 kilobyte (kb) from the nearest protein-coding gene [Figure 1c];

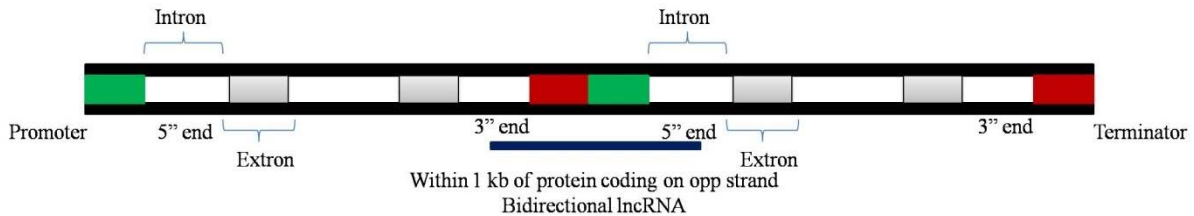


Figure 1c: Bidirectional lncRNA formed from within 1 kb of protein coding on opposite strand

d) *Intergenic lncRNAs*: located at least 1 kb far from the closest protein-coding gene, in-between the protein-coding genes [Figure 1d]. They form the largest group;

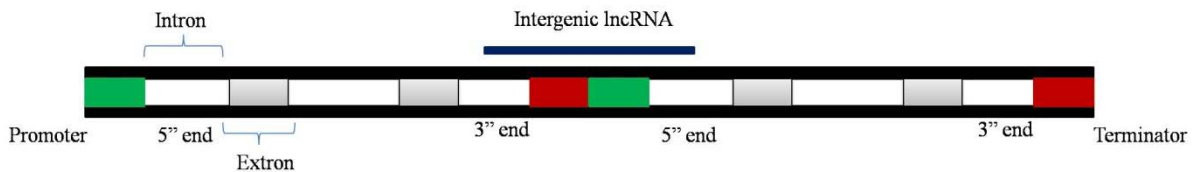


Figure 1d: Intergenic lncRNA synthesized from within 1 kb of protein coding on same strand

e) *Intronic lncRNAs*: overlapping either the sense or antisense intronic areas of the protein-coding genes (Figure 1e) [7,8,9].

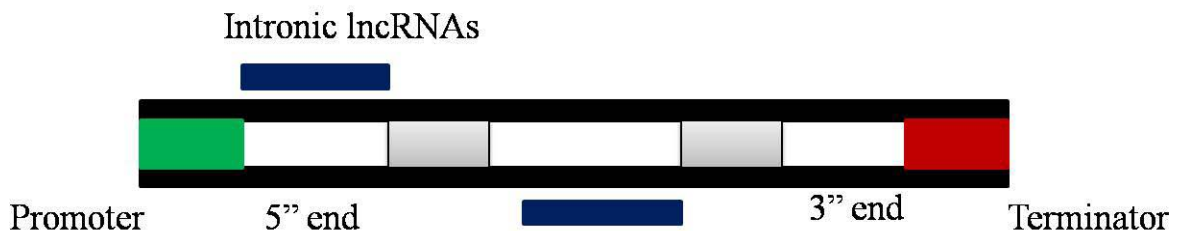


Figure 1e: Intronic lncRNA synthesized from intronic region of coding gene either same or opposite side

LncRNAs regulate gene expression through epigenetic regulation (chromatin modification & DNA methylation), transcription, and post transcription processing by acting as scaffolds, guides, decoys or

repressors, sponges serving as competing endogenous RNAs (ceRNAs) for signaling pathways, and enhancer RNAs. They are involved in pre- mRNA splicing [Table 1] [1,4, 6, 9, 7, 10, 11,12, 13].

Table 1: Actions of Long non-coding RNA

Sl no	Action type Long non-coding RNA	Function
1.	LncRNAs scaffolds	Platforms on which multiple enzymatic proteins can be transiently assembled in functional units such as ribonucleoprotein complex (RNP), heterogenous nuclear ribonucleoproteins (hnRNAs) etc. Their interaction is dynamic and exerts regulatory functions during mRNA processing.
2.	LncRNAs guides	Physically direct the RNAs to specific genomic region by binding to regulatory or enzymatically active proteins such as transcription factors, chromatin modifiers etc and regulate gene expression either in cis or trans sites.
3.	LncRNA decoys	Limit the availability of specific regulatory factors by acting as a molecular sink and sequester RNA-binding proteins, transcription factors, microRNAs, catalytic proteins and subunits of larger modifying complexes. They titrate these factors away from interacting with their native targets, decreasing their bioavailability, inhibiting their normal functions
4.	LncRNA sponges	Impair miRNAs, explained by competing endogenous RNA (ceRNA) hypothesis. According to which lncRNAs sequester miRNAs and reduce the availability of miRNA for the target mRNAs. The miRNAs play an important role in post transcriptional regulation of protein coding genes and mRNAs. LncRNAs actively compete with specific protein-coding mRNA that interact with intracellular pool of miRNAs acting as sponges or ceRNA for miRNAs, silence them and reduce the post-transcriptional activity.
5.	Signalling lncRNAs	Associated with specific signalling pathways or events such as cellular stress leading to transcription activation of specific genes.
6.	Enhancer lncRNAs	Enhance and promote gene activity by altering the 3 dimensional configuration of DNA.

