„OVIDIUS" UNIVERSITY OF CONSTANTA
DOCTORAL SCHOOL OF MEDICINE
FIELD OF DENTISTRY

DOCTORAL THESIS

SUMMARY

SCIENTIFIC COORDINATOR
PROF. UNIV. BADEA VICTORIA

PhD STUDENT
CIRCO RAZVAN

CONSTANTA
2021

„OVIDIUS" UNIVERSITY OF CONSTANTA

DOCTORAL SCHOOL OF MEDICINE

FIELD OF DENTISTRY

INTERLEUKIN 1 BETA AS A MARKER FOR HIGHLIGHTING THE INFLAMATORY PROCESS OF CHRONIC PERIODONTITIS IN PATIENTS WITH CHRONIC AUTOIMMUNE THYROIDITIS

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CONTENT TABLE

ABREVIATIONS

CP = chronic parodontitis

IL = interleukine

TNF = tumor necrosis factor

PGE = prostaglandines

CAT = chornic autoimmune thyroiditis

RANK L = receptor activator of nuclear factor kappa-B ligand

OPG = osteoprotegerin

HsPs = Heat Shock Proteins

ANCA = Antineutrophil cytoplasmic antibodies

ATPO = antithyroperoxidase antibodies

ATG = antithyroglobulin antibodies

TSH = „ thyroid stimulating hormone"

FT4 = „ thyroxine/free- thyroxine"

ECLIA = Electrochemiluminiscence - Immune Assay

ANOVA = Analysis of variance

Pr = Coeficientul Pearson

ANA = antinuclear antibodies

OHIs = simplified oral hygene index

ECHEM = Enzime Chemo - Analysis

SCIENTIFIC PAPERS PUBLISHED DURING THE DOCTORAL REASEARCH

1. „Deficient dental hygiene in patients with chronic autoimmune thyroiditis and periodontal disease – pathological correlations" **- Răzvan Circo,** Seila Ibadula, Olesea Scrinic, Marian Beciu, Eduard Circo, International Scientific Conference on Social Sciences, 6th SWS International Scientific Conference on Social Sciences, CONFERENCE **PROCEEDINGS**, ISCSS 2019, Volum 6, Book number 3, pg. 445 – 455.
   Revista: ISI - PROCEEDINGS
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   DOI: 10.5593/SWS.ISCSS.2019.3/S12.072
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2. „Evoluția etapizată a bolii parodontale la pacienții cu tiroidită cronică autoimună – corelații patologice" **-** Eduard Circo, Ibadula Seila, Olesea Scrinic, Cristina Goșu, **Răzvan Circo**, Romanian Medical Journal, vol. LXVII Suppl.2, 2020; (67), pg. 65 – 70.
   Revista: BDI - B+ CNCSIS/CNCS
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3. „Chronic periodontitis in a group of patients with chronic autoimmune thyroiditis – particularities of expression" **- Răzvan Circo,** Cristina Goșu, Victoria Badea, Romanian Medical Journal, vol. LXVIII, No. 2021; 68(1), pg. 92 – 101.
   Revistă: BDI - B+ CNCSIS/CNCS
   ISSN: 1220 – 5478; **e – ISSN:** 2069 – 606X.
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   https://rmj.com.ro/articles/2021.1/RMJ_2021_1_Art-16.pdf

4. „Antithyroid antibodies – a possible involvement in the development of chronic periodontitis" - **Răzvan Circo,** Marian Beciu, Cristina Goșu, Doina Raducan, Victoria Badea, Romanian Medical Journal, vol. LXVIII, 2021, 68(2), pg. 278 – 285.
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   ISSN: 1220 – 5478; **e – ISSN**: 2069 – 606X.

DOI: 10.37897/RMJ.2021.2.23
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5. „Interleukine 1β – in serum and saliva in patients with chronic autoimmune thyroiditis associating chronic periodontitis – particularities of expression” **- Răzvan Circo,** Seila Ibadula, Cristina Circo, Victoria Badea, International Scientific Conference on Social Sciences, 8th SWS International Scientific Conference on Social Sciences, ISCSS 2021 [Currently being published according to „INTERNATIONAL MULTIDISCIPLINARY SCIENTIFIC CONFERENCE ON SOCIAL SCIENCES, ART AND HUMANITIES'' – Section: 13. SOCIAL SCIENCES: Section Digital societies, Transformations and Healthcare. ISCAH21/C/56452/26.08.2021].
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1. „Modificări dento-maxilare la adulții hipotiroidieni” - **Răzvan Circo**, Cristina Goșu, Al X – lea Congres al Asociației de Endocrinologie Clinică din România, 02–05 septembrie 2015, Constanța.
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   - **Oral presentation**

2. „Modificări dento-maxilare la copiii cu hipotiroidism” - Cristina Goșu, **Răzvan Circo –**- Al X – lea Congres al Asociației de Endocrinologie Clinică din România, 02–05 septembrie 2015, Constanța.
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3. „Periodontal disease in patients with chronic autoimmune thyroiditis – particularities of expression” - **Răzvan Circo,** Cristina Goșu, Seila Ibadula, Eduard Circo – Al XXVI-lea Congres National de Endocrinologie, cu participare internațională, Sibiu, 27-30 iunie 2018; Acta Endocrinologica, The International Journal of the Romanian Society of Endocrinology, vol. XIV, supliment 1, iunie 2018, pg.163 IF:0,449.
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4. „Tiroidita cronică autoimună și boala parodontală: itercondiționări patologice” - **Răzvan Circo,** Goșu Cristina, Ibadula Seila – Al XIII – lea Congres al Asociației de Endocrinologie Clinică din România, 05–08 septembrie 2018, Teatrul Elisabeta, București.
   Volum de rezumate: N2/2018, Ediția 13/2018, ISSN: 2457-6883.
   - **Oral presentation**

5. „Antinuclear antibodies, chronic autoimmune thyroiditis, periodontal disease – pathological correlations” - **Răzvan Circo,** Victoria Badea, Cristina Goșu, Eduard Circo – 21st European Congres of Endocrinology, 18 – 21 May 2019, Lyon, France.
   - **Poster**
6. „Evaluarea indicelui de igienă orală – utilitatea diagnostică evolutivă și de pronostic în boala parodontală asociind tiroidita cronică autoimună” - **Circo Răzvan,** Scrinic Olesea, Circo Cristina, Ibadula Seila – Al XIV-lea Congres al Asociației de Endocrinologie Clinică din România (AECR), Sinaia, 05–07 septembrie 2019.
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   - **Oral presentation**

INTRODUCTION

Periodontal disease is a condition with infectious determinism, initiating inflammatory and autoimmune processes, in intricate evolutionary stages, affecting 10% to 60% of adults (21,64,66).

The subgingival plaque initiates CP through microbial toxins creating an inflammatory response that will alter through cytokines the epithelial cells and fibroblasts in the periodontium. Both in the tissue and salivary, but also in the serum of patients with CP were identified IL-1, IL-6, TNF-α, PGE2, with tissue alterations of autoimmune and inflammatory background (272,307), similar processes to those encountered in the thyroid tissue of patients with chronic autoimmune thyroiditis (269,270). The causal interrelationship between the two diseases seems likely as long as autoimmunity can be induced by genetic, endogenous and / or environmental factors. The systemic associations of PC are varied, involving collagen diseases, coronary heart disease, osteoporosis, diabetes, the background being the gene polymorphism encountered in CP (273). Regulation of the immune response of lymphocyte to infectious aggression in CP has similarities with the intrinsic mechanisms found in CAT (270). For thyroid patients, is also added the impact of thyroid dysfunction, mainly of hypothyroidism (269). The pathogenesis of CAT, same as CP, raises a series of hypotheses that can often be intricated.

The way that the thyroid dysfunction is involved and the complex mechanisms of immunity, still raises many unknowns (270).

The immune response to periodontopathic bacteria / bacteria, the main causative agent, is complemented by the immune response to autoantigens, such as type I collagen and / or HSP60 heat shock protein, triggering ANCA antibodies involved in delayed apoptosis and a direct toxic effect on antigen carrier cells. (141,142).

Cytokines are key modulators in the inflammatory process and alteration of tissue homeostasis in both thyroiditis and periodontal connective tissues. (268) Cytokine nucleotide polymorphism and receptor gene coding are factors that control the risk, severity, initiation and progression of periodontal lesions (270,307).

The titer of interleukins, including IL-1β determined in various biological fluids, can be used in the diagnosis of immune disorders and in the monitoring of treatments only in correlation with complementary clinical and paraclinical data (285).

II. PERSONAL CONTRIBUTIONS

The main objective of this paper is to study the incidence and particularities of periodontal clinical lesions encountered in patients with chronic autoimmune thyroiditis. Intercorrelation of periodontal lesions with a number of pathological parameters encountered in patients with CAT and serum TSH level, as a marker of thyroid functional status and serum levels of antithyroid antibodies - ATPO and ATG, as well as their correlation with salivary values of IL-1β, constant identified cytokine in periodontal lesions (271) was considered to be a specific element of multidisciplinary study.

