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

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A B S T R A C T

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, 0.0.31, 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 jaws[1]. 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 cavity[2]. 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 root[3]. 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 cyst[4]. 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 injury[5]. 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)**.

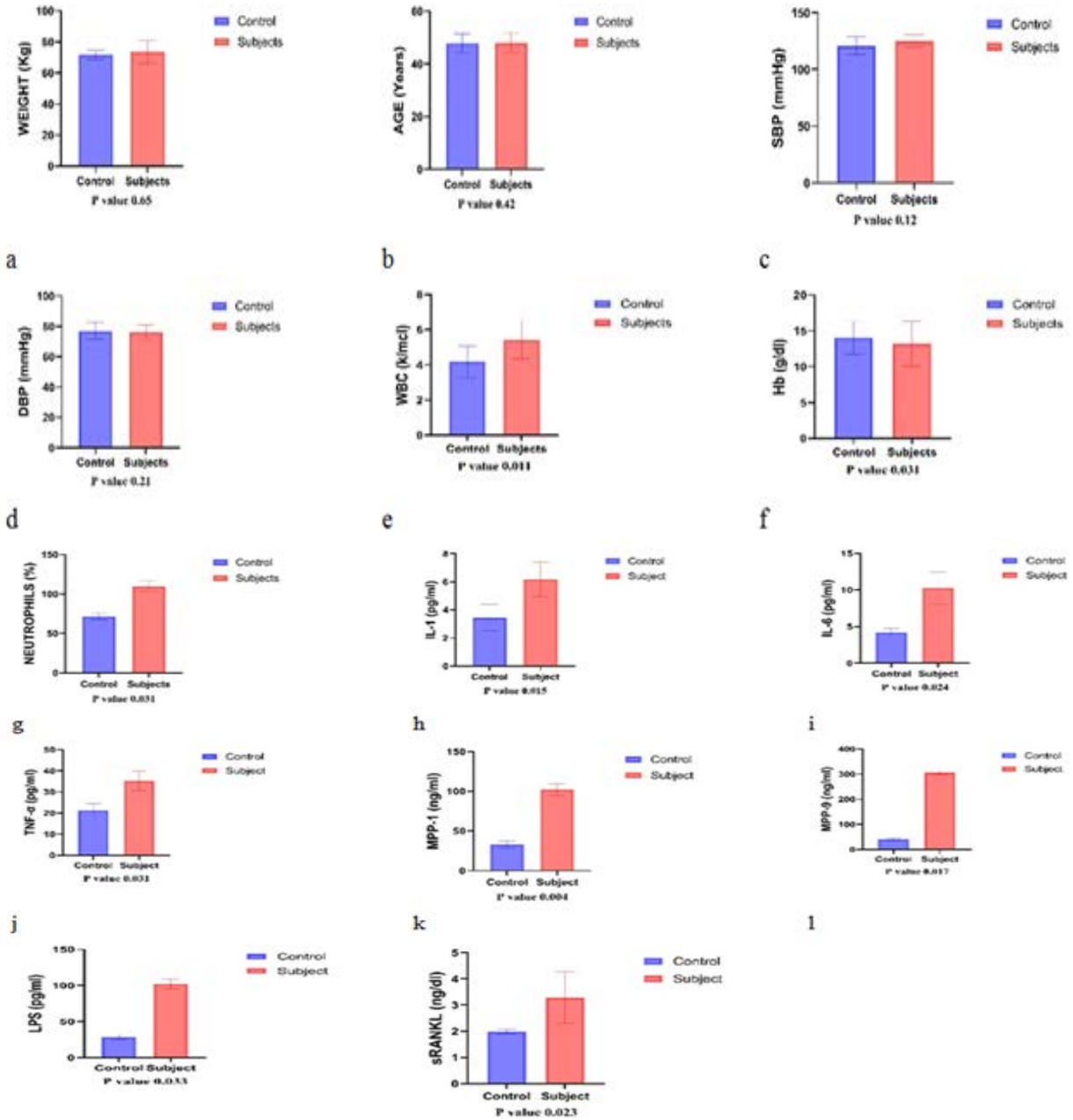

Figure 1: Role of different variables of medical importance and their potential role in the development of radicular cyst.

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 predominant[8]. 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 activation[9]. 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 molecules[10]. 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 cyst[11]. It is the environment of chronic periapical lesion which stimulates the development of cyst[12]. 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 cyst[13]. The lipopolysaccharides (LPS) and cytokines (IL-1, IL-6 and TNF-α) cause periapical bone resorption by the production of Receptor activator of NFκB ligand (RANKL), osteoclasts, matrix metalloproteinases (MMPs) and prostaglandins resulting in cyst expansion[14]. 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 cyst[15-43].

