

**University Of Medicine And Pharmacy Of Craiova
Doctoral School**



THESIS

**STUDIES ON ODONTO-PERIODONTAL CHANGES IN
ENDOCRINE DISEASES**

SUMMARY

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INTRODUCTION

In the perspective of the relations between endocrinology and dentistry, it is necessary to have a complex approach of the stomato-endocrine correlative study and the odonto-periodontal changes in order to adopt a pathogenically different therapeutic attitude.

Patients with endocrine disorders and multiple comorbidities require special attention. Endocrine pathology evolves with impairment of swallowing, masticatory and phonetic functions, involving numerous changes on the odontal and periodontal tissues. Moreover, we can say that oral tissues serve as a sensitive indicator for many nutritional and metabolic disorders. [1]

The activity of the endocrine system starts in different stages of postnatal odontogenesis, so its role is to regulate in the genetic program, the growth and development of the body, and therefore of the dento-maxillary apparatus as an integral part of it. [2,3,4]

During the embryogenesis of the buccal-dental elements, the role of the endocrine glands is unknown, the only known information is the influence of the thyroid. On the other side of the spectrum, in genetic diseases with endocrine implications (Langdon-Down syndrome, Turner syndrome, Klinefelter syndrome), oral and dental malformations are constantly present. [5]

In the postnatal period - also characterized by growth and differentiation phenomena - the effect of endocrine glands on the oral-dental elements is manifest, being important especially in terms of trophicity but also in the following stages (maturity, climacterium, senescence). [6,7]

THE STAGE OF KNOWLEDGE

1. News On The Interrelation Between Endocrinopathies And Odonto-Periodontal Changes

The endocrine system acts on the constituent elements of the oral cavity: on the hard tissues represented by bones and teeth but also on the soft tissues represented by lips, gums and tongue. Initially, the first mechanism begins during embryogenesis and follow one another throughout the developmental stages of the body. [8,9]

In hypopituitarism, craniofacial development is in harmony with skeletal development. Thus the skull and the face show a slowed development, with the mention that the face is smaller compared to the skull. There are numerous studies on the developmental abnormalities of the face and skull in growth hormone deficiency. [10,11]

In idiopathic pituitary dwarfism, the teeth are small (microdentition) in harmony with generalized microsomia. Trophic and growth disorders in myxedema, Turner syndrome, Klinefelter's syndrome or other gonadal dysgenesis produces inequalities in tooth size, making micro-, macro- and normodontics coexist. [12]

Hyperpituitarism - excess growth hormone that appeared in childhood has the effect of symmetrical growth of the mandible and jaw, tongue and teeth, and tooth eruption is accelerated. The teeth are large with long roots, with a tendency to spacing. Hyperkimentosis can occur which causes the roots to grow in size. [13,14,15,16].

In adults, excess growth hormone produces the oro-facial appearance of acromegaly with disproportionate growth of facial bones. [17,18]

In severe hyperthyroidism there is a rapid bone demineralization that can be evaluated radiologically by a process of osteoporosis in the jaws. [19,20].

2. Clinical Features Of Importance In The Relationship Between Endocrinopathy - Periodontal Disease

Both number, position, and structural abnormalities are considered favoring factors in the occurrence of periodontal inflammation. [21]

Crowded dento-alveolar abnormalities favor the retention of food debris, due to the lack of self-cleaning and the difficulties of artificial cleaning. Dento-alveolar abnormalities with spacing are accompanied by flattening phenomena of the interdental papillae and dystrophic phenomena. [22]

Maxillary compression is accompanied by gingival hypertrophy, overload in the lateral areas with demineralization of the interdental septa, and deep covered occlusion may be accompanied by lesions of the marginal periodontium on the palatal face of the upper frontals caused by direct contact with the incisor margin. [23]

3. Paraclinical Aspects Periodontal Disease – Endocrinopathies

Gingival tissue and gingival fluid have been shown to contain a complex set of immune components that not only irrigate the gingival sulcus but are also released into the oral cavity [23]. Gingival fluid has been shown to be derived from gingival capillary beds (serum components) and from both resident inflammatory cells that migrate. This fluid contains a number of immune, inflammatory and adaptive immune molecules, but also cells whose role is to contribute to the host-bacteria interaction in this ecological niche. [23]

PERSONAL CONTRIBUTION

4. Working Hypothesis

The working hypothesis for this research started from the clinical finding according to which patients with endocrine diseases present a series of specific odonto-periodontal changes, but also with a series of peculiarities depending on the associated comorbidities. Based on this finding, we established the general objective of the doctoral thesis, namely the recognition and early diagnosis of

craniofacial, dental and periodontal abnormalities in patients with endocrine disorders, in order to develop prophylactic measures and / or institute early therapy in order to avoid complications.

