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# METHODS OF DIAGNOSIS AND INTERDISCIPLINARY TREATMENT OF CONGENITAL EDENTATIONS

**323.01 DENTISTRY**

**Summary of the thesis of Doctor Habilitatus in Medical Sciences**

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The thesis was elaborated within the Department of Prosthetic Dentistry "Ilarion Postolachi" of "Nicolae Testemitanu" State University of Medicine and Pharmacy.

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# LIST OF ABBREVIATIONS

TMJ – Temporomandibular joint.
AXIN2 – Gene involved in tooth formation and eruption.
BMP – Bone Morphogenetic Protein.
C – Canine.
CBCT – Cone Beam Computed Tomography.
CNC – Cranial neural crest cells.
CNV – Variation in the number of genetic copies.
CT – Classical computed tomography.
DLX1, DLX2 – Homeobox genes involved in dental morphogenesis.
DNA – DNA, genetic material.
IC – Central incisor.
ICD – International Classification of Diseases.
IL – Lateral incisor.
M1 – First molar.
M2 – Second molar.
MAS – Association of Dentists of the Republic of Moldova.
MSX1, MSX2 – Genes involved in craniofacial development.
NGS – Next-generation genetic sequencing.
OPG – Panoramic dental radiography.
p – Statistically significant value.
PAX9 – Gene involved in the development of dentition.
PCR – Polymerization Chain Reaction.
PM1 – First premolar.
PM2 – Second premolar.
SD – Standard deviation in statistical tables.
SDM – Dento-Maxillary Dentistry: dental specialty.
SNP – Single nucleotide polymorphism.
SPSS – Program used for statistical analysis.
TSG – Complex approach in rehabilitation.
TGF-β – Transformer Beta Growth Factor.
WES – Whole exome sequencing.
WHO – World Health Organization.
$\chi^2$ – Statistical test for the significance of differences between groups.

# INTRODUCTION

**Topicality and importance of the researched problem**

Congenital edentulousness is a medical and socio-human problem. There are numerous studies that refer to congenital edentations associated with hypodontia, oligodontics, and anodontias. [1]. The complexity of the treatment depends on the determining factors and the group of specialists involved, at different age stages of these patients[2]. In the Republic of Moldova, patients with congenital edentulousness are addressed at different ages, although early diagnosis allows the prevention of complications in the development of the dento-maxillary apparatus. [3, 4]. The great diversity of syndromic forms over several decades has been the subject of numerous scientific researches that provide for the complex interdisciplinary rehabilitation of the dento-maxillary apparatus [5]. The clinical examination contributes to the choice of therapeutic management and to the evaluation of the results over time [6–8].

Such an experimental study is useful for evaluating the extent of congenital edentations and for identifying limiting anatomical factors, such as the temporomandibular joint, the position of the teeth on the dental arch and the vertical size of the occlusion, in relation to the age and type of dentition. The precise paraclinical detection of dental follicles and the method of interdisciplinary treatment will offer us the possibility of rehabilitating the anatomical, functional and aesthetic structures of patients with congenital edentulousness [9]. The evaluation and integration of the patient's psychosocial and emotional status is an essential condition for obtaining optimal results in interdisciplinary treatment, especially in the context of rehabilitation of the functions of the dental system, constituting at the same time a relevant scientific component of the present study [10].

**Research hypothesis**

Congenital edentulous diseases have a multifactorial etiology, in which malocclusions, malformation symptoms and syndromes, genetic factors and morpho-functional particularities significantly influence the pattern of clinical manifestation, and the application of an early diagnosis model, including through the integration of prenatal investigations, and an individualized interdisciplinary therapeutic approach leads to the improvement of clinical, functional and Prosthetic results, as well as quality of life patients.

**Purpose of the study**

Evaluation and methodological identification of diagnosis and interdisciplinary treatment in patients with congenital edentulousness.

**General objectives of the thesis**

1. Evaluation of the epidemiological particularities of patients with malocclusions associated with congenital edentulousness.
2. Identification and argumentation of methods for the early detection of congenital edentulousness, including by integrating prenatal investigations into a pilot study.
3. Development and systematization of the algorithm for clinical and paraclinical diagnosis of congenital edentulousness.
4. Analysis of the impact of dental absences on the functions of the dental system.
5. Evaluation of morpho-functional peculiarities in various stages of development of the dento-maxillary apparatus.
6. Investigating the role of genetic factors by analyzing genes involved in dental development.

7. Substantiation of an interdisciplinary treatment model adapted to congenital edentulousness, depending on the age and severity of the case.

**General research methodology**

The present research was conceived as a complex, interdisciplinary study, structured on several successive and interconnected methodological stages, meant to ensure the achievement of the proposed goal – the evaluation of the research sample, the methodical identification of the diagnosis and the substantiation of an interdisciplinary treatment in patients with congenital edentulousness.

*Type of study.* The research had a mixed design, combining the observational epidemiological component (cross-sectional, for assessing the particularities of prevalence and distribution of congenital edentations in the studied population) with the clinical analytical component (prospective, for monitoring the evolution of patients undergoing the developed interdisciplinary treatment and diagnostic protocol).

**Research stages.**

1. The stage of documentation and critical analysis of the specialized literature, which allowed the outlining of the theoretical framework and the identification of the existing scientific gap at national level regarding the early diagnosis and interdisciplinary approach of congenital edentulousness.
2. The stage of selection of the research sample and the formation of the study groups, based on rigorously defined inclusion and exclusion criteria.
3. The epidemiological evaluation stage, aimed at establishing the particularities of malocclusions associated with congenital edentations in the examined population.
4. The clinical and paraclinical diagnosis stage, in which complementary investigation methods were applied.
5. The stage of elaboration and implementation of the interdisciplinary clinical treatment protocol.
6. The stage of statistical processing and interpretation of the data, followed by the formulation of conclusions and practical recommendations.

Research methods used included:

- *clinical method*, by direct examination of patients (anamnesis, exooral and endooral examination, evaluation of the functions of the dento-maxillary apparatus).
- *paraclinical diagnostic methods*, including radiological investigations (orthopantomography, cephalometric radiography, cone beam computed tomography) and analysis of study designs.
- *the epidemiological method*, for determining the incidence and particularities of the distribution of congenital edentulousness in the sample studied, including by applying a survey addressed to the group of predisposed patients.
- *the comparative method*, by relating the results obtained to the data from the international literature.
- *the statistical-mathematical method* for processing the collected quantitative data, testing the statistical significance of the differences between the batches and validating the research hypotheses.
- *interdisciplinary method of evaluation and treatment*, which involved the collaboration of the specialties involved in the management of congenital edentulousness (orthodontics, oro-maxillofacial surgery, dental prosthetics, medical genetics, as the case may be), to develop a unitary clinical protocol.

The methodological approach described allowed obtaining original data, the first study of this type conducted in the Republic of Moldova, thus contributing to the scientific substantiation of new methods of early diagnosis and an interdisciplinary treatment adapted to the particularities of the local population.

**Limitations of the study**

Although the research was designed and carried out with methodological rigor, over an extended period of 10 years, which ensured a solid longitudinal follow-up of patients and a consistent temporal validation of the results, including a component of genetic investigations, it is nevertheless necessary to mention some inherent limits to any scientific approach of this magnitude:

1. Limits related to the study sample. The research was conducted on a sample from a specific geographical area (Republic of Moldova), which may influence the degree of generalization of the results to other populations, with different ethnic, genetic or socio-economic profiles. Being an inaugural study at national level, the sample size, although statistically relevant and strengthened by the long duration of the research, does not allow for undifferentiated extrapolations at the global population level.
2. Limitations related to the interdisciplinary nature of the approach. The implementation of the interdisciplinary clinical protocol depended on the availability and effective collaboration of related medical specialties (orthodontics, oro-maxillofacial surgery, dental prosthetics, medical genetics), which, in certain specific situations, could influence the uniformity of the full application of the protocol to all patients included in the study.
3. Limits on diagnostic imaging technological resources. Although modern paraclinical methods were used throughout the 10 years of research, the technological evolution in this interval determined a certain heterogeneity of the diagnostic imaging equipment available at various stages of the study, which is natural for a longitudinal study of such magnitude.
4. Limits related to the complexity of multifactorial etiology. Although the study included genetic investigations, the complex nature of congenital edentations, determined by the interaction of genetic, epigenetic and environmental factors, makes it difficult to establish with absolute certainty the weight of each etiological factor, which remains an area open to further research at the in-depth molecular level.

**Scientific novelty and originality:** For the first time in the Republic of Moldova, cases of congenital edentulousness were investigated. The results of the research conducted allowed the revelation of the clinical and paraclinical particularities in patients with congenital edentulousness and their interdisciplinary treatment possibilities.

**The scientific problem solved in the thesis** consists in the development of methods for early diagnosis of congenital edentations and the elaboration of the complex treatment algorithm at different ages of development of the stomatognathic system.

**Applicative value of the study:** Conducting an in-depth study of the parameters of congenital edentulousness significantly supplemented the knowledge regarding this anomaly of the stomatognathic system; the essential aspects that could determine the appearance and progression of the given pathology were highlighted. At the same time, new diagnostic methods have been developed, and interdisciplinary treatment has been established for patients with congenital edentulousness, which will reduce the number of registered cases of this anomaly of the dento-maxillary apparatus among the population of the Republic of Moldova.

**Main scientific results submitted for support:**

1. Epidemiological study of congenital edentations according to the addressability of patients in the Republic of Moldova
2. Detection of congenital edentates in the number of patients with dental malocclusions.
3. Study of dental occlusion in patients with congenital edentulousness.
4. Genetic evaluation and non-syndromic screening in patients with dental agenesis.
5. Methods of early diagnosis of congenital edentulousness.
6. Methods of paraclinical diagnosis of patients with malocclusions in different periods of growth.
7. Interdisciplinary treatment of patients with congenital edentulousness.

**Implementation of scientific results.**

The results of the study, the basic concepts and the practical recommendations developed were implemented in the research, instructive-methodical process within the PI of the "Nicolae Testemitanu" University of Pharmacy, at the clinical bases of the Department of Prosthetic Dentistry "Ilarion Postolachi" within the dental clinic, "SoloDent" and at the Institute of Mother and Child.

**Approval of the results obtained.**

The research was presented: XVIII – XX Congresses of the Association of Dentists of the Republic of Moldova – 2022-20 24. Ukrainian National Dental Congress, October 22-23, 2021.International Congress "Effective strategies for the development of dentistry, challenges and decisions during the Covid 19 pandemic", Kazakhstan, October 13, 2021.
XIV - XX International Congress of the Romanian Society of Oral Rehabilitation, - November 202-2025, Iasi, Romania. Euro invent, Romania, Iași, Timișoara -2024-2026. World Dental Federation Congress 2024. The Consecrated Conference of 75 years since the foundation of the Nicolae Testemitanu University of Medicine and Pharmacy within the Faculty of Dentistry 2020. Conference Dedicated to "Professor Pavel Godoroja" at the Academy of Sciences of the Republic of Moldova – 2024. Med Espera Congress, Chisinau -2026.

**Publications on the topic of the thesis:**

The basic materials published for the thesis were in 79 scientific papers, including 1 monograph, 1 chapter in monographs, 48 articles, 3 in international scientific collections, 4 in the papers of international scientific conferences, 3 papers of national scientific conferences, 4 patents of inventions, 9 patents of inventions, patents, certificates of registration, materials at invention salons, 9 participations with communications at scientific forums 7 2 national.

**Volume and structure of the thesis:** The paper includes: 233 pages and consists of: introduction, 3 chapters, general discussions, general conclusions, and practical recommendations. The thesis is illustrated with 9 tables, 102 figures and 4 annexes., bibliographic index (304 titles). The results obtained are published in 79 scientific papers.

**Keywords:** congenital edentulousness, genes, malocclusion, malformities syndromes, agenesis, hypodontia, oligodontics, anodontias, occlusion, combined treatment.

## 1. GENETIC AND MORPHOLOGICAL FOUNDATIONS OF TOOTH DEVELOPMENT AND ERUPTION.

Tooth eruption is a coordinated biological process, fundamental in the development of the dental system. Complex mechanisms such as root elongation, periodontal development, and alveolar bone remodeling are involved during this process [11,12].

In embryogenesis, dental development begins in the sixth evolutionary week, with the formation of the dental lamina – a thickening of the oral epithelium. This generates dental buds that penetrate the mesenchyme, causing the initiation of the process of dental morphogenesis [13].