The general objectives of the study were:

→ the incidence and specificity of periodontal lesions encountered among patients with CAT;

→ correlations regarding the severity of periodontal lesions with thyroid function and the serum level of thyroid auto-antibodies;

→ appreciation under this aspect of the staged evolution of PC in correlation with the variables studied in patients with CAT;

→ correlation of the salivary level of IL-1β in patients with CT with the parameters studied from a clinical, hormonal and thyroid autoimmunity point of view;
→ specifying a possible aggravating role in the genesis of periodontal lesions of altered thyroid function, the serum level of thyroid autoantibodies, the stimulation of the inflammatory / destructive process performed by IL-1β;
→ possible involvement of serum-dosed IL-1B in systemic effects in patients with CAT with and without PC.
→ the perspective in this sense of the potential "targeted" treatment on the cytokine IL-1β, useful in BP, but also in CAT.

Research directions

In order to achieve the objectives of the doctoral research, the following studies were made:

Study 1: Chronic periodontitis in a group of patients with chronic autoimmune thyroiditis - particularities of expression, compared to a control group of patients with periodontal disease, without thyroid damage - clinical study.

Study 2: Staged evolution of chronic periodontitis in a group of patients with chronic autoimmune thyroiditis - pathogenic intercorrelations with the index of oral hygiene.

Study 3: Antithyroid antibodies - a possible involvement in the development of chronic periodontitis.

Study 4: Serum and salivary interleukin 1β evaluated in patients with chronic autoimmune thyroiditis associated with chronic periodontitis.

Chapter 2. General research methodology

The doctoral thesis consisted of a clinical observational analytical study correlated with the evaluation of specific biological constants of patients with CT and CAT: TSH, ATPO, ATG, IL-1β.

The clinical diagnosis of periodontal lesions was made in accordance with the clinical and radiological criteria proposed by the 1999 International World Workshop for the Classification of Periodontal Disease (23).

The following stages were followed in the study methodology of the patients:
- identification of the patient with periodontitis;
- identification of periodontal lesions from a clinical point of view and of the altered dental attachment, appreciated as intensity and number of affected teeth;
- identification of factors associated with potential pathological effect on oral and systemic health;
- anticipating the multifactorial involvement of pathological conditions in the rate of progression of periodontitis.

CP staging attests to the dynamics of lesions in relation to a series of pathogenic factors that can become therapeutic targets (271,304). In this sense, biomarkers can help to clarify the diagnosis in even early stages of the disease, can help in assessing the staging and the degree of disease involvement, as well as in assessing the effectiveness of specific therapeutic methods (307).

Patient selection criteria

Inclusion criteria:

- the existence of periodontal lesions.

- for selected patients with chronic autoimmune thyroiditis, the diagnosis was made based on clinical examination, thyroid ultrasound imaging and serum values (TSH, FT4, ATPO, ATG) obtained by ECLIA dosing methods (electrochemiluminescence); these data were analyzed retrospectively - observational from the personal file of the patients with their permission.

The exclusion criteria Patients with other autoimmune, inflammatory, neoplastic diseases, diabetes, malformative or systemic genetic diseases with potential periodontal pathogenic effect, women during pregnancy, smokers, aggressive periodontitis, lack of written consent were not admitted to the study.

Statistical analysis of data

Data collected was expressed as mean ± standard deviation for numerical variables and as frequency for categorical variables; T was performed test for continuous variables assessed comparatively. The value $p < 0.001$ was considered intensely significant, and $p < 0.05$ to state a statistical correlation. The ANOVA test was used to analyze the differences between the group averages.

The experimental data were processed using the IBM SPSS Statistics statistical processing program 23.

Chapter 3. STUDY 1 - Chronic periodontitis in patients with chronic autoimmune thyroiditis - features of expression

3.1. Working hypothesis. Objectives

The identification of periodontal lesions compared to patients with CAT without thyroid damage could provide useful information on the involvement of autoimmune thyroid disease in periodontal disease and could be the basis for the study of identifying possible risk factors in the development of periodontal lesions in patients with CAT.

3.2. Material and method

A group of patients with CAT and CP (n = 109) and a control group (n = 91) with CP without thyroid damage (group 2) were examined from a dental point of view.

3.3. Results

The analysis of the data obtained in group 1 and group 2 through the individualized study of each type of lesion revealed a series of differences with different statistical significance depending on the age group and sex of the patients.

A comparative distribution of the percentage values with their statistical significance between the two study groups is shown in table 3.

Table 3. Statistical significance of the lesion type in the two study groups - comparatively

Type of lesion	Group 1 n = 109 (%)	Group 2 n = 91 (%)	P
1. Bleeding sites percentage			
Spontaneous	45,8 % (n = 50)	42,8 % (n = 39)	NS
On probing	38,5 % (n = 42)	60,4 % (n = 55)	p < 0,001
2. Presence of bacterial plaque and tartar deposits	87,1 % (n = 95)	90,1 % (n = 82)	NS

Continuare tabelul 3			
3. Recession of the gingival margin	93,5 % (n = 102)	67 % (n = 61)	p < 0,001
4. Dental mobility			
1st grade	20,2 % (n = 22)	34 % (n = 33)	p < 0,05
2nd grade	48,6 % (n = 53)	17,5 % (n = 31)	p < 0,001
3rd grade	29,3 % (n = 32)	30,7 % (n = 16)	NS
5. Depth of periodontal pockets on probing			
1st grade	13,7 % (n = 15)	30,7 % (n = 28)	p < 0,001
2nd grade	48,6 % (n = 53)	29,6 % (n = 27)	p < 0,001
3rd grade	27,5 % (n = 30)	14,2 % (n = 13)	p < 0,001
6. Involvement of radicular furcation	57,8 % (n = 63)	11 % (n = 10)	p < 0,001
7. Modified dental oclusion	71,5 % (n = 78)	19,7 % (n = 18)	p < 0,001

NS – statisticaly non- significant

Priority impairment of the group of patients with associated chronic autoimmune thyroiditis suggests an additional pathogenic effect in these patients in the development of periodontal disease, compared to normal thyroid patients.

Table 4. Involvement of serum thyroid autoantibody levels in the initial and evolved periodontals lesions - statistical significance - Study Group 1 (n = 109)

	ATPO (mean values)	ATG (mean values)
Recession of the gingival margin (n = 102)	143 ± 22	511 ± 27
Modified dental oclusion (n = 78)	636 ± 24	604 ± 31
p	< 0,001	NS

Quantitative variations and fluctuating particularities of autoantibody action, characteristics of autoimmune diseases in general as well as individual responsiveness to the action of these autoantibodies may explain the heterogeneity of periodontal lesions in patients with CAT (146,150).

The study group (n = 109) aimed to correlate periodontal lesions with serum thyroid hormone levels (Table 5).

Table 5. Correlation of thyroid dysfunction in patients with initial periodontal lesions and evolved.

Study group (n = 109)	Normal function [TSH: 0,24 – 4,2 mUI/ml]	Hypothyroidism [TSH: 24 ± 8,12 mUI/ml]	Thyrotoxicosis [TSH: 0,08 – 0,04 mUI/ml]
Recession of the gingival margin (n = 102)	57 % (n = 56)	27 % (n = 97)	18 % (n = 18)
Modified dental oclusion (n = 78)	52 % (n = 67)	15 % (n= 19)	11 % (n = 14)
p	NS	0,05	NS

Taking into account the increased prevalence of both diseases, further studies in this regard are fully motivated.

3.4. Discussions

Statistically significant values (p <0.001) in favor of the older age group were observed in case of bleeding, spontaneous and probing, the presence of bacterial plaque and tartar deposits, mobility of grade 2 and 3, depth of the periodontal pocket, grade 1, involvement of radicular furcation and altered dental occlusion. Weak statistical significance

(p <0.05) was recorded for gingival margin recession, grade 1 mobility and grades 2 and 3 of depth of periodontal pockets were considered statistically insignificant in favor of the older age group.

In terms of differences in patient sex (Table 1) statistically significant values (p <0.001) in favor of women compared to men were recorded for spontaneous bleeding. Statistical significance (p <0.001) in favor of men was observed for probing bleeding, grade 2 dental mobility and altered dental occlusion. Poor statistical significance was recorded for recession of the gingival margin, dental mobility grade 3, depth of periodontal pockets grade 3. There were no statistically significant differences in the presence of bacterial plaque, dental mobility grade 1, depth of periodontal pockets at grade 1 probing and involvement of radicular furcation.