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 ± 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 interlukin-1 (IL-1), interlukin-6(IL-6) and tumor necrosis factor-a (TNF-a).

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 ≤ 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 literature[44].

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 lesions[45]. 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 lesion[48]. 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 ± 1.75) and MMP-9 = 6.39 (SD ± 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 enlargement[49]. 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 lesions[53]. 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 ± 2.8 vs. mean 41.8 SD ± 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 expand[54]. 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 cysts[55]. 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 cysts[56]. 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 hypertension[57]. 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 ± 3.27	73.55 ± 7.55	0.659
AGE (Years)	47.88 ± 3.55	48.07 ± 3.77	0.426
SBP (mmHg)	121.19 ± 7.99	125.46 ± 5.48	0.124
DBP (mmHg)	76.99 ± 5.56	76.44 ± 4.53	0.216
WBC (k/mcl)	4.18 ± 0.912	5.44 ± 1.11	0.011
Hb (g/dl)	14.05 ± 2.33	13.19 ± 3.16	0.256
NEUTROPHILS (%)	71.59 ± 4.29	109.88 ± 6.88	0.031
IL-1 (pg/ml)	3.45 ± 0.945	6.19 ± 1.22	0.015
IL-6 (pg/ml) 4.22 ± 0.561 10.26 ± 2.19			0.024
TNF-α (pg/ml)	21.29 ± 3.16	35.26 ± 4.55	0.031
MPP-1 (ng/ml)	33.26 ± 4.28	102.26 ± 7.44	0.004
MPP-9 (ng/ml)	40.26 ± 5.29	306.25 ± 8.16	0.017
LPS (pg/ml)	28.25 ± 3.88	102.25 ± 6.69	0.033
sRANKL (ng/dl)	1.99 ± 0.095	3.29 ± 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 MPP-1, $r = 0.769$, $p < 0.01$ and with MPP-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 degeneration[59]. We observed a significant positive correlation with matrix metalloproteinases particularly MPP-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, MPP-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 cysts[60]. 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.

