

Unveiling the Enigmas of Radicular Cysts: A New Perspective on Their Development and Progression

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ABSTRACT

Introduction: Radicular cysts can therefore be described as the most frequently encountered inflammatory odontogenic cysts which arise in response to infection and inflammation of the tooth. Nonetheless, they still rank among the most obscure concepts in oncology and as far as the particular mechanisms that congenital oncology as well as its development are concerned, these matters are still very much a topic of conjecture. It therefore follows that this study wishes to offer a new milestone of how these pathophysiological entities affects cyst formation within the radicular context given the varying inflammatory/immune markers assessments.

Materials and Methods: This case-control study included 100 participants, divided into two groups: pa control group with fifty study subjects and the second group of study subjects with radicular cysts n= 50. The following biomarkers were tested: Interleukins 1 (IL-1), interleukins 6 (IL-6), tumour necrosis factors- α (TNF- α), matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 9 (MMP-9), lipopolysaccharide (LPS), soluble receptor activator of nuclear factor kappa-B ligand (sRANKL). Certain physical and biochemical variables such as white blood cell count, haemoglobin, neutrophil, age, weight index, systolic blood pressure and diastolic blood pressure were also considered. Inferential data was tested using t-test of two samples and compared the results against a set p-value of < 0.05.

Results: In comparison to the control group, the subject group was of similar weight age, SBP, DBP and or haemoglobin. However, results got some changes in the pro and anti-inflammatory cytokines such as IL-1, IL-6, TNF- α , MMP-1, MMP-9 and LPS, sRANKL, neutrophils were found significant with p value of 0.015, 0.024, 0.031, 0.004, 0.017, 0.033 respectively.

Conclusion: In the case of radicular cysts, some of these factors have been highlighted, such as inflammatory cytokines, matrix metalloproteinases and a part of immune response. Relatively higher levels of pro-inflammatory cytokine such as IL-1, IL-6, TNF- α and MMP-3 observed in the subjects suggest inflammatory and remodelling based concept of cyst development. From these findings it will possible to do more that may enable the researcher to come up with even more refined intervention measures to control radicular cysts.

1. Introduction

Radicular cyst is a cyst of jaw which originates from rest of Malassez present in the periodontal ligament due to inflammatory process after pulp death. Radicular cyst is the most common odontogenic cyst having frequency of 52% to 68% of all the cysts affecting the jaws¹. The prevalence of radicular cyst is highest in third decade of life and is more common in men than women. They are more common in maxilla than mandible. Usually, it is a symptom less lesion of jaw but sometimes may grow slowly and represents as a symptomatic swelling visible in oral cavity². On radiograph, the radicular cyst usually appears as an oval or pear shaped unilocular radiolucency around the apex of non-vital tooth and sometimes around the lateral side of root³. It is very difficult to distinguish the radicular cyst from periapical granuloma on the basis of radiograph alone but if the radiolucent

area is greater than 2cm then it may be more likely a cyst⁴. Histologically, the radicular cyst is lined by stratified squamous epithelium which is derived from odontogenic epithelium called rest of Malassez. Radicular cyst is usually present at the apex of tooth which has become on vital after caries, pulp necrosis or physical injury⁵. It is named as apical, lateral or residual radicular cyst depending on the position of cyst in association with the involved tooth: apical radicular cyst is located around the apex of involved tooth; lateral radicular cyst is present on the lateral side of involved tooth and residual cyst develops in the jaw even after the extraction of offending tooth^{6,7}. Usually radicular cyst develops within untreated chronic periapical granuloma but all granulomas do not proceed to radicular cyst. Mostly they are associated with permanent dentition and are rarely seen in deciduous teeth (**Figure 1**).