The specific analysis of periodontal lesions according to the age group criterion recorded significant values (p <0.001) in favor of the older age group for gingival margin recession, dental mobility grade 1 and grade 3, depth of periodontal pockets when probing for 3rd degree of severity, in the involvement of the radicular furcation and the modified dental occlusion. Statistical significance had a low value (p <0.05) in the case of spontaneous bleeding and bacterial plaque with tartar deposition.

No significant values were recorded for probing bleeding and grade 2 dental mobility.

Statistically significant differences (p <0.001) obtained in favor of men for spontaneous bleeding and grade 1 dental mobility and depth of periodontal pockets – 1st grade.

The differences had a low statistical significance (p <0.05) in the case of recession of the gingival margin, grade 2 dental mobility, depth of periodontal pockets at probing - grade 2 and altered dental occlusion. There were no statistically significant differences in the other types of lesions.

The possible involvement of the mean serum level of thyroid autoantibodies in the performance of periodontal lesions was assessed differently for ATPO / ATG (Table 4) the result having statistical significance (p <0.001) only for ATPO.

A possible involvement of thyroid dysfunction in patients with CAT in the development of periodontal lesions proved insignificant for the same types of lesions, initially - recession of the gingival margin - and aggravated - altered dental occlusion, in patients with normal function and those with thyrotoxicosis in the study group. 1. Statistical significance was weakly significant (p <0.05) only for hypothyroidism in favor of gingival margin recession.

3.5. Conclusions

1. Clinical data studied comparatively between the two groups of patients with chronic periodontitis, with and without associated autoimmune chronic thyroiditis, reveal a heterogeneity of the distribution of recorded lesions, statistical significance being recorded primarily for the elderly in both groups and being heterogeneous function of the sex of the patients.
2. The comparative assessment of periodontal lesions considered aggravated found a preponderance of them especially among patients with associated thyroid damage suggesting an additional pathogenic effect in these patients compared to patients without thyroid damage.

Chapter 4. STUDY 2 - Staged evolution of chronic periodontitis in a group of patients with chronic autoimmune thyroiditis - pathogenic intercorrelations with the oral hygiene index

4.1. Working hypothesis. Objectives

Multifactorial etiopathogenesis with many common coordinates, both for CAT and CP raises the suspicion of pathogenic interconditioning between the two diseases as a substrate infection, thyroid dysfunction and the development of autoimmunity, a fact postulated for several decades (268,270).

4.2. Material and method

Periodontal lesions found in patients in the two previously studied groups (n = 109; n = 91) were characterized by severity and magnitude, given the staged evolution of the disease (62), under the influence of hypothyroidism and thyroid autoantibodies. (287) with potential impact on bacterial plaque, and indicative of oral hygiene, initiator of the inflammatory / autoimmune process (269,294,295,297).

Patients were classified according to the severity of periodontal lesions:

→ Mild CP - with gingival bleeding, recession of the gingival margin, tartar deposition: group 1 - 35 cases, group 2 - 27 cases;

→ CP of medium intensity - according to the probing depth of the periodontal pockets with affected dental attachment: group 1 - 58 cases, group 2 - 52 cases;

→ Severe CP, with root fork and modified dental occlusion: group 1 - 16 cases, group 2 - 12 cases.

The oral hygiene index was assessed in the range of values: 0 - 1.2 (low); 1.3 - 3 (medium); 3.1 - 6 (increased), including plaque and tartar index.

The study of nonspecific autoimmunity was performed by qualitatively dosing ANA antinuclear antibodies by EliA Symphony test.

4.3. Results:

Medium-intensity periodontal lesions prevailed in both groups (Figure 1).

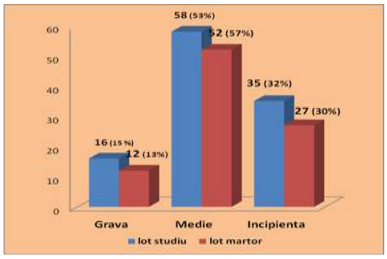


Figure 1. Periodontal disease study group/control group

The distribution of periodontal lesions according to the sex of the patients had the following characteristics (Figure 2).

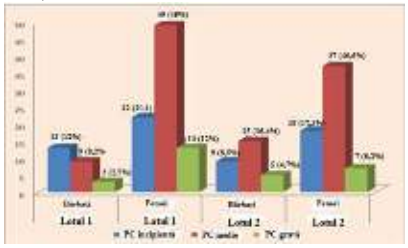


Figure 2 Comparative distribution of parodontal lesions depending on sex

According to the age criterion, the intensity of periodontal lesions had the following distribution.

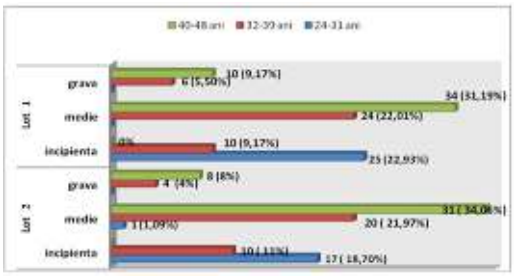


Figure 3 Comparative distribution of parodontal lesions depending on age

Monofactorial linear regression (Pearson's r coefficient) tested the dependency ratios between OHI-s and patients' age (Figure 4), thyroid function (TSH) (Figure 5) and thyroid autoimmunity (ATPO, ATG) (Figure 6).

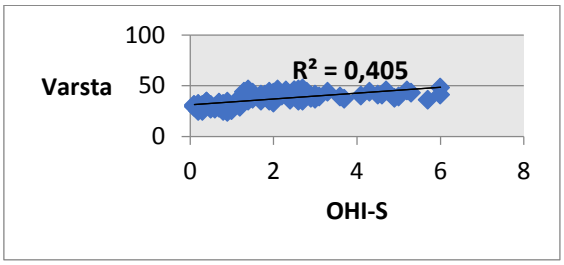


Figura 4 Correlations between age and OHI-s (Pearson's – r coefficient)

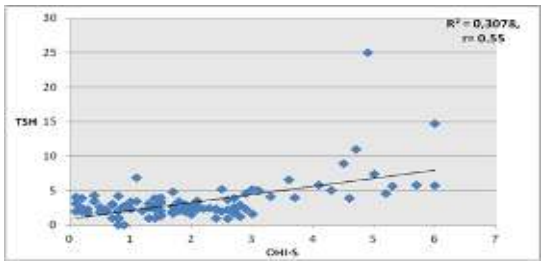


Figura 5 Correlations between TSH and OHI-s (Pearson's – r coefficient)

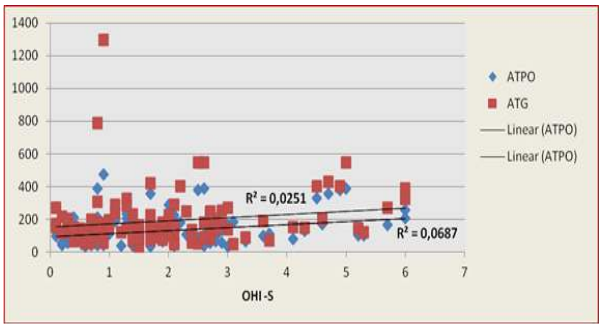


Figura 6 Correlations between ATPO, ATG and OHI-s (Pearson's – r coefficient)

The multifactorial linear regression calculation established the following correlations between OHI-s and TSH, ATPO and ATG (Figure 7).

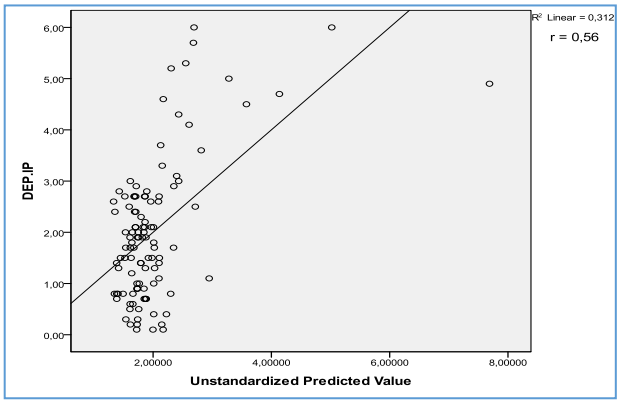


Figure 7. Correlations between OHI-s, TSH, ATPO and ATG (multifactor linear regression)

Applying the calculation by multiple linear regression, the following statistical correlations were obtained between OHI-s and TSH, ATPO, ATG and patients' age (Figure 8).

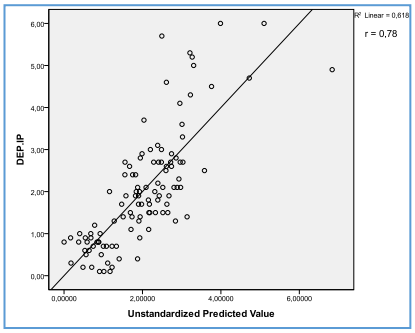


Figure 8 Correlation between OHI-s-TSH, ATPO, ATG – ab and age (linear multiple regression)

4.4. Discussions

All three categories of lesions were found more frequently in patients in group 1 compared to patients in the control group (p = 0.043).