LncRNAs act in nucleus or cytoplasm or both, exhibiting three types of interactions: RNA-RNA, RNA-DNA, and RNA-proteins. Their partners of communication include RNA binding proteins (RBPs), transcription factors, chromatin-modifying complexes, nascent RNA transcripts, mature mRNA, microRNA, DNA, and chromatin. [1, 7, 9, 14]

In the nucleus where they are mainly localized, they regulate epigenetics of protein-coding genes and alter their expression through chromatin remodeling complexes [such as polycomb repressive complex 2 (PRC 2), H3K9 methyl transferases] and DNA methylation patterns. They control the gene expression at the transcription level, act as decoys, bind to the DNA target sequences, act as alternative splicing regulators (antisense transcripts), are involved in splicing malfunctioning, and act as decoys for splicing [7,15]. The cis-acting lncRNAs are close to transcription site, and trans-acting lncRNAs are on distant genes of chromosomes [1].

In the cytoplasm, they interact with target mRNAs or miRNAs through miRNA response elements via base pairing. They may stabilize or decoy the target transcripts, thus promoting or repressing the translation of transcripts to proteins [7]. Cytoplasmic lncRNAs act as sponges and promote micro peptide formation [10, 16].

a) *Synthesis of LncRNA*

LncRNAs originate and are predominantly located in the nucleus. Tissue specific RNA polymerase I, II or III transcribe lncRNAs. They are 5' capped, 3' polyadenylated, have exon/intron length, and undergo splicing of multiple exons through canonical genomic splice motifs. They resemble protein-coding mRNAs, but lack or have a small number of open reading frames. The exon length of lncRNA is the same as protein-coding mRNAs but has fewer exons that are less expressed than protein-coding mRNAs. As the span of lncRNA is more than 200 bp, they can fold into more complex three dimensional structures unlike, miRNA. The complex structure of lncRNAs determines their specific interaction with transcription factors, histone and chromatin-modifying genes affecting the expression level of a broad spectrum of genes [9, 8,10,17].

b) *Functions of LncRNA*

LncRNAs affect numerous biological processes such as embryological development, stem-cell biology, development, and differentiation [6]. They are tissue or cell type-specific as indicated by gene expression profiling, possessing a varied expression to different pathophysiological conditions, and tumors. They regulate cell proliferation, survival, apoptosis, invasion, metastases, glycolysis, angiogenesis, growth, tumor-

stroma signaling or genomic stability, thus serving as potential diagnostic, prognostic biomarkers, and therapeutic targets [5,8,10,13,18,19,20].

LncRNAs are dysregulated in several neurological disorders and cancers, demonstrating both oncogenic and tumor-suppressive roles [12,21]. LncRNA Hox antisense intergenic RNA (HOTAIR), for example, functions as an oncogene in breast cancer, colorectal cancer, pancreatic cancer, etc, and increased levels are associated with reduced survival rates [20]. On the other hand, maternally expressed gene 3 (MEG3) is up-regulated in breast, hepatic cancer, and plays an oncogenic role. In contrast, it is down-regulated in tongue squamous cell carcinoma (TSCC) and plays a tumor-suppressor role [4]. The present article reviews the expression of lncRNAs in OSCC mainly, with a note on its presentation in oral potentially malignant disorders (OPMDs).

Gibb et al. state that in the normal oral mucosa 325 lncRNAs are expressed. In OPMDs, around 164 lncRNAs are aberrantly expressed. Jia et al. studied 3590 differently expressed lncRNAs in TSCC, and found that 1785 were up-regulated, and 1805 were down-regulated [3,4,22]. Yu et al. detected 1572 abnormally expressed lncRNAs with 882 up-regulated, and 690 down-regulated lncRNAs [4]. A study on head and neck squamous cell carcinoma (HNSCC) showed that 84 out of 3199 lncRNAs had an impact on survival rates of the patients [1]. Studies done by Gao et al. showed six upregulated lncRNAs such as lnc 122-PPP2R4-5, SPRR2D-1, FAM46A-1, BL2-4:1, and MBL2-4:3 (associated with high nodal status) in TSCC and two down-regulated lncRNA viz AL355149.1-1 and STXPB5-1[17].

II. LNCRNAs UPREGULATED DURING OSCC PROGRESSION

a) *LncRNA H19*

First identified long non-coding RNA, coded by gene H19 located in chromosome 11p15.5 in close association with insulin growth factor (IGF) 2 gene. LncRNA H19 is a transcription factor of the H19/IGF 2 genome blotting cluster, directly activated by c-MYC and down-regulated by p53 contributing to cell growth and proliferation [23].

The combination of H19 and enhancer of zest homolog 2 (EZH2) affects signal transduction of β -catenin/glycogen synthase kinase three beta (GSK 3 β)/epithelial- mesenchymal transition (EMT) in TSCC, promoting lymph node metastasis and poor prognosis. MiRNA-138 and 630 down-regulate EZH2 and are suppressed by lncRNA H19. Thus H19 and Hox antisense intergenic RNA (HOTAIR) can up-regulate EZH2 decreasing the E-cadherin levels, enhancing the invasive potential of SCC cells with H19 expression

being higher in metastatic tumors than non-metastatic [23].

