



Research Article

Estimation of Salivary IL-6 Level in relation of Periodontal Status in Patients with Hyperthyroidism

Eman Habib Kadhom*, Nada Jafer MH. Radhi

Department of Pediatric and Preventive Dentistry, College of Dentistry, University of Baghdad, Baghdad, Iraq

* Corresponding author's email: lyman.Habeeb1202a@codental.uobaghdad.edu.iq

ABSTRACT

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Keywords: Carbimazole, Gingival index, Hyperthyroidism, Interleukin-6, Plaque index, Periodontal disease.



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Background: The overproduction of thyroid hormones is known as hyperthyroidism. Increased susceptibility to caries and periodontal disease are two potential oral symptoms. The interleukin-6 (IL-6) was observed to significantly increased in the hyperthyroid group. According to multiple research, IL-6 dysregulation has been linked to a number of oral disorders, including periodontal diseases. The study aimed to evaluate periodontal health status in relation to IL6 among hyperthyroidism patients.

Subjects and Methods: The sample was composed of 90 female patients aged 25-45 years attending endocrine disorder center in al-Najaf Governorate/Iraq which include hyperthyroid group and healthy group, the hyperthyroid patients were diagnosed by specialist and under treatment with carbimazole. The clinical examination of periodontal health status assessment was performed according to WHO (2013) in addition to evaluation the Plaque and gingival condition. The Saliva was collected to evaluate IL-6 concentrations.

Results: The plaque index (PLI) in the study group was more than the control with a significant difference ($P < 0.05$). The gingival index (GI) in the study was more than the control but with no significant difference ($P > 0.05$). Both periodontal pocket depth (PPD) and clinical attachment loss (CAL) were higher in the study group than in the control group, with a significant difference. IL-6 was higher in the study group than in control with a significant difference. There was a positive non-significant correlation between PPD and CAL with IL-6 in hyperthyroid patients.

Conclusion: The results of the present study showed that individuals with hyperthyroidism are at risk for periodontal disease; these patients have high levels of both periodontal disease and IL6.

Introduction

The thyroid gland has a major impact on every system in the body, including the oral cavity, and regulates metabolism to a substantial extent. The oral cavity is affected by excess or insufficient thyroid hormone, high levels of triiodothyronine and

thyroxin in the serum and low levels of thyroid-stimulating hormones are the characteristics of hyperthyroidism, three main causes of hyperthyroidism are toxic multinodular goiter, toxic adenoma, and Graves' disease (1). Treatment options for

hyperthyroidism include thyroid surgery, radioactive iodine ablation of the thyroid gland, and antithyroid drugs such as methimazole. Carbimazole is an antithyroid drug well renowned for treatment of Graves' disease (toxic diffuse goiter) and other diseases causing hyperthyroidism such as toxic nodular goiter. It is a "thionamide" drug; a derivative of 3-carbomethoxy methimazole group. After ingestion, carbimazole is metabolized in the liver to methimazole (2). Methimazole diminishes the formation of thyroid hormones; after two, four and six weeks of its administration (3). Methimazole induces depression of bone marrow (BM) and results in aplastic anaemia, agranulocytosis and thrombocytopenia which consequently induce adverse effects on the periodontal tissues (such as; periodontal ligament, cementum, and alveolar bone) and cause rapid increase in the rate of periodontal destruction (4). In a case report study, methimazole intake induced neutropenia in some patients with subsequent gingival ulceration and necrosis (5). Clinical presentations of hyperthyroidism range from asymptomatic to thyroid storm. The patient's preference and the advantages versus dangers in a particular clinical circumstance determine the treatment to be administered (6). Periodontitis is a common inflammatory periodontal disease affecting a wide range of population all over the world. The cause systematically or locally such as bacteria releases chemicals which activate the innate immune system to release proinflammatory cytokines contributing to more progression. Regardless of the reason but activates the acquired immune system leading to more progression of periodontitis. As the immune response goes on, released cytokines and chemokines can damage the periodontal ligaments, gingiva, and alveolar bone. There are many types of cytokines and chemokines in periodontitis, this study included the IL-6 (7). Numerous types of cytokines and chemokines have been studied extensively for their crucial involvement in the inflammatory process of periodontitis (8-10). The proinflammatory cytokines (Interleukin-6) are produced in thyroid dysfunction (5). And many recent studies found that IL-6 increased in hyperthyroidism patients (11-13). There are some studies conducting there was correlation between hyper thyroidism and periodontal disease and increased periodontitis in thyroid dysfunction (14-16). Therefore, the purpose of this study was to investigate the association between periodontal health status and IL6 in hyperthyroidism patients.

