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EVALUATION OF SALIVARY PROCALCITONIN LEVELS IN CHRONIC PERIODONTITIS PATIENTS WITH HYPOTHYROIDISM BEFORE & AFTER NON SURGICAL PERIODONTAL THERAPY - A CLINICAL STUDY.

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Conflicts of Interest: Nil

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Abstract:

Periodontitis is a highly prevalent oral disease among the middle aged to elderly people. Bidirectional relationship of periodontitis with various systemic conditions has been reported with thyroid dysfunction as one among them. Procalcitonin is considered as an inflammatory marker that is raised during infectious & inflammatory conditions. It can be measured in biological fluids like serum and saliva.

Aim: The study aimed to compare the levels of Salivary Procalcitonin in Chronic Periodontitis patients with Hypothyroidism before & after non-surgical periodontal therapy.

Settings and design: This was a randomized interventional study, wherein thirty patients participated.

Materials and methods: Thirty hypothyroid patients with chronic periodontitis aged between 35-50 years were equally divided into Group A (oral hygiene instructions) and Group B (NSPT+ oral hygiene instructions) selected from an outpatient department from general hospital in Hyderabad. A written informed consent was obtained from all the patients and the study was approved by institutional ethical committee. Statistical Analysis used: Comparison within the groups was done by Paired *t*-test and between the groups by Independent sample *t*-test. $P<0.05$ was considered of statistical significance. Results: Intergroup assessment showed better improvement of clinical and biochemical variables in Group B when compared to Group A which was statistically significant. Conclusion: Successful periodontal therapy results in a decrease in the procalcitonin levels along with improvement in clinical parameters. Hence, chronic periodontitis patients with hypothyroidism can benefit from non surgical periodontal therapy with reduction in inflammatory burden.

Keywords: Chronic periodontitis, Hypothyroidism, Procalcitonin, Non-surgical periodontal therapy

Introduction

Periodontitis is a multi-factorial disease caused by the plaque micro-organisms. Although bacteria are primary etiological agents in periodontitis, host response to the infection sustaining is crucial to disease progression. Host inflammatory cells respond to the microorganisms of dental plaque by secreting a number of chemokines and inflammatory cytokines, whose production is amplified by several bacterial virulence factors, thereby leading to the destruction of periodontal tissues. Periodontal disease results in increase in inflammatory mediators that causes tissue break down, such as Acute Phase Proteins (APP) or Acute Phase Reactants (APR), cytokines, pro-inflammatory cytokines, anti-inflammatory cytokines, prostaglandins which are part of the host immune response.[1,2] Conventional disease diagnostic techniques lack the capacity to identify highly susceptible patients who are at risk for future breakdown. Need for advanced diagnostic parameters in oral and periodontal diseases have led to the development of methods by which periodontal disease risk can be identified and quantified by objective measures such as biomarkers. The inflammatory biomarker level in biologic fluids may be a useful indicator of the inflammatory activity which may reflect the extent of periodontal tissue breakdown, the severity of disease and its progression. Procalcitonin is one such biomarker that has been associated with the periodontal diseases. It is the precursor protein of calcitonin that is mainly secreted by the C cells of thyroid gland. It behaves as an acute phase reactant with normal range being 0.01ng/ml that increases upto 0.5 to 1.0ng/ml during infectious and inflammatory conditions.

The recent studies have demonstrated the role of thyroid dysfunction in disturbing the periodontal tissues leading to their destruction. Hypothyroidism is a condition where the thyroid gland function and production of hormones is reduced (TSH levels > 4.5mIU/L). This condition affects bone healing, causes decreased recruitment, maturation

and activity of bone cells leads to reduction of bone resorption and formation. Oral manifestations of hypothyroidism include poor periodontal health, delayed wound healing, delayed dental eruption, altered tooth morphology, macroglossia and salivary gland enlargement.

The present study was designed to estimate the levels of salivary ProCT in chronic periodontitis patients and compare its levels in chronic periodontitis patients with hypothyroidism before and after non-surgical periodontal therapy.

Materials and Methods:

This was a randomized, interventional, single blinded clinical trial, wherein thirty hypothyroid patients with chronic periodontitis were recruited. The study was conducted from June 2017 to February 2018. Prior approval was obtained from the institutional ethical committee. Information regarding the study was explained to the subjects prior to the sample collection and written informed consent was taken.

The samples were equally categorized into two groups – Group A (15 hypothyroid patients with chronic periodontitis that received oral hygiene instructions) & Group B (15 hypothyroid patients with chronic periodontitis that received non-surgical periodontal therapy along with oral hygiene instructions).