H19 acts as a ceRNA increasing the level of miRNA lethal(let)-7a targets, a chief regulator of high-mobility group AT-hook 2 (HMGA 2) in the process of tumor metastasis. H19 / let-7a/HMGA2 / EMT axis plays a principal role in the regulation of invasion, metastasis, and is associated with poor prognosis in TSCC [4]. H19 over-expression in endothelial cells stimulated angiogenesis. H19 regulates expression of tumor growth factor (TGF)- β , which promotes cancer cell migration through enhanced adhesion with extracellular molecules. Notch and hepatocyte growth factor regulated signaling of H19.

Blocking of Notch and HGF inhibited H19. The inhibition of H19 decreased cell resistance to Fulvestrant and Tamoxifen [10,22,24]. Thus H19 plays a role in reducing the susceptibility of cells to chemotherapeutic drugs.

b) *Hox antisense intergenic RNA- HOTAIR*

HOTAIR is highly conserved nuclear lncRNA, a transcript of 2.2 kb, transcribed from the (Homeobox C) HOX C locus at chromosome 12 but functions at transit close to HOX D locus on chromosome 2 that induces silencing of transcription [3].

The domain 5' of HOTAIR binds PCR 2, which includes EZH2, SUZ 12, and EED (both polycomb proteins) to the HOX D locus and inhibits its expression. EZH2 is a histone H3 lysine 27 methyl transferase (H3K27me 3) enzyme that catalyzes trimethylation of H3K27, a histone modification associated with long-term transcription repression [23]. EZH2 is a critical epigenetic regulator for various biological processes such as cell proliferation, cell cycle, metastases, and oncogenesis [6,16].

HOTAIR prefers to occupy a guanine-adenine (GA)-rich DNA motif on chromatin, which allows direct interaction of lncRNA transcript to specific genomic sites (has both cis and trans-regulatory mechanism) [20, 23]. Also, the 3' domain of HOTAIR binds the histone demethylase lysine-specific histone demethylase (LSD)1. This evidence suggests that HOTAIR serves as a platform for two different histone modification complexes [3].

It promotes tumor cell invasion and metastasis by recruiting EZH2 and repressing E-cadherin in OSCC [11]. HOTAIR is differently expressed in the saliva of patients with OSCC with metastases and without metastases [3]. According to Dai et al., HOTAIR 7 is highly expressed in TSCC associated with cell proliferation, apoptosis, metastases, and invasion [4].

High expression of HOTAIR in laryngeal SCC is associated with tumor size greater than 0.9 cm, poor differentiation, lymph node metastasis, resistance to apoptosis, advanced clinical stages, and also drug

resistance with EZH2 serving as a potential mediator [3,8,20].

HOTAIR is highly expressed in hypoxia and regulates angiogenesis through vascular endothelial growth factor A (VEGF A) directly through its promoter sequence or by modifying the levels of glucose-regulated protein- 78 (GRP 78) and angiopoietin 2 (ANG-2) in nasopharyngeal carcinoma [10].

c) *Ferritin Heavy Chain 1 Pseudogene 3: FTH1P3*

FTHIP3 is mapped to chromosome 2p23.3 with a length of 954 nucleotides, it is ferritin pseudogene with a misannotated 3' un-translated region (UTR), which is closely associated with iron-responsive elements (IREs). It affects the post-transcriptional structured cis-acting RNA regulatory elements in the 5' or 3' UTRs of mRNAs. FTH1P3 harbors miR-224-5p cognate site, sponging miRNA 224-5p and consequently modulates the expression of frizzled class receptor five, which acts as an oncogene in OSCC. miRNA 224-5p is a potential tumor suppressor that is suppressed by FTHIP3 in OSCC, contributing to oncogenesis.

FTH1P3 is coexpressed with plasminogen activator urokinase (PLAU) and targets OSCC associated genes, including matrix metalloproteinase (MMP) 1, 3, 9, PLAU and interleukin 8 (IL 8) which are essential regulators of tumorigenesis. Ectopic and overexpression of FTH1P3 facilitates cell proliferation, colony formation, tumor progression, metastases, and worsens survival rate in OSCC cases [6,11,22,23,24].

d) *Urothelial Cancer-associated 1- UCA1*

Located on chromosome 19p13.12, UCA1 regulates the expression of various genes mainly through wingless-homeobox gene (WNT)/ b-catenin signaling pathway. The lncRNA is upregulated in OSCC, promoting cellular proliferation and tumor-lymph node-metastasis (TNM) staging. UCA1 functions as a sponge to miR-184 inhibiting it, miRNA-184, in turn, has an inhibitory effect on phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of Rapamycin (mTOR) signaling pathway. As a ceRNA, UCA 1 represses the effect of miRNA-184 promoting tumor progression, suppressing the influence of cisplatin-induced apoptosis and chemosensitivity in TSCC cells. UCA1 acts by inhibiting the cisplatin-activated PI3K/Akt signaling pathway, though, in TSCC, UCA1 promotes lymph node metastases more than cell proliferation.