Subjects and Methods

The sample was composed of 90 female aged 25-45 years attending an endocrine disorder center in Al- Sader Medical City in al-Najaf Governorate/Iraq. The sample includes two group each group consist of 45 female. The study group, including hyperthyroid female patients while the control group contain 45 healthy females, the hyperthyroid patients were diagnosed by specialist and under treatment with carbimazole, and the study group includes female patients diagnosed with hyperthyroidism one year ago and more. A Ministry of Health authorization was obtained to review these patients' ethical status. Additionally, Prestudy data from medical records were used to determine the type of thyroid malfunction, how long the patient had been ill, the drugs they were taking, and their medical history. For this study, the samples had to meet the

following requirements: they shouldn't have had any other systemic illnesses, they shouldn't have been taking any other medications than those for thyroid dysfunction, and they shouldn't have been pregnant or smokers. Method of randomization was simple randomization method. According to WHO (2013) (17) guidelines, examinations were conducted on each patient under standardized circumstances. The general information, which included name, age, gender, and dental and medical histories, was entered on a particular form before the examination so personal file contained information was registered. Each patient was inspected in an appropriate chair with a headrest and artificial headlight. This study was started in December 2021.

Salivary Sample

The Unstimulated whole saliva was collected in screw-capped tubes according to the instruction of Tenovou and Lagerlof (1996)(18). Saliva was collected at morning 10-12 am. It was performed under standardized conditions following the instructions. The female should not have eaten or drunk (except water) 1 hour before collection. Saliva should have been collected at the same time during the day. The female should not have smoked or undergone heavy physical stress before collection, a fixed collection time (5 min). The female should have sat in a relaxed position. Samples containing blood should be neglected. The participants in the study drooled their saliva into the tubes with screw-capped caps. After that, the saliva was centrifuged for ten minutes at (3000 rpm). The supernatant produced was placed in Eppendorf tubes, where it was labelled and sealed before being frozen at -80 C° for further examination. The collection of saliva was before oral examination.

Clinical examination

Dental plaque was recorded during the oral examination use plaque index (19), gingival condition according to gingival index (20), periodontal pocket depth and clinical attachment loss (17). A color coded periodontal probe been used with this index Community Periodontal Index (CPI) It can be used as a screening or monitoring tool to determine the periodontal treatment needs of either a community or an individual so this index was designed to assess the treatment needs of specific groups. The CPI system is designed to obtain an estimate of the accumulated destruction of the periodontal attachment and thereby permits comparisons between population groups. Gingivae of all teeth present in the mouth should be examined by carefully inserting the tip of the WHO CPI probe between the gingiva and the tooth. The sensing force used should be no more than twenty g. A practical test for establishing this force is to ask examiners to place the probe point under their thumbnail and press until blanching occurs. All teeth present should be probed and scored in the corresponding box. The codes for scoring bleeding and pocketing are given as following.

Pocket scores

- 0 = Absence of condition.
- 1 = Pocket 4–5 mm.
- 2 = Pocket 6 mm or more.
- 9 = Tooth excluded.
- X = Tooth not present.

Information on loss of attachment collected from the index teeth. The CPI system is intended to estimate the accumulated damage of the periodontal attachment and thus allow comparisons between population groups. It is not designed to describe the full extent of loss of attachment in an individual. Loss of attachment is recorded by dividing the mouth in sextants, defined by tooth numbers. The most reliable method of examination for loss of attachment in each sextant is to record this immediately after recording the pocket scores. The extent of loss of attachment is recorded using the CPI probe and applying the following codes:

- 0 = 0–3 mm
- 1 = 4–5 mm (CEJ within black band)
- 2 = 6–8 mm (CEJ between upper limit of black band and 8.5 mm ring)
- 3 = 9–11 mm (CEJ between 8.5 mm and 11.5 mm ring)
- 4 = 12 mm or more (CEJ beyond 11.5 mm ring)
- X = Excluded sextant
- 9 = Not recorded

Biochemical analyses

After allowing frozen saliva samples to thaw at room temperature, an enzyme-linked immune sorbent assay (ELISA) kit was used to measure IL6 levels in the saliva. This method was based on the Biotin double antibody sandwich technology (Shanghai YL Biont).

