



## TRICHO-DENTO-OSSEOUS SYNDROME: A BRIEF REVIEW FOR DENTISTRY

### Síndrome trico-dento-óssea: uma breve revisão para odontologia

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#### ABSTRACT

**Introduction:** Tricho-dento-osseous syndrome is a ultra-rare ectodermal dysplasia related to genetic alterations in the *DLX3* gene of interest to the health sciences due to its clinical manifestations. **Aim:** To synthesize the scientific evidence about tricho-dento-osseous syndrome, especially for dentistry. **Methods:** A bibliographic search was performed in the MEDLINE / PubMed, Web of Science and Scopus databases. A search strategy with descriptors was applied to all databases mentioned to reach scientific articles. The articles reached in all databases had their titles and abstracts read in search of adaptation to the proposed objective. There was no restriction on the year of publication, country or language. **Literature review:** Patients diagnosed with this syndrome have dental enamel defects and severe taurodontism, especially in the permanently lower first molars. In addition to these signs, other manifestations may be associated, such as curly hair, increased bone density and changes in craniofacial bones. The diagnosis of tricho-dento-osseous syndrome can be challenging due to the heterogeneity and wide phenotypic variation presented by patients with *DLX3* mutations, since this gene is associated with several functions, especially related to cell differentiation and biomineralization. In addition, it is necessary to consider that other dental anomalies may be confused with tricho-dento-osseous syndrome, especially cases of imperfect amelogenesis associated with taurodontism. **Conclusion:** For dentistry, oral manifestations caused by this syndrome become relevant for diagnostic and therapeutic purposes, although there are no clinical protocols for dental management of this patients.

**Keywords:** Tricho-dento-osseous syndrome. Ectodermal dysplasia. Oral manifestations. Review literature as topic.

#### RESUMO

**Introdução:** A síndrome trico-dento-óssea é uma displasia ectodérmica ultra-rara relacionada a alterações genéticas no gene *DLX3* de interesse para as ciências da saúde devido à suas manifestações clínicas. **Objetivo:** Sintetizar as evidências científicas sobre a síndrome trico-dento-óssea, especialmente para odontologia. **Materiais e métodos:** Uma pesquisa bibliográfica foi realizada nas bases de dados MEDLINE/PubMed, Web of Science e Scopus. Uma estratégia de busca com descritores foi aplicada em todas as bases de dados mencionadas para alcançar os artigos científicos. Os artigos alcançados em todas as bases de dados tiveram seus títulos e resumos lidos em busca da adequação ao objetivo proposto. Não houve restrição quanto ao ano de publicação, país ou idioma. **Revisão de literatura:** Os pacientes diagnosticados com essa síndrome apresentam defeitos no esmalte dentário e taurodontismo severo, principalmente nos primeiros molares permanentemente inferiores. Além desses sinais, outras manifestações podem estar associadas, como cabelos crespos, aumento da densidade óssea e alterações nos ossos craniofaciais. O diagnóstico da síndrome trico-dento-óssea pode ser desafiador devido à heterogeneidade e ampla variação fenotípica apresentada pelos pacientes com mutações em *DLX3*, uma vez que esse gene está associado a várias funções, principalmente relacionadas à diferenciação e biomineralização celular. Além disso, é necessário considerar que outras anomalias dentárias podem ser confundidas com a síndrome trico-dento-óssea, principalmente nos casos de amelogênese imperfeita associada ao taurodontismo. **Conclusão:** Para a odontologia, as manifestações orais causadas por essa síndrome tornam-se relevantes para fins diagnósticos e terapêuticos, embora não existam protocolos clínicos para o tratamento odontológico específico destes pacientes.

**Palavras-chave:** Doenças genéticas inatas. Displasia ectodérmica. Manifestações bucais. Literatura de revisão como assunto.

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## INTRODUCTION

The tricho-dento-osseous syndrome (TDOS) is an ultra-rare syndromic condition with an autosomal dominant inheritance. It is an uncommon ectodermal dysplasia resulting from interactions between epithelium and mesenchyme. Ectodermal dysplasias are hereditary changes in tissues that develop from the embryonic ectoderm, leading to inadequate tissue differentiation. With wide phenotypic variation, TDOS causes changes in the hair, teeth and bones of affected individuals<sup>1-3</sup>.