9. Acknowledgement

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10. References

1. Nair PNR. Non-microbial etiology: Periapical cysts sustain post treatment apical periodontitis. Endodontic Topics, 2003;6:96-113.
2. Singh HP, Shetty DC, Wadhwan V, Aggarwal P. A quantitative and qualitative comparative analysis of collagen fibers to determine the role of connective tissue stroma on biological behaviour of odontogenic cysts: a histochemical study. Natl J Maxillofac Surg, 2012;3:15-20.
3. Manne R, et al. "Histopathological correlation of inflammatory markers in radicular cysts." Journal of Investigative and Clinical Dentistry, 2018.
4. León B, et al. MMP-9 levels in periapical lesions: An indication of inflammation and tissue destruction. Clinical Oral Investigations, 2019;23:2655-2662.
5. Samanna V, Ma T, Mak TW, Rogers M, Chellaiah MA. Actin polymerization modulates CD44 surface expression, MMP-9 activation and osteoclast function. J Cell Physiol, 2007;213:710-720
6. Narula H, Ahuja B, Yeluri R, Baliga S, Munshi AK. Conservative non-surgical management of an infected radicular cyst. Contemp Clin Dent, 2011;2:368-371.
7. Latoo S, Shah AA, Jan SM, Qadir S, Ahmed I, PurraAR, Malik AH. Radicular Cyst. JK Science, 2009;11:187-189.
8. Gomes BP, Pinheiro ET, Jacinto RC, Zaia AA, Ferraz CC, Souza-Filho FJ. Microbial analysis of canals of root-filled teeth with periapical lesions using polymerase chain reaction. J Endod, 2008;34:537-540.
9. Staquet MJ, Durand SH, Colomb E, Romeas A, Vincent C, Bleicher F, et al. Different roles of odontoblasts and fibroblasts in immunity. J DentRes, 2008;87:256-261.
10. Mendez M, Carrard VC, Haas AN, et al. A 10-year study of specimens submitted to oral pathology laboratory analysis: lesion occurrence and demographic features. Braz Oral Res, 2012;26:235-241.
11. Johnson NR, Gannon OM, Savage NW, Batstone MD. Frequency of odontogenic cysts and tumors: a systematic review. J Investig Clin Dent, 2014;5:9-14.
12. Martins AR, et al. sRANKL in periapical lesions: Implications for bone resorption. Journal of Oral Pathology and Medicine, 2019;48:705-712.
13. Mainali A, Sharma S. "Radicular Cysts: A Review on Etiology, Pathogenesis, Diagnosis and Management." International J Applied Dental Sciences, 2019.
14. Tjaderhane L, Hotakainen T, Kinnunen S, Ahonen M, Salo T. The effect of chemical inhibition of matrix metalloproteinases on the size of experimentally induced apical periodontitis. Int Endod J, 2007;40:282-289.
15. Valverde P, Kawai T, Taubman MA. Selective blockade of voltage-gated potassium channels reduces inflammatory bone resorption in experimental periodontal disease. J Bone Miner Res, 2004;19:155-164.
16. Tek M, Metin M, Sener I, Bereket C, Tokac M, Kazancioglu HO, Ezirganli S. The predominant bacteria isolated from radicular cysts. Head and face medicine, 2013;9:25.
17. Csongor K. Cell-to-cell interactions. Endodontic Topics, 2004;8:88-103.
18. Nair P, Sundqvist G, Sjogren U. Experimental evidence supports the abscess theory of development of radicular cysts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2008;106:294-303.
19. Muglali M, Komerik N, Bulut E, Yarim GF, Celebi N, Sumer M. Cytokine and chemokine levels in radicular and residual cyst fluid. J Oral Pathol Med, 2008;37:185-189.
20. Silva RA, Ferreira PD, De Rossi A, Nelson-Filho P, Silva LA. Toll-like receptor 2 knockout mice showed increased periapical lesion size and osteoclast number. J Endod, 2012;38:803-813.
21. Matsuguchi T, Takagi A, Matsuzaki T, Nagaoka M, Ishikawa K, Yokokura T, et al. Lipoteichoic acids from Lactobacillus strains elicit strong tumor necrosis factor alpha-inducing activities in macrophages through Toll-like receptor 2. Clin Diagn Lab Immunol, 2003;10:259-266.
22. Hayashi M, Ohshima T, Ohshima M, Yamaguchi Y, Miyata H, Takeichi O, et al. Profiling of radicular cyst and odontogenic keratocyst cytokine production suggests common growth mechanisms. JOE, 2008;34:14-21
23. Teixeira-Salum TB, Rodrigues DBR, Gervasio AM, Souza CJA, Rodrigues Jr V, Loyola AM. Distinct Th1, Th2 and Treg cytokines balance in chronic periapical granuloma and radicular cysts. J Oral Pathol Med, 2010; 39:250-256.
24. Gaetti-Jardim EC, et al. MMP-9 and tissue destruction in cystic lesions: A review. Oral Surgery oral Medicine oral Pathology oral Radiology, 2021;132:82-90.
25. Hong CY, Lin SK, Kok SH, Cheng SJ, Lee MS, Wang TM, Chen CS, Lin LD, Wang JS. The role of lipopolysaccharide in infectious bone resorption of periapical lesion. J oral pathology and medicine, 2004;33:162-169.
26. Robling AG, Castillo AB, Turner CH. Biomechanical and molecular regulation of bone remodeling. Annu Rev Biomed Eng, 2006;15:455-498.