Statistical analysis

Data description and analysis were performed using an Independent Sample T-test: a parametric test of the difference between two groups; results were displayed as a mean, standard error to determine the significance level at a p-value of (0.05).

Results

The results found that both Periodontal pocket depth (PPD) and Clinical attachment loss (CAL) was higher in the study group than those in control with significant difference as seen in (table 1). Plaque index (PLI) in the study group is more than the control with a significant difference (P<0.05), and the Gingival index (GI) in the study is more than the control but with no significant difference (P>0.05), as seen in (table 2).

The results found that IL-6 was higher in the study group than those in the control with a significant difference, as seen in (table 3). The result found that the correlation between interleukin-6 and Periodontal pocket depth and Clinical attachment loss was weak positive non-significant in the study group, as seen in (table 4).

Table 1: Mean values and statistical difference of Periodontal pocket depth and Clinical attachment loss among study and control groups

Variables	Groups				T test	P value
	Study		Control			
	Mean	SE	Mean	SE		
Periodontal pocket depth	5.21	0.108	4.013	0.201	5.06	0.0001
Clinical attachment loss	1.339	0.302	0.100	0.100	3.89	0.00027

Table 2: Mean values and statistical difference of Plaque index and Gingival index

Groups	Plaque index				Gingival index			
	mean	±SE	T-test	P value	mean	±SE	T-test	P value
Study	1.116	0.027	2.653	0.007 Sig.	1.020	0.027	0.151	0.880 NS
control	1.033	0.012			1.014	0.028		

Table 3: Mean values and statistical difference of salivary interleukin-6 among the study and control groups

	Groups				T-test	P value
	Study		Control			
	Mean	±SE	Mean	±SE		
interleukin-6	11.847	0.451	9.274	0.453	4.025	0.000120

Table 4: Correlation between periodontal parameters and interleukin-6

Groups		IL-6	
		r	p
Study	Periodontal pocket depth	0.062	0.688
	Clinical attachment loss	0.059	0.698
Control	Periodontal pocket depth	0.317	0.034
	Clinical attachment loss	0.317	0.034

Discussion

The human periodontal disease is a global problem. So that, age, gender and area of residence are among the most important risk factors that can impact progression and severity of periodontal diseases (21).

In clinical examination of periodontal status, the need for reliable indices that not only clarify the etiological factors of the disease, but also provide a virtual image on the manpower and financial recourses seems to be gaped by the Community Periodontal Index of Treatment Needs (CPITN) proposition in 1982 and the rapid acceptance of this instrument that provided the scientific community with an enormous amount of epidemiological data collected through this index. However, based on the limitations identified by several authors during years of research, the World Health Organization (WHO) proposed a few changes to the CPITN in 1987 and again in 1997, but the instrument’s diagnostic criteria were basically unaffected by these modifications(22). The CPI has proven to be a useful tool for planning periodontal treatment needs, establishing population periodontal health goals, and evaluating changes in the periodontal status of a given population after a program implementation (23-26). In 2017 there was workgroup reported new classification of Periodontal and Peri-Implant Diseases of Periodontal health and gingival diseases and conditions (27, 28). In the present study preferred to use 2013 for several advantage more practical, employs scoring system and used for large population while in 2017 depend on stage and grade of the disease and one of

the restrictions and challenges was the requirement for a dental x-ray confirmation, which is unavailable because the endocrine center lacks a specialized dental facility.

According to the findings of the present study, the majority of hyperthyroid patients had greater periodontal disease and Several studies support this(14, 29, 30) .

Also agreed with several Iraqi studies showing that individuals with thyroid disorders had high rates of caries experience and periodontal disease increased with increasing the duration of illness and advancing age(31, 32).

This may be caused by adverse consequences from long-term use of anti-thyroid drugs by patients. In study was carried out in 2020 to assessed the potential effect of carbimazole on histological structure of periodontal tissues forming the dentoalveolar complex (periodontal ligament, cementum, and alveolar bone) in rats, the study showed Carbimazole had deleterious effect on structure and homeostasis of periodontal tissues forming the dentoalveolar complex, in the present study, which was conducted on human's patients, supports that result(33).