The heterogeneity of phenotypes makes it difficult to accurately diagnose of TDOS, although changes in dental elements may be consistent in differentiating it from other syndromes with oral manifestations<sup>4,5</sup>. The diagnosis often occurs in the first year of life, when the first signs of the syndrome can be observed. Also, wide phenotypic variation may be due to environmental combined to genetic factors. The onset of TDOS are mutations different regions of the distal-less homeobox 3 (*DLX3*) gene<sup>2,4</sup>.

Thus, considering the importance of TDOS for dentists and the need to understand oral manifestations, this review aims to synthesize the scientific evidence about tricho-dento-osseous syndrome, especially for dentistry.

## METHODS

A bibliographic search was carried out in the MEDLINE/PubMed, Web of Science and Scopus databases. A search strategy with descriptors was applied in all the aforementioned databases to reach the scientific articles: “dentistry” [MeSH terms] AND “tricho-dento-osseous syndrome” [MeSH terms]). The articles reached in all databases had their titles and abstracts read in search of adequacy to the proposed objective. There were no restrictions on the year of publication, country or language.

As it is an ultra-rare syndrome, little evidence is available in the databases. We selected studies available fully that addressed relevant aspects about the trico-dento-osseous syndrome for dental sciences, involving a historical, molecular and clinical perspective.

## LITERATURE REVIEW

Retrospectively, the first scientific evidence of TDOS was reported by Robinson et al.,<sup>6</sup> Lichtenstein and Warson<sup>7</sup> and Lichtenstein et al.<sup>8</sup> The authors initiated case studies that investigated phenotypic characteristics in individuals and families with enamel hypoplasia, seeking to understand what other changes were associated with this dental defect.

Moving forward in the timeline, with the consolidation of TDOS as a syndrome, Quatromani et al.<sup>9</sup> and Shapiro et al.<sup>10</sup> initiated the first studies to identify clinical variations. In their results, based on clinical evidence, the authors suggested the first classification for TDOS into three subtypes according to the phenotypic variation presented. Also, the same authors started discussions about genetic mutations and heterogeneity observed in TDOS.

Seow<sup>11</sup> published a literature review that included and evaluated case reports of TDOS and imperfect amelogenesis. This was one of the pioneering studies in understanding the phenotypic variations of TDOS and an initial toe in discussions about the differential diagnosis between this syndrome and other dental anomalies. In the same year, Seow<sup>12</sup> investigated the relationship between the severity of taurodontism, TDOS, and imperfect amelogenesis. The author was a pioneer in identifying that severe taurodontism is associated only with TDOS and is unrelated to imperfect amelogenesis.

DLX3 gene mutations are the molecular explanation to TDOS. Molecular and genetic approaches to TDOS had their milestones with the identification of mutations in *DLX3* gene, located on chromosome 17q21, in families with TDOS<sup>13-15</sup>. In addition to these, Wright et al.<sup>16</sup> researched phenotypic and genotypic variations in TDOS. In their findings, the authors identified that hair alterations, enamel defects and taurodontism have wide clinical variation, even with high penetrance in patients diagnosed with TDOS.

The DLX3 protein is related to craniofacial growth and development, acting on the standardization of embryonic ectoderm, hair follicles, and dental amelogenesis. DLX3 is a transcription factor important to bone, tooth and hair embryogenesis. Mutations localized in different regions of *DLX3* are associated with the clinical manifestations range of the syndrome, justifying the occurrence of mild to severe cases<sup>2,3,17</sup>.

The alterations that affect the C-terminus region of DLX3 might be associated with the severity of some manifestations in patients diagnosed with TDOS, indicating that certain *DLX3* mutations are associated with low or high severity phenotypes of this syndrome. Variations in that region are important to the failure of the binding of DLX3 protein with DNA to exercise its activity as a transcription factor<sup>18,19</sup>.

DLX3 protein is associated with tissue biomineralization throughout the human skeleton, regulating the deposition of minerals in tissues. In knockdown models for *DLX3*, it is observed that there is a negative modulation of the expression of enamel mineral matrix genes, crucial to amelogenesis<sup>20,21</sup>.

Besides, some *DLX3* mutations identified can cause late cell senescence, modifying bone aging and decreasing bone loss. Studies in experimental models indicate that the osteogenic potential of mesenchymal stem cells may increase when *DLX3* genetic mutations are present. These findings can be interpreted as a possible cause for bone density changes observed in some patients with TDOS<sup>3</sup>.