In OSCC, it is co-expressed with numerous metabolism- related genes. UCA1 enhances the Warburg effect via mTOR activation followed by activation of signal transducer and activator of transcription 3 (STAT 3) and repression of miR-143. The Warburg effect results in increased hexokinase 2 (HK2) levels and a consequent increase in glycolysis.

Tonghan Zhang et al. discovered the regulation effects of UCA1/miR-124/Jagged 1 (JAG1) axis on

tongue cancer which activates Notch pathway [4,5,8,12,13,14,21,25,23].

e) *Metastases associated lung adenocarcinoma transcript 1- MALAT1*

MALAT1 or nuclear enriched abundant transcript 2 (NEAT2), is a long intergenic non-coding RNA that maps on chromosome 11q13 [23] and is 8.7 kb 203 long. It is very stable due to its triple-helical and nuclear retention element (ENE) like structure located in the nucleus and plays a role in RNA metabolism. Expression of cell cycle genes such as E2F1 transcription factors and the G1/S phase requires MALAT 1. It promotes mitosis through transcription factor B-MYB. MALAT-1 depleted cells are sensitive to p53 levels, indicating that p53 is one of the key molecules involved in the downstream effects of MALAT1.

MALAT 1 acts as a sponge to miRNA- 125 b, which upregulates STAT 3 expression promoting OSCC development. It plays a role in EMT in OSCC cells, promoting cell migration and invasion. Its knockdown suppressed N-cadherin and vimentin but induced E-cadherin expression in vitro. In a tongue cancer cell line, MALAT1 targeted miRNA-124 and promoted cancer growth through modulation of JAG1. Studies have shown that upregulated MALAT 1 induced cervical lymph node metastasis in TSCC by increasing BCL2 associated X (BAX) expression.

Upregulated MALAT 1 interacts with EZH2 inducing b-catenin expression activating Wnt/b-catenin signaling pathway, upregulating MMP-7, inducing EMT, enhancing the invasion, and inhibiting apoptosis capacity of TSCC cells. Down-regulation of apoptosis-related genes BNIP3L (pro-apoptotic BCL-2 family protein) and Neuregulin 1 (NRG1) is noted. Increased levels of MALAT 1 also incite mitogen activated protein kinase (MAPK) and PI3K/Akt.

MALAT 1 functions as ceRNA for miRNA-320a, which suppresses forkhead box M1 (FOXM1). FOXM1 is involved in new vessel growth in hypoxic conditions associated with fibroblast growth factor-2 (FGF-2) expression [4,6,14,19,21,25].

f) *Opa-interacting protein five antisense RNA 1-OIP5-AS1*

Emerges from chromosome 15q15.1 on the strand opposite to OIP5 gene and is involved mainly in the regulation of neurogenesis during development. OIP5-AS1 is an oncogene that serves as a ceRNA by sponging multiple miRNAs such as miR-340-5p, miR-217, miR-200b-3p, miR-223, miR-410, miR- 378a, and miR-338-3p. miRNA 338-3p is a tumor suppressor that modulates the expression of neuropilin 1(NRP1). NRP1 is a co-receptor for VEGF and functions as an oncogene in multiple types of cancers. OIP5-AS1 functions as miR-338-3p 'sponge' to trigger NRP1 expression and thus the progression of OSCC. Overexpression of NRP1

promotes EMT by stimulating the nuclear factor-kappa B (NF-kb) pathway.

Knockdown of OIP5-AS1 decreased the levels of NRP1 and significantly inhibited OSCC cell proliferation, migration, invasion, retarded tumor growth, and colony formation [19].

g) *Colon cancer-associated transcript-1-CCAT1-S or cancer-associated region long non-coding RNA-5-CARLO-5*

CCAT1-S is a 2628 nucleotide lncRNA located on chromosome 8q24.21. CCAT1 mediates cell proliferation by inhibiting expression of cyclin-dependent kinase (CDK) inhibitor 1A (CDK N1A) mRNA, the main regulator of G0-G1 phase by increasing the expression of p16, p21, and p27 and thus cell proliferation. Silencing of CCAT1 by siRNA leads to induction of phase 1 cell cycle arrest, increased levels of E-cadherin, and decreased levels of fibronectin and vimentin required for EMT. CCAT1 interacts with transcriptional enhancer c-MYC promoter region through chromatin looping and increases its expression. CCAT1 functions as a ceRNA for miRNA-155-5p, let-7b-5p, and miRNA-490-3p by sequestration and miRNA-218-5p by epigenetic regulation.

27% of oral tumor show overexpression of CCAT1 associated with increased expression of c-MYC; and down-regulation of miRNA-155-5p and let 7b-5p. Oral cancer patients with an increased level of CCAT1 are associated with tobacco use, poor prognosis, and aggressive phenotype [6].

h) *THOR- CG8846 gene product from transcript CG8846-RA*

IGF 2 mRNA binding protein 1 (IGF2BP1), an oncogene belongs to a conserved family of RNA-binding proteins present mainly in the cytoplasm. They bind to mRNAs that regulate protein synthesis of k-RAS, MYC gene family, CD44, phosphatase and tensin homolog (PTEN) and IGF 2. It plays a pivotal role in cell proliferation, polarization, metabolism, morphology,

differentiation, and migration. IGF2BP1 regulates the radio-/chemo-resistance of cancer cells by increasing the expression of multidrug resistance mutation 1 (MDR1).