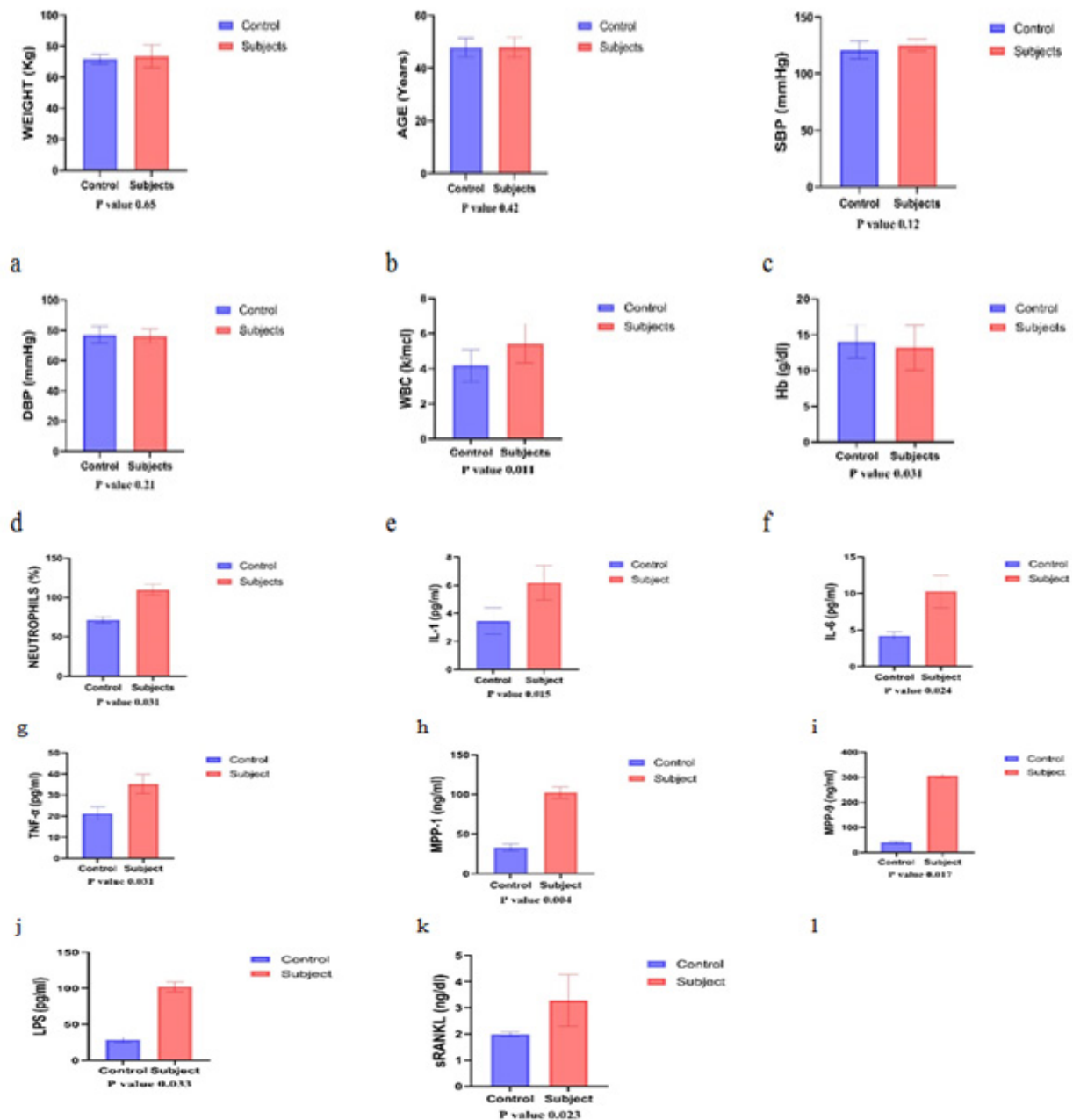


Figure 1: Role of different variables of medical importance and their potential role in the development of radicular cyst.

Initially, the oral microflora enters the tooth pulp through carious cavity but due to the local environment of root canals the gram-negative anaerobic microorganisms become predominant⁸. At a later stage, the infected pulp becomes polymicrobial community and has several pathogenic and biological properties. These microorganisms may cause mitogenic activity, antigenicity, enzymatic breakdown, chemotaxis and host defence activation⁹. The microorganisms present in the root canal system advance towards periapex releasing their products (endotoxin) and triggers the various host defence reactions consisting of activation of several

types of cells, antibodies, intercellular messengers and effector molecules¹⁰. The microbial elements and host defence system clash with each other and damage the periapical tissue causing the development of various types of periapical pathologies including radicular cyst¹¹. It is the environment of chronic periapical lesion which stimulates the development of cyst¹². Under the influence of bacterial lipopolysaccharides various pro-inflammatory cytokines, enzymes and growth factors are released around the apex of involved tooth which stimulate the rest of Malassez in periodontal ligament to form the stratified squamous epithelium lined cyst¹³. The lipopolysaccharides (LPS) and cytokines (IL-1, IL-6 and TNF- α) cause periapical bone resorption by the production of Receptor activator of NF κ B ligand (RANKL), osteoclasts, matrix metalloproteinases (MMPs) and prostaglandins resulting in cyst expansion¹⁴. The aim of this study is to investigate the role of Lipopolysaccharide, inflammatory cytokines (IL-1, IL-6, TNF- α) and Matrix metalloproteinases (MMP-1 and MMP-9) in the development of radicular cyst¹⁵⁻⁴³.