To demonstrate the working hypothesis and meet the general objective, we established the following specific objectives: identifying patients with odonto-periodontal changes of endocrine cause in order to early diagnose the degree of damage to the teeth and periodontium; elaboration of prophylactic measures and / or establishment of early therapy in order to avoid complications, use of cephalometric measurements in the investigation of genetically determined variables or influenced by the existence of metabolic or endocrine diseases; elaboration of the diagnosis which represents a synthesis based on objective data of the clinical examination, corroborated with the paraclinical examinations; establishing a histological diagnosis of dental changes caused by the presence of endocrine disease, establishing a histological and morphopathological diagnosis of periodontal changes caused by the presence of endocrine disease, performing an immunohistochemical assessment of the cell population involved in periodontal inflammatory reactions, local vascular changes and the process fibrosis.

5. Clinical-Statistical Study Of The Incidence Of Odonto-Periodontal Changes In Endocrinopathies And Metabolic Diseases

The first direction of research was to conduct a clinical-statistical study to analyze metabolic and hormonal changes in patients selected in the study in order to establish correlations between biochemical and hormonal investigations, endocrinopathic status and consequences on the dento-maxillary apparatus. Moreover, some correlations were established that derive between odonto-periodontal changes and socio-demographic variables.

In assessing social status, it was corroborated with oro-dental changes and altered facial appearance, phonation or mastication. The group of patients for the clinical-statistical study included 210 patients who presented to the Dentistry Clinic of the Faculty of Dentistry Craiova, for various treatments. Patients were examined

clinically and radiologically, and an observation sheet was prepared. General data, data on socio-economic status, reason for presentation and oral status of patients were collected. The behavioral factors studied were smoking, poor oral hygiene, consumption of sweets and carbonated beverages and reduced accessibility to dental services.

The collateral diseases present in the study group show the presence of dyslipidemias and cardiovascular damage (hypertension, ischemic heart disease, atrial fibrillation).

6. Imaging study

The second direction of research was to perform cephalometric measurements in the investigation of genetically determined variables or influenced by the existence of metabolic or endocrine diseases. In this sense, a series of relations were established on the harmonious development or dento-maxillary disharmony in vertical and transversal plane, but also some relations on the development of horizontal mandibular branches and facial mass, with the analysis of bone structures in sagittal and transversal direction. The craniofacial morphological changes induced by the growth hormone deficiency were analyzed, but also in the case of administration of hormonal supplements to patients with growth hormone deficiency.

From the analysis of the correlation coefficients between the cephalometric variables and age we can say that they have a high predictive value: jaw length, mandible length and posterior base of the skull. The average values of the prognosis angle of the mandible and that of the maxilla have low values compared to the normal, standardized ones.

The craniofacial morphological characteristics in patients with Turner syndrome observed by us are: reduction of the posterior base of the skull, retraction of the mandible and maxilla, posterior rotation of the mandible and maxilla and reduction of the length of the mandible and maxilla.

7. Histological And Immunohistochemical Study Of Odonto-Periodontal Changes In Endocrinopathies And Metabolic Diseases

The research aimed to highlight dental or periodontal changes in patients with endocrine disorders, assessed by histological or immunohistochemical examination.

The histological study involved the microscopic examination of hard dental tissues or fragments of gingival mucosa, following their rigorous preparation by processes of tooth decalcification, fixation, dehydration, clarification, embedding, cutting and staining of preparations. To highlight the constituent elements, staining with HE or trichromic GS was performed. The immunohistochemical study aimed to identify cells specific to periodontal inflammation, using specific immunohistochemical markers.

Immunohistochemistry is a specific method, as it uses the antigen-antibody reaction, targeted identification of certain proteins, enzymes or other tissue structures. Through this study we wanted to prove that there is a correlation between changes in the main constituents of gingival tissue and the degree of damage to the marginal periodontium.

Most of the cases studied highlighted areas of demineralized dentin, with enlarged dentinal tubules, with aspects of microcystic cavities.

