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CORRELATION BETWEEN PERIAPICAL CHOLESTEROL, SERUM LOW DENSITY LIPOPROTEINS AND HIGH-SENSITIVITY C REACTIVE PROTEIN LEVELS: A HISTO-BIOCHEMICAL ANALYSIS

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ABSTRACT

Aim

Periapical cholesterol crystals (PCC) have been implicated in refractory periapical pathological processes and untoward healing with a yet unidentified mechanism of cholesterol crystallization. There also exists a knowledge gap regarding the association of PCC with hyperlipidaemia. Recently, studies have proposed a similar mechanism of cholesterol crystallization in periapical region as of atherosclerosis. Thus aim of the present study is to correlate the presence of PCC with levels of established markers of atherosclerosis namely low density lipoproteins (LDL) and high-sensitivity C-reactive protein (hsCRP).

Methods

31 consenting patients of the age group 30 - 65 years, requiring surgical endodontic management were included. Pre-surgically, all patients were advised routine haematological investigations that included a hsCRP assay and LDL test. Subsequently, all patients underwent endodontic treatment followed by periapical curettage. The curetted tissues were subjected to histological examination to detect cholesterol crystals. The existence of cholesterol crystals was correlated with serum values of LDL and hsCRP.

Results

In the present study, patients with PCC neither exhibited elevated LDL nor elevated hsCRP values. Statistical analysis performed using Pearson Correlation Coefficient showed no significant correlation between PCC and serum LDL (p value 0.579) and also between PCC and serum hsCRP (p value 0.540) values.

Conclusion

The correlation between PCC, serum LDL and hsCRP values was insignificant. Authors also propose that mechanism of cholesterol crystallization in periapical lesions may not be similar to that of atherosclerosis as there was no observed elevation of its established markers.

KEYWORDS : : atherosclerosis, inflammation, cardiovascular disease, endothelium,, lipids, pulpitis.

Introduction

Refractory periapical lesions (RPL) are an enigma, which needs to be completely understood to resolve the pathology. Nair had enumerated etiological processes for RPL, one among which is presence of PCC [1]. The incidence of PCC in odontogenic pathosis is between 18-44% [2]. Owing to the use of fat solvents in histological processing, PCC appear as clefts. Routine nonsurgical endodontic treatment is unlikely to resolve these crystals existing in the periapical area [3].Although its presence has been observed for a long time, the significance of PCC is yet to be fully appreciated [4]. Nevertheless, to the best of authors' knowledge, no study has correlated PCC with systemic diseases.

Atherosclerosis or atherosclerotic vascular disease is a condition characterized by chronic vascular inflammation and associated endothelial dysfunction. In a chronically inflamed state, vascular endothelium expresses several types of adhesion molecules that are chemotactic to monocytes. The recruited monocytes enter the intima and engulf excess modified LDL following which phagolysosomal damage ensues resulting in leakage of the contents into cytoplasm. Consequently cytokines, the key mediators of chronic vascular inflammatory response, come into play producing a low grade vascular inflammation which is crucial for initiating the atherosclerotic process [5]. This low-grade chronic vascular inflammation (assessed by hsCRP assay) and elevated levels of serum LDL are essential for atherosclerotic plaque stability [6].

A comprehensive assessment of chronic apical periodontitis (in which PCC exists) and atherosclerosis has revealed certain common factors. Both the conditions exhibit presence of foamy macrophages, increased incidence in elderly people [7], control of disease progression with statins [8,9,10] and Presence of cholesterol crystals (in both periapical lesions and atherosclerotic plaque). Furthermore, Slutzky-Goldberg et al 2013, had proposed that the mechanism of cholesterol crystallization in periapical lesions could be similar to that of atherosclerosis. Also Glodny et al. 2013, had positively correlated chronic apical periodontitis and aortic atherosclerotic burden using whole-body computed tomographic examination [11].

Therefore, the present study aims to correlate the presence of PCC with atherosclerotic markers i.e. serum LDL and hsCRP levels.