2. Materials and Methods

Fifty male patients with diagnosed radicular cyst (RC) associated with root canal failure teeth were enrolled for the present study from the period of September 2013 to November 2015. The normal pulp tissue of fifty healthy teeth extracted for orthodontic treatment served as control. Informed consent was taken from the entire participants of the study. Patients having history of antibiotic therapy in past three months or having diseases that interfere with periodontal status such as liver disease, hypertension, diabetes etc. and smokers were excluded from this study. Tissue homogenates of radicular cyst and normal pulp were prepared and stored at -70°C for the assessment of different biochemical variables. All the protocols performed in this study were approved by research ethical committee School of Pain and Regenerative Medicine (SPRM), The University of Lahore.

2.1. Analytical assays

Different biochemical assays were performed through their specific protocols. Lipopolysaccharides (LPS) were measured through spectrophotometer. Whereas, soluble receptor activator of nuclear factor Kappa- β ligand (sRANKL), interleukins (ILs) and matrix metalloproteinases (MMPs) were measured through commercially available ELISA kit methods provided by Abcam S' and Enzo Laboratories.

2.2. Statistical analysis

Independent samples t-test was also used to test the hypothesis where control group comprised 50 subjects and the subject group comprised 50 subjects. This parametric test was conducted to test hypotheses that exist as to whether the differences in the mean inflammatory markers and protein expressions in the groups were significant. The cut off point for significance was set at 0.05. Descriptive statistics were evaluated by SPSS software, version 25 and the p-value of less than 0.05 was considered biomechanical significant.

3. Results

Several clinical and biochemical markers were compared between the Control group which consisted of fifty subjects and the subject group of fifty subjects suffering from radicular cysts. The analysis of variance indicated nonsignificant p values for

weight: For the number of PVCs, the F statistic was $F(1,168) = 0.659$; for age, $F(1,168) = 0.426$; SBP $F(1,168) = 0.124$; DBP $F(1,168) = 0.216$; and Hb $F(1,168) = 0.256$. However, in the case of several markers, the difference was revealed out to be significant between the subject group and control group. In the present study, there was a significant raise in the mean count of WBC at 5.44 ± 1.11 k/mcl in the patients of radicular cyst compared to the control group with the mean count of 4.18 ± 0.912 k/mcl with p-value 0.011. The subject group also showed a higher neutrophil % $109.88 \pm 6.88\%$ as compared to the control group with mean 71.59 ± 4.29 , $p = 0.031$. Regarding acute phase reactants significant increase was found of interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α).

The levels of IL-1 in the subject group is significantly higher 6.19 ± 1.22 pg/ml than that of the control which is 3.45 ± 0.945 pg/ml 'P' value 0.015. Similarly, the IL-6 and TNF- α concentration was also found significantly high in the subjects as compared to the control group which was 10.26 ± 2.19 pg/ml and 35.26 ± 4.55 pg/ml respectively while in control subjects it was 4.22 ± 0.561 pg/ml and 21.29 ± 3.16 pg/ml respectively with $p = 0.021$. The mean concentrations MMP-1 and MMP-9 in their serum samples were significantly higher than the control group; MMP - 1 – 102.26 ± 7.44 ng/ml; MMP - 9- 306.25 ± 8.16 ng / ml; (Mean Comparisons $p = 0.004$ and $p = 0.017$). Concentration of Serum Lipopolysaccharide (LPS) in the subject group was higher than that of the control group 102.25 ± 6.69 pg/ml vs 28.25 ± 3.88 pg/ml respectively, $p \leq 0.033$. And finally, the level of sRANKL was also significantly higher in subject group (3.29 ± 0.99 ng/dl) as compare to control group (1.99 ± 0.095 ng/dl) with p value 0.023. These findings also have implications for the role of inflammatory biomarkers genes, immune effector numbers and other matrix disintegrating enzyme in radicular cyst biology.

4. Discussion

In this work, there is the identification of new knowledge on the basic inflammatory and immune processes related to radicular cysts. From the discriminant analysis of a number of biomarkers above, it can be seen that the changes of the inflammatory mediators, matrix metalloproteinases (MMPs) and other immune factors in the subject groups are significantly different from that in the control groups. These results are consistent with the emergent knowledge of the molecular pathways that mediate cyst formation and development in the kid kidneys. None of the systemic parameters such as weight, age, SBP and DBP were significantly different between control and subject groups. This means that factors such as hypertension or obesity are not directly correlated with the occurrence of radicular cysts in accordance to the cystic diseases literature⁴⁴.