Although the number of male patients (n = 54) was lower than that of female patients (n = 146), the probability of influencing CP severity according to gender was reduced in both group 1 (p = 0.051), as well as in group 2 (p = 0.058).

In terms of patients' age, an average interdependence was established between OHI-s and age (r = 0.63; p = 0.018) (Figure 3, Figure 4).

Thyroid function determined in hypothyroidism an average interdependence between sOHI and TSH (r = 0.55; p = 0.0003) (Figure 5).

Analyzing the relationship between the parameters obtained in the study of TCA characteristics in patients in the study group by multifactorial linear regression was found a directly proportional relationship between OHI-s and TSH, ATPO, ATG (r = 0.56; p = 0.001) (Figure 6, Figure 7).

Along with these parameters, their interdependence was much closer considering the age of the patients (r = 0.78; p <0.001) (Figure 8).

The presence of the two types of antibodies exerts a much more intense effect on sOHI in the study group compared to the control group (Pr = 96.28%; r = 0.87; p = 0.00372).

The influence of the listed parameters on IH-s increases significantly if the age of the patients is taken into account (Pr = 94.6%; r = 0.997; p <0.001) and the serum TSH level (Pr = 92.4%; r = 0.55; p = 0.0003).

In the case of patients with CP from the two groups, the presence of ANA did not correlate with the severity of periodontal lesions (p = 0.10). However, the interpretation of this result must take into account the limiting aspect of the low number of cases for this parameter in the study.

4.5. Conclusions

1. The oral hygiene index as a marker of bacterial plaque in the initiation and progression of chronic periodontitis correlated with inadequate oral hygiene measures was considered a useful study parameter on the causal interrelationships CP / CAT, being known that the gingival defense barrier is structurally and functionally altered in thyroid disease.

2. The evaluation in the ANOVA test on the parameters studied with potential effect on the oral hygiene index finds an intensified effect exerted by the presence of both types of thyroid autoantibodies, the serum TSH level characteristic of hypothyroidism and proportional to age, in the study group compared to the control group. These differences

found between the averages of the groups of values studied emphasize the multifactorial involvement in the realization of periodontal lesions with increased intensity in patients with autoimmune thyroiditis.

Chapter 5. STUDY 3 - Antithyroid antibodies - a possible involvement in the development of chronic periodontitis

5.1. Objectives

Highlighting the presence of periodontal lesions in patients with chronic autoimmune thyroiditis and correlating them with the specifics and particularities of the distribution of antithyroid autoantibodies.

5.2. Material and methods:

The study group included a number of 133 patients diagnosed with chronic autoimmune thyroiditis by clinical examination, thyroid ultrasound and serum level dosage (ECHEM) of thyroid autoantibodies.

Criteria for assessing periodontal lesions: patients were examined from the point of view of dental status identifying lesions characteristic of chronic periodontitis according to their classification according to the recommendations of the European Periodontology Federation (62) and according to the concept of dynamic assessment of stage evolution of chronic periodontitis (20,23). Periodontal lesions were identified and classified according to their specificity and severity as: mild, moderate intensity and severe.

5.3. Results

The distribution of periodontal lesions, often intricate in the same patient, had the following percentage values of the type of lesion found among patients with CP associated with CAT (Table 2).

Table 2. Incidence of types and distribution of periodontal lesions - patients with chronic autoimmune thyroiditis

Periodontal lesions		**Patients with CP (n = 133)**	%
1. Bacterial plaque/Tartar deposits		120	90,22
2. Bleeding			
	Spontaneous	50	37,59
	On probing	83	62,4
3. Recession of marginal pockets		103	77,44
4. Dental mobility			
	1st grade	90	67,67
	2nd grade	37	27,81
	3rd grade	6	4,51
5. Depth of parodontal pockets - probing			
	Mild 1 – 2 mm	44	33,08
	Moderate 3 – 4 mm	76	57,14
	Severe > 5 mm	13	9,77
6. Radicular furcation			
	1st grade < 3 mm	77	57,89
	2nd grade > 3 mm	44	33,08
	3rd grade - complete penetration	12	9,02
7. Modified dental oclusion		25	18,8

Patients with CAT and periodontal lesions were classified according to the specificity of autoantibody expression as incidence and mean serum level (Table 3):

Table 3. Antithyroid antibodies - distribution characteristics (n = 133)

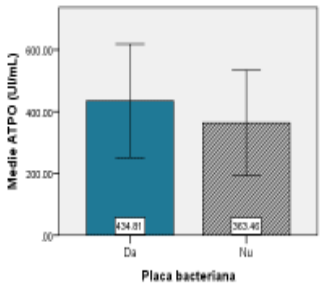
	ATPO	**ATG**	**ATPO + ATG**
Patients number	46	19	68
Percentual value (%)	34,58	14,28	51,12
Mean value of serum level of autoantibodies	332 ± 206	553 ± 271	612 ± 108

The presence of **bacterial plaque** was identified in a number of 120 patients.

Table 4. ATPO / ATG distribution - Bacterial plaque

	Bacterial plaque	N	Mean	Std. Deviation	Std. Error Mean
ATPO (UI/mL)	Da	120	434.81	183.80	16.78
	Nu	13	363.46	170.46	47.28
ATG (UI/mL)	Da	120	269.13	148.26	13.53
	Nu	13	216.46	98.25	27.25

The graphical representation of the obtained values is shown in Figure 1 for ATPO and Figure 2 for ATG.



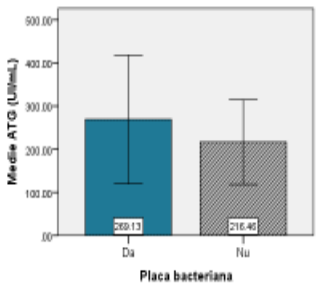


Figure 1 ATPO/Bacterial plaque

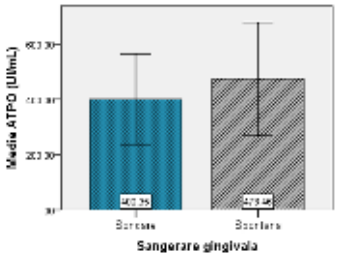
Figura 2 ATG/ Bacterial plaque

Gingival bleeding was explored by probing and identified in 83 patients. A number of 50 patients presented with spontaneous bleeding, declared by them through self-observation (Table 5).

Table 5. ATPO/ATG distribution– Gingival bleeding

	Gingival bleeding	N	Mean	Std. Deviation	Std. Error Mean
ATPO (UI/mL)	Probing	83	400.35	164.07	18.01
	Spontaneous	50	473.46	204.76	28.96
ATG (UI/mL)	Probing	83	251.06	139.04	15.26
	Spontaneous	50	285.44	152.66	21.59

Differences in mean ATPO / ATG values in terms of gingival bleeding are plotted (Figure 3; Figure 4).



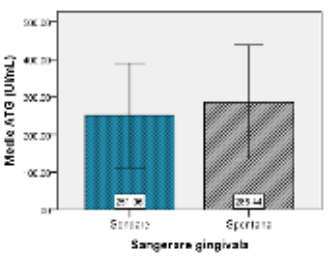


Figure 3 ATPO – Gingival bleeding

Figure 4 ATG – Gingival bleeding

Gingival recession as an evolutionary stage beyond the initial gingivitis lesions was described in 103 patients. For 30 patients this characteristic lesion of periodontal pathology could not be specified (Table 6).

Table 6. ATPO/ATG distribution – Gingival recession

	Gingival recession	N	Mean	Std. Deviation	Std. Error Mean
ATPO (UI/mL)	Yes	103	447.57	179.54	17.69
	No	30	360.07	182.20	33.27
ATG (UI/mL)	Yes	103	270.52	149.45	14.73
	No	30	241.53	126.79	23.15

The different distribution of thyroid autoantibody values among patients with gingival recession (n = 103) and among those without gingival recession (n = 30) is shown graphically in Figure 5 and Figure 6, respectively.

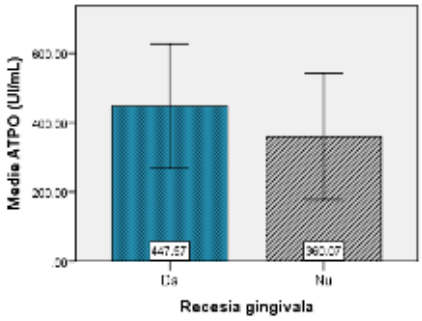


Figure 5 ATPO – Gingival recession

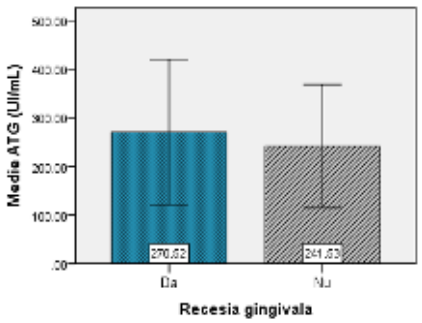


Figure 6 ATG – Gingival recession

Evaluation of dental mobility, aggravated evolutionary stage of periodontal lesions was gradually assessed by the meaning and extent of mobility - grade 1 - vestibulo-oral mobility; grade 2 - vestibulo-oral and proximal mobility; grade 3 - vestibulo-oral, proximal and axial mobility (Table 7).