Randomisation procedure

An investigator (PSK) randomly distributed the study samples into Groups A & B and was also responsible for monitoring the non-surgical periodontal therapy and oral hygiene instructions being given to the patients. Another investigator (AM) performed the non-surgical periodontal therapy who was blinded to the randomization procedure.

Inclusion criteria

Recently diagnosed hypothyroid patients (under medication) having moderate to severe alveolar bone loss with Clinical attachment loss (CAL) $\geq$ 5mm and probing depth (PD) $\geq$ 6mm in multiple sites of all four quadrants of the mouth participated in the study.

Exclusion criteria

Smokers, pregnant and lactating women, patients with any other bacterial infections or systemic diseases having undergone any periodontal therapy within past 6months and those on antibiotics within past 3months were excluded from the study.

Clinical parameters

All patients were subjected to oral examination with William's calibrated periodontal probe. The indices taken were Gingival Index (GI), Bleeding on Probing (BOP), Probing Pocket Depth (PPD), Clinical Attachment Level (CAL).

Biochemical Variables

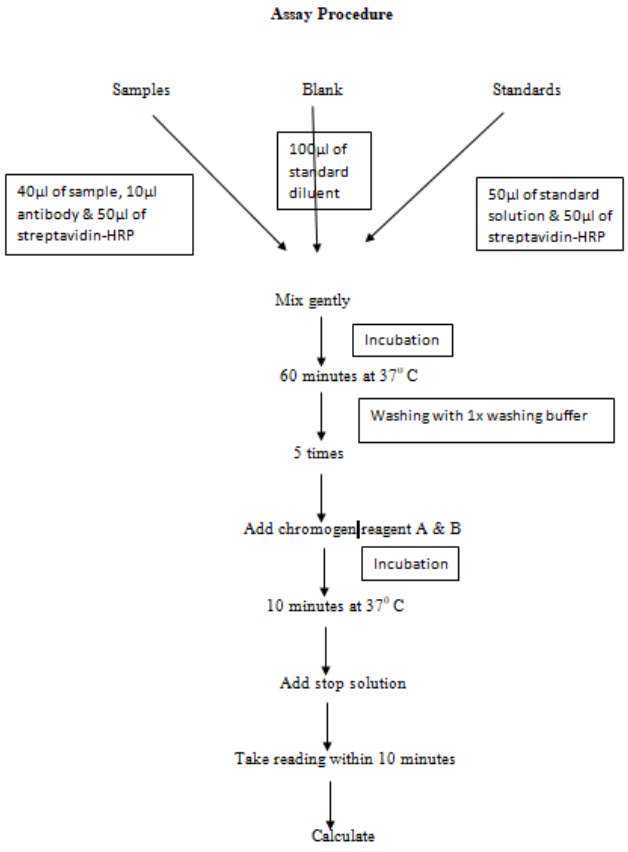
Sample collection – Patients were instructed to refrain from eating, drinking beverages (except water), chewing gum one hour before sample collection.

About 3-5ml of unstimulated whole salivary samples were obtained by expectorating into polypropylene tubes. Upon collection, sample is immediately aliquot and stored at -80^0 C. Centrifugation is done at 1500-2000 rpm for 10min at 4^0 C. The supernatants were collected carefully and assayed. All the reagents, buffers and samples were brought to room temperature prior to use.

ProCT assessment was done at baseline and 3 months after NSPT using the quantitative commercial ELISA kit by GenxBio Health Sciences Pvt. Ltd.

Reagents used – ProCT microplate, washing concentrate (20X), Standard protein detection antibody, streptavidin-HRP concentrate, chromogen solutions A and B, stop solution, assay diluent

Outcome measures – The primary outcome measures assessed was salivary procalcitonin levels and the secondary outcome measures were BOP, GI, PPD and CAL.




Glass funnel


Collection tube


Sample collection


Armamentarium

ELISA kit


Reagents used

RESULTS

Intragroup comparison – There was significant improvement in the clinical variables assessed in Group A and all the variables in Group B.

Intergroup comparison – There was marked improvement in both the clinical ad biochemical parameters in Group B as compared to Group A.