**Table 1.** Signaling of protein factors involved in tooth development, the dysfunction of which can lead to modeling defects [14, 15]

| Stage of tooth development | Protein factors involved in epithelial signaling | Protein factors involved in mesenchymal signaling |
|---|---|---|
| **Initiation stage** | Fogs, Bmps, Shh, Pitx2, Wits | Pax9, Pt., Msx1, Msx2, Bmp4, Lhx6, Lhx7, Lefl, Dlx1, Dlx2, Gli1, Gli2, Barx1 |
| | ↓ | |
| **Bud stage** | Bmp, Fgf, Wnts, Shh, Pdgf, p21, Msx2, Lefl, Tgf-β | Pax9, Bmp, Dlx1, Dlx2, Msx1, Lhx6, Lhx7, Lefl, Gli1, Gli2, Gli3, Barx1, Fgfs |
| | ↓ | |
| **Cup stage** | Bmp, Fgf, Wnts, Shh, Pdgf, p21, Msx2, Lefl, Tgf-β | Pax9, Bmp, Dlx1, Dlx2, Msx1, Lhx6, Lhx7, Lefl, Gli1, Gli2, Gli3, Barx1, Bmp4, Msx2, Fgfs |
| | ↓ | |
| **Bell stage** | Bmp, Fgf, Wnts, Shh, Pdgf, p21, Msx2, Lefl, Tgf-β | Pax9, Bmp, Dlx1, Dlx2, Msx1, Lhx6, Lhx7, Lefl, Gli1, Gli2, Gli3, Barx1, Bmp4, Msx2, Fgfs |

For example, PAX9 is essential for determining dental initiation sites, and MSX1 contributes to the maintenance of BMP4 expression, which plays a central role in cell differentiation [16]. Mutations in these genes are associated with various forms of congenital edentations [17,18].

Research has identified FGF and WNT as activators and BMP as inhibitors of pladome formation [19]. Other tooth-related genes that are expressed at the initiation stage include MSX1, MSX2, DLX1, DLX2, and LEF1, but dental development is stopped at the initiation stage only when both MSX1 and MSX2 genes or both DLX1 and DLX2 genes are inactivated [17, 20].

During the "initiation stage," we understand the molecular and cellular processes that determine the exact type, position, and orientation of each tooth on the developing jaws. The cooperation of the WNT7b and SHH genes delimits the oral (non-odontogenic) epithelium from the dental (odontogenic) epithelium and thus restricts the expression of SHH to the dental epithelium [21]. The first morphological indication of dental development on dental lamina is the formation of ectodermal placodes, i.e., embryonic epithelial thickenings preceding the local appearance of an ectodermal organ [22, 23].

Dental plaques secrete molecules from all four families of growth and transcription factors (BMP, FGF, SHH, and WNT), which induce the expression of many genes (e.g., PAX9, MSX1/2, RUNX2, BMP, FGF, Activin, LEF1, DLX1, BARX1, LHX6/7, GLI1/2/3) into the mesenchyme (figure 4). BMPs and FGFs activate MSX1, while FGFs induce PAX9 and RUNX2 expression [24]. PAX9 expression is required for mesenchymal condensation [25]. In contrast to the initiation stage, in the early stage, several mutations of key genes (e.g., LEF1, MSX1, PAX9) have been reported that affect odontogenesis. [26, 27].

BMP4 is an important candidate for a mesenchymal signal that induces the transition from the bud to the head stage. If BMP4 is absent from the mesenchyme, the specific dental genes LEF1, MSX1 and PAX9 are not expressed, and dental development is stopped at the bud stage.

Most of the signaling molecules that regulate epithelial-ectomesenchymal interactions during tooth development are members of the TGF (transforming growth factors), FGF, BMP, Hedgehog, EDA, Notch, and WNT families. The ectomesenchymal expression of MSX1 and PAX9 remains strong from the initiation stage to the bell stage. Tightly overlapping expression patterns of the PAX9 and Msx1 genes are consistent with a role in epithelial-mesenchymal interactions.

In addition to major signaling pathways, the expression of transcriptional factors plays a crucial role in cell differentiation. For example, LEF1, activated within the WNT pathway, regulates cell proliferation in the mesenchymal and contributes to the establishment of coronary polarity [26]. Other genes, such as PITX2 or EDA, are involved in the development of enamel structure and

polarized formation of the dental organ [28]. Also, epigenetic factors and microRNAs have begun to be recognized as elements of fine regulation of gene expression in odontogenesis, contributing to the mechanisms by which genetic information is interpreted and used in tissue development [29]. Data from the literature have shown that mutations in many of these genes cause dental abnormalities in both mice and humans [30].

Tissue recombination experiments have shown that the earliest odontogenic potential is found in the dental epithelium rather than in CNC cells, and that modeling information for tooth initiation and type is present in the oral ectoderm prior to epithelial thickening. This acquisition by ectomesenchymal cells was demonstrated when mouse embryonic molar mesenchyme was combined with chick embryonic epithelium, thus resulting in the formation of dental germs [31].

The reciprocal, accurate, spatio-temporal orchestration of epithelial/mesenchymal communication is significant, as the loss of these interactions results in dental abnormalities, as observed in the absence of teeth in birds and at the level of the lower jaw [32].

Developmental defects usually occur in tooth tissues as a result of mutations in genes that code for signaling molecules and transcription factors. These developmental defects can occur alone (isolated, as represented by hypodontia in PAX9 mutants) or in combination with defects of other tissues (syndromic, as manifested by hypodontia due to mutations in many genes, such as MSX1, AXIN2, EDA, PITX2 and SHH) the iredity of tooth characteristics is subject to universal genetic rules; however, very few traits are inherited in a Mendelian manner; Most dental polymorphisms are controlled by more than 300 genes. Some of them, such as EDA (ectodysplasin), HED (ectodermal dysplasia), MSX1, and PAX9, play key roles in determining dentition phenotype [23, 30, 33, 34].

**Table 2. Frequency of absence of diverse types of teeth (% of cases) in patients with mutations in genes associated with dental agenesis**

| GENE | M2 | M1 | PM2 | PM1 | C | THE | IC | M2 | M1 | PM2 | PM1 | C | THE | IC |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **AXIN2** | 50,0 | 33,3 | 83,3 | 56,3 | 31,3 | 62,5 | 8,3 | 37,5 | 37,5 | 83,3 | 35,4 | 18,8 | 47,9 | 66,7 |
| **PAX9** | 86,6 | 69,1 | 70,6 | 32,5 | 30,9 | 27,8 | 6,7 | 86,6 | 43,8 | 50,5 | 14,4 | 11,3 | 11,9 | 41,2 |
| **EDA** | 19,6 | 8,7 | 47,8 | 41,3 | 50,0 | 84,8 | 19,6 | 17,4 | 10,9 | 67,4 | 45,7 | 34,8 | 91,3 | 89,1 |
| **WWTP** | 23,3 | 20,0 | 53,3 | 50,0 | 50,0 | 66,7 | 6,7 | 20,0 | 13,3 | 63,3 | 33,3 | 23,3 | 66,7 | 36,7 |
| **WNT10A** | 40,7 | 26,0 | 82,4 | 64,2 | 40,2 | 64,7 | 6,4 | 44,6 | 24,5 | 77,9 | 50,0 | 33,3 | 42,2 | 53,4 |
| **WNT10B** | 25,0 | 25,0 | 50,0 | 50,0 | 58,3 | 83,3 | 50,0 | 25,0 | 33,3 | 66,7 | 8,3 | 50,0 | 91,7 | 66,7 |
| **LRP6** | 40,6 | 6,3 | 68,8 | 59,4 | 65,6 | 93,8 | 0,0 | 46,9 | 3,1 | 75,0 | 37,5 | 43,8 | 71,9 | 78,1 |
| **MSX1** | 30,7 | 14,0 | 84,2 | 75,4 | 13,2 | 39,5 | 15,8 | 46,5 | 33,3 | 88,6 | 29,8 | 14,0 | 21,1 | 50,9 |

**Note:** The homologous teeth in the right and left hemiarch were analyzed together.

Despite our extensive knowledge of the spatiotemporal expression of specific genes during tooth formation, no gene has yet been directly experimentally or naturally correlated with ontogenesis or the absence of a specific tooth [14, 35].

## 2. RESEARCH MATERIALS AND METHODS

The prevalence of congenital edentations varies by continent and gender. The highest values were reported in Europe (4.6% in men and 6.3% in women) and Australia (5.5% in men and 7.6% in women), compared to the Caucasian population in North America (3.2% in men and 4.6% in women). Analyses show that congenital edentations are 1.37 times more common in women than in men. The most commonly affected teeth are the second mandibular premolar, followed by the maxillary lateral incisor and the second maxillary premolar [39]. The occurrence of congenital edentations was divided into three main groups: common (P2(I) > I2(s) > P2(s)), less common (I1(I) > I2(i) and P1(s) > C(s) and M2(I)) and rare (M2(s) and M1(s) > C(I) > M1(i) and I1(s)). The unilateral appearance of

congenital edentations is more common than the bilateral appearance. However, edentulousness with agenesis of the maxillary lateral incisors is more common than unilateral edentulousness. The general prevalence of congenital edentations in the jaw is comparable to that of the mandible, but a marked difference was found between both jaws in terms of tooth type. The absence of one or two permanent teeth is found in 83% of the subjects with a practical application of the results of the meta-analysis is the estimation of the need for dental treatment.

The present study was carried out in the dental clinic No.1 Department of Prosthetic Dentistry "Ilarion Postolachi" and the dental clinic "SoloDent" based on clinical and paraclinical examinations, photometric, biometric, radiological, occlusion, intrauterine and genetic examinations were studied in a number of 3692 patients, of which, 3567 malocclusion patients according to the Angle classification, out of the 3567 - 100 patients detected with congenital edentulousness. Prenatal ultrasound evaluation with intrauterine follicle identification of 15 pregnant ladies and 5 patients with exploratory genetic analysis, genes involved in odontogenesis. Their recordings were examined to detect congenital edentulousness of permanent teeth in both dental arches, including the third molar. The data were recorded according to gender, age, number of missing teeth, location in each jaw and laterality. Congenital edentulousness has been clinically diagnosed and defined as lack of crypt formation or detection of crown mineralization in panoramic X-rays and conical beam dental 3D computed tomography.

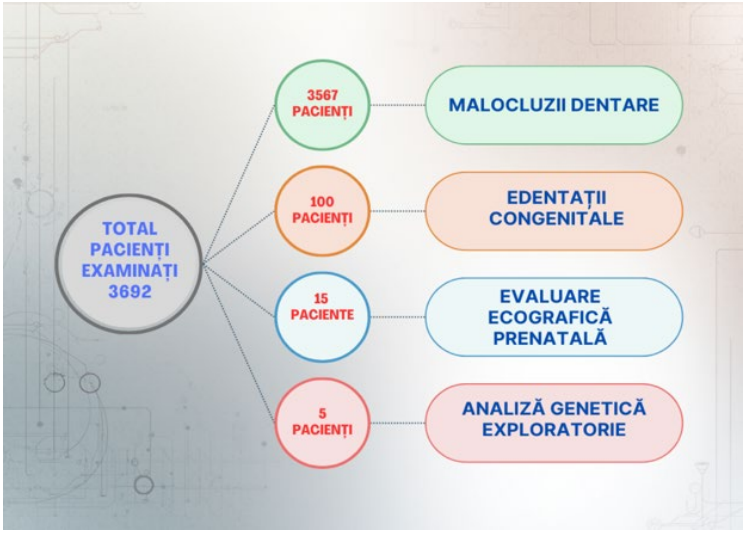


**Figure 1. Distribution of the study group.**

The data was processed automatically using open-source programs, namely RStudio, version 2024.09.1+394 (https://www.rstudio.com/) and Python, version 3.12.3 (https://www.python.org/). The use of these modern tools, recognized in academia and research, has allowed for rigorous, efficient, and fully reproducible analysis of the dataset. Their choice has made a key contribution to ensuring the transparency of the analytical process, the validity of the results and the possibility of independent replication. The source codes used for data processing and analysis are available and can be made available, providing the opportunity to verify the results or integrate the methodology into similar future research.

For the characterization of numerical variables, we calculate the fundamental descriptive statistics: minimum value, maximum value, arithmetic mean accompanied by standard deviation, median and interquartile range (IQR). These measures of central tendency and dispersion allowed a detailed and precise description of the distribution of each variable, facilitating the identification of extreme values, possible asymmetries and deviations from normality. For the comparison of two independent groups in terms of the distribution of quantitative variables, the nonparametric Mann-

Whitney-Wilcoxon test was used, due to its robustness and insensitivity to the presence of extreme values.

The graphical representation of the numerical variables was achieved by means of box-plot diagrams, which provided an intuitive visualization of the central trends, dispersion, and differences between the groups.

As for the categorical variables, we determined the absolute and relative frequencies, being accompanied by 95% confidence intervals for estimating the proportions. This statement allowed for a robust statistical characterization of data distribution within each category. For a clear and comparable visual representation, bar charts were used, which contributed to a better understanding of the distribution of categories and differences between groups.

For the testing of hypotheses regarding categorical variables, Pearson's Chi-square test was applied. In all cases, regardless of sample size or frequency distribution, the Monte Carlo simulation variant was used, generating 100,000 random samples, for a robust p-value estimate. This approach was preferred to ensure the validity of statistical testing even under conditions of low frequencies or imbalance between categories. Statistical analyses were performed using a significance level set at 0.05 according to standard conventions. In interpreting the results, p-values below this threshold were considered as indices of statistically significant differences or correlations. In addition to the statistical significance, the practical relevance of the results was also considered, assessed in relation to the specifics of the study, the size of the effects obtained and the potential impact on clinical decisions or public health strategies.