Table 7. ATPO/ATG distribution – dental mobility

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
ATPO (UI/mL)	Grade 1	90	386.29	159.99	352.78	419.80	60.00	800.00
	Grade 2	37	500.19	198.97	433.85	566.53	45.00	910.00
	Grade 3	6	604.83	193.93	401.32	808.35	414.00	830.00
ATG (UI/mL)	Grade 1	90	247.88	135.92	219.41	276.35	115.00	690.00
	Grade 2	37	291.03	155.56	239.16	342.89	118.00	720.00
	Grade 3	6	338.83	181.44	148.43	529.24	125.00	570.00

Figure 7 and Figure 8, respectively, reproduce the gradually assessed differences in the distribution of mean ATPO / ATG values as a function of pathological dental mobility (Figure 7; Figure 8).

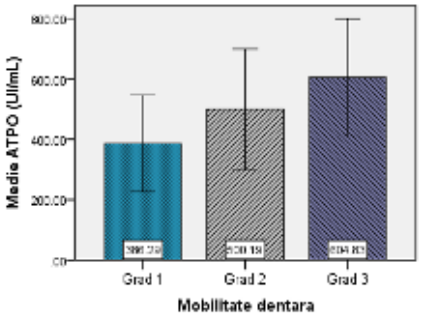


Figure 7 ATPO – Dental mobility

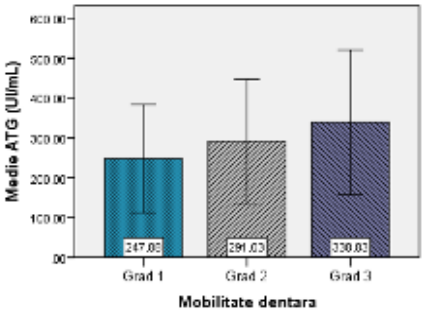


Figure 8 ATG – Dental mobility

Exploration of periodontal pockets classified the level of clinical dental attachment by probing depth at six sites / tooth: light 1 - 2 mm; average 3 - 4 mm; severe> 5 mm (Table 8).

Table 8. ATPO/ATG distribution – depth of parodontal pockets

		N	Mean	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
ATPO (UI/mL)	Mild	44	365.18	25.39	313.97	416.39	60.00	800.00
	Moderate	76	443.36	20.85	401.82	484.89	45.00	910.00
	Severe	13	549.15	47.22	446.26	652.04	283.00	830.00
ATG (UI/mL)	Mild	44	238.50	19.18	199.83	277.17	128.00	608.00
	Moderate	76	271.12	17.55	236.15	306.08	115.00	720.00
	Severe	13	308.54	40.35	220.63	396.45	125.00	570.00

The mean values of the serum ATPO / ATG level assessed comparatively depending on the result of probing the periodontal pockets are shown graphically (Figure 9; Figure 10).

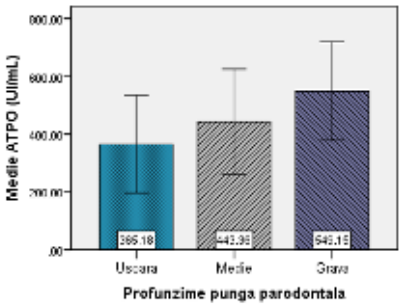


Figure 9 ATPO – Depth of parodontal pockets

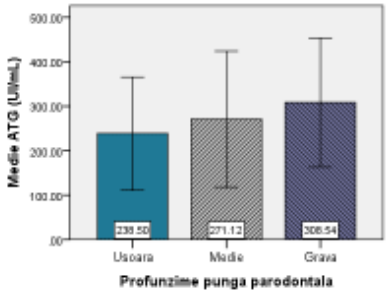


Figure 10 ATG - Depth of parodontal pockets

The root fork evaluated by the horizontal penetration of the probe was classified according to the depth and direction of the probe penetration: grade 1 <3 mm; grade 2 > 3 mm; grade 3 at the end between two dental roots (Table 9).

Table 9. ATPO/ATG distribution – radicular furcation

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
ATPO (UI/mL)	Gr.1	77	393.84	167.69	355.78	431.91	60.00	870.00
	Gr.2	44	446.70	190.89	388.67	504.74	45.00	910.00
	Gr.3	12	576.75	179.33	462.81	690.69	283.00	830.00
ATG (UI/mL)	Gr.1	77	246.22	141.46	214.11	278.33	116.00	690.00
	Gr.2	44	286.43	147.15	241.70	331.17	115.00	720.00
	Gr.3	12	295.67	151.86	199.18	392.16	125.00	570.00

The compared average ATPO / ATG values corresponding to the three groups of patients gradually classified according to the degree of root fork are plotted (Figure 11; Figure 12).

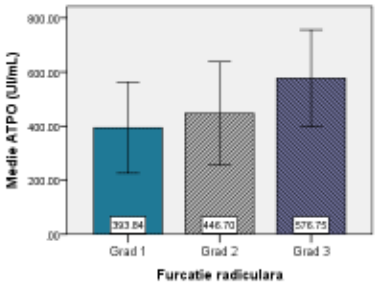


Figura 11 ATPO – Radicular furcation

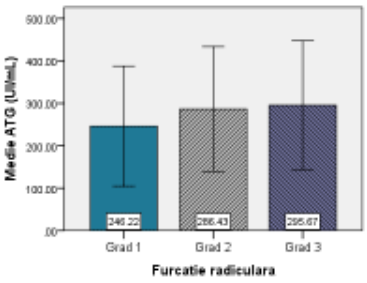


Figura 12 ATG – Radicular furcation

The major impairment of dental attachment assessed by the presence **of modified dental occlusion** was assessed differently in terms of the distribution of the average serum level of thyroid autoantibodies - ATPO / ATG depending on its presence and absence (Table 10).

Table 10. ATPO/ATG distribution – modified dental occlusion

	Modified dental occlusion	N	Mean	Std. Deviation	Std. Error Mean
ATPO (UI/mL)	Yes	25	508.12	194.77	38.95
	No	108	409.25	176.14	16.95
ATG (UI/mL)	Yes	25	289.20	131.39	26.28
	No	108	258.15	147.57	14.20

Graphically, the distribution of ATPO / ATG values depending on the presence / absence of modified dental occlusion are shown in Figure 13 - for ATPO and Figure 14 - for ATG.

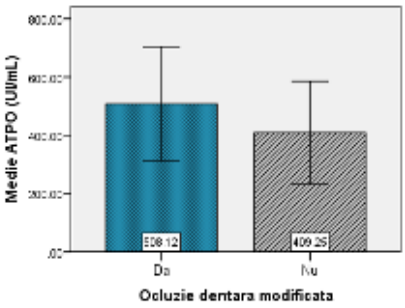


Figura 13 ATPO – Modified radicular furcation

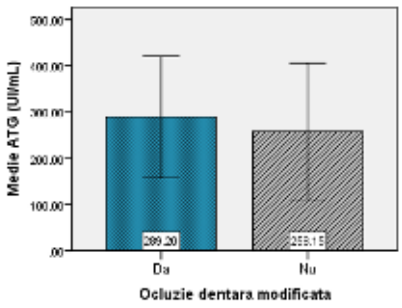


Figura 14 ATG – Modified radicular furcation

According to the staged classification of periodontal lesions according to their evolution, the mean ATPO / ATG values were analyzed differently by assessing the totality of **lesion types** summed in CP - mild, medium, severe (Table 11).

Table 11. ATPO/ATG distribution – lesion type

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
ATPO (UI/mL)	Mild	36	367.25	169.94	309.75	424.75	60.00	800.00
	Moderate	65	430.05	181.96	389.81	470.29	45.00	910.00
	Severe	32	552.94	160.39	467.47	638.40	283.00	830.00
ATG (UI/mL)	Mild	36	252.61	135.45	206.78	298.44	128.00	608.00
	Moderate	65	257.83	148.68	224.95	290.70	115.00	720.00
	Severe	32	320.75	140.06	246.11	395.39	125.00	570.00

The different distribution of the average ATPO / ATG values regarding the evolutionary stages of CP - mild, moderate, severe - is shown graphically - Figure 15 and Figure 16, respectively.