THOR stabilizes the binding of IGF 2 mRNA with IGF2BP1. It regulates IGF2/mitogen activated kinase/extracellular signal-regulated kinases (IGF2/MEK/ERK) signal pathway in TSCC cells by increasing cell cycle-related proteins cyclin D 1 and E1. THOR functions as a negative prognostic marker by increasing cell proliferation; attenuates cisplatin sensitivity in nasopharyngeal carcinoma; regulates osteosarcoma stemness and mobility [26].

i) *Long Intergenic Non-Protein Coding RNA, Regulator of Reprogramming- lncRNA-ROR*

Located on chromosome 18q21.31, lncRNA-ROR is 2.6 kb long non-coding RNA and consists of retrotransposons elements such as long interspersed nuclear elements (LINE), short interspersed nuclear elements (SINE) and long terminal repeater (LTR) elements. The location of lncRNA-ROR is a binding site for pluripotency transcription factors such as Sox2, Oct4, and Nanog. lncRNA-ROR acts as ceRNA for miRNA 145-5p at post-transcriptional level, modulating the expression of target genes c-MYC, KI, SOX2, and Oct 4 impacting the differentiation of human embryonic stem cells. It also sponges miRNA-205 increasing the half-life of Zinc Finger E-Box Binding Homeobox 2 (ZEB2), thus promoting EMT. lncRNA-ROR is a suppressor of p53 during DNA damage by interacting with hnRNP I, thus directly inhibiting p53 mediated cell cycle arrest and apoptosis [6].

The other lncRNAs associated with OPMDs is presented in table 2 [4,27,28,29]; and OSCC progression in relation to angiogenesis in table 3 [4,6,10,18,21,23,25,29], cell proliferation in table 4 [4,15,19,23,25,27,30,31,32], metastasis in table 5 [1,4,6,8,16,18,22,25,31,33,35], and chemoresistance in table 6 [4,13,29].

Table 2: Long-coding RNAs involved in OPMDs

Sl no	Name of Lnc RNA	Function	Expression in OPMDs/OSCC
1.	Nuclear enriched abundant transcript 1-NEAT 1	Oncogene regulates miR365/ Regulator of G protein signalling 20 (RGS20) pathway and up regulates cyclin dependent kinase (CDK) 6 through miRNA-107	Over expression: transformation of OPMD to OSCC. Elevating proliferation, invasion, nodal metastases and inhibiting apoptosis in OSCC. <i>Not found in saliva.</i>
2.	Long intergenic non-protein coding RNA 974-LINC00974	Oncogene- Areca nut constituents have shown to activate the TGF-/p-Smad2 pathway mediated by LINC00974, leading to enhanced myofibroblastic activity	Higher expression: increases oral fibrinogenesis in OSF and mediates progression of OSF to OSCC.
3.	Long intergenic non-protein coding RNA 511-LINC00511	ceRNA for miRNA 765 increasing the expression of Laminin subunit gamma 2 (LAMC2), weakening the inhibitory effect of miRNA-765	High expression: Higher grades of dysplasia in leukoplakia and progression to malignancy. Increases cell proliferation and invasion in TSCC. <i>An early biomarker.</i>

Table 3: Long-coding RNAs affecting angiogenesis

1.	Hyaluronan synthase 2 antisense 1-Lnc HAS2-AS1	Marker for hypoxia	Increased HAS2-AS1 induces HIF-1a increased production of hyaluronan synthase which in turn increases EMT and OSCC tumour metastases.
2.	HIF-1a co-activating RNA- lncRNA HIFCAR	Complexes with HIF-1a, recruitment of HIF1a and p300 that target promoters in OSCC.	Complex is induced by hypoxia, stabilizing and activating HIF1-a resulting in angiogenesis
3.	Long intergenic non-coding RNA 668-LINCO 0668	Acts as a ceRNA for miRNA-297 which inhibits VEGF A promoting angiogenesis	Up regulation: Associated with cell proliferation, tumor invasion of OSCC. Knockdown suppressed tumor growth and reduced the expression of proliferation antigen ki-67
4.	FOX C1 upstream transcript-FOXCUT or long intergenic non-protein coding RNA 1379- LINC01379	Influences the expression of matrix metalloproteins (MMP) 2, 7, 9 and VEGF A	Over-expressed in OSCC, associated with cell proliferation, angiogenesis, colony formation and invasion.
5.	Long non-coding RNA MIR31	Hypoxia-inducible lncRNA and acts as HIF-1 α co-activator increasing angiogenesis	Enhanced levels are associated with poor clinical outcomes and poor prognosis in oral cancer.
6.	Long non coding RNA p 21- LncRNA-p21	Binds to hnRNP-K complex and suppresses the expression of p53 regulated genes. Induced by hypoxia inducible factor-1a (HIF 1a) directly during hypoxia, increases levels of GLUT-1 and lactate dehydrogenase in turn increasing glycolysis in cancer cells.	Up regulated in OSCC