The Ethics Committee of the Institutional Evaluation Committee of the State University of Medicine and Pharmacy «Nicolae Testemitanu» approved the inclusion in the study. Descriptive and comparative statistical analyses were conducted using statistical tests which are essential tools used in research to evaluate and interpret the collected data. They help us determine whether there are significant differences between groups or variables and draw conclusions about the results obtained.

**Table 3. Inclusion and exclusion criteria**

| INCLUSION CRITERIA | EXCLUSION CRITERIA |
|---|---|
| Photometric, biometric and radiological paraclinical examinations | Traumatic history of dento-maxillary teeth or permanent tooth extractions |
| Dental malocclusions associated with congenital edentulousness | Dental inclusions (including teeth without confirmed agenesis) |
| Presence of one or more non-erupted teeth with suspected image-confirmed agenesis | Odontomas or other odontogenic formations that prevent the eruption |
| Prenatal evaluations (fetal morphological ultrasound – second trimester) | Dental abnormalities associated with cleft lip and palate |
| Confirmation of the involvement of genes associated with dental agenesis (MSX1, PAX9, AXIN2) | Ectopic eruption of other teeth without congenital toothlessness |
| Presence of malformities syndromes with dental expression | Chronic local inflammatory processes that cause secondary tooth loss |
| Indication for interdisciplinary treatment (orthodontic-surgical-prosthetic-implant) | Tooth loss acquired through complicated caries or periodontal disease |

### 2.1 Clinical examination of patients with congenital edentulousness.

The detailed evaluation of patients with congenital edentulousness is essential in establishing a correct, coherent and phased treatment plan. This stage must include both the preprosthetic and prosthetic aspects, with the ultimate goal of restoring the functionality of the dento-maxillary apparatus and facial aesthetics. The clinical examination is conducted in two main stages. The first stage, contact, takes place during the first consultation and involves collecting general information

and examining the dento-maxillary apparatus. The second stage, also called the final stage, focuses on establishing the diagnosis, formulating the pre- and prosthetic therapeutic plan, as well as determining complex treatment approaches. In this phase, photometric, biometric and radiological paraclinical methods are integrated, in order to base clinical decisions on objective bases.

The relevance of the clinical examination is strongly influenced by the moment of the patient's presentation in the dental office and by a series of determining factors, including: the patient's age, the stage of eruption of the temporary and permanent dentition, the shape and size of the dental arches, the type of occlusion, the vertical size, the presence of malocclusions associated with edentulism, genetic factors involved, the positioning of the teeth and roots in the arches, as well as the morphology and distribution of congenital edentulousness.

**2.2. Cervicofacial examination**

The cervicofacial examination is an essential element of the complex diagnosis. The analysis of facial morphology is performed by inspection, palpation, auscultation, and percussion. Auscultation of the temporomandibular joint (TMJ) allows the detection of abnormal noises such as crackling, crackling or rubbing that occur during the opening and closing movements of the mouth and that may suggest the presence of occlusal or degenerative disorders at the joint level. In addition, percussion performed in the exooral area may signal systemic disorders such as severe hypocalcemia, with clinical relevance in the context of abnormal formation of dental structures [43, 44].

**2.3. Facial examination**

The facial examination performed clinically and photographically and must meet all requirements. In the patients examined, we use the Onyx Ceph computer program for facial analysis, where facial landmarks are indicated, examining the proportions of the face in different planes. Transverse symmetry refers to the position of the mandible in relation to other facial structures.

**2.4. Oral examination**

The oral examination is performed primarily clinically. The clinical examination will be completed with the examination of study models and x-rays, after which periodontal and gnathological examinations will also be performed. For some authors, the shape of the dental arch is genetically predetermined, while others consider it to be the reflex of muscle activity [45].

**2.5. Examination of study models.**

The examination of study designs was used to obtain additional data, difficult to collect by the endooral clinical examination, as well as to apply metric methods that cannot be performed directly to the patient. Initially, each model was analyzed individually, to verify the correctness of the execution and to validate the information obtained through the clinical examination (tooth appeal, their position, etc.). Subsequently, the models were examined in occlusion. These allowed the evaluation of the symmetry of the dental arches, the available space, and the dimensions of the teeth, as well as the realization of the measurements necessary to calculate the length of the anterior arch of the arches.

**Intraoral scanning.**

The intraoral scanner is a method consisting of an intraoral scanner, computer, and software. It creates a 3D digital model of scanned objects that can be teeth, dental arches, impressions, and plaster dental models. With the introduction of the intraoral scanning technique, the disadvantages of conventional impression techniques, such as dimensional changes in impression materials, storage problem, and dental calculation errors are overcome. In addition, it is easier to take fingerprints in patients with vomiting reflexes by using the intraoral camera. The development of digital models makes it possible to obtain more precise 3D diagnostic information, to communicate between the

laboratory and the orthodontist and prosthetist, to create virtual configurations and to plan the treatment and manufacture of fixed or custom-made devices. Orthodontists and prosthetists are able to plan treatment on the digital model, control the positioning of appliances, fixed and removable prostheses, and occlusally analyze models before and after orthodontic-prosthetic treatment.

Intraoral scanning allows archiving study models, evaluation of intra- and interocclusal relationships, diagnosis and treatment planning, virtual simulation, 3D realization of aligners and CAD/CAM retaining systems, positioning of orthodontic appliances, and performing prosthetic treatment.

However, inter-arch measurements such as overjet, overbite, molar relationship, and canine relationship should be checked on digital models in occlusion. It takes longer to scan the full arch in routine practice which can be considered as a disadvantage of this technique.

**2.6. Radiological examination**

When analyzing the space in a child with mixed dentition, it is necessary to assess the size of the permanent unerupted teeth in order to calculate the necessary space. There are several methods of appreciation:

Measurement of teeth on X-rays. For this purpose, there must be a correct X-ray image, which is easier to obtain on panoramic X-rays. Regardless of the type of X-ray, it is necessary to compensate for the width of the X-ray image. This is done by measuring an object that can be seen both on the X-ray and on the model, namely the first temporary molar. In this way, a simple relationship of proportionality can be expressed.

With the help of the Onyx program, each tooth in the radiological cliché is measured with a special measurement method that demonstrates in the table the width of each tooth, the diameter of the unerupted tooth and what is the space necessary for the eruption of the permanent tooth. These measurements can be performed on all dentures in different age periods.

**2.7 Prenatal evaluation of fetal dentition development**

The research included the stage of prenatal evaluation of fetal dentition development, with the aim of analyzing the formation of future teeth. This was performed in the second ultrasonographic investigation, carried out at 20 weeks of gestation according to the "Standard for the supervision of pregnant women with physiological evolution of pregnancy in outpatient conditions", approved at the meeting of the Council of Experts of the Ministry of Health on 30.03.2023 (report no. 1) and formalized by the Order of the Ministry of Health no. 311 of 11.04.2023. A detailed evaluation of fetal morphology was pursued, including the identification of potential dental and mandibular anomalies, essential for the assessment of craniofacial development. Pregnant women with mono-fetal pregnancy in physiological evolution at 20 years of age were subjected to ultrasonographic examination.

The examination was performed with the Volfson E10 ultrasound scanner, in 2D mode, equipped with a convex transducer, suitable for seasonal age, by transabdominal approach. Sagittal and axial projections of the craniofacial region were used for an optimized visualization of the facial profile. These projections were necessary for the evaluation of the bone structures and positions of the dental buds in relation to the structures of the jaw and mandible structures, thus providing detailed information on morphological development. The facial profile of the fetus was observed to identify possible genetic syndromes, maxillomandibular abnormalities and the positioning of the alveolar dental buds. At 20 weeks of pregnancy, the dental buds are visualized as small hyperechoic formations, located in the implantation areas of the maxillary and mandibular arches. In ultrasound images, they appear as white and well-defined structures, reflecting sound waves due to the increased

density of these tissues. This hyperechoic character allows the buds to be differentiated from the surrounding soft tissues, providing a clear picture of them. The dental buds appear aligned in a linear arrangement, characteristic of the position of future teeth. Linear alignment is an indicator of the symmetrical and normal development of tooth buds, characteristic of this 20-week gestation period. The linear arrangement of tooth buds is an important benchmark for aligning future tooth structures and can highlight potential deficiencies early.

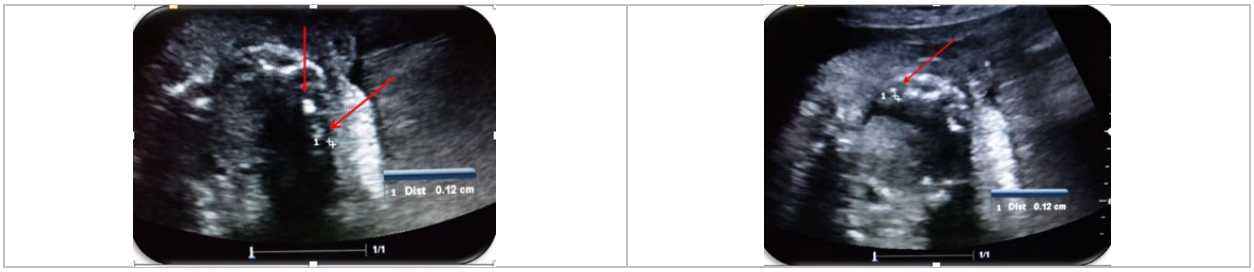


**Figure 2. Sagittal ultrasound section of the fetal craniofacial region highlighting the alveolar dental buds.**

**Note:** Dental buds appear as hyperechoic structures, well defined, located at the level of the alveolar arches. The linear and symmetrical alignment corresponds to the physiological stage of development at 20 weeks of gestation.

**2.8 Methods of treatment in age and edentulousness in patients with congenital edentulousness**

The chapter highlights that congenital edentulousness, although they are not life-threatening conditions, produce major functional (chewing, phonation), aesthetic and psychosocial consequences, with a direct impact on the quality of life. In pediatrics and adolescence, the key to therapeutic success is the phased approach, correlated with biological age, type of dentition (temporary, mixed, permanent) and severity of edentulousness, within an interdisciplinary plan (orthodontic-prosthetic, sometimes surgical-implantological). The treatment is dynamic: it simultaneously follows the development of the dento-maxillary system and the temporary rehabilitation of the gaps, until the opportune moment for definitive solutions.

In temporary dentition and at the beginning of the mixed period, the strategy is prophylactic and morpho functional. The role of morpho functional appliances (mobile or functional) in correcting dental position, guiding occlusion, stimulating jaw growth, and preventing the worsening of dento-maxillary anomalies is emphasized. These devices do not only aim at "alignment", but at the functional remodeling of the dental system, so that further development takes place under the most physiological conditions possible.

The objectives of prosthetic treatment are clearly defined: prophylaxis of associated anomalies, maintenance/recovery of spaces, protection of remaining teeth and supporting tissues, restoration of physiognomy, improvement of mastication and phonation, prevention of temporomandibular dysfunctions and establishment of age-appropriate solutions in partial edentulousness. In the choice of prosthetic means, the chapter insists on the bio functional principle: overuse should be avoided, and aggregation/restorations should allow pulp and root maturation, respecting the child's particularities (large pulp chamber, open apex, ongoing eruptions). In the same sense, functional occlusion becomes the most important criterion for all stages of prosthetic rehabilitation.

Regarding the type of restoration, the chapter discusses the alternative fixed versus removable prostheses, the decision being dependent on the location of the defect, the condition of the pillar teeth, the type of occlusion, the available space and the growth rate. Fixed restorations (crowns/bridges, inlays, physiognomic or non-physiognomic variants) are useful in selected situations, including

special solutions (telescoping, maintenance/stabilization elements) in extended anodontias. However, removable partial dentures play an essential role at growing ages due to their adaptability, the possibility of combining with orthodontic retention and hygienic advantages, provided that correct fixation and periodic monitoring are conducted.

An important component is space management: either spaces are opened for subsequent prosthetic restorations or orthodontically closed, followed by dental recontouring/reconstruction (e.g. canine substitutions). The choice is made through integrated analysis: age, sagittal/vertical malocclusion, degree of crowding, facial profile, and aesthetic parameters of the substitute tooth (shape, size, color, level of eruption). The chapter emphasizes the role of imaging investigations (especially orthopantomography and CBCT, where necessary) for the evaluation of tooth buds, eruption space and potential for maintenance/creation of spaces.

During the growth period, replacement prostheses, and active devices (with screws, springs, vestibular arches, inclined planes) are presented as tools for prevention and correction: they can control the vertical size, limit dento-alveolar extensions, guide the eruption and support orthodontic treatment. The need for dispensary surveillance (periodic check-ups every 8–10 months) and changing the prostheses according to the growth rate is emphasized, to avoid side effects and maintain the effectiveness of the therapy.