Recently, c.533 A > G as a *DLX3* mutation that may cause decreased differentiation of dental pulp odontogenic cells was reported, indicating an influence of this gene on dentin formation and mineralization. One year later, that same group found that microRNA-675 positively acts in the process of odontogenic cell differentiation. It modulates *DLX3* gene expression by inhibition of its promoter methylation<sup>22,23</sup>.

Dental and craniofacial manifestations are frequently in this syndrome. TDOS manifests clinically widely in affected individuals, however, some characteristics are frequently observed. Curly or wavy hair has been identified in a series of studies with patients diagnosed with TDOS and some authors consider it one of the characteristics that drive the investigation and diagnosis of this syndrome in children. However, scientific evidence reports that capillary changes are not present in all individuals with TDOS, have wide phenotypic variation among individuals within the same family and may change after childhood, as some lose this characteristic over time<sup>3,5,24</sup>.

On the other hand, taurodontism and enamel hypoplasia are characteristics strongly associated with diagnoses with TDOS. Nevertheless, taurodontism (pulp chamber enlargement) still causes divergences in the clinical diagnosis between amelogenesis imperfecta and TDOS. This diagnostic confusion, exemplified by the clinical case reported by Hegde and Srikanth<sup>25</sup>, should take seriously the fact that it is possible to observe a mild degree of taurodontism in patients with imperfect amelogenesis, although severe cases of taurodontism are associated with TDOS. However, it is still not possible to understand whether it is an imperfect threat, an incomplete expression of TDOS or a spectrum of disease<sup>4,5,26,27</sup>.

Changes in dental enamel may be considered the most significant in patients diagnosed with TDOS. They include teeth with a color change in shades between yellow and brown. In addition, a drastic reduction in enamel thickness can be found, ranging from 12.5% to 60% of

the thickness of a healthy tooth. Histologically, it is common to observe zones of aprismatic enamel, hypocalcified and with less amount of mineral matrix, together with changes in dentinal tubules and Tomes granular layer<sup>4,28,29</sup>.

Currently, it is understood for diagnostic purposes that generalized enamel hypoplasia and severe taurodontism characterize TDOS and allow differential diagnosis of imperfect amelogenesis, since severe taurodontism is not common in the latter and both conditions are present in all individuals with TDOS. When assessing taurodontism, its occurrence in the permanent lower first molar is a change strongly associated with a true dental anomaly and its severity can be measured radiographically by the relationship between the dimensions of the root and the crown of the tooth<sup>4,24,30</sup>.

Craniofacial manifestations remain poorly understood in patients with TDOS. Dolichocephalic profile, maxillary retrognathism, and mandibular prognathism were identified in patients with TDOS; however, studies measuring such cephalometric characteristics suggest that such alterations may be the result of environmental and genetic factors unrelated to TDOS. Besides, it is necessary to consider that the inclusion of patients with different phenotypic severities of TDOS may make statistical analyzes difficult to determine significant craniofacial changes<sup>24,31</sup>.

Kula et al.<sup>31</sup> found that the length of the mandibular body, the size and the angle of the skull base were greater in patients with TDOS, as well as the thickness of some craniofacial bones and lower visibility of the frontal sinuses. On the other hand, Nguyen et al.<sup>24</sup> found no differences in skull base size and angle. However, similarly to Kula et al.<sup>31</sup> identified larger measurements on mandibular body length, as well as higher measurements of lower facial third height compared to standard values. Nguyen et al.<sup>24</sup> also did not verify mandibular prognathism in patients with TDOS comparing to their controls. However, he indicated the possibility of a skeletal class III appearance when there is a retracted jaw.

Associated with severe taurodontism (in primary or permanent dentitions) and enamel hypoplasia, individual and family case reports indicate that patients diagnosed with TDOS may have brittle nails, increased skull bone density (bone sclerosis), severe dental attrition and abscesses<sup>4,32</sup>.

The other clinical manifestations that can be identified in patients diagnosed with TDOS are variable and not completely understood. Unusually, Mayer et al.<sup>33</sup> reported a case of severe atopic dermatitis in a patient diagnosed with TDOS. Similarly, Al Kaissi et al.<sup>34</sup> reported a case of melorheostosis mimicking TDOS in a patient with similar phenotypic characteristics. In addition to these findings, two studies indicate an association between chromosome 17q21 deletion and the occurrence of TDOS associated with cognitive disorders and osteogenesis imperfecta, making room for new correlations between *DLX3* genetic alterations and other conditions<sup>35,36</sup>.

It is essential for the diagnosis and management of patients with TDOS to observe other characteristics besides enamel hypoplasia and taurodontism, such as changes