Table 4: Long non-coding RNAs affecting Cell proliferation

1.	Colon Cancer Associated Transcript 2-CCAT2	Regulates WNT/b-catenin/ GSK-3b	Increased expression: Cell proliferation, higher grade of tumour cell and pathological stage (stage II/III) of OSCC, but does not affect metastases.
2.	Long intergenic non-protein coding RNA 939 or lncRNA RP5-916L7.2	Targets miR-328-5p and miR-939-5p	Up regulation enhances cell proliferation and inhibits cell apoptosis in TSCC.
3.	Cancer Susceptibility 9- CA SC 9	Regulation of p-AKT, p-mTOR, P62 and BCL-2	Over expression: Inhibition of apoptosis, promotes cell proliferation, increases local recurrence in OSCC cases.
4.	MYC-induced long non-coding RNA-MINCR	Oncogene: activates the Wnt/ β -catenin signalling pathway	High expression: promotes cell proliferation and regulates G0/G1 stage in OSCC.
5.	Long non-coding RNA Protein Disulfide Isomerase Family A Member 3 Pseudogene 1- LncRNA PDIA3P	Up regulates miR-185-5p target gene cyclin D2 (CCND2) by competitively sponging miR-185-5p and then activating CCND2 signalling pathways involved in cell cycle progression from G1 to S phase	Up-regulation results in OSCC cell proliferation, tumor growth, increased Ki-67 index and decreased the survival rates. <i>Prognostic biomarker</i> to distinguish patients with higher risks of OSCC progression.
6.	Long non-coding RNA Taurine upregulated gene 1-LncRNA TUG 1 & 338	Induced by higher levels of notch 1. Acts a sponge of miR-145 that regulates Wnt/b-catenin signalling pathway. TUG 338 dysregulated down stream factors STAT 1, ATK and caspase 3.	Upregulated TUG increased cell proliferation and decreased apoptosis.
7.	Long Intergenic non-coding RNA 261-LINC00261	Regulates expression of Ectonucleotide Pyrophosphatase/ Phosphodiesterase (ENPP) 4 and ENPP5 that are involved in tumor development. Low expression of ENPP2 increases reactive oxygen species level that promotes tumor cell apoptosis.	Up-regulation inhibits apoptosis. Decreased expression shows better prognosis in TSCC

Table 5: Long non-coding RNAs affecting metastases

1	HOXA transcript at the distal tip- HOTTIP	Activation of HOX A gene	High expression: advanced clinical stage, tumour size and metastases. Independent prognostic factor
2	A disintegrin and metalloproteinase with a thrombospondin type 1 motif 9 antisense 2- ADAMTS9-AS2	ce RNA for miRNA 600 which reduces EZH2 levels	Up regulation decreased miR-600 levels, increasing EZH2 function, promoting migration and invasion through TGF- β 1 mediated EMT process in TSCC. Expression being more in lymph node metastatic TSCC than non-metastatic TSCC.
3	Krueppel-like factor 8 (KLF 8) regulated Long non coding AC132217.4	KLF8 binds to the upstream sequence of AC132217.4, activating its expression and interacts with the 3' UTR of IGF2 mRNA increasing its stability, leading to increased IGF2 levels	Upregulation: promoted cell migration and EMT by upregulating IGF2, activating AKT signalling in OSCC promoting lymph node metastases.
4.	Long Intergenic Non-Protein Coding RNA 958- LINC00958	ceRNA for miRNA 185-5p, silencing YWHAZ, that promotes apoptosis and inhibits cell proliferation.	Up regulation of LINC00958 downregulates YWHAZ promoting proliferation and metastases of OSCC.
5.	Long intergenic non-protein-coding RNA 673- LINC00673	Action in OSCC yet to be determined.	Up regulation: increases tumour size, muscle infiltration, clinical stage, survival and recurrence rate in TSCC. <i>Early biomarker for OSCC.</i>
6.	Long intergenic non-coding RNA 00152- LINC00152	Binds to EZH2, silences the expression of p15 and p21 inducing tumor cell cycle progression	High expression: correlates with TSCC progression, advanced stage, relapse and invasion.
7.	Small nucleolar RNA host gene 20- LncRNA SNHG20	Regulates SNHG20/miR-197/LIN 28 axis	Over expression: higher TNM stage, lesser tumor differentiation and poor overall survival in OSCC.
8.	Long non coding RNA small nucleolar RNA host gene 1- LncRNA SNHG 12	Sponge for miR-195-5p leading to over expression of Notch2 and Hes	Up regulation: enhances cell growth, invasion and EMT in esophageal squamous cell cancer.
9.	Long non coding HNF1A antisense RNA 1-LncHNF1A-AS1	Promotes mechanical expression of Notch 1 and Hes 1	High levels associated with cell proliferation, migration and poor prognosis in OSCC.
10.	Colorectal Neoplasia Differentially Expressed-CRND E	decreases expression of miRNA 384 which targets Kristen rat sarcoma (K-RAS), cell division cycle (CDC) 42 and insulin receptor substrate 1 (IRS 1) genes	Up-regulation: Accelerates the cell cycle, promotes the proliferation and invasion in TSCC.
11.	Cancer Susceptibility 15- CA SC 15	inhibits miRNA- 33a-5p	Increased levels promotes proliferation and migration in TSCC cells
12.	Lnc GIF2IRD2P1 and Inc PDIA3F	Targets MMP 3, 9, PLAU, IL-8 and PDIA3P	Over expression: progression and metasatsets of OSCC.
13.	Lnc RNA GIHCG	GIHCG is the gene inhibitor of miR-200b/200a/429 expression and inhibits expression of miRNA 429	Up-regulation: accelerates cell cycle, promotes proliferation and metastasis in TSCC.
14.	X-inactive specific transcript-XIST	regulates oncogene E2F3 by spongeing miR-34a-5p and miR-137	Up-regulation: promotes cell growth, EMT and poor overall survival of HNSCC.
15.	Deleted in lymphocytic leukemia 1 (DLEU 1)	Increases the expression of hyaluronan synthase 3 (HAS 3) and CD 44 and interacts with HA-CD44 signalling. upregulates CDH1 that codes for E-cadherin.	Over expression: increases proliferation, migration, invasion, metastasis, xenograft formation, inhibits apoptosis and leads to progression in OSCC cells.
16.	Long intragenic non-coding RNA 312- LINC00312 or NAG7	NAG7 transcript is translated into protein—estrogen receptor repressor-10 (ERR-10) and functions as both coding and non-coding RNA	Up-regulation: inhibits proliferation (G1/S arrest) and increases cell adhesion, motility and invasion. Positively correlates with lymphnode metastases and negatively correlates with clinical stage and tumour size.