But the subject group showed a highly significant increase in the count of white blood corpuscles WBC (p value = 0.011) and percentage of neutrophils (p value 0.031) suggesting an improved immunity. High WBCs and neutrophils suggest inflammation and neutrophils are relevant in the initial phase of defense and in the damage to cystic lesions⁴⁵. The significant rise in the level of interleukin-1 (IL-1) ($p = 0.015$) and interleukin-6 (IL-6) ($p = 0.024$) in the subject group reaffirms the key position of these cytokines in the inflammatory process of the radicular cysts. IL-1 is a potent pro-inflammatory cytokine which is

involved in self-promoting feedback mechanisms and stimulates osteoclastogenesis, whereas IL-6, although primarily implicated with inflammation, is also implicated with osteoclast induction and bone resorption. The current investigations have also revealed that both IL-1 and IL-6 are involved in the generation of the inflammatory milieu typically identified in PA lesions by playing the middleman roles in immune reactions and tissue remodelling^{46,47}. These data are in agreement with increased levels revealed in the present investigation, suggesting that the given cytokines facilitate the cyst enlargement by stimulating inflammation. Tumor necrosis factor-alpha (TNF- α), which was also considerably higher in the subjects ($p = 0.031$), is also one of the most perfect examples of the markers of inflammation and bone resorption. TNF- α has been investigated for its capability to stimulate osteoclast population and bone resorption in cystic and granulomatous diseases. A work by Mendes et al. (2019) also showed that TNF- α is highly expressed in periapical cysts signifying its role in the destruction of the tissue and growth of the lesion⁴⁸. As was established above, our results corroborate with this and therefore we endorse the view that TNF- α could be a target for the treatment of cystic lesions. Subject MMP-1 = 4.09 (SD \pm 1.75) and MMP-9 = 6.39 (SD \pm 2.14) were independently higher of the subject group comparing to the control group ($p = 0.004$ and $p = 0.017$ respectively). These are characterized by protease activity, which are involved in the degradation of ECM molecules with a view of exerting remodelling and expansionary effect on cystic lesions. MMP-1 (collagenase) depolymerises a form of collagen, which is a major structural protein of the ECM; tissue disintegration and cyst enlargement⁴⁹. MMP-9 (gelatinase) goes particularly to the basement membrane, which also adds to tissue degradation and tumors' penetration into the neighbouring structures.

We observed the pronounced increase of these MMPs in our study, which also corresponds to the recent investigations in which the increased MMP activity was associated with the aggressive behaviour of odontogenic cysts^{50,51}. Higher levels of LPS in the subject group ($p = 0.033$) support bacterial-induced pathogenesis of radicular cysts. LPS is a component of the outer membrane of Gram-negative bacteria, which induce strong inflammatory response through interacting with plethora of proteins, primarily through TLR4 that results in production of cytokines IL-1 and TNF- α ⁵². Studies described this bacterial component as being associated with CA strictly in terms of a source of antigens that go on to perpetuate the immune response that enables cystic lesion growth. LPS levels increased significantly in present study which is in consistent with recent finding revealing the role of microbial products in the enhancement of periapical lesions⁵³. Soluble receptor activator of nuclear factor kappa B ligand otherwise referred to as sRANKL, takes part in osteoclast differentiation and activation, which in turn results in bone resorption.

Since we noted a highly significant increase in serum sRANKL concentration in the subject group compared with that in the controls [mean 48.0, SD \pm 2.8 vs. mean 41.8 SD \pm 2.6 for the control group, $p = 0.023$], we conclude that the protein is involved in the formation of RCs. sRANKL after binding with its receptor RANK increases the activity of osteoclast precursors and stimulate bone resorption. This is evident in the process of

cystic expansion in which bone resorption enables the lesion to expand⁵⁴. Recent researches presented over a decade have proved that sRANKL is overexpressed in periapical and radicular cysts actually demonstrating its involvement in osteolytic processes. This can be hypothesized since the antagonism of the sRANKL pathway may have a therapeutic effect on the halt of cyst progression.