Methodology

Ethical clearance to this study was issued by Institutional Review Board of Ragas Dental College and Hospital, Chennai, India. The study was performed in accordance to the Declaration of Helsinki, 2007 and written consent was obtained from all participating subjects. 31 consenting adults of the age group 30 -65 years, requiring surgical endodontic therapy of maxillary or mandibular anterior tooth/teeth were included. Patients with uncontrolled diabetes mellitus, hypertension, established history of ischaemic heart disease, bleeding disorders or other conditions contraindicating surgical endodontic therapy, were excluded from the study.

Pre-surgical haematological investigations, inclusive of hsCRP and LDL tests, were performed one week prior to surgical intervention, performed at nearby private laboratory. hsCRP assay was done by immunoturbidimetric method and lipid profiles measured using CHOD-POD enzymatic method. Pre-surgical radiographs were procured. Endodontic treatment was initiated, canals were cleaned, shaped(with Mani K type files and 5% sodium hypochlorite irrigant),

obturated(Densply GP 2%taper) using lateral compaction technique and subsequently periapical curettage followed by apicoectomy was performed in a single visit. Full thickness mucoperiosteal flaps were elevated and bony defect was located. Window opening was created using osteotomy burs (SSW HP-701, SSW HP-8) with copious saline irrigation. Periapical tissue was curetted and immediately placed in formalin for fixation. Flaps were repositioned and sutured using non-absorbable black braided silk sutures ((ETHICON).

The samples were histologically processed in the Department of Oral & Maxillofacial Pathology, Ragas Dental College. Initial grossing procedure followed by subsequent placement of samples in varying concentrations of alcohol (60%,70%,80%,90%,100%), xylene(4 stations) and paraffin wax(2 stations) was performed. The prepared soft tissue blocks were sectioned using soft tissue microtome and stained with Eosin and Hematoxylin stains [12]. 10x and 40x magnifications were used for identification of PCC.

The results were tabulated and statistically analysed using Pearson correlation coefficient.

Results

Among the 31 periapical specimens studied, four specimens exhibited PCC (an incidence of 12.5%)[FIGURE 1] out of which two specimens also displayed haemosiderin pigment. Two patients who had elevated serum levels of LDL revealed concomitant presence of foamy macrophages in their periapical specimen [FIGURE 2]. Neither patients with elevated LDL exhibited PCC nor any patients with PCC showed elevated serum LDL levels.S In all the 31 cases, hsCRP findings were within the normal range. Statistical analysis revealed no correlation between PCC and serum LDL (p value 0.579), serum hsCRP (p value 0.540) values.

Discussion

The origin of periapical cholesterol crystals was proposed by various authors in the past including disintegrating red blood corpuscles of stagnant blood vessels within the lesion (Browne 1971); (ii) lymphocytes and macrophages (Trot et al, 1973); and (iii) circulating lipids (Shear 1963) [13]. Cholesterol crystals were present in 28.5% of cases in Shear's studies, 30% in Trott's studies and 43.5% in Browne's studies [13].

Shear in 1963 proposed an interesting theory regarding the role of circulating LDL in PCC formation. According to his theory, blood vessels at the site of inflammation are thin walled and fragile. When low density lipoproteins pass through these thin-walled vessels, it cleaves into cholesterol and its esters which are retained in the site of inflammation [13]. But this theory was refuted by the results of our study as no correlation could be established between serum LDL and PCC.

Trott had suggested that considerable accumulation of cholesterol crystals in periapical lesions can occur through disintegration of plasma cells, macrophages and lymphocytes all of which take part in the inflammatory process [13]. He also found a close association between haemosiderin and periapical cholesterol, but his regression analysis showed that only 35% of cholesterol accumulation can occur by this association [13].

In this study, patients having PCC neither exhibited elevated LDL nor hsCRP levels. However all patients with elevated LDL showed concomitant presence of foamy macrophages in the periapical specimens without cholesterol crystals. These findings suggest that the mechanism of periapical cholesterol accumulation may be different from that of atherosclerosis where elevated levels of serum LDL and foamy macrophages play significant roles.