17.	Long Intergenic Non-Protein Coding RNA 460- LINC00460.	Acts as a sponge to miR-206, a tumour suppressor that down regulates AKT/ERK signalling pathway. miR-206 also regulates the expression of Stanniocalcin 2 (STC 2) which is associated with poor cancer prognosis.	High expression of LINC00460, STC2 and poor expression of miR-206 was associated with high nodal metastases in HNSCC
18	KTN1- antisense 1- KTN1-AS1or C14orf33	Acts as a ceRNA and sponges miR-153-3p which dysregulates SNAIL1 and ZEB2 involved in EMT	Up regulation promotes cell proliferation, migration, EMT and invasion in OSCC. <i>Used as a biomarker to identify high risk cases.</i>
19.	LOC541471	unknown	Up regulation results in increased lymphnode metastases and perineural invasion.
20.	RP5-894A10.6	unknown	Upregulation results in poor prognosis in OSCC cases. <i>Can be used as a biomarker to identify high risk cases of OSCC</i>

Table 6: Long non-coding RNAs affecting chemoresistance

1.	Chemotherapy-induced lncRNA 1-CILA1	Activates Wnt/b catenin pathway	High levels of CILA-1 and low levels of phosphorylated b-catenin increased cisplatin resistance in TSCC patients, promoted EMT and invasiveness.
2.	KCNQ1 overlapping transcript 1-KCNQ1OT1	Transcriptionally silences KCNQ1 locus by regulating histone methylation, ceRNA to miRNA 211-5p that regulates Ezrin (also known as cytovillin or villin-2) /focal adhesion kinase (Fak)/Src (non receptor tyrosine kinase) signalling pathway	High expression: chemoresistance in TSCC
3.	Long non coding RNA- lnc-p23154	Possess complementary sequence to miR-378a-3p promoter region. miRNA 378-3p targets 3'UTR of Glut1, inhibiting its expression & in turn glycolysis. Lnc-p23154 interacts with miR-378a-3p promoter to repress its transcription, and then increases Glut1 expression.	Over expression: Increased tumor size, clinical stage, lymph node metastasis and decreased sensitivity of phenformin in OSCC patients.

III. LNCRNAs DOWN-REGULATED DURING OSCC PROGRESSION

a) *Maternally expressed gene 3- MEG3*

Mapped to chromosome 14q32.2, MEG 3 is expressed in normal human tissues and possesses tumor suppressor properties. Its expression is lost, especially in cases of HPV-related OSCC due to gene deletion and promoter hypomethylation or hypermethylation of intergenic differentially methylated region. Decreased expression of MEG 3 results in the upregulation of the WNT pathway increasing the levels of b catenin. MEG3 increases the levels of p53 protein and regulates the downstream expression of p53 target genes. Notch 1 and Hes 1 are inhibited by MEG 3 blocking cell proliferation and metastasis.

Studies have revealed that miRNA-26a can increase the expression of MEG3 in TSCC tissues by targeting DNA methyltransferase 3B (DNMT3B) transcript inhibiting cell proliferation and triggering apoptosis. Down-regulation of MEG3 and miRNA-26a results in the increased malignant potential of OPMDs and poor OSCC prognosis [1,4,5,6,23].

b) *Nuclear 270 factor- kappa beta interacting long non-coding 271 RNA- NKILA*

NKILA helps in phosphorylation of nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor α ($I\kappa B\alpha$) and inhibits activation of NF- κB . Low levels in cancer promote EMT through TNF- α signaling and increase malignant potential in OPMDs. Reduced levels of NKILA are associated with decreased disease-free survival rates and overall survival rates [2,4,6].

c) *Long non-coding ribo-nucleic acid phosphatase and tensin homolog pseudogene 1- lnc RNA PTENP 1:*

LncRNA PTENP1 modulates PTEN expression by acting as a sponge for miRNA-17, miRNA-21, miRNA-214, miRNA-19, and miRNA-26, which suppress PTEN expression. Enhanced expression of PTEN can reverse the Warburg effect by PI3K independent or dependent mechanisms inhibiting glycolysis in cancer cells.