The gingival mucosa showed changes in all cases studied in the epithelium, accompanied by changes in the underlying chorion, the degree of changes observed being variable in intensity depending on the clinical diagnosis but also in relation to the presence of inflammatory process and its persistence. The gingival epithelium in cases of hypothyroidism diagnosed with gingivitis or PMCP, generally presented a normal appearance from a histological point of view, this being a stratified squamous epithelium, having in the spinous layer a smaller or larger number of cell rows, the superficial layer being lacking keratinization or showing ortho or parakeratinization. Occasionally, among the keratinocytes of the basal and spinal layers, we noticed the presence of proinflammatory cells, especially lymphocytes, migrated from the chorion. CD3-positive T lymphocytes were present in the chorion

of the gingival mucosa in variable numbers in all cases studied, but their number was increased in cases of gingivitis compared to cases of PMCP. CD68-positive macrophages were present in the chorion of inflamed gingival mucosa, most commonly located in chronic inflammatory infiltrates along with lymphocytes and plasma cells, or with diffuse arrangement in connective tissue. Immunohistochemical reactions for MMP2 were different in intensity compared to the diagnosis of periodontal disease.

8. General Discussions

The clinical-statistical study showed an increased prevalence of patients diagnosed with thyroid pathology, [24,25,26,27] supported by experimental data in the literature indicating the increased prevalence of oro-dental changes in thyroid pathology. [7,28,29,30]

It is known that the incidence of thyroid disease is increasing predominantly in women, but in our study the sex distribution of patients with thyroid disease is relatively equal.

The behavioral factors studied were: smoking, poor oral hygiene, consumption of sweets and carbonated beverages, and reduced accessibility to dental services. A predominance of these factors was noted in females. Our study agrees that poor oral hygiene remains a high-frequency behavioral factor among the general population in our country. [31]

Functional abnormalities of the endocrine glands produce various effects [32] the most common being cardiovascular damage. This finding is in agreement with our study, which noted a predominance of patients with endocrine disorders associated with ischemic heart disease and hypertension.

From the analysis of the correlation coefficients between the cephalometric variables studied by us and age, we can say that they have a high predictive value: jaw length, mandible length and posterior base of the skull. The prognosis angles of the jaw (S-N-Ss) and mandible (S-N-Sm) show low values in our group compared

to the control group, but the low value is specific to growth hormone deficiency. [33]

In the group of patients with Turner syndrome, the decrease in the angle of maxillary and mandibular prognathism is about 100 compared to normal values (135.4°) and even lower than the values in the Cazzola study which mentions an average value of 125°. [34,35,36,37]

Given that the IMPA angle refers to the balance and harmony of the anterior face in the lower segment, we can say that the group with Turner syndrome has a balanced and harmonious face. The low value of this angle in children with growth hormone deficiency indicates that this group can be included in the dolichocephalic typology.

Alterations in thyroid hormone levels from hypothyroidism or hyperthyroidism have a significant impact on periodontal tissue, causing soft tissue edema, demineralization and pathological growth of alveolar bone, or altering the response of periodontal tissue to pathogenic germs,[38] changes sustained by the results of our study.

Data from the literature state that in periodontal disease, MMP-2 is expressed in fibroblasts in the chorion of the gingival mucosa, in epithelial keratinocytes, as well as in macrophages and endothelial cells [39]. In all cases with endocrine diseases diagnosed clinically and radiologically with periodontal disease taken by us in the study, the gingival mucosa showed epithelial changes in the chorion, with the presence of chronic inflammatory lymphoplasmacytic infiltrates that indicate chronicity and evolution of pathological processes.

9. General conclusions and innovative contributions

The chosen research topic is topical, as the inter-relationship between dentistry and endocrine is a constant scientific concern. The oro-dental clinical manifestations associated with endocrine pathology of different etiologies must be known and identified by each dentist.

This doctoral thesis aims to participate in the attempt to establish the best therapeutic attitude regarding the treatment of odonto-periodontal lesions in patients with endocrine disorders, especially since they are also associated with a number of comorbidities.