The chapter also includes contemporary measures of temporary rehabilitation, such as adhesive bridges (including Maryland type), with indications, contraindications, advantages, and conditions of success related to the selection of the case and the accuracy of the clinical-technical stages. These solutions are especially valuable in young permanent teeth, offering minimally invasive and reversible restorations, while preserving more complex future options. In pediatric practice, modern prosthetic solutions are also mentioned, better tolerated (e.g. flexible prostheses), which are useful in frontal/lateral edentulousness, with the role of maintaining space and guiding the eruption of permanent teeth.

For older ages and the end of growth, we move on to the orthodontic-surgical-prosthetic paradigm, in which endoosseous implants can be used after alignment and the formation of spaces, with rigorous evaluation of bone volume, soft tissues and the risk of infraocclusion in continuous growth. Implant-specific prosthetic principles are described: osseointegration assessment, the importance of peri-implant soft tissues, complete and functional impression, correct recording of intermaxillary relationships, as well as the choice of fixation method (screwed vs cemented) according to biomechanical and maintenance criteria, for long-term stability.

**Figure 3. Intrametric photometric examination of the patient with congenital edentations of teeth 1.2, 2.1.**

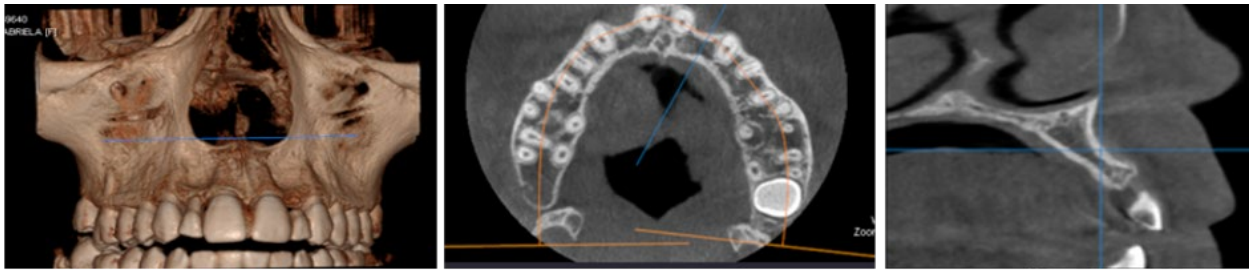

**Figure 4. 3-dimensional radiography with the conical beam and evaluation of the tissue in the frontal region.**

**Figure 5. Fixation of temporary crowns in the region of teeth 1.2 and 2.2 after implant treatment.**

Overall, the chapter formulates a guiding idea: the treatment of congenital edentates must be planned by age stages, be prophylactic in the initial stages, adaptable in growth and definitively only after the stabilization of the development of the stomatognathic system. Rehabilitation is not a singular act, but a controlled path, oriented towards maintaining function, aesthetics, and occlusal rehabilitation, so that in adulthood the patient benefits from stable, predictable solutions with a favorable long-term prognosis.

## 3. RESULTS OF RESEARCH ON CLINICAL, AESTHETIC AND GENETIC PARTICULARITIES IN CONGENITAL EDENTULOUSNESS.

Congenital dental agenesis is not a simple numerical absence, but the expression of a disturbance of craniofacial morphogenetic programming. Odontogenesis is a process strictly regulated by epithelia-mesenchymal interactions, genetically controlled by networks of transcription factors and molecular signaling pathways (WNT, BMP, SHH). Any dysfunction in these mechanisms can alter the initiation, progression, or differentiation of the tooth bud.

His own research has shown that dental agenesis associated with malformities formations cannot be interpreted in isolation. They constitute phenotypes integrated into complex craniofacial pictures, where clinical expressiveness reflects genetic and epigenetic imbalances with an impact on the development of the entire dento-maxillary system.

### 3.1 Genetic dimension of dental agenesis.

Homeobox genes and genes involved in embryonic signaling pathways play a central role in the determinism of agenesis.

**PAX9,** regulates the development of the dental mesenchyme and the progression of the bud stage. Its mutations frequently cause agenesis of molars and premolars, stopping dental development before the hood phase.

**MSX1**, located on chromosome 4p16.2, is essential for epithelium-mesenchymal interaction. Mutations lead to selective hypodontia (second premolars, lateral incisors) and can be associated with cleft lip and palate.

**AXIN2**, a regulator of β-catenin degradation in the WNT pathway, engages in severe forms of oligodontia and is associated with a predisposition to colorectal neoplasia.

**WNT10A** is one of the major genes involved in both non-syndromic hypodontias and ectodermal dysplasia's.

**DLX, LHX, RUNX2, EDA, EDAR,** participates in the modeling of the ectomesenchyme of the first gill arch and in the differentiation of dental and craniofacial structures.

Current data support the heterogeneous nature of transmission: autosomal dominant with incomplete penetrance, autosomal recessive, linked to the X chromosome, polygenic pattern.

Brook's proposed model of microdontia–hypodontia continuity is supported by clinical observations, suggesting the existence of a critical threshold of dental germ development.

**3.2 Agenesis isolated by number.**

**Hypodontias**

It represents the congenital absence of 1–6 teeth and is the most common numerical abnormality. The overall prevalence varies between 1.6–9.6%, being more common in permanent dentition.

The most affected teeth: the three molars (which are not taken into account, but it is shown that their non-formation leads to problems with the development of the dental arches), the two mandibular premolars and the maxillary lateral incisors.

Clinical expressiveness is variable and includes associated microdonation, delayed eruption, retention of temporary teeth, malposition and dental rotations, bullfighting, short roots.

**Oligodontics**

Defined by the absence of more than 6 permanent teeth, it is rare (≈0.1–0.2%). It is frequently associated with: reduced coronary size, enamel abnormalities, delayed eruption, ectodermal damage, MSX1, PAX9 and WNT10A mutations are frequently involved.

**Subtotal and total anodontias**

Extensive forms are rare and almost always associated with ectodermal dysplasia. Genetic mechanisms frequently involve EDA, EDAR, EDARADD, and genes from the WNT family.

**3.3 Associated malformities syndromes**

Dental agenesis is frequently part of complex syndromic pictures: ectodermal dysplasia, Down syndrome, Turner syndrome, Tricho-dento-bone syndrome (DLX3), Papillon–Lefèvre, Langerhans cell histiocytosis, cleft lip-maxillo-palate, cleido-cranial dysostosis.

In orofacial clefts, hypodontias is present in about 80% of cases, on the cleft side, the maxillary lateral incisors being the most frequently absent.

Chromosomal syndromes (Down, Turner) present: delayed eruption, microdontia, short roots, pseudoprognatated class III malocclusion.

**3.4 Associated dental abnormalities.**

Dental agenesis rarely occurs in isolation. In the studied group, significant associations were identified with short roots, maxillary canine ectopy, infraocclusion of temporary molars, enamel hypoplasia, reduction of mesiodistal dimensions, tooth rotations, ectopic eruptions. These associations suggest the existence of a common developmental instability, genetically regulated.

**3.5 Analysis of data from the research group.**

These data confirm that partial edentulousness diagnosed in children and adolescents frequently coexists with other dental and developmental abnormalities, such as decreased root length, ectopic eruptions, reduction in the mesiodistal size of the crowns, morphological changes and enamel hypoplasia. These comorbidities can simultaneously influence the development of the dento-maxillary apparatus and the occlusal architecture, suggesting the existence of common etiopathogenic mechanisms that govern the formation and differentiation of dental structures. In this perspective, the presence of edentations seems to be not just an isolated entity, but part of a broader spectrum of craniofacial development abnormalities.

In the study, 100 patients with congenital edentulousness were analyzed. For each subject, 83 variables were collected and evaluated, including sociodemographic data (sex, age, domicile),

edentulous characteristics (number of missing teeth, type and location of agenesis), particularities of dental eruption (early or delayed eruptions), type of malocclusion and occlusal scheme, facial features (facial symmetry, vertical size, lip relationship, chin protrusion) as well as cephalometric parameters analyzed according to the methodology Steiner. An additional objective aimed at evaluating the genetic components involved in dental agenesis, an aspect investigated by analyzing genes with a role in odontogenesis.

The results obtained suggest the existence of possible relationships between dental agenesis and occlusal features. However, it should be noted that the prevalence of class III and class II division 2 malocclusions – types in which differences in the frequency of edentations have been noted – remains low in the general population, and their manifestation is largely influenced by genetic predisposition. It is also relevant that most previous studies have been based on the Angle classification, a predominantly qualitative system that focuses on the anteroposterior relationship of the first permanent molars, without sufficiently integrating other essential features of occlusion, such as the position of the front teeth or their alignment in relation to the occlusion plane. In the context of dental agenesis, compensatory mobility of the remaining teeth – often a mesial migration – can alter the molar interocclusal ratio, generating classification errors in the Angle system. Considering these limitations, the present study aimed to investigate the relationships between congenital edentations and quantifiable occlusal indicators, in a non-random but consecutive sample, and included in the analysis both permanent molars and wisdom molars, which in the previous literature were frequently excluded.

The gender analysis demonstrated an interesting pattern: hypodontias and oligodontics were more common in females, while severe forms, such as subtotal edentulousness, showed a male predominance. These observations are illustrated in Figure 30 and suggest potential biological and genetic differences, which are worth exploring in future studies.

Figure 6 illustrates the relative distribution of the main types of dental agenesis by sex, highlighting statistically significant differences between groups (Chi-Squared Test, Monte Carlo: $\chi^2 = 12.01$; $p = 0.00236$). The results demonstrate a clear pattern of segregation of phenotypes in relation to sex, with important implications for understanding the etiological mechanisms of congenital edentulousness.

In the case of subtotal edentulousness, the proportion of male patients is dominant (88.9%), while women are affected in a much smaller proportion (11.1%). This unbalanced ratio suggests that severe forms of agenesis could be influenced by genetic or epigenetic factors with greater penetrance in males, through mechanisms related to craniofacial development or hormonal variables involved in odontogenesis.

On the other hand, hypodontias and oligodontics are predominantly found in females, with identical values of relative prevalence (69.2%), compared to 30.8% in males. This distribution indicates an increased susceptibility of girls to mild and moderate forms of agenesis, which may reflect subtle differences in eruptive dynamics, dental maturation, or specific interactions of genes involved in dental development (e.g., MSX1, PAX9, AXIN2).

Overall, the figure confirms the existence of a phenotypic profile differentiated by sex, in which: the male gender presents extensive forms of edentations (subtotal), the female gender manifests more frequently form of low or moderate severity (hypodontia and oligodontia).

The statistical significance of the differences ($p < 0.01$) supports the hypothesis that sex is a relevant predictor factor in the expression of congenital edentulousness, which justifies the integration of this parameter in the screening, diagnosis, and interdisciplinary treatment planning

algorithms.

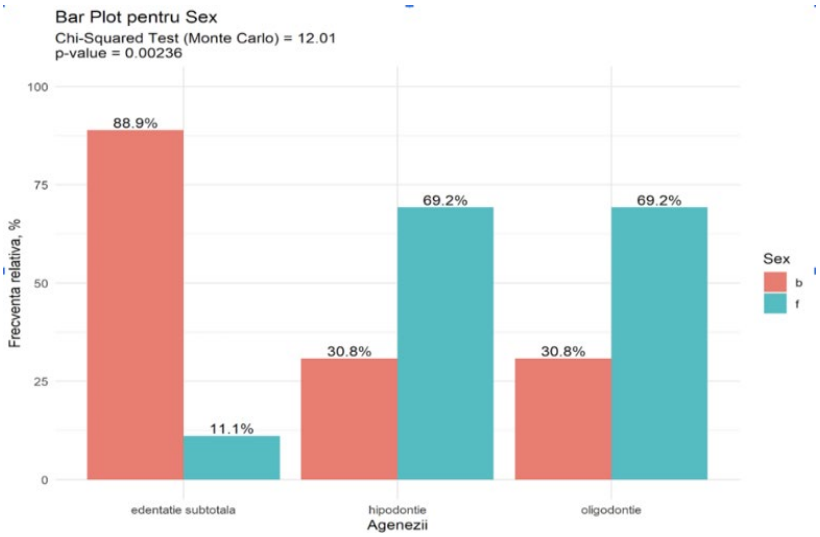


**Figure 6. Pilot study between genders in different types of dental agenesis.**

Figure 7 shows the relative distribution of the main types of dental agenesis according to the area of residence of the patients, analyzing three categories: the municipality of Chisinau, the rest of the Republic of Moldova and abroad. The Chi-square test (Monte Carlo) indicates a value $\chi^2 = 4.37$, with a $p = 0.3124$, which signifies the absence of a statistically significant association between the type of agenesis and the geographical area of origin. Although the differences do not reach the threshold of statistical significance, the phenomenological distribution provides relevant information for the national epidemiological context.

In the case of subtotal edentulousness, the distribution is balanced between the municipality of Chisinau (44.4%) and the rest of the Republic of Moldova (55.6%). This distribution suggests that severe forms of congenital edentations are uniformly found in the population, without indicating an urban or rural concentration. The lack of major differences may reflect the similar access to pediatric dental services or the genetic character of these forms.

For hypodontia, the data show a higher concentration in Chisinau (64.1%), followed by the rest of the republic (32.1%), while cases from abroad are rare (3.8%).