Decreased expression of lncRNA PTENP1 is observed in progressive OPMDs [5].

d) *Growth Arrest-Specific Transcript 5 antisense 1- GAS 5- AS1*

GAS 5 induces apoptosis, is down-regulated in HNSCC, and is associated with poor prognosis. It predicts the response to radical chemotherapy and plays an essential role in the pathogenesis of oral submucous fibrosis (OSF) and its progression to malignancy [4,3,8,22].

e) *Prostate Androgen Regulated Transcript 1- PART 1*

Located on chromosome 5q12, PART 1 functions as a ceRNA for miRNA- 301b, which regulates Nuclear Receptor Subfamily 3 Group C Member 2 (NR3C2). Down-regulated NR3C2 promotes cell proliferation, EMT, and metastases. PART1/mir-301b/NR3C2 axis may be associated with TSCC. Androgens regulate PART 1 which is a tumor suppressor. Studies have found less expression of androgen receptor (AR) mRNA in OSCC specimens compared to healthy tissues. ARs might be involved in lessening the progression of OSCC and PART 1 is regulated by androgens, PART 1 study may also be involved in the pathogenesis of OSCC [32,38].

f) *Long Intergenic Non-Protein Coding RNA 472- LINC00472*

LINC00472 acts as a sponge to miRNA-503 that regulates the expression of Gremlin 2, DAN Family BMP Antagonist (GREM2), which is an antagonist of bone morphogenetic proteins (BMP). BMP activates the Notch signaling pathway and Wnt/b-catenin signaling. Higher expression of LINC00472 is associated with a better prognosis [32].

IV. APPLICATIONS

Identification of up-regulated or down-regulated lncRNAs in the progression of OSCC is essential as their expression can be altered using appropriate RNA interference machinery such as short hairpin RNAs, miRNAs, siRNAs, oligonucleotides that are complimentary to target lncRNAs, etc. Molecule inhibitors that act by preventing the interaction of lncRNAs with the protein partners, blocking the binding or changing the secondary structure of the lncRNAs are tried. For instance, silencing of MALAT1 in TSCC, lung adenocarcinoma, cervical cancer, etc. by short hairpin RNA reduced the migration and invasive abilities of cancer cells. Blocking of MALAT1 increased the levels of miRNA 195, which decreased PDL-1 expression in B-cell lymphoma cases, decreasing apoptosis of CD 8+ cells; proliferative and metastatic abilities of the cancerous cells [39]. Down-regulation of UCA1, MALAT1, HOTAIR, and FOXCUT by using siRNAs resulted in decreased cell proliferation and increased apoptosis in OSCC [8]. lncRNAs are used as gene therapy drugs to deplete cancer stem cells or reverse their phenotype, thus

increasing their sensitivity to radiation and chemotherapy [2].

V. CONCLUSION

lncRNAs function as regulators in the conversion of OPMDs to OSCC, affect angiogenesis, cell proliferation, metastases, and predict chemoresistance. Through reverse-transcriptase polymerase chain reaction, they can be detected in plasma and saliva, and thus serve as biomarkers. Identification of PAC3 in saliva helps in early diagnosis of OSCC, salivary gland tumors, and metastatic disease [8]. Markers such as LINC00974 and NEAT 1 etc, predict the progression of OPMDs. Expression of lncRNAs such as HOTAIR, MALAT 1, etc. found in saliva can help predict metastatic status in OSCC cases. High levels of CILA 1, KCNQ10T1, etc. predict chemoresistance in OSCC cases. Studies have found that specific siRNAs are used to alter the lncRNAs, regulating their expression in OSCC cases that works for a better prognosis. These features facilitate a thought to research these lncRNAs for good treatment options.

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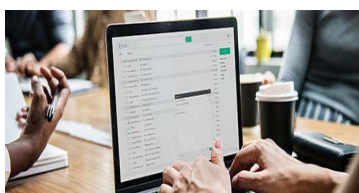
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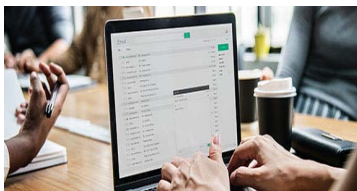
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- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
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- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

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The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

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- a) A title which should be relevant to the theme of the paper.
- b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
- c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
- d) An introduction, giving fundamental background objectives.
- e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
- f) Results which should be presented concisely by well-designed tables and figures.
- g) Suitable statistical data should also be given.
- h) All data must have been gathered with attention to numerical detail in the planning stage.

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- i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
- j) There should be brief acknowledgments.
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- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."



Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Topics	Grades		
	A-B	C-D	E-F
<i>Abstract</i>	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
<i>Introduction</i>	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
<i>Methods and Procedures</i>	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
<i>Result</i>	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
<i>Discussion</i>	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
<i>References</i>	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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