Based on the current knowledge in these fields, from this doctoral thesis can be formulated some important conclusions and elements of originality:

1. The cephalometric study demonstrates the presence of aberrant craniofacial aspects in both groups, respectively subjects with growth hormone deficiency and subjects with Turner syndrome, with reduction of the posterior base of the skull, shortening of the mandible and jaw, retraction of the mandible and maxilla.
2. The retraction of the mandible and maxilla is best highlighted by the values of the angles SNA and SNB, easy to calculate on the lateral telerradiography.
3. By comparing the values of the skull base in the two groups, we find that higher values of the anterior skull base and the posterior skull base are found in subjects with Turner syndrome.
4. We also find that in patients with growth hormone deficiency, both the anterior base of the skull and the posterior base of the skull have lower values than in subjects with Turner syndrome.
5. The angle of ANBo representing the relationship between the maxilla and the mandible has lower values in the group with growth hormone deficiency than in the group with Turner syndrome, and both groups have lower values than normal values.
6. Mandibular relationships assessed by S-N-Sm⁰ angle indicate lower angle values in subjects with growth hormone deficiency.
7. The interincisive angle is low in both groups compared to normal values, which confirms the presence of class I or class II malocclusions, division 1.
8. The recognition of these cephalometric variables and their calculation is the starting point in orthodontic therapy in patients with growth hormone deficiency and Turner syndrome, but also a possibility to monitor and follow over time the evolution of treatment.

9. The degree of changes in the epithelium and changes in the underlying chorion varied with respect to the clinical diagnosis of periodontal disease, the changes being more pronounced in patients with PMCP, as opposed to those in whom the clinical diagnosis was gingivitis.

10. The gingival epithelium appeared as a stratified squamous epithelium having in the spinous layer a smaller or larger number of cell rows, the superficial layer being devoid of keratinization or having ortho or parakeratinization.

11. The presence of thin interpapillary epithelial ridges, which sink deep into the chorion, creating the appearance of "retepegs", is a rarer aspect in cases with gingivitis and with a much higher frequency in cases with PMCP. This may indicate a possible destruction of the subepithelial basement membrane, so a chronic inflammation.

11. In the chorion, we noticed the presence of a chronic inflammatory infiltrate, consisting mainly of lymphocytes and plasma cells, with macrophages present in variable numbers and with the presence of a small number of polymorphonuclear cells.

12. Fibrosis was present in all cases studied, the degree of fibrosis being more intense in cases with gingivitis as opposed to cases with PMCP, indicating an advanced stage of gingivitis, but also a gingival hypergrowth.

13. We noticed an increased number of capillaries in the conjunctival papillae but also in the deep chorion, the angiogenesis vessels appearing with small lumen and hypertrophied endothelial cells, with voluminous nuclei, indicating an incipient inflammation.

14. Microhemorrhages, consisting of the presence of extravasated blood in the connective tissue, were frequently observed in all cases with hypothyroidism regardless of the clinical diagnosis of periodontal disease, indicating the discontinuity of the walls of small vessels in the gingival connective tissue, so a chronic inflammation.

15. Histological examination of the gingival mucosa in the case of Addison's disease revealed necrosis of the gingival epithelium in some areas, while in other areas the epithelium showed acanthosis and hyperkeratosis.
16. In the case of Turner syndrome, the gingival mucosa appeared thickened, with an acanthosis, thick and parakeratotic epithelium and the presence of a massive fibrosis, with thick bands of collagen fibers in the chorion.
17. Immunolabeling with anti-CD3 antibody showed the presence of T lymphocytes in the chorion of the gingival mucosa in variable numbers in all cases studied, their number being increased in cases with gingivitis.
18. CD20-positive B lymphocytes were present in appreciable numbers in the inflammatory infiltrates of the chorion in all cases studied regardless of the type of periodontal disease, but also in large numbers spread diffuse in the chorion.
19. In all cases studied, CD68-positive macrophages were present in variable numbers in the chorion of the inflamed gingival mucosa, a higher number of macrophages being noticed in cases with PMCP periodontitis.
20. In patients with a clinical diagnosis of gingivitis, MMP-2 showed a positive reaction in the endothelial cells of blood vessels, but also in some fibroblasts in the chorion.
21. The immunohistochemical response to MMP-2 in PMCP cases has been found to be highly positive in chorionic cells, fibroblasts and some proinflammatory cells, but also in blood vessel endothelial cells, especially in congested vessels and neofunction capillaries. turgid endothelium, which denotes a chronicity of these inflammatory lesions.
22. We consider changes in the gingival mucosa found in our study to be nonspecific for endocrine diseases, the important trigger of periodontal disease remaining the specific bacterial plaque, but the evolution of the disease is influenced by overlapping systemic diseases, certain physiological conditions such as menopause and side effects of some drugs.
23. There is a variability of oro-dental clinical manifestations associated with endocrine pathology of different etiologies.

24. The recognition by the dentist of the signs and symptoms at the oro-dental level entangled with endocrine pathology is the starting point in the application of an adequate and personalized dental treatment to each patient with endocrine disease.

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