4.1. Pearson's coefficient correlation matrix

The results are presented in (Table 1 and Table 2) that indicates a correlation between clinical markers (weight, age, systolic and diastolic blood pressure) and biomarkers like leukocyte count, Haemoglobin, Neutrophils and other inflammatory mediators for example IL 1, IL, 6, TNF, α , MMP-1 and MMP-9, LPS and sRANKL. Correlation analysis revealed that weight had a moderate relationship with systolic BP and haemoglobin; $r = 0.425$ and $r = 0.326$ respectively; thus, weight could play a role in determining BP and Haemoglobin in patients with radicular cysts⁵⁵. These findings are in concordance with the literature recommending the need to control weight as a way to protect against hypertension as well as maintain haemoglobin levels. Nonetheless, the other cytokines like IL-1, IL-6 also known to be inflammatory markers were present in lesser intensity suggesting that weight may not play a major role inflammatory processes occur in radicular cysts⁵⁶. Age was found however to have a reasonably significant positive relationship with the systolic blood pressure with 0.325 coefficient and diastolic blood pressure with a coefficient of 0.265. This implies that there is a rise in the blood pressure with age in the patients, these finding are in line with previous findings where age has been identified as a strong predictor for hypertension⁵⁷. However, the present analysis revealed that age had displayed only low significance with inflammatory mediators such as IL-6, TNF- α etc.; it implies that, cytokine production may not necessarily be determined by age in a situation of radicular cysts. There was a high positive correlation between cytokines; IL-1, IL-6 and TNF- α respectively, IL-6 and TNF- α had very high correlation ($r = 0.958$ $p < 0.001$)⁵⁸.

Table 1: Expression of Different Variables And Their Impending Role To Develop Radicular Cyst.

VARIABLES	CONTROL (n=50)	SUBJECTS (n=50)	P-VALUE (<0.05)
WEIGHT (Kg)	71.59 \pm 3.27	73.55 \pm 7.55	0.659
AGE (Years)	47.88 \pm 3.55	48.07 \pm 3.77	0.426
SBP (mmHg)	121.19 \pm 7.99	125.46 \pm 5.48	0.124
DBP (mmHg)	76.99 \pm 5.56	76.44 \pm 4.53	0.216
WBC (k/mcl)	4.18 \pm 0.912	5.44 \pm 1.11	0.011
Hb (g/dl)	14.05 \pm 2.33	13.19 \pm 3.16	0.256
NEUTROPHILS (%)	71.59 \pm 4.29	109.88 \pm 6.88	0.031
IL-1 (pg/ml)	3.45 \pm 0.945	6.19 \pm 1.22	0.015
IL-6 (pg/ml)	4.22 \pm 0.561 10.26 \pm 2.19		0.024
TNF- α (pg/ml)	21.29 \pm 3.16	35.26 \pm 4.55	0.031
MPP-1 (ng/ml)	33.26 \pm 4.28	102.26 \pm 7.44	0.004
MPP-9 (ng/ml)	40.26 \pm 5.29	306.25 \pm 8.16	0.017
LPS (pg/ml)	28.25 \pm 3.88	102.25 \pm 6.69	0.033
sRANKL (ng/dl)	1.99 \pm 0.095	3.29 \pm 0.99	0.023

Table 2: Pearson S' Correlation Coefficients Matrix Of Different Variables And Their Impending Role To Develop Radicular Cyst.

VARIABLES	weight	age	SBP	DBP	WBC	Hb	Neut.	IL-1	IL-6	TNF- α	MPP-1	MPP-9	LPS	sRANKL
Weight		.235	.265	.425	.125	.326	.125	.265	.147	.235	.126	.234	.025	.032
Age			.265	.325	.235	.245	.152	.015	.023	.014	.023	.025	.321	.159
SBP				.625**	.184	.025	.265	.352	.014	.265	.0325	.014	.325	.235
DBP					.235	.236	.235	.235	.025	.326	.014	.235	.026	.023
WBC						.025	.526*	.011	.235	.634**	.256	.234	.214	.026
Hb							.025	.421*	.023	.525*	.235	.659*	.125	.652
Neutrophils								.235	.452	.265	.211	.235	.452	.235
IL-1									.635*	.435**	.736*	.835*	.635*	.841**
IL-6										.458*	.769**	.958***	.654*	.569**
TNF- α											.652*	.958**	.568*	.565*
MPP-1												.546**	.925*	.765**
MPP-9													.658*	.661**
LPS														.856*
sRANKL														