Although statistically insignificant, this model can be explained by: an earlier detection of mild forms of agenesis in urban areas, due to better access to specialized consultations, a higher rate of presentation in university centers for orthodontic and pedodontics evaluations, the possibility for families in rural areas to come late for treatment, which reduces the reporting of mild forms.

As for oligodontics, there is a notable preponderance among patients from Chisinau municipality (76.9%), compared to only 15.4% in the rest of the republic and 7.7% among patients from abroad. This distribution, although not statistically significant, is clinically relevant, suggesting that moderate forms of dental agenesis are evaluated and treated within university centers, which may reflect both the increased addressability in the urban area and the complexity of cases requiring interdisciplinary diagnosis.

Overall, the figure indicates that the area of residence is not a significant determinant of the severity of congenital edentulousness, but the phenomenological distribution reveals: the predominance of moderate and severe forms in urban areas, increased addressability at university centers for complex cases, potential underreporting of mild forms in rural areas.

These data support the need to strengthen screening and early diagnosis programs at national level, especially in environments where access to specialized dental services is limited.

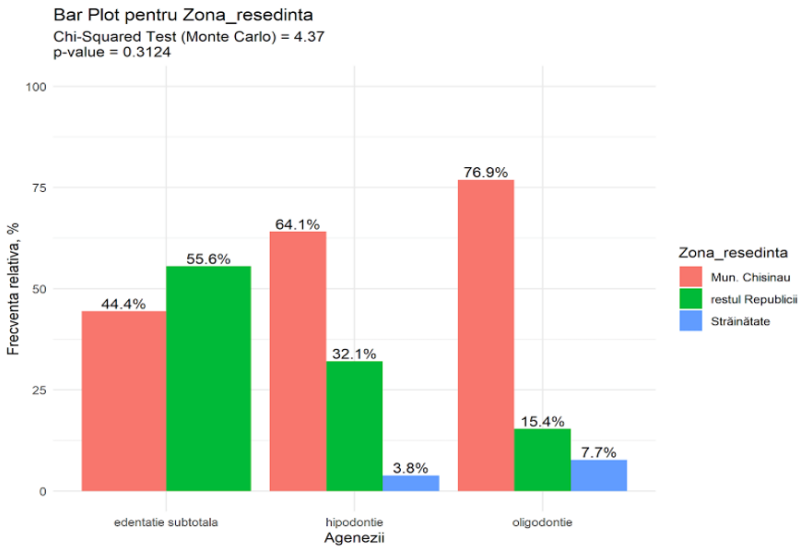


**Figure 7. Study by area of residence.**

Figure 8 shows the distribution of aesthetic perception among patients with subtotal edentulousness, hypodontia, and oligodontics. Although differences are observed between groups, the Chi-square test (Monte Carlo) did not reveal a statistically significant association between the type of agenesis and aesthetic concerns ($\chi^2 = 3.72$; $p = 0.1692$).

From a descriptive point of view, patients with **hypodontia** reported the most frequent aesthetic impact (75.6%), which is explained by the frequent involvement of the upper lateral incisors, a critical region for facial aesthetics. In **subtotal edentulousness**, aesthetic concerns are present in 55.6% of patients, while **oligodontics** presents an almost balanced distribution between those aesthetically affected and those who are not affected (53.8% vs. 46.2%).

Overall, the results suggest that aesthetic perception does not depend exclusively on the numerical severity of agenesis, but on the location of the missing teeth and the associated morphological changes, even if the relationship does not reach the threshold of statistical significance.

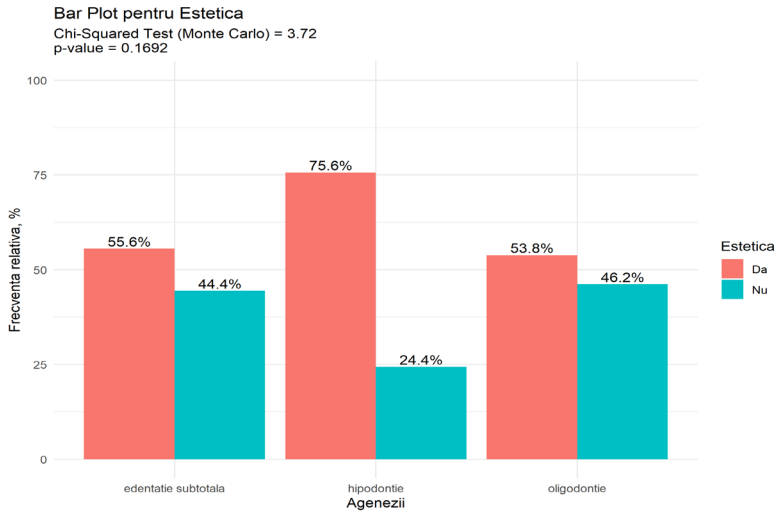


**Figure 8. Examination of the aesthetics of patients with dental agenesis.**

In 1899, Angle introduced his famous classification of malocclusion, which remains relevant today. According to the World Health Organization, malocclusions are the third most common oral health problem after tooth decay and periodontal disease.

The etiology of malocclusions is complex and multifactorial, involving genetic, environmental, and ethnic factors. Genetic factors play a significant role, with certain types of malocclusions, such as class III, being commonly found within the same family, suggesting a strong

link between genetics and malocclusion. The ethnic factor is also relevant, with examples such as the bimaxillary protrusion, which affects several people of African descent. On the other hand, functional adaptations to environmental factors influence dental structures and surrounding tissues, leading to various malocclusion problems.

Therefore, malocclusion is considered a multifactorial condition, without having a single cause of stability. The involvement of agenesis in dental malocclusions causes partial edentulousness that can falsify dental malocclusion depending on the skeletal development class and the position of both front and lateral teeth. In the sample, we detected malocclusions in subtotal edentations by class 44.4% in patients with Class I and II after Angle and 11.1% in class III. In oligodontics 61.5% class I, 15.4% in class II and 23.1% in class III after Angle. In patients with hypodontia, 79.5% with class I, 17.9% with class II and 2.6% with class III.

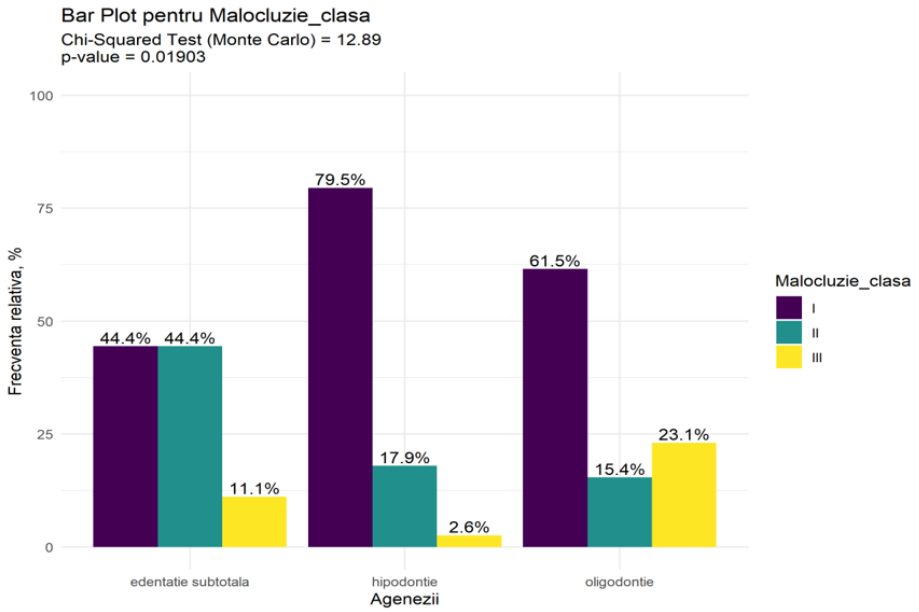


**Figure 9. Forms of malocclusion after Angle in dental agenesis.**

Dental occlusion in patients with congenital edentulousness is the direct expression of the disturbance of the development of the facial skeleton and the morpho functional balance of the stomatognate system. The absence of the dental bud not only influences the lack of dental unity but also causes the insufficient development of the corresponding alveolar segment, a reduction in the thickness of the cortical blade and a change in the shape of the dental arches, which inevitably leads to occlusions of the pathological dental arches. These changes are clinically reflected by masticatory, phonetic, aesthetic disorders and by imbalances at the level of the temporomandibular joint, with progressive functional impact.

The analysis of the forms of occlusion in the study highlights a clear correlation between the severity of congenital edentations and the type of occlusal imbalance. In hypodontia, orthognathic occlusion predominates (75.6%), but there is already an incidence of deep occlusion of 21.8% and open occlusion of 2.6%, indicating the onset of vertical changes. In oligodontics, imbalances become more pronounced: deep occlusion increases to 38.8%, and open occlusion to 15.4%, with a decrease in the proportion of orthognathic occlusion to 53.8%, which reflects the progressive destabilization of intermaxillary relationships. In subtotal edentulousness, the picture is dominated by deep occlusion (66.7%), and the rest of the cases present orthognathic occlusion (33.3%), confirming that the numerical severity of congenital edentates directly correlates with the severity of occlusal involvement. The distribution of forms of occlusion demonstrates that congenital edentations is not only a number anomaly, but a determining factor of the pathological remodeling of the stomatognathic system.

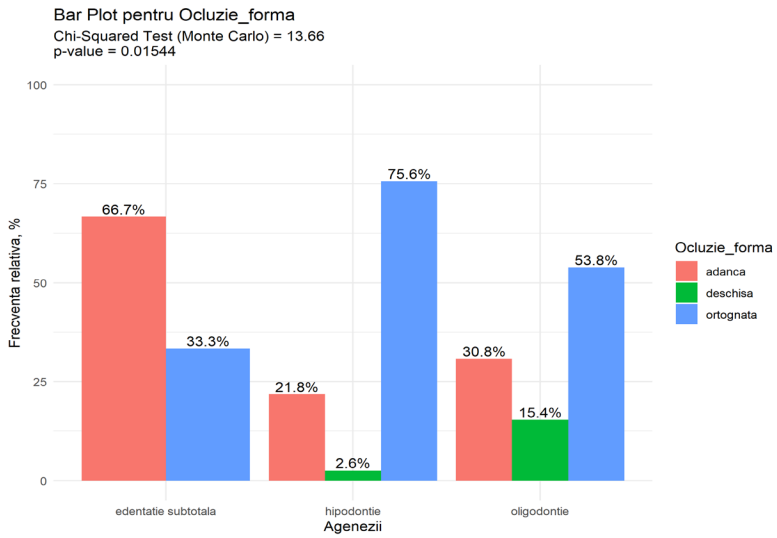


**Figure 10. By the type of dental occlusion in different forms of agenesis.**

### 3.6 The agenesis of each tooth detected in the patients studied.

The analysis of the distribution of agenesis by dental units demonstrates that congenital edentations present a differentiated topographic pattern, depending on the type and severity of the damage (subtotal edentulousness, hypodontia, oligodontia). For an important part of the teeth examined, the Chi-square tests with Monte Carlo simulation confirm statistically significant associations between the category of agenesis and dental status (present/absent), which supports the existence of stable "phenotypic signatures". In particular, wisdom teeth appear as elements with maximum variability and high susceptibility, and the increase in the frequency of their agenesis in severe forms (oligodontics) reflects the intensity of the disruption of dental organogenesis.

At the same time, the investigated group highlights a clinically relevant contrast: certain dental groups show selective vulnerability (premolars, third molars and, in some situations, specific posterior teeth), while others behave as phenotypically preserved structures, with very low rates of agenesis and/or without significant differences between groups (e.g., teeth with increased developmental stability). This dualism suggests a differentiated genetic control, with variable effects on the fields of dental development and with clinical expression modulated by the severity of agenesis, confirming the uneven character of dento-maxillary damage in congenital edentulousness.

From an applicative perspective, tooth-to-tooth mapping provides a useful tool for case stratification, anticipation of occlusal imbalances and substantiation of interdisciplinary decisions (orthodontic, prosthetic, surgical), including in relation to the development of alveolar ridges and maintenance of the vertical dimension of occlusion.