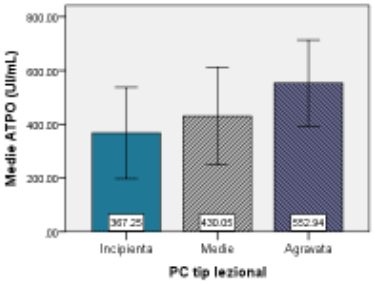


Figure 15 ATPO – CP lesion type

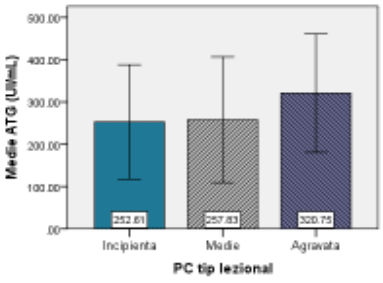


Figure 16 ATG – CP lesion type

5.4 Discussions

The distribution of periodontal lesions, with significant diversity and frequency variations among patients with CAT (n = 133) emphasizes the association of the two diseases highlighted by clinical observation (190,193,194,197,198,202,267,269) lesions depending on the evolutionary stage being differently classified (231).

We find that significant differences are between the mean ATPO values recorded in patients with mild lesions and those with severe lesions (p = 0.003), as well as between the values recorded in patients with moderate intensity lesions compared to the values recorded in patients with severe lesions (p = 0.003). = 0.036), but not between the values recorded in patients with mild and moderate lesions (p = 0.234) (Table 15).

Table 15. ATPO – Multiple variables comparisons - Bonferroni

	Sig.		
	(I) CP lesion type		
(J) CP lesion type	Mild	Moderate	Severe
Mild		.234	.002
Moderate	.234		.036
Severe	.002	.036	

5.5. Conclusions

1. Identifying the involvement of the thyroid autoimmune process in the performance of periodontal lesion types is a priority in favor of the serum ATPO level. There were average values of ATPO with statistical significance for gingival bleeding, gingival recession, depth of probing periodontal pockets proportional to its severity, the presence of root fork priority for grade three, compared to grade one, altered dental occlusion. For the mean serum ATG level, no statistically significant values were obtained correlated to the same type of periodontal lesions found on examination of the oral cavity of the patients studied.
2. The presence of significantly increased mean values of ATPO among patients with periodontal lesions classified as severe, suggesting different implications of thyroid autoantibodies - ATPO with effects systemic and thus implications in extra-thyroid complications, including chronic periodontitis, and ATG with destructive activity focused primarily on the thyroid tissue.

Chapter 6. STUDY 4 - Serum and salivary interleukin 1β in patients with chronic autoimmune thyroiditis associated with chronic periodontitis

6.1. Introduction. Working hypothesis. Objectives.

The identification of quantitative and / or qualitative differences in markers specific to the pathogenic mechanisms of the two diseases, such as IL-1β in serum - for systemic effects - and in saliva - for local effects, could explain the potentiation of the two diseases, both with an increased incidence at the level of the population, in the staged realization of the characteristic tissue lesions.

Interleukin titers determined in various biological fluids can be used in the diagnosis of immune disorders and in the monitoring of treatments only in correlation with complementary clinical and paraclinical data.

6.2. Material and method

The study group included a number of 70 patients diagnosed with chronic autoimmune thyroiditis (TCA) according to the protocol and methodology outlined above.

The recorded lesions determined the classification of patients:

→ CP - mild: tartar deposition, sites of spontaneous and probing bleeding, recession of the gingival margin (n = 20 - 28.57%);

→ CP - of moderate intensity: the presence of periodontal pockets; loss of dental attachment (n = 14 - 20%);

→CP - severe: root fork, modified dental occlusion, alteration of masticatory function (n = 12 - 17.14%).

6.3. Results:

The median IL-serum values (pg / ml) was 2,257, and that of IL-saliva (pg / ml) 38,855 with a significant difference in values (p <0.001) (Table 40; Figure 23).

Table 40. Values of IL-serum/IL-saliva: median values

	Statistic	
	IL serum (pg/ml)	ILsaliva (pg/ml)
Mean	3.292	37.980
Median	2.257	38.855
Std. deviation	2.860	18.116
Minimum	.180	9.552
Maximum	10.548	69.781
Range	10.368	60.229
Interquartile Range	3.588	30.746
Skewness	.992	-.040
Kurtosis	-.231	-1.282

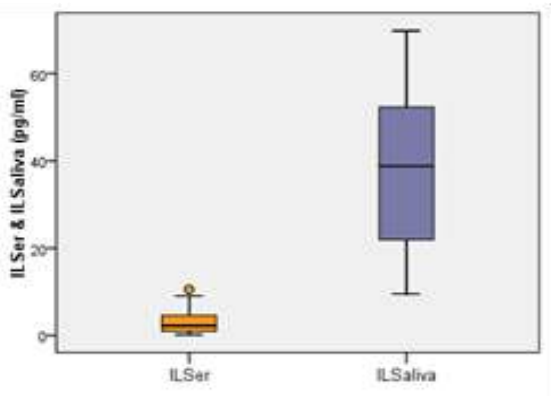


Fig. 23 IL-serum/IL-saliva: comparative median values

No significant differences were found between the median values of serum IL level corresponding to the four study groups (patients without periodontal lesions and patients with PC) (p = 0.764> 0.05), respectively the distribution of values was the same within the groups (p = 0.440> 0.05) (Figure 24).

The median values of IL in saliva at the level of the four studied groups had a statistically significant different distribution (p <0.001 <0.05) (Table 43; Figure 25).

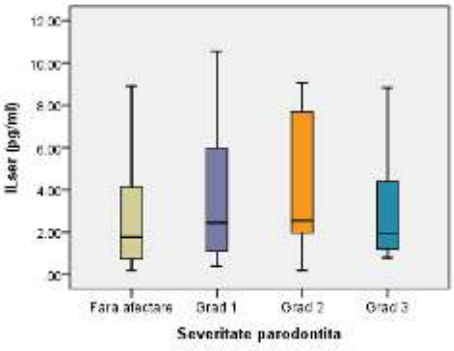


Figure 24 IL-serum: comparative values

Table 43. IL-saliva: values distribution

		Statistical			
		Severity of periodontitis			
		No involvement	Grade 1	Grade 2	Grade 3
ILsaliva (pg/ml)	Mean	24.475	39.255	47.824	51.381
	Median	21.476	36.815	51.229	60.484
	Standard Deviation	12.810	15.641	15.035	17.485
	Minimum	9.749	9.552	9.754	12.094
	Maximum	57.469	69.781	66.731	65.086
	Range	47.720	60.229	56.977	52.992
	Interquartile Range	20.618	24.005	11.875	17.351
	Skewness	.867	.158	-1.539	-1.558
	Kurtosis	.139	-.431	2.552	1.461

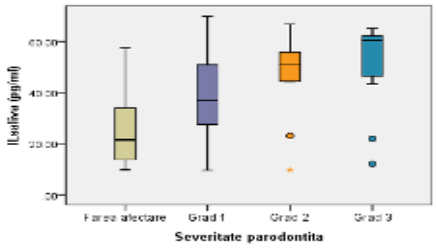


Figure 25 IL-salivary: comparative values

No statistically significant differences were found regarding the involvement of thyroid function (normal - TSH: 0.27 - 4.2 IU / ml; hypothyroidism - TSH> 4.3 IU / ml) in the achievement of serum IL-1β in serum - median values 1,971 / 2,730 (0.088 p> 0.05 / 0.291 p> 0.05) (Table 45; Figure 26).

Table 45. IL 1β serum – thyroid functional status

		Statistic	
		Funcție tiroidiană	
		Normofuncție	Hipotiroidism
ILser (pg/ml)	Medie	3.105	3.573
	Mediana	1.971	2.730
	Deviația std.	2.911	2.810
	Minimum	.180	.188
	Maximum	10.548	8.910
	Range	10.368	8.722
	Interquartile Range	3.510	4.020
	Skewness	1.184	.772
	Kurtosis	.197	-.572

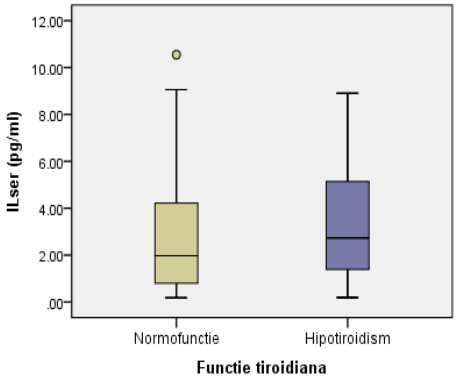


Figure 26 IL 1β serum – thyroid functional status

Also in saliva - median values 43,136 / 36,703 (0.807 p> 0.05 / 0.557 p> 0.05) without statistical significance (Table 47; Figure 27).