These relationships suggest that inflammatory processes in the development of radicular cysts are very interdependent. IL-6 also showed significant correlation with the MMPs which are MMP-1, $r = 0.769$, $p < 0.01$ and with MMP-9, $r = 0.958$, $p < 0.001$; these proteins play a major role of matrix turnover which is a key factor in cyst growth and tissue degeneration⁵⁹. We observed a significant positive correlation with matrix metalloproteinases particularly MMP-9 with various inflammatory cytokines and LPS which were IL-6 ($r = 0.958$; $p < 0.001$) and TNF- α ($r = 0.568$; $p < 0.01$). Moreover, MMP-9's positive association with sRANKL ($r = 0.856$; $p < 0.01$) support the observation that this protein is involved in bone resorption and tissue repair, essential in the formation of radicular cysts⁶⁰. Lipopolysaccharide (LPS), a bacterial endotoxin, revealed a statistically significant positive correlation with sRANKL ($r = 0.856$; $p < 0.01$); thus, bacterial infection may be involved in the activation indifferent RANKL signalling pathway in the bone resorption shown in radicular cysts. Moreover, a moderate relationship between sRANKL and other inflammation mediators including IL-1 ($r = 0.841$, $p < 0.01$) and IL-6 ($r = 0.569$, $p < 0.01$) also supports the notion that inflammation and remodelling are cardinal cystogenic events. The following clinical research variables have presented material facts, as illustrated in this correlation matrix analysis these findings attempt at establishing new-a-pert relationship between clinical variables, inflammatory markers and matrix metalloproteinases concerning the pathophysiology of radicular cysts. Such insights may help design new therapy approaches that may engage anti-inflammatory and tissue remodelling signals in order to improve the management and treatment of radicular cysts.

5. Conclusion

Altogether, it is clear from his present work that there is an intricate kinetic relationship between the inflammatory mediators among the individual bacterial components within the cysts as well as the matrix-degrading enzymes. The increased concentration of IL-1, IL-6, TNF- α , MMP-1, MMP-9, LPS and sRANKL indicate that inflammation, tissue degradation and bone resorption are the main processes that contribute to the growth of cystic lesion. These results are in consonance with recent developments in the knowledge of periapical diseases and may hold salutary therapeutic implications for the cure of radicular cysts. The current study projects the role of LPS

in the activation of inflammatory cytokines and MMPs. The raised levels of LPS in patient group might increase the levels of MMPs and cytokines resulting in the degradation of bone matrix and basement membrane which may contribute in the development of radicular cyst. The results of present study may conclude that higher levels of MMP-1 and MMP-9 are actively involved in the destruction of periapical tissue and pathogenesis of radicular cyst. This study opens a new window of opportunity for the diagnosis, monitoring and treatment of chronic periapical lesions. Further studies are required to establish the destructive role of MMPs in periapical lesions while inhibitors of matrix metalloproteinases may be of clinical use in the treatment of radicular cyst.

5.1. Declarations

5.1.1. Ethics approval and consent to participate: All the participants were informed of the purpose of the study, methods to be used, possible harms and benefits, besides any adverse effects of participating in the study were explained to the participants and the participants made their contribution willingly. All participants' identities were kept confidential and their privacy was respected; information gathered was also aggregated in order to maintain anonymity. Bottom of Form

5.2. Consent of publication

We confirm that this work represents original research and has not been published previously and is not under submission for publication elsewhere. Further, all the participants have given their informed consent for using anonymous data in publications that will emanate from this research. All names, places organizations and other details have been disguised to provide the users' anonymity and institutions' anonymity. The authors also understand and adhere to the Publication Statement of the journal and make a voluntary consent to undergo the editorial process involved in the reviewing and publishing of this piece of work.

5.3. Availability of data and materials

The datasets generated and/or analysed during the current study, titled "Unveiling the Enigmas of Radicular Cysts: The raw data or raw facts and the PowerPoint presentations, which were slides; "Perception of Their Development Journey: A New Perspective on Their Development and Progression", can be

provided by the corresponding author on request for a reasonable explanation. Any collected data pertinent to the conclusion of this study has been archived competently regarding institutional and ethical standards to safeguard the identification of the participants and integrity of data information.

For further inquiries or access to the datasets and materials, please contact:

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6. Conflict of interest

Authors declare no conflict of interest.

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8. Author's contributions

Conception and design of the study: AM and MW. Acquisition of data, analysis and interpretation of data: JI, AZ and MW. Drafting the article: AM, JI, MW, AZ. Revising the article critically for important intellectual content: AM, JI, MW, AZ. Final approval of the version to be submitted: AM and MW. All authors contributed equally and have read and agreed to the published version of the manuscript.

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