50% of patients with cholesterol crystals revealed haemosiderin pigment, suggesting a positive role for erythrocytes as suggested by Browne [13]. Browne had postulated that cholesterol from disintegrating red blood cells tend to accumulate in inflamed periapical tissues due to relative lack of lymphatic drainage [13]. Arwill and Heyden (1973) also demonstrated that cholesterol crystallization can occur in congested capillaries when periapical area is inflamed [13]. Once cholesterol is deposited in the periapical tissues, they excite a foreign body giant cell reaction. Histological sections have shown dense masses of multinucleate giant cells surrounding cholesterol clefts [13].

Brzostek et al. 2004, showed that people in the age group of 30-65 years expressed higher atherosclerotic risk factors such as hypercholesterolemia, systolic hypertension, overweight, smoking, C reactive proteins and depression [14]. Accordingly, an age range of 30-65 years was selected for the study.

This study is unique in being the first invivo attempt to assess the relevance of periapical PCC to distant hyperlipidaemic and atherosclerotic events in the body. Also it is the first of its kind to question the role of serum LDL in periapical cholesterol crystal formation. The other sources can be erythrocytes (Browne, 1971) or from locally dying inflammatory cells (Trott et al, 1973) or may be from a newer source that is yet to be postulated.

The small sample size is an inherent weakness of this study which can be partly attributed to the limited number of patients opting for surgical endodontic procedures compared to extraction. To the best of authors' knowledge, only limited studies on PCC exist. Despite the small sample size and the negative results, the novel idea behind this study will help in further research pertaining to the source of origin and methods to eliminate periapical cholesterol crystals; thereby reducing the incidence of RPL.

Conclusion

Within the limitations of this in vivo study, it can be concluded that

1. Correlation between the presence of PCC, serum LDL and hsCRP values was insignificant.
2. The occurrence of haemosiderin in specimens containing PCC may suggest a possible role of erythrocytes in the origin of PCC.
3. It is unlikely that the process of periapical cholesterol crystallization be similar to that of atherosclerosis.

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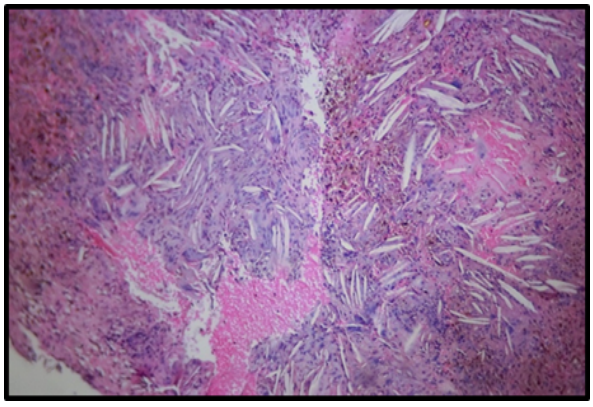

FIGURE 1 –HISTOLOGY OF PERIAPICAL TISSUE SHOWING CHOLESTEROL CLEFTS UNDER LIGHT MICROSCOPE- 10X MAGNIFICATION(E & H STAIN). Souce: Dept. of oral and Maxillofacial Pathology, Ragas Dental College.

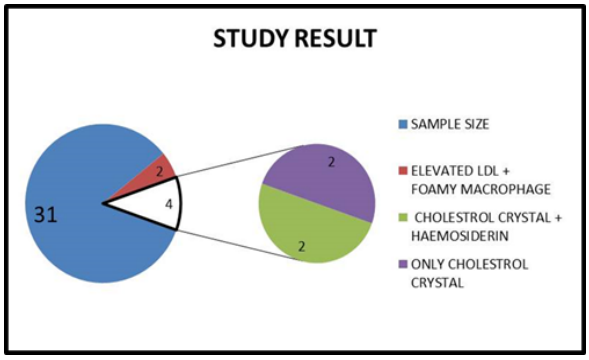

FIGURE 2 – STUDY RESULT

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