Table 47. IL 1β saliva – thyroid functional status

		Statistic	
		Thyroid function	
		Normofuncțion	Hypothyroidism
ILsaliva (pg/ml)	Mean	38.936	36.546
	Median	43.136	36.703
	Std. deviation	19.350	16.328
	Minimum	9.552	12.094
	Maximum	69.781	65.086
	Range	60.229	52.992
	Interquartile Range	33.174	28.761
	Skewness	-.131	.075
	Kurtosis	-1.392	-1.087

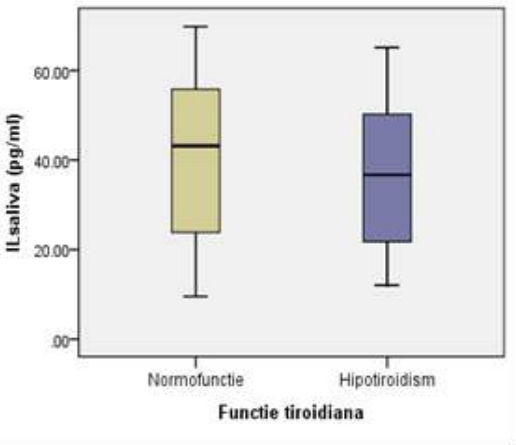


Figure 27 IL 1β saliva – thyroid functional status

The median values for IL-serum were: 2,067; 2,352; 2,541 (0.853 p> 0.05; 0.967 p> 0.05), taking into account the age criterion, the patients being assessed according to the mentioned age categories (Table 49; Figure 28).

Table 49. IL 1β serum – age correlation

		Statistical		
		Age yearsi)		
		(22-40]	(41-60]	(61-75)
ILserum (pg/ml)	Mean	3.205	3.428	2.916
	Median	2.067	2.352	2.541
	Std. deviation	2.837	3.066	2.122
	Minimum	.180	.188	.803
	Maximum	8.860	10.548	6.501
	Range	8.680	10.360	5.698
	Interquartile Range	3.912	3.941	3.786
	Skewness	.957	1.013	.434
	Kurtosis	-.277	-.356	-1.280

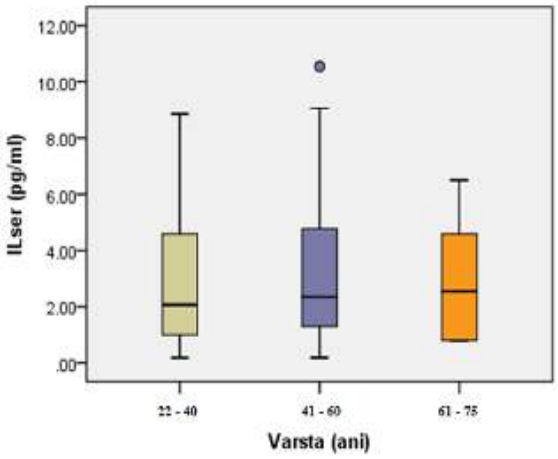


Figure 28 IL 1β serum – age correlation

For salivary IL assessed in the same manner - differentiated by age groups, the median values were: 35,847; 40,821; 43,379 (0.853 p> 0.05; 0.444 p> 0.05) (Table 51; Figure 29).

Table 51. IL 1β saliva – age correlations

		Statistic		
		Age (years)		
		(22-40]	(41-60]	(61-75)
ILsaliva (pg/ml)	Meam	33.934	40.026	39.006
	Median	35.847	40.821	43.379
	Standard deviation	16.483	18.108	22.211
	Minimum	10.188	9.749	9.552
	Maximum	57.469	69.781	62.263
	Range	47.281	60.032	52.711
	Interquartile Range	33.796	32.101	46.240
	Skewness	-.141	-.021	-.255
	Kurtosis	-1.514	-1.285	-1.843

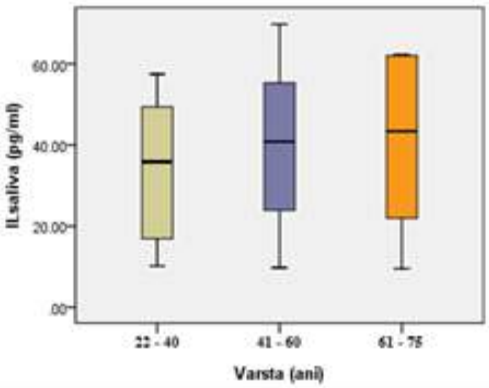


Figure 29 IL 1β saliva – age correlation

In the "nonparametric correlation" analysis, no correlation of serum IL / IL saliva was also established with the age of the patients (rho = - 0.011, p = 0.929; rho = 0.198, p = 0.100) (Table 53).

Table 53. Correlation coefficient ILserum/Il saliva/patients age

			IL serum (pg/ml)	**Age (years)**
Spearman's rho	**ILserum (pg/ml)**	Correlation Coefficient **rho**	1.000	-.011
		Sig. (2 - tailed) **p**	.	.929
		N	70	70
	Age (years)	Correlation Coefficient	-.011	1000
		Sig. (2 - tailed)	.929	.
		N	70	70
			ILsaliva (pg/ml)	**Age (years)**
Sperman's rho	**ILsaliva (pg/ml)**	Correlation Coefficient **rho**	1.000	.198
		Sig. (2 - tailed) **p**	.	.100
		N	70	70
	Age (years)	Correlation Coefficient	.198	1.000
		Sig. (2 - tailed)	.100	.
		N	70	70

For IL - serum the following values were recorded: 2,352 women; 1,682 men (0.306 p> 0.005; 0.585 p> 0.05); (Table 54; Figure 30)

Table 54. IL serum – patients sex correlations

		Statistic	
		Sex	
		Women	Male
ILserum (pg/ml)	Mean	3.332	3.050
	Median	2.352	1.682
	Std. deviation	2.851	3.055
	Minimum	.180	.188
	Maximum	10.548	9.059
	Range	10.368	8.871
	Interquartile Range	3.539	5.399
	Skewness	1.003	1.133
	Kurtosis	-.155	-.113

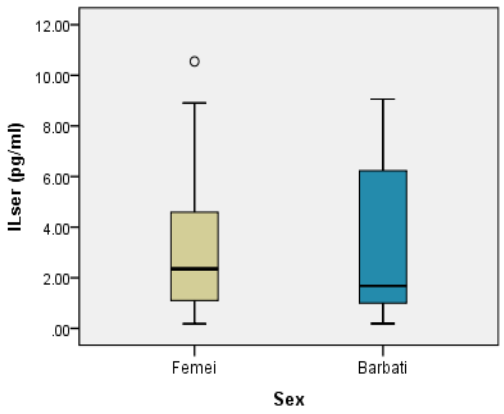


Figure 30 IL serum – Patients sex correlations

Correlations between nonparametric values of thyroid autoantibodies (ATPO; ATG) and IL-1β values measured in serum and saliva had the following distribution (Table 66).

Table 66. Nonparametric correlations ATPO, ATG, IL-1β.

			ATPO (UI/L)	**IL serum (pg/ml)**
Spearman's rho	ATPO (UI/L)	Correlation Coefficient **rho**	1.000	.199
		Sig. (2 - tailed) **p**	.	0.099
		N	70	70
	ILserum (pg/ml)	Correlation Coefficient	.199	1.000
		Sig. (2 - tailed)	.099	.
		N	70	70
			ATG (UI/L)	**IL serum (pg/ml)**
Spearman's rho	**ATG (UI/L)**	Correlation Coefficient **rho**	1.000	-.116
		Sig. (2 - tailed) **p**	.	.337
		N	70	70
	IL serum (pg/ml)	Correlation Coefficient	-.116	1000
		Sig. (2 - tailed)	.337	.
		N	**70**	**70**
			ATPO (UI/L)	**IL saliva (pg/ml)**
Sperman's rho	**ATPO (UI/L)**	Correlation Coefficient **rho**	1.000	.035
		Sig. (2 - tailed) **p**	.	.772
		N	70	70
	IL saliva (pg/ml)	Correlation Coefficient	.035	1.000
		Sig. (2 - tailed)	.772	.
		N	70	70
			ATG (UI/L)	**IL saliva (pg/ml)**
Spearman's rho	**ATG (UI/L)**	Correlation Coefficient **rho**	1.000	-.348
		Sig. (2 - tailed)	.	.003
		N	70	70
	ILsaliva (pg/ml)	Correlation Coefficient	-.348	1.000
		Sig. (2-tailed)	.003	.
		N	70	70

A significant, but weak to moderate correlation was obtained between ATG and IL - saliva (rho = 0.348, p = 0.003).

6.5. Conclusions

1. The presence of IL-1β in serum and saliva in patients with chronic autoimmune thyroiditis with and without chronic periodontitis attests to the inflammatory and autoimmune lesion substrate common to the two diseases.