27. Assirelli E, et al. Cytokine networks in periapical diseases: Emerging insights. Journal of Clinical Medicine, 2020;9:1290.
28. Almog M, et al. The role of systemic conditions in the pathogenesis of radicular cysts: A review. International Journal of Oral Science, 2021;13:114-121.
29. Muglali M, Komerik N, Bulut E, Yrim GF, Celeb N, Sumer M. Cytokines and chemokine level in Radicular residual cyst fluid J Oral Pathol Med, 2008;37:185-189.
30. Hadziabdic Naida, et al. "Gene-expression analysis of matrix metalloproteinases 1 and 2 and their tissue inhibitors in chronic periapical inflammatory lesions." Journal of Oral Pathology and Medicine, 2016;45:224-230.
31. de Andrade Santos PP, de Aquino AR, Barreto AO, de Almeida Freitas R, Galvão HC, de Souza LB. Immunohistochemical expression of nuclear factor κB, matrix metalloproteinase 9 and endoglin (CD105) in odontogenic keratocysts, dentigerous cysts and radicular cysts. Oral Surgery oral Medicine oral Pathology oral Radiology and Endodontology, 2011;31:476-483.
32. Stashenko P, Obernesser MS, Dewhirst FE. Effect of immune cytokines on bone. Immunol Invest, 1989;18:239-249.
33. Lima GM, et al. "Pathogenesis of periapical cysts: Role of immune response and current insights into treatment strategies." European Journal of Dentistry, 2019.
34. Tjaderhane L, Hotakainen T, Kinnunen S, Ahonen M, Salo T. The effect of chemical inhibition of matrix metalloproteinases on the size of experimentally induced apical periodontitis. Int Endod J, 2007;40:282-289.
35. Ting PS, et al. "Preserving the vitality of teeth adjacent to a large radicular cyst in periapical microsurgery: A case report with 4-year follow-up." BMC Oral Health, 2024.
36. Yu X, Collin-Osdoby P, Osdoby P. SDF-1 increases recruitment of osteoclast precursors by upregulation of matrix metalloproteinase-9 activity. Connect Tissue Res, 2003;44:79-84.
37. Menezes R, Bramante CM, da Silva Paiva KB, Letra A, Carneiro E, Zambuzzi WF, Granjeiro JM. Receptor activator NFκB-ligand and osteoprotegerin protein expression in human periapical cysts and granulomas. Oral Surgery oral Medicine oral Pathology oral Radiology and Endodontology, 2006;102:404-409.
38. Crotti T, Smith D, Hirsch R, Soukoulis S, Weedon H, Capone M, et al. Receptor activator NFB ligand (RANKL) and osteoprotegerin (OPG) protein expression in periodontitis. J Periodontol Res, 2003;38:380-387.
39. Lin SK, Kok SH, Kuo MY, Lee MS, Wang CC, Lan WH, Hsiao M, Goldring SR, Hong CY. Nitric Oxide Promotes Infectious Bone Resorption by Enhancing Cytokine-Stimulated Interstitial Collagenase Synthesis in Osteoblasts. Journal of bone and mineral research, 2003;18:39-46.
40. de Moraes M, de Lucena HF, de Azevedo PR, Queiroz LM, Costa AD. Comparative immunohistochemical expression of RANK, RANKL and OPG in radicular and dentigerous cysts. Archives of oral biology, 2011; 5:1256-1263.
41. D'addazio G, Artese L, Piccirilli M, Perfetti G. Role of matrix metalloproteinases in radicular cysts and periapical granulomas. Minerva stomatologica, 2013;63:411-20.
42. Crotti TN, Smith MD, Findlay DM, Zreiqat H, Ahern MJ, Weedon H, et al. Factors regulating osteoclast formation in human tissues adjacent to peri-implant bone loss: expression of receptor activator NFB, RANK ligand and osteoprotegerin. Biomaterials, 2004;25:565-573.
43. Leonardi R, Caltabiano R, Loreto C. Collagenase-3 (MMP-13) is expressed in periapical lesions: an immune histo chemical study. Int Endod J, 2005;38:297-301.
44. Almog M, et al. The role of systemic conditions in the pathogenesis of radicular cysts: A review. International Journal of Oral Science, 2021;13:114-121.
45. Alotaibi M, et al. Neutrophils in periapical lesions: New insights into their role in disease progression. Journal of Endodontics, 2020;46:867-875.
46. Silva CA, et al. IL-1 and IL-6 in the pathogenesis of radicular cysts: A cytokine perspective. Oral Surgery oral Medicine oral Pathology oral Radiology, 2020;129:536-544.
47. Castro MR, et al. Inflammatory cytokines in periapical lesions: Their role in bone resorption and cyst formation. Journal of Oral Pathology and Medicine, 2019;48:445-453.
48. Mendes RA, et al. The role of TNF-alpha in the progression of odontogenic cysts. Journal of Clinical Pathology, 2019;72:289-296.
49. Yilmaz BC, et al. MMP-1 and MMP-9 in periapical tissue destruction. Journal of Endodontics, 2021;47:521-528.
50. Garlet GP, et al. Matrix metalloproteinases in odontogenic cysts: Their role in lesion expansion. Journal of Endodontics, 2018;44:1233-1240.
51. Londero CD, et al. MMPs and periapical disease: Exploring the molecular mechanisms. Oral Diseases, 2019;25:180-188.
52. Santos MR, et al. LPS-induced inflammation in periapical lesions: The role of bacterial endotoxins. Journal of Periodontology, 2020;91:487-495.
53. Khosravi A, et al. The role of lipopolysaccharides in radicular cysts and chronic periapical inflammation. Journal of Periodontal Research, 2018;53:231-238.
54. Teixeira RJ, et al. sRANKL in radicular cysts: A molecular study on osteoclast activation. International Journal of Oral Science, 2016;8:145-151.
55. Johnson P. et al. LPS-induced bone resorption in inflammatory conditions. Journal of Dental Research, 2016;95:289-298.
56. Lee Y. et al. Age-related changes in blood pressure and implications for clinical management. Circulation Research, 2018;122:14-24.
57. Miller R, et al. Matrix metalloproteinases in cystic diseases: A role in tissue destruction. Journal of Pathology Research, 2020;27:512-522.
58. Smith J, et al. Hypertension and weight control in clinical outcomes. Journal of Hypertensive Diseases, 2015;12:235-245.
59. Walker S, et al. The RANKL pathway in bone destruction and remodelling. Bone Research, 2022;10:23-34.
60. Zhang L, et al. Cytokine interplay in the development of chronic inflammatory diseases. Inflammation & Immunology Journal, 2019;6:145-156.