**Table 4. Percentage distribution of agenesis on each tooth according to the type of congenital edentations**

| Tooth | Subtotal Edentulousness (%)Absent / Present | Hypodontia (%)Absent / Present | Oligodontia (%)Absent / Present |
|---|---|---|---|
| 1.8 | 44.4 / 55.6 | 16.7 / 83.3 | 92.3 / 7.7 |
| 1.7 | 44.4 / 55.6 | 1.3 / 98.7 | 15.4 / 84.6 |
| 1.6 | 44.4 / 55.6 | 2.6 / 97.4 | 0 / 100 |
| 1.5 | 66.7 / 33.3 | 11.5 / 88.5 | 23.1 / 76.9 |
| 1.3 | 22.2 / 77.8 | 100 / 0 | 100 / 0 |
| 1.2 | 44.4 / 55.6 | 75.6 / 24.4 | 69.2 / 30.8 |
| 1.1 | 11.1 / 88.9 | 2.6 / 97.4 | 0 / 100 |
| 2.1 | 66.7 / 33.3 | 100 / 0 | 100 / 0 |
| 2.2 | 55.6 / 44.4 | 28.2 / 71.8 | 53.8 / 46.2 |
| 2.3 | 77.8 / 22.2 | 0 / 100 | 0 / 100 |
| 2.4 | 55.6 / 44.4 | 3.8 / 96.2 | 0 / 100 |
| 2.5 | 55.6 / 44.4 | 9.0 / 91.0 | 7.7 / 92.3 |

| | | | |
|---|---|---|---|
| **2.6** | **44.4 / 55.6** | **3.8 / 96.2** | **0 / 100** |
| **2.7** | **22.2 / 77.8** | **1.3 / 98.7** | **0 / 100** |
| **2.8** | **44.4 / 55.6** | **14.1 / 85.9** | **84.6 / 15.4** |
| **3.8** | **44.4 / 55.6** | **26.9 / 73.1** | **84.6 / 15.4** |
| **3.7** | **77.8 / 22.2** | **98.7 / 1.3** | **76.9 / 23.1** |
| **3.6** | **33.3 / 66.7** | **19.2 / 80.8** | **15.4 / 84.6** |
| **3.5** | **66.7 / 33.3** | **21.8 / 78.2** | **30.8 / 69.2** |
| **3.4** | **33.3 / 66.7** | **1.3 / 98.7** | **7.7 / 92.3** |
| **3.3** | **66.7 / 33.3** | **0 / 100** | **0 / 100** |
| **3.2** | **22.2 / 77.8** | **1.3 / 98.7** | **0 / 100** |
| **3.1** | **22.2 / 77.8** | **3.8 / 96.2** | **7.7 / 92.3** |
| **4.1** | **22.2 / 77.8** | **1.3 / 98.7** | **15.4 / 84.6** |
| **4.2** | **33.3 / 66.7** | **2.6 / 97.4** | **7.7 / 92.3** |
| **4.4** | **33.3 / 66.7** | **1.3 / 98.7** | **7.7 / 92.3** |
| **4.5** | **66.7 / 33.3** | **19.2 / 80.8** | **38.5 / 61.5** |
| **4.6** | **44.4 / 55.6** | **14.1 / 85.9** | **0 / 100** |
| **4.7** | **44.4 / 55.6** | **5.1 / 94.9** | **15.4 / 84.6** |
| **4.8** | **44.4 / 55.6** | **24.4 / 75.6** | **100 / 0** |

### 3.7 Tooth eruption in dental agenesis.

Table 5 presented includes 15 cases investigated at 20 weeks of gestation and contains the following parameters: age of the pregnant woman, weight and height, BMI, gestational age, obstetric history, comorbidities (genital inflammation, urological pathologies, obesity, endocrine pathologies, cardiovascular diseases). The age of pregnant women varies between 17 and 43 years, which allows the inclusion of both young pregnant women and those of advanced maternal age. The BMI indicates an important variability: there are cases with normal values, but also multiple situations of overweight and obesity (BMI > 30). Most pregnancies are assessed at 20 weeks, according to the standardized protocol. This anthropometric diversity is relevant in the context of the evaluation of fetal development, as maternal nutritional status and possible metabolic pathologies can influence craniofacial development. From the analysis of the columns on the associated pathology, it is observed: The presence of cases of genital inflammation. Isolated cases of urological conditions. A considerable number of patients with obesity. Cases with endocrine pathologies. Some pregnant women have cardiovascular disease (CVS). These data are important in interpreting the results because: endocrine and metabolic disorders can influence mineralization processes; Maternal obesity may be associated with an increased risk of developmental abnormalities; chronic inflammation may impact the intrauterine environment.

**Table 5. Clinical-demographic characteristics of pregnant women included in the prenatal evaluation of fetal dentition development (20 weeks gestation)**

| NR. DR | VÂRSTA | GREUTATEA | ÎNĂLȚIMEA | IMC | SĂPTĂMINĂ | SĂPTĂMINĂ | NĂȘTERI | INFLAMAȚIE GENITALĂ | INFLAMAȚIE UROLOGIE | OBEZITATE | ENDOCRINE | SCV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 20 | 53 | 163 | 199 | 27 | 1 | 1 | Da | Nu | Nu | Nu | Nu |
| 2 | 30 | 78 | 165 | 287 | 26 | 2 | 2 | Nu | Nu | Da | Da | Nu |
| 3 | 35 de ani | 64 | 162 | 244 | 21 de ani | 1 | 1 | Da | Nu | Nu | Nu | Nu |
| 4 | 43 | 59 | 160 | 230 | 28 de ani | 3 | 3 | Da | Nu | Nu | Da | Da |
| 5 | 19 | 74 | 164 | 275 | 24 | 1 | 1 | Nu | Da | Nu | Nu | Nu |
| 6 | 28 de ani | 89 | 160 | 348 | 25 | 3 | 3 | Nu | Nu | Da | Da | Da |
| 7 | 22 | 68 | 167 | 244 | 21 de ani | 1 | 1 | Nu | Nu | Nu | Nu | Nu |
| 8 | 17 ani | 48 de ani | 160 | 187 | 29 | 1 | 1 | Nu | Da | Nu | Nu | Nu |
| 8 | 32 | 58 | 162 | 22.1 | 28 de ani | 2 | 2 | Nu | Nu | Nu | Nu | Nu |
| 10 | 26 | 65 | 152 | 28.1 | 38 de ani | 1 | 1 | Nu | Nu | Nu | Nu | Nu |
| 11 | 42 | 78 | 165 | 287 | 36 | 7 | 4 | Da | Nu | Nu | Nu | Da |
| 12 | 37 | 89 | 172 | 30.1 | 30 | 2 | 2 | Da | Nu | Nu | Da | Nu |
| 13 | 32 | 78 | 160 | 305 | 38 de ani | 3 | 3 | Da | Da | Nu | Nu | Nu |
| 14 | 22 | 89 | 158 | 357 | 36 | 1 | 1 | Nu | Nu | Da | Nu | Nu |
| 15 | 19 | 62 | 164 | 23.1 | 29 | 1 | 1 | Da | Nu | Nu | Nu | Nu |

Correlation with the development of fetal dentition at the 20th week, visualization of dental buds is an indirect marker of ectodermal development and integrity of craniofacial morphogenetic processes. In the context of the table, the group includes pregnant women with a variable biological profile, which allows the assessment of dental development under various physiological conditions. The absence of mention of major abnormalities suggests that, in most cases, the alignment and visualization of the dental buds were in accordance with the gestational age. The presence of risk factors (obesity, endocrine pathology) provides the premise for further comparative analyses on the potential influence on dental development. The prenatal evaluation at 20 weeks of gestation allows the identification and morphological assessment of the dental buds, representing a valuable tool for the early detection of possible dento-maxillary anomalies. The analyzed group presents a significant biological heterogeneity, including pregnant women with metabolic and inflammatory risk factors, which provides an adequate framework for investigating the relationship between maternal status and fetal dentition development. The integration of dental evaluation within standard morphological ultrasound contributes to an interdisciplinary approach, with potential for development in the direction of prenatal screening of dento-craniofacial anomalies.

**3.8 Vertical dimension of occlusion in congenital edentulousness.**

Analysis of the vertical dimension of occlusion in relation to the type of agenesis and congenital edentulousness directly correlated with the severity of dental arch damage. The data obtained demonstrate that the changes in the vertical dimension are not accidental but reflect the adaptation of the stomatognathic system to the loss of dental units and the consequent occlusal imbalance.

In subtotal edentulousness, reduction of vertical dimension is the dominant feature in most patients. The extensive absence of teeth causes a decrease in posterior occlusal support and the appearance of a secondary hypodivergent facial pattern, frequently associated with changes in the lower level of the face. The lack of cases with enlarged vertical size in this group confirms the reductive character of the impact of subtotal edentulousness on vertical facial development.

In hypodontia, it is found that vertical balance is maintained in most cases, the normal size being dominant. This finding suggests that mild forms of agenesis do not significantly disturb intermaxillary relationships, with dento-alveolar compensatory mechanisms sufficient to preserve facial proportions. Reduction in vertical size occurs to a lesser extent, and its increase is rare, indicating a limited impact of hypodontia on vertical parameters.

In oligodontics, the picture becomes more complex and variable. Although normal vertical size remains relatively common, the increased proportions of both reduction and enlargement of vertical dimension reflect the instability of morphological equilibrium in severe forms of congenital agenesis and edentulousness. The multiple absence of teeth can generate changes in the occlusal plane. This variability suggests the existence of different adaptive mechanisms, dependent on the topographic distribution of absent teeth in congenital edentulousness.

Figure 78 shows the distribution of the vertical occlusal size. In patients with subtotal edentulousness, the decreased vertical occlusal size is dominant, being present in 88.9% of cases. Normal size is observed in 11.1 % of patients, while enlarged size is not found in this group. This distribution suggests a strong correlation between subtotal edentations and reduction in occlusal vertical size.

In hypodontia, the situation is different. Normal vertical occlusal size is the most common, being present in 73.1% of cases, indicating minimal impact on occlusal balance. The decreased size is seen in 24.4% of patients, suggesting that in some cases, reducing the number of teeth may contribute to the decrease in vertical size. Enlarged size is exceedingly rare in this group, being present in only 2.6% of patients.

In the case of oligodontics, the distribution is more balanced. Normal size is found in 46.2% of patients, but there are also a significant proportion of patients with reduced size, respectively 30.8%. Also, the enlarged size is present in 23.1% of cases, indicating a greater variability of this characteristic depending on the particularities of each patient.

These results suggest a clear relationship between the severity of dental agenesis and changes in the occlusal vertical size. While patients with subtotal edentations most commonly show a reduction in this size, those with hypodontia tend to have a normal size, and in oligodontics an increased variability is observed.

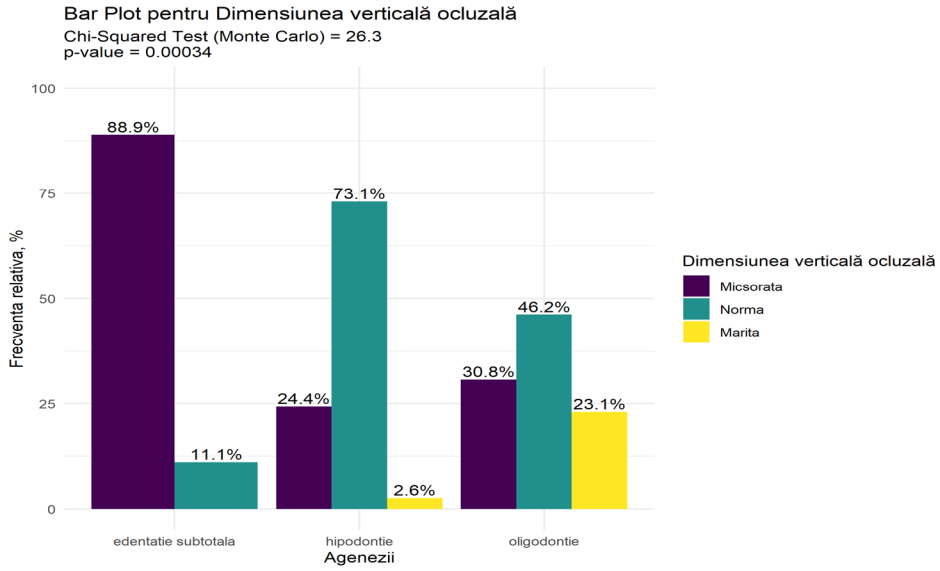


**Figure 11. Distribution of the occlusal vertical dimension in dental agenesis.**

Steiner analysis is one of the most widely used cephalometric methods in orthodontics, providing a rigorous framework for evaluating the sagittal relationships between the jaw, mandible, and base of the skull. Through the ANS, SNB and ANB angles, it allows the assessment of the anteroposterior position of the bone bases and the identification of the skeletal imbalances underlying the malocclusions. The ANB angle is a synthetic indicator of the maxillo-mandibular relationship: values within the norm reflect a harmonious skeletal balance, increased values are suggestive of a

skeletal class II relationship (maxillary protrusion and/or mandibular retrusion), and low or negative values indicate a skeletal class III tendency (maxillary retrusion or mandibular prognathism). In addition, the analysis of the position of the incisors in relation to the reference lines, including the reference to the S-line, allows the integration of dental components in the evaluation of the aesthetics of the profile and occlusal functionality.

The distribution of Steiner cephalometric values according to the type of dental agenesis highlights a correlation between the severity of congenital edentulousness and changes in skeletal relationships. In subtotal edentulousness, decreased values predominate (55.6%), while the rest of the cases fall within the norm, without registering increased values. This trend suggests an increased frequency of class III sagittal discrepancies or a relative reduction in the maxillo-mandibular ratio, secondary to occlusal collapse and insufficient development of alveolar support.