2. The identification of values whose median is significantly increased in favor of salivary IL-1β compared to the median serum IL-1β values suspects an intensified local effect in the components of the oral cavity in patients with chronic autoimmune thyroiditis. Differences in quantitative values of salivary IL-1β between patients with CP and those without periodontal lesions do not exclude the pathological involvement of CAT on inflammatory substrate suggesting differences in the evolutionary phase of periodontal disease.

3. The lack of a statistical correlation of the median serum and salivary IL-1β values with the age and sex of patients, thyroid function, median thyroid autoantibody median values differentiated according to their value ranges, emphasizes the possibility of local production of IL-1β at the gingival level.

4. The presence of increased values of salivary IL-1β, having a significantly increased distribution according to the degree of presentation of periodontal lesions emphasizes the staged evolution of the disease.

Chapter 7. Final conclusions and general contributions

1) The increased incidence of periodontal lesions encountered in patients with chronic autoimmune thyroiditis suspects etiopathogenic overlap for the two common diseases and evolutionary mechanisms.

2) A number of variables such as age, sex of patients, thyroid functional characteristics, varied profile of thyroid autoantibodies as entities and quantity as well as poor oral hygiene may be directly or correlatively involved in affecting the components of the oral cavity.

3) The classification of periodontal lesions according to their intensity and extent from incipient lesions to severe lesions, emphasizes the dynamics of their evolution with variations in intensity, duration of expression, particularities of expression for both potentially harmful factors and inflammatory and autoimmune response of the patient.

4) The multifactorial, dynamic and cumulative interpretation over time of periodontal lesions in patients with chronic autoimmune thyroiditis must be adapted to each patient perceived as at an evolving stage of the disease. This point of view allows therapeutic attitudes of collaboration and in accordance with the evolutionary risks as well as an individualized prognosis regarding the lesion status appreciated in real time.

5) All three categories of periodontal lesions - mild, moderate, severe - were found more frequently among patients with chronic autoimmune thyroiditis, mild lesions being found primarily in the young age group, and severe ones increasing in incidence in proportion to the age of patients.

6) Evaluation of periodontal lesions according to the sex of patients found differences for some variables studied in terms of lesion intensity but lack of statistical significance for thyroid autoantibodies, thyroid function, inflammatory process assessed serum and salivary. The small number of male patients can be considered a limiting element of the study.

7) The oral hygiene index as a marker of bacterial plaque in the initiation and progression of chronic periodontitis correlated with inadequate oral hygiene measures is a useful study parameter on causal CP / CAT intercorrelations, the gingival defense barrier being structurally and functionally altered in thyroid diseases.

8) By monofactorial linear regression, an average interdependence of the oral hygiene index was obtained with the age of the patients, the hormonal profile characteristic of hypothyroidism, without a relationship with the average level of thyroid autoantibodies. The assessment of the study parameters by multifactorial linear regression found a direct proportional relationship of the oral hygiene index with the mean serum TSH, ATPO and

ATG, their interdependence being closer considering the age of patients as a cumulative element of the duration of periodontal disease and autoimmune thyroid disease.

9) The multifactorial dynamic and cumulative analysis of periodontal lesions in patients with autoimmune thyroid disease emphasizes a multifactorial involvement in the performance of periodontal lesions, all these potential factors can be studied.

10) If thyroid dysfunction usually associates trophic changes in the components of the oral cavity, under normal thyroid function the role of thyroid autoantibodies in the periodontal destructive process is still vaguely defined, as they have as an evolutionary feature individualized quantitative fluctuations.

12) Inequality in expression and involvement of ATPO compared to ATG in the development of PC in patients with CAT is underlined by the presence of significantly increased mean values of ATPO among patients with periodontal lesions classified as aggravated suggesting different implications of thyroid autoantibodies - ATPO with systemic effects and thus implications in extra-thyroid complications, including chronic periodontitis, and ATG with destructive activity focused primarily on the thyroid tissue.

13) Clinical observations related to a possible specific mechanism of involvement of thyroid autoantibodies in periodontal disease often associated with thyroid autoimmune disease are important in signaling the existence and complexity of the inflammatory-autoimmune process that characterizes both diseases. The interference of autoimmunity with thyroid dysfunction recognized as an important etiopathogenic factor in the development of CP requires clarifications such as the cause-effect ratio, evaluating the decrease of immune tolerance, as a general process characteristic of autoimmune diseases, and the involvement of destructive inflammatory tissue.

16) Significantly increased median values of salivary IL-1β compared to the median serum IL-1β value suspect an intensified local inflammatory effect in the oral cavity in patients with chronic autoimmune thyroiditis.

17) Lack of a statistical correlation of the median value of serum and salivary IL-1β with a number of variables studied to evaluate possible implications in the autoimmune / inflammatory process, such as age, sex of patients, thyroid function assessed at the level of hormonal components thyroid, the median values of thyroid autoantibodies assessed differently as a range of values - emphasizes the possibility of local production of IL-1β at the gingival level.

19) The significant distribution of the median salivary IL-1β values according to the intensity of the periodically assessed periodontal lesions emphasizes the staged evolution of the disease, proportional to the intensity of the inflammatory process.

20) The presence of salivary IL-1β in patients with CAT without periodontal lesions implies the interpretation of a possible subclinical stage of the development of chronic periodontitis imposing dispensary and prophylaxis measures adapted to patients with autoimmune thyroid disease.

21) The titer of interleukins, including IL-1β, determined in various biological fluids may be a diagnostic element in immune diseases and in the monitoring of treatments only in correlation with complementary clinical and paraclinical data.

22) The distribution of some variables appreciated in the four studies presents significant results for the same variable evaluated on different groups of patients, having as common element the autoimmune thyroid damage and the absence or presence of periodontal lesions. The individual variability of the studied constants is the expression of the particularities of manifestation and evolution of periodontal disease in the context of the presence of chronic autoimmune thyroiditis.

23) The communicated results prove by their variability and diversity the current limits of the detailed knowledge of the inflammatory and autoimmune process that characterizes chronic periodontitis. The possibility of IL-1β becoming a "therapeutic target" justifies research efforts in this regard.

Chapter 8. Originality and future perspectives

Originality of the study

- Identification of periodontal lesions in a high percentage of cases in patients with chronic autoimmune thyroiditis;
- Specifying some etiopathogenic entanglements and some common evolutionary mechanisms for the two diseases;
- Assessing the staged evolution of chronic periodontitis depending on the extent and degree of damage to the periodontium, emphasizing the dynamics of its evolution;
- Interpretation of periodontal lesions in dynamic and multifactorial, adapted for each patient as being in an evolutionary moment of the disease, with an individualized prognosis regarding the dental lesion status appreciated in real time;
- The expression variability of the same constant studied in groups of different patients interpreted in the context of the variability and versatility of the autoimmune pathology imposing an individualized diagnostic and therapeutic concept;
- The usefulness of the oral hygiene index in assessing periodontal lesions and the risks of bacterial plaque in patients with chronic autoimmune thyroiditis, the gingival defenses being altered in thyroid diseases.
- The potentially unequal involvement of thyroid autoantibodies in the pathogenesis of chronic periodontitis and the systemic effects of thyroid disease, including periodontal lesions, which are correlated and associated primarily with serum ATPO levels;
- Identification of IL-1β in serum and saliva in patients with chronic autoimmune thyroiditis with or without chronic periodontitis and their correlation with the systemic inflammatory process and in the oral cavity, common to both diseases;
- The presence of IL-1β in serum and saliva in patients with CAT without CP emphasizes the subclinical evolution and the risk of developing periodontal lesions;
- Significant distribution of the median salivary IL-1β values according to the intensity of periodontal lesions gradually assessed, a result that emphasizes the staged evolution of the disease, proportional to the intensity of expression of the inflammatory process;
- Specification of an intensified inflammatory effect in the periodontium, proportional to the severity of periodontal lesions gradually assessed, by identifying significantly increased median values of salivary IL-1β compared to serum IL-1β, suspecting a local production of IL at the gingival level in the context of chronic thyroiditis autoimmune;
-The usefulness of determining IL-1β titer in saliva in patients with chronic periodontitis associating chronic autoimmune thyroiditis with the interpretation of values in the clinical context as an element of diagnosis and treatment monitoring.

Future perspectives

- Additional specification on the status of IL-1β in saliva in patients with chronic periodontitis as a cause / effect process;
- Implementation of a protocol for the investigation of salivary IL-1β and the establishment of a range of values useful in the stage diagnosis of chronic periodontitis and in the patient's dispensary;
- Extensive collaboration with medical specialties having as object of activity inflammatory diseases with autoimmune substrate, chronic periodontitis can be an element of early diagnosis for these diseases.
- Clinical observations and the results of statistical correlations on the studied variables are motivations for extensive population studies on the association of chronic periodontitis with chronic autoimmune thyroiditis and the etiopathogenic mechanisms common to the two diseases.

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