Many attempts were carried out to ameliorate the side effects of carbimazole and enhance periodontal regeneration. Regenerative or reparative medicine which refers to the utilization of cell-based therapy in treatment of destructive diseases has received much attention (34).

According to the findings, IL-6 levels are significantly greater in the hyperthyroid group than in the healthy group and that agree with several studies(11-13) .In study was carried out in 2022 concluded that the pro- inflammatory cytokines play a major role in the pathogenicity of hyperthyroidism(12). Iraqi study conducted in 2022 found that IL-6 increase in hyperthyroid patient and decrease after treatment with carbimazole drug(35). Processes, including cell division, apoptosis, differentiation, and survival, which are influenced by IL6. IL-6 has a variety of activities in the immunological, endocrine, neurological, and hematological systems, including inflammation, bone metabolism, and blood pressure regulation(4) . In addition, it is affecting the function of B lymphocytes, stimulating the body to produce autoantibodies and stimulates the incidence of hyperthyroidism(13).

There was a positive correlation between IL6 and (PPD, CAL) in hyperthyroid patients this agree with a study that found thyroid hormone-related periodontitis is strongly influenced by the serum and salivary levels of proinflammatory cytokines, including tumor necrosis factor (TNF)- and interleukin (IL-6)(30).The development of periodontitis in a setting of thyroid dysfunction leads to an even greater increase in the destruction of connective tissue the explanation Several studies showed that thyroid hormones play an important role in bone resorption by influencing osteoprotegerin (OPG) and receptor activator of nuclear factor kappa-B ligand (RANKL) mechanism (36). The cytokines that were produced due to thyroid dysfunction might have been the initiators of an amplified inflammatory cascade. In combination with endotoxins produced by germs in dental plaque this might lead to higher local inflammatory mediator concentrations, including cytokines and prostaglandins, higher concentrations of matrix metalloproteinase and of other proteinases with destructive effects on bone and conjunctive tissue, in the end leading to osteoporosis and periodontal breakdown(16).

As a result of the present study's findings, it is clear that both the thyroid dysfunction and healthy group's female participants had periodontal disease, but the thyroid dysfunction group's female

participants had worse periodontal health and more clinical attachment loss than the healthy group's female participants. These results came in agreement with the result of another study (37) . Therefore, take into consideration during clinical practice that periodontal disease has additional hidden causes, all of which are clearly related.

According to the findings, PLI was higher in the study group than in the healthy group, with a significant difference. Dental plaque's microbial biofilm may have contributed to the onset and maintenance of periodontal disease; genetic and environmental host factors affect the disease's progression; as a result, the amount of tissue destruction is typically inversely correlated with dental plaque levels, host defenses, and associated risk factors(38). At the same time, suffering from a periodontal disease indicates the ignorance of those patients Regardless of their systemic disease. For this cause, dental education is important for people to improve their knowledge and attitude toward oral health. In addition to that, the severity of these dental diseases will increase with age and duration of illness; therefore, special preventive programs need to be designed for those patients. In order to help people, recognize periodontal disease in its earliest stages, it is important to increase public awareness of the condition (39). The public periodontal awareness and knowledge is still struggling, the solution requires hared resources and multiple approaches (40).

Pre-study was conducted to minimize limitations in this study as much as possible. The method for collecting saliva, the oral examination, the facilities, the supplies, the time needed, and the storage of the sample in a deep freezer have all been tested; additional research is required to evaluate larger sample sizes and to test additional types of biomarkers. The small sample size was due to limited duration for sample collection which was affected by withdrawal some patients, finding a patient who meets all the criteria is challenging in a limited period of time because time constraints due to the limited expire date of ELSA kit. The visual and tactile investigations were only methods used during clinical dental examination, while for instance, radiographs were not use, due to the fact that the patient was being treated in an endocrine center and dental radiography was unavailable.

Conclusion

The results of the present study showed that individuals with hyperthyroidism are at risk for periodontal disease; these patients have high levels of both periodontal disease and IL6, and there was a weak positive non-significant correlation between the two.

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This research did not receive any specific fund.

Conflict of Interest

No conflict of interest

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