The mean salivary ProCT levels (primary outcome measure) increased from 0.10 ± 0.04 at baseline to 0.13 ±0.04 at 3 months in group A, but it was 0.14 ± 0.06 at baseline and decreased to 0.09±0.04 in Group B.
Overall the improvement in salivary ProCT was more in Group B as compared to Group A(p=0.000).
In addition, the mean gingival index decreased from 0.99 to 0.86 after 3 months in Group A and from 0.86 to 0.27 in Group B. The mean probing depth was reduced from 6.07 to 5.82 after 3 months in Group A and from 6.44 to 5.41 in Group B. The mean clinical attachment levels decreased from 6.91 to 5.94 in Group A and from 6.71 to 5.64 in Group B after 3 months.

Therefore, when intergroup comparison was done regarding secondary outcome measures, greater improvement was observed in Group B when compared with Group A.

Table 1: Intragroup comparison of GI, PD, CAL & Procalcitonin Levels in Group A

Parameters	TIME	MEAN	SD	P value
Gingival index	BASELINE	0.99	0.22	0.367
	3 MONTHS	0.86	0.23	NS
Probing Depth	BASELINE	6.07	1.06	0.524
	3 MONTHS	5.82	0.99	NS
Clinical Attachment Loss	BASELINE	6.19	1.29	0.521
	3 MONTHS	5.94	1.17	NS
Procalcitonin Level	BASELINE	0.10	0.04	0.000
	3 MONTHS	0.13	0.04	S

*p<0.05 is statistically significant. SD- Standard Deviation, P- Probability value

Table 2: Intragroup comparison of GI, PD, CAL & Procalcitonin Levels in Group B

Parameters	TIME	MEAN	SD	P value
Gingival index	BASELINE	0.86	0.13	0.000
	3 MONTHS	0.27	0.10	S
Probing Depth	BASELINE	6.44	1.77	0.020
	3 MONTHS	5.41	0.78	S
Clinical Attachment Loss	BASELINE	6.71	1.73	0.016
	3 MONTHS	5.64	0.68	S
Procalcitonin Level	BASELINE	0.14	0.06	0.000
	3 MONTHS	0.09	0.04	S

*p<0.05 is statistically significant. SD- Standard Deviation, P- Probability value

Table 3: Intergroup comparison between in GI, PD, CAL and Procalcitonin Levels in Group A and Group B

Parameters	TIME	Group A		Group B		P value
		MEAN±SD difference	% of Mean change	MEAN±SD difference	% of Mean change	
Gingival index	BASELINE 3 MONTHS	0.13±0.01	-13.13	0.59±0.03	-68.60	0.003 *
Probing Depth	BASELINE 3 MONTHS	0.25±0.07	-4.12	1.03±0.99	-15.99	0.042 *
Clinical Attachment Loss	BASELINE 3 MONTHS	0.25±0.12	-4.04	1.07±1.05	-15.95	0.033 *
Procalcitonin Level	BASELINE 3 MONTHS	0.03±0.00	30.00	0.05±0.02	-35.71	0.000 *

*p<0.05 is statistically significant. SD- Standard Deviation, P- Probability value

Discussion

Periodontal diseases are a group of diseases that cause inflammation and destruction of the investing and supporting structures of the teeth (such as the gingiva, periodontal ligament, alveolar bone and cementum). Periodontal diseases occur due to a complex interplay of bacterial infection and host response often modified by behavioral, genetic factors and various systemic conditions.[3]

In recent years there has been a shift in interest from understanding periodontal manifestations of systemic diseases to linking the role of periodontal infections with various systemic diseases.[4,5] The association between periodontal and systemic diseases, especially those causing hormonal disturbances such as diabetes mellitus and thyroid dysfunction had received great attention in periodontal literature in recent years. Many in vivo models that demonstrated the role of cytokines in pathophysiology had demonstrated that a given inflammatory stimulus results in the generation of a complex cascade of cytokine release.[6]

Thyroid hormones play a role in the maintenance of homeostasis of the body by regulating normal physiologic growth and development, skeletal maturation and bone turn over. Furthermore, they are involved in the maintenance of immune function in response to environmental stimuli and stress‐mediated immunosuppression.