In hypodontia, most patients (74.4%) present values within normal limits, which indicates the maintenance of skeletal balance in mild forms of agenesis. The low proportion of decreased values and the minimal incidence of increased values demonstrate that hypodontia, in the absence of an extensive distribution of missing teeth, does not significantly influence the anteroposterior relationships of the bone bases. On the other hand, a more variable distribution is observed in oligodontia: although more than half of the cases remain normal, the equal proportions of the decreased and increased values (23.1%) indicate an instability of the sagittal balance, with the possibility of the appearance of both class II and class III skeletal patterns.

Overall, Steiner's analysis confirms that the severity of congenital edentations influences not only the dental component, but also the vertical and sagittal skeletal relationships. Severe forms of congenital edentations are associated with greater variability in cephalometric parameters, suggesting that multiple absence of the dental follicle may interfere with the growth and shaping of the maxillary bases. From a clinical perspective, these data emphasize the need for detailed cephalometric evaluation in interdisciplinary treatment planning, as occlusal rehabilitation must be correlated with skeletal peculiarities to ensure long-term functional and aesthetic stability.

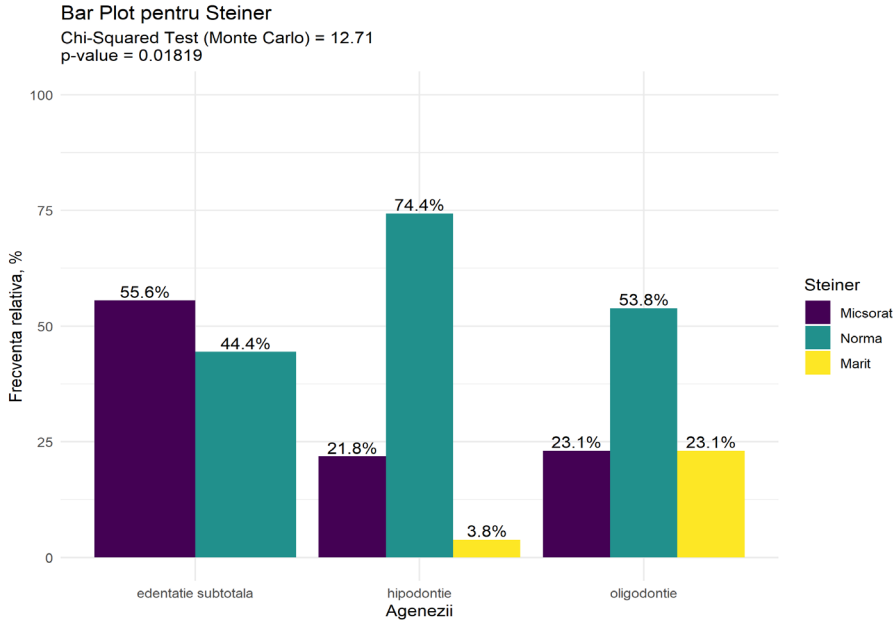


**Figure 12. Distribution in agenesis: the cephalometric method according to Steiner**

**3.8 Genes studied congenital edentulousness.**

Within the group of patients with congenital edentulousness, results of genetic investigations previously performed in specialized centers were available in a subgroup of 5 patients. These

molecular analyses were brought by the patients and were integrated into the clinical evaluation of the study.

The online catalogue of inherited human diseases, Online Mendelian Inheritance in Man (OMIM), is one of the most important databases for correlating clinical phenotypes with the genetic substrate. Currently, around 16,000 pathological entities with hereditary transmission are described, but the molecular etiology has only been elucidated for some of them. The identification and cloning of the genes involved is a fundamental step in understanding the pathogenic mechanisms, subsequently facilitating the development of modern strategies for molecular diagnosis, family screening and personalized therapeutic intervention.

In the context of dental agenesis, genetic research has highlighted the essential role of genes involved in regulating odontogenesis and epitheliomesenchymal interactions during embryonic development. In the analyzed study, in patients who presented results of genetic investigations, changes were identified at the level of key genes involved in dental morphogenesis.

**MP4 (Bone Morphogenetic Protein 4)** encodes a bone morphogenetic protein belonging to the TGF-β family, with a key role in the initiation and differentiation of the tooth bud. It participates in the regulation of cell proliferation and in establishing the pattern of development of dento-alveolar structures, and its variations can influence both the number and morphology of teeth.

**PAX9** is a member of the paired box (PAX) transcription factor family, playing an essential role in the formation of posterior teeth. Mutations in this gene are frequently associated with hypodontias and oligodontics, especially in permanent molars, and are considered among the best-documented genetic causes of non-syndromic dental agenesis.

**MSX1**, located on chromosome 4p16.2, belongs to the homeobox family and participates in controlling the differentiation of mesenchymal cells during dental development. Alterations in this gene can lead to the absence of incisors and premolars, being associated with both isolated forms of agenesis and syndromic manifestations.

**AXIN2** is an important regulator of the Want/β-catenin signaling pathway, which is essential for the initiation and progression of odontogenesis. AXIN2 mutations are correlated with severe forms of oligodontics and, in certain cases, may have systemic implications, with associations with predispositions for other pathologies being described. The data obtained confirms the existence of a molecular substrate in the etiology of congenital edentulousness. These results reinforce the hypothesis that the congenital absence of teeth is not only a local developmental anomaly, but the expression of a complex genetic disorder, with implications for dental morphogenesis. The integration of genetic evaluation in the study of congenital edentations contributes to the deepening of the understanding of etiopathogenic mechanisms and opens perspectives for early diagnosis and individualized early treatments.

### 3.9 Treatment distribution in patients with partial edentulousness

Congenital edentulousness represents a therapeutic challenge both by the complexity of the clinical manifestations and by their impact on the functional and aesthetic development of the dento-maxillary apparatus. The congenital absence of one or more teeth influences the development of dental arches, occlusion, chewing, phonation, and facial appearance, which is why the management of these patients requires a phased approach and the collaboration of several dental specialties. Figure 92 presents the multidisciplinary protocol for the treatment of congenital edentulousness, organized in successive stages of interdisciplinary treatment. The dental approach in congenital edentations begins with prophylactic measures, which include primary, secondary, and tertiary prophylaxis, followed by orthodontic treatment with mobile or fixed appliances. Depending on clinical needs, the

management continues through oro-maxillofacial interventions, implantological or orthognathic type, and the final stage is represented by Prosthetic-prosthetic rehabilitation, performed by mobile or fixed prosthesis. The structure of the scheme highlights the phased and interdisciplinary nature of the treatment, adapted to the particularities of each patient with congenital edentulousness. Also, an interdisciplinary examination, with the orthodontist, Prosthetic dentist and oro-maxillofacial surgeon, is recommended for planning the combined treatment plan.

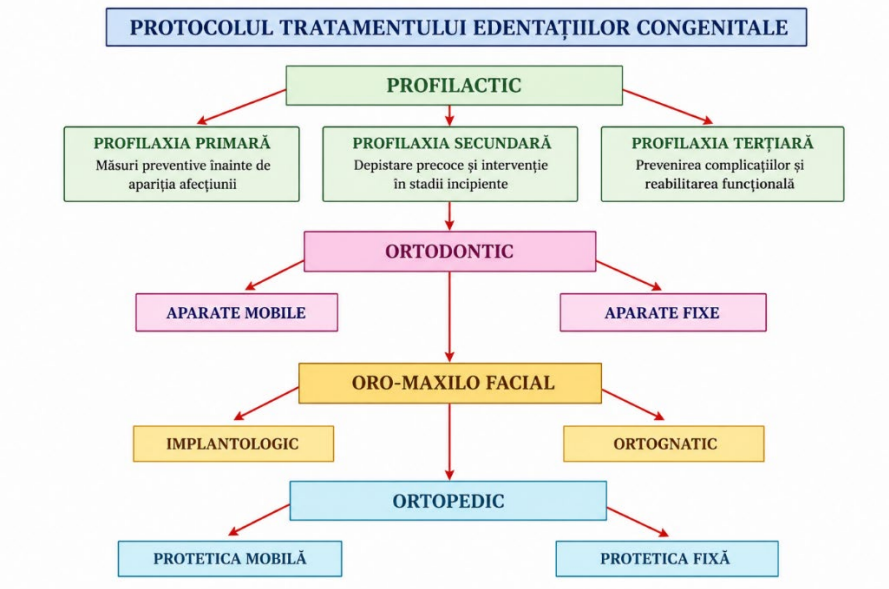


**Figure 13. Protocol for the treatment of congenital edentations**

1. Prophylactic treatment in congenital edentations aims to prevent occlusal imbalances, tooth migration and complications that may arise from the congenital absence of one or more teeth.
2. In cases of dental eruption guidance, orthodontic intervention can be early to guide the eruption of permanent teeth and maintain a functional occlusion and treatment of the development of dental arches, orthodontic treatment in congenital edentations is an essential component in the multidisciplinary management of patients with congenital edentulousness.
3. Oro-maxillofacial rehabilitation of congenital edentations is a high-performance option, aimed at restoring the functional balance of the stomatognate system. In the congenital absence of teeth, the alveolar bone needs to be carefully planned for interdisciplinary treatment through gnathological and implantological methods.
4. In the context of congenital edentulousness, the choice of Prosthetic treatment is a critical stage in the oral rehabilitation process, being influenced by factors such as the number of missing teeth, the distribution of edentulousness, the quality of bone support, the shape of the alveolar process, the patient's age and the individual functional and aesthetic context. Treatments include dento-dental or implant fixed prosthetic restorations, partially or totally mobile prosthesis and mixed solutions (fixed and mobile combined), the indications for treatment depend on the complication and severity of congenital edentulousness[295]

# 4. GENERAL DISCUSSION

The study conducted on a group of 3692 patients with dento-maxillary anomalies showed a significant correlation between dental agenesis and multiple clinical, cephalometric, and genetic features, with important implications in the diagnosis and interdisciplinary treatment of congenital edentulousness.

A predominance of females was found in the hypodontia and oligodontics forms, while subtotal edentations was more common in male patients. In the present study, an association was observed between the presence of dental agenesis and certain types of malocclusion, especially Class III and Class II division 2, which suggests the hypothesis of the existence of common mechanisms involved in dento-maxillary development.

Regarding the gender distribution, the results are consistent with the meta-analysis by Khalaf et al., which estimated an overall prevalence of hypodontias of 6.4% and a higher risk in women (OR = 1.22; 95% CI: 1.14–1.30), as well as with the study by Gracco et al. on 4,006 patients, in which the prevalence was 9.1% in women and 8.7% in men [47, 48].

The results on the aesthetic impact are consistent with the observations of Kerekes-Mathe et al., who showed that the clinical and aesthetic impact of hypodontias is determined not only by the number of missing teeth, but also by their location and by changes in the shape and size of the remaining teeth, aspects that significantly influence the dentofacial appearance [1].

In the analyzed group, the changes in the facial profile were more evident in the extended forms: the protrusive position of the lips was observed in 88.9% of patients with subtotal edentulousness, in 38.5% of those with oligodontia and in 21.8% of those with hypodontia, the same trend being found for the protrusion of the chin. Class I after Angle prevailed in all forms of agenesis in our group, with no significant differences between the groups analyzed.

The analysis of the right maxillary segment 1.2–1.8 revealed an uneven distribution: tooth agenesis 1.2 was identified in 75.6% of patients with hypodontias and 69.2% of those with oligodontics, for 1.5 the frequencies were 66.7% in subtotal edentulousness, 23.1% in oligodontics and 11.5% in hypodontia, and for 1.8 they reached 92.3% in oligodontics, 44.4% in subtotal edentations and 16.7% in hypodontia.

This distribution corresponds to the hierarchy described by Polder et al. and Khalaf et al., in which the lateral incisor and the second maxillary premolar are among the frequently absent teeth, while the canine, first premolar, and molars one and two are less often affected; in Khalaf's meta-analysis, mild, moderate, and severe forms accounted for 81.6%, 14.3%, and 3.1%, respectively [46, 47].

In our study, tooth 3.5 showed the highest frequency of agenesis among the analyzed teeth, being absent in 66.7% of patients with subtotal edentulousness, in 21.8% of those with hypodontia and in 30.8% of those with oligodontics. The results are comparable to the meta-analysis conducted by Polder et al. in 48,274 people, in whom the prevalence of second mandibular premolar agenesis was 2.91–3.22% in the general population, this being the most frequently affected tooth [47].

Regarding the prenatal evaluation of the development of dental buds, the study group included 15 pregnant women aged between 17 and 43 years, of which 46.7% had genital inflammation, 26.7% endocrine pathologies, and 20.0% had obesity, urological or cardiovascular diseases. The ultrasound evaluation performed around the 20th week aimed at visualizing the fetal dental buds, but the small size of the group does not allow establishing a causal relationship between maternal pathology and the appearance of congenital edentulousness.

Early eruption was identified in 11.1% of patients with subtotal edentulousness and 20.5% of those with hypodontia, while no case was recorded in oligodontics.

Delayed eruption was more frequent, being observed in 55.6% of patients with subtotal edentulousness, in 23.1% of those with hypodontia and in 38.5% of those with oligodontia.