Thyroid stimulating hormone (TSH) modulation takes place by the immune cells in two ways- one is by the direct effect of TSH on cells of the immune system, the second being an indirect effect mediated by TSH‐induced thyroid hormone. The production of TSH by leukocytes gives a reasonable assumption that it may act like a cytokine‐like regulatory molecule within the immune system.[7] **Hodkinson CF et al 2009** have shown that there is a positive association of thyroid hormone with markers of inflammation such as interleukin‐1 (IL‐1), IL‐2, IL‐6, natural killer T cells, memory helper T‐cells, tumor necrosis factor‐α (TNF‐α), and transforming growth factor-β.[8]

Thyroid diseases may affect the status of periodontal diseases especially in the hypothyroid conditions. Uncontrolled thyroid disease may lead to periodontal destruction. Meta-analysis by **Wang and Cohen in 2011**, stated that periodontal treatment is safe in controlled conditions.[9]

Several studies have investigated the relationship between hypothyroidism and periodontitis which were clinically significant. In the present study, at the baseline the periodontal parameters like gingival index, probing pocket depth and clinical attachment level were higher in test group with mean values: 0.86±0.13, 6.44±1.77, 6.71±1.73 respectively. This was in support of a similar study conducted by **Venkatesh Babu et al 2016** where clinical parameters such as gingival index, probing pocket depth and clinical attachment level were significantly higher in the study group (thyroid dysfunction) than the control healthy subjects.[10] Similar studies were also obtained in a study conducted by **Kadhim et al 2012** who found that patients with thyroid disorders have poor periodontal health, more clinical attachment loss compared with healthy individuals.[11]

This study showed the presence of ProCT in saliva and its correlation with the degree of periodontitis in hypothyroidism. We hypothesized that periodontitis in hypothyroidism may act as a stimulus for ProCT production, since endotoxin is a potent stimulator for the production of ProCT and can promote the systemic release of calcitonin precursors from nearly all tissues of the body.[12]

Advances in the use of oral fluids as possible biological samples for objective measures of current disease state, treatment monitoring, and as prognostic indicators have

boosted saliva to the forefront of technology.[13] Saliva is considered to be mirror of the body where it can be used to diagnose both the oral diseases and systemic conditions as well.[13] Several inflammatory mediators of tissue destruction have been detected in whole saliva of periodontitis patients.

The results of our study showed a higher value in the salivary ProCT levels in both the groups (A and B) of subjects with chronic periodontitis at baseline with mean values of 0.10+0.04 and 0.14+0.06 respectively. This is in accordance with a study conducted by **Hendek et al 2015** where mean values of salivary ProCT was lowest in the healthy group followed by the gingivitis group, the chronic periodontitis group and highest in the generalized aggressive periodontitis group.[14] **Savas et al 2016** showed that PCT was significantly elevated along with ESR, CRP in patients with thyroid dysfunction irrespective of their thyroid dysfunction type suggesting that inflammation plays a pivotal role in the pathogenesis of thyroid dysfunction.[15]

Yousefimanesh et al 2015 reported a correlation between clinical parameters and PCT Level but that salivary PCT concentration changed without predictable and significant pattern and concluded that PCT might not be a valuable marker for the existence of periodontal disease. These results are contradictory to our present study.[16]

This study was an interventional study where all the clinical parameters and salivary ProCT were re-estimated after 3 months of non-surgical periodontal therapy in group B. The results showed a significant improvement in the clinical parameters and a decrease in the ProCT levels. This was similar with a previous study conducted by **Paschalina Goutoudi et al 2012** where periodontal treatment showed improvement in all clinical parameters in chronic periodontitis patients.[17]

In the control group where the patients were treated with hypothyroid medication and oral hygiene instructions (without non-surgical periodontal therapy), the improvement in the clinical parameters after 3 months was not significant and there was a significant increase in the ProCT level. The differences in clinical parameters following non-surgical periodontal therapy were statistically significant between control & test groups indicating that there is no influence of hypothyroid medication on the inflammatory marker level in the control group. **Bassim et al 2008** investigated ProCT levels in saliva and serum of persons with periodontitis and type 2 diabetes and showed that ProCT was influenced by Periodontitis severity, but not by glycemic control.[18]

Overall, the present study confirms the increase of salivary PCT in subjects with chronic periodontitis and hypothyroidism and reduction of salivary PCT after treatment. Even after excluding the other factors leading to the increased levels of salivary PCT, the result of the present study demonstrate elevated salivary PCT levels in chronic periodontitis with hypothyroidism thus further strengthening the fact that as periodontal destruction increases, the levels of salivary PCT also increases. In chronic periodontitis subjects, periodontal therapy helps to decrease salivary PCT levels, which is statistically significant between chronic periodontitis subjects at base line, after phase **LIMITATIONS**

Age group included in the study was 35-50 with predominance of females. The study group with no hypothyroid medication would be desirable to observe the effects of periodontal therapy on salivary ProCT levels.

Conclusion

Chronic periodontitis patients with hypothyroidism can benefit from non surgical periodontal therapy with a reduction in the inflammatory burden. Further studies should be conducted with larger sample size to achieve the better results.

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