Reduction in vertical facial and occlusal size was predominant in subtotal edentulousness, being identified in 88.9% of patients, compared to 24.4% in hypodontias and 30.8% in oligodontics.

In hypodontia, normal size predominated (73.1%), while oligodontics showed the greatest variability: 46.2% of patients had normal values, 30.8% decreased values and 23.1% increased.

Decreased cephalometric values predominated in subtotal edentulousness, being identified in 55.6% of patients, compared to 21.8% in hypodontia and 23.1% in oligodontia.

Normal values predominated in hypodontias (74.4%) and oligodontics (53.8%), but oligodontics showed greater variability, increased values being identified in 23.1% of patients.

The pilot study aimed to identify changes in the BMP4, PAX9, MSX1 and AXIN2 genes, involved in odontogenesis by regulating epitheliomesenchymal interactions and BMP and WNT signaling pathways.

For BMP4, positive results were recorded in 33.3% of patients with subtotal edentations and in 15.4% of those with oligodontics, while in hypodontias no positive results were identified; However, the high proportions of untested patients, of 46.2% in hypodontias and 38.5% in oligodontics, limit the comparison of groups.

In our study, positive PAX9 result was identified in 33.3% of patients with subtotal edentations and 15.4% of those with oligodontics, without positive results in hypodontia ($\chi^2 = 25.79$; $p = 0.00024$).

MSX1 variants were identified in all patients evaluated in the subtotal edentulous group, compared to 35.9% of those with hypodontia and 53.8% of those with oligodontia.

AXIN2 variants were identified in 44.4% of patients with subtotal edentations and in 15.4% of those with oligodontics, without positive results in the hypodontia group.

The results obtained in the study on the methods of diagnosis and interdisciplinary treatment of congenital edentations allowed us to outline a complex picture of how the congenital lack of teeth influences craniofacial development, the functions of the stomatognathic system and the aesthetic balance of the face.

The analysis of the patient group revealed an important variability of clinical manifestations, correlated both with the severity of dental agenesis and with individual genetic particularities.

Hypodontia, oligodontics and subtotal edentations have been shown to be different expressions of the same dysregulated morphogenetic mechanism, determined by complex interactions between the genes responsible for dental differentiation and local growth and development factors. A balanced phenotype predominates in hypodontia, with effective functional adaptations, occlusion close to normal and discrete facial asymmetries. Oligodontics, by affecting a greater number of dental units, produces more obvious morphological disturbances, with changes in the vertical dimension, dental migrations, and occlusion disorders.

Subtotal edentations are the most severe form, characterized by obvious facial decompensations, reduction of alveolar support and alteration of facial aesthetics, with expressed lips and prominent chin.

At the genetic level, the analysis of the expression of the MSX1, PAX9, AXIN2 and BMP4 genes confirmed their direct involvement in the etiopathogenesis of congenital edentulousness. Thus, the interdisciplinary approach proved to be essential for achieving stable and functional results. The

early identification of congenital edentations, during the period of mixed dentition, allows interventions that can prevent occlusal imbalances and subsequent facial asymmetries. At the same time, modern imaging examination (CBCT, digital orthopantomography) has provided essential information for differentiating between real agenesis and included or non-erupted teeth, avoiding diagnostic errors.

In conclusion, the comparative analysis of the results obtained demonstrates that the severity of congenital edentations determines the degree of functional, morphological, and aesthetic impairment.

The results obtained in the study on the methods of diagnosis and interdisciplinary treatment of congenital edentations allowed us to outline a complex picture of how the congenital lack of teeth influences *craniofacial development*, the functions of the stomatognathic system and the aesthetic balance of the face. The analysis of the patient group revealed an important variability of clinical manifestations, correlated both with the severity of dental agenesis and with individual genetic particularities. Hypodontia, oligodontics and subtotal edentations have been shown to be different expressions of the same dysregulated morphogenetic mechanism, determined by complex interactions between the genes responsible for dental differentiation and local growth and development factors.

A balanced phenotype predominates in hypodontia, with effective functional adaptations, occlusion close to normal and discrete facial asymmetries. Oligodontics, by affecting a greater number of dental units, produces more obvious morphological disturbances, with changes in the vertical dimension, dental migrations, and occlusion disorders. Subtotal edentations is the most severe form, characterized by obvious facial decompensations, reduction of alveolar support and alteration of facial aesthetics, with expressed lips and prominent chin. This clinical progression confirms that the severity of edentations is directly proportional to the degree of functional and morphological impairment.

Cephalometric and photometric analysis revealed clear relationships between the occlusal pattern and the distribution of edentulousness. Deep occlusion, commonly found in severe forms, reflects a compensatory adaptation to the loss of vertical and alveolar support. The decrease in the vertical size of the face, associated with the asymmetry of the dental arches, accentuates the aesthetic and functional imbalance, affecting not only chewing, but also phonation and facial expressiveness. In moderate forms of oligodontics, a compensating capacity is observed by adapting the occlusion and maintaining vertical ratios, which underlines the importance of early diagnosis and early orthodontic intervention.

At the genetic level, the analysis of the expression of the MSX1, PAX9, AXIN2 and BMP4 genes confirmed their direct involvement in the etiopathogenesis of congenital edentulousness. MSX1 and PAX9 have been shown to be genes with a significant role in the formation of tooth buds, determining various phenotypes depending on the degree of expression or mutations present. AXIN2, although less frequent in the analyzed group, has a major clinical significance, being associated with extensive forms of agenesis and having syndromic potential. BMP4, with a modulatory role, participates in the regulation of *epithelial-mesenchymal* signals, influencing the process of mineralization and dental differentiation. This genetic correlation emphasizes the multifactorial nature of congenital edentations and the need to include genetic testing in the modern diagnostic algorithm.

The interdisciplinary approach has proven to be essential for achieving stable and functional results. The collaboration between the orthodontist, the oro-maxillofacial surgeon, the prosthetic

specialist, and the geneticist allowed the development of personalized therapeutic solutions, adapted to the severity of the case and the patient's age. In mild cases, space maintainers and preventive orthodontic treatments played a key role in guiding the eruption and maintaining vertical dimensions.

These results demonstrate that therapeutic success depends on the integration of functional, morphological and genetic approaches into a common framework. The study also highlighted the importance of early diagnosis. The early identification of congenital edentations, during the period of mixed dentition, allows interventions that can prevent occlusal imbalances and subsequent facial asymmetries. Modern imaging examination (CBCT, digital orthopantomography) has provided essential information for differentiating between real agenesis and included or non-erupted teeth, avoiding diagnostic errors. The integration of genetic and imaging investigations into a unitary diagnostic protocol is one of the most important directions for the modernization of pediatric and orthodontic dentistry.

The results obtained confirm that congenital edentations should be regarded not only as a simple dental absence, but as an expression of a complex disorder of *craniofacial development*. The impact of these changes goes beyond the aesthetic sphere, influencing the functions of the dento-maxillary apparatus, psycho-emotional development, and the patient's quality of life. In this context, treatment cannot be limited to morphological rehabilitation but must also aim at restoring the overall functional and *aesthetic balance*.

In conclusion, the comparative analysis of the results obtained demonstrates that the severity of congenital edentations determines the degree of functional, morphological, and aesthetic impairment. Genetic factors play a decisive role in the deceptive development of the stomatognathic system and the entire body. The development and use of an interdisciplinary protocol, based on early diagnosis, genetic assessments and integrated treatment planning, will provide the best prospects for a complete and sustainable interdisciplinary rehabilitation of patients with congenital edentulousness. The research thus contributes to the scientific substantiation of a modern model of treatment of congenital edentulousness.

## GENERAL CONCLUSIONS

1. The epidemiological peculiarities of congenital edentations highlight a statistically significant female predominance ($p = 0.002$) and an uneven distribution of clinical forms, with a predominance of hypodontia.
2. Early detection is essential, in the context in which the severity of edentulousness increases with the number of missing teeth, the differences between forms being significant ($p < 0.001$).
3. The interdisciplinary clinical and paraclinical diagnosis allows the correct evaluation of occlusal relationships, which are significantly influenced by the type of edentulism ($p < 0.05$).
4. Congenital edentations cause obvious craniofacial changes, especially on the vertical dimension and facial profile, with a statistically significant impact ($p < 0.001$).
5. Interdisciplinary treatment demonstrates efficiency in restoring the functions of the dento-maxillary apparatus, being correlated with the clinical particularities and severity of the case.
6. The step-by-step algorithm, adapted to the age and type of edentulousness, ensures continuity and predictability in treatment, having extensive practical applicability.
7. The genetic component plays a decisive role in the appearance of congenital edentulousness, with significant associations being identified for genes involved in odontogenesis ($p \leq 0.006$).

8.

## RECOMMENDATIONS

1. Strengthening the interdisciplinary approach through close collaboration between orthodontists, oro-maxillofacial surgeons, prosthetists, geneticists, and pediatricians, to develop integrated diagnostic and treatment protocols.
2. Use of modern genomic sequencing methods to identify genetic mutations involved in dental agenesis and to establish phenotype-genotype correlations.
3. Creation of national and regional registries with patients diagnosed with congenital edentulousness, useful for large-scale epidemiological and genetic studies.
4. Elaboration of standardized clinical guidelines for the early diagnosis and phased treatment of congenital edentulousness, adapted to the stages of development of the dento-maxillary apparatus.
5. Expansion of the use of advanced imaging techniques (CBCT, MRI, high-resolution ultrasound) for the evaluation of dento-alveolar structures and dental mineralization.
6. Integration of digital technologies (CAD/CAM, 3D printing, artificial intelligence) in personalized treatment planning and simulation of dental development.
7. Developing educational and prevention programs for dentists, students, parents, and children, with a focus on the importance of early diagnosis.
8. Developing individualized therapeutic protocols, adapted to the age, type, and severity of dental agenesis, with a focus on maintaining functionality and aesthetics.
9. Stimulating fundamental and applied research in the field of molecular biology, tissue engineering, and regenerative medicine for innovative solutions to replace missing congenital teeth.
10. Future directions: – deepening the relationship between gene mutations involved in dental development and the risk of systemic pathologies; – development of predictive models assisted by artificial intelligence for population screening; – applying the concept of "personalized medicine" in dentistry, by integrating genetic, clinical and imaging data into therapeutic plans.

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# LIST OF PUBLICATIONS AND PARTICIPATION IN SCIENTIFIC FORUMS

of Mr. **Solomon Oleg,** doctor of medical sciences, associate professor, for the thesis of doctor habilitatus in medical sciences, with the theme: Methods of diagnosis and interdisciplinary treatment of congenital edentations, specialty 323.01 Dentistry

"Ilarion Postolachi" Department of Prosthetic Dentistry,

"Nicolae Testemitanu" State University of Medicine and Pharmacy

from the Republic of Moldova

## SCIENTIFIC PAPERS

**1. Monographs:**

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## SUMMARY

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**” Methods of diagnosis and interdisciplinary treatment of congenital edentations”**

**Thesis of Doctor Habilitatus of Medical Science, 323.01 Dentistry. Chișinău 2026**

**Thesis structure:** The thesis comprises 206 pages and consists of an Introduction, three chapters, General Discussion, General Conclusions, and Practical Recommendations. It is illustrated with 9 tables, 102 figures, and 4 appendices, and includes a bibliography comprising 301 references. The research findings have been published in 78 scientific papers.

**Key words:** congenital edentulousness, malformations, dento-maxillary apparatus, diagnosis, interdisciplinary treatment, clinical protocol.

**Field of study:** Dentistry, congenital dentitions.

**The purpose of the paper:** Evaluation of the sample, methodical identification of the diagnosis and interdisciplinary treatment in patients with congenital edentulous teeth.

**Objectives of the study:** Evaluation of the epidemiological characteristics of patients with malocclusions associated with congenital dentitions. Highlighting the methods of early detection of congenital edentations. Elaboration of clinical and paraclinical diagnostic methods. The normal development of the multiple and complicated functions of the dento-maxillary apparatus in congenital edentations. The study and development of a predominantly interdisciplinary treatment of congenital edentations.

**The scientific novelty of the study:** it consisted in the elucidation of the clinical particularities of congenital dentitions, taking into account their increasing incidence. For this purpose, an interdisciplinary clinical protocol was developed, as well as a survey of the group of patients predisposed to the appearance of congenital edentations, a study conducted for the first time in the Republic of Moldova.

**The scientific problem solved:** the development of new diagnostic methods and the establishment of interdisciplinary treatment for patients with congenital edentulous teeth that will reduce the number of registered cases of this anomaly of the dento-maxillary apparatus among the population of the Republic of Moldova.

**The theoretical significance and the applied value of the study:** The research results allowed revealing the clinical and paraclinical particularities of patients with congenital edentulousness and

the possibilities of their interdisciplinary treatment. Carrying out an in-depth study of the parameters of congenital edentations, will significantly supplement the knowledge about this anomaly of the dento-maxillary apparatus, specific to the respective geographical region, the essential aspects that could determine the appearance and progression of the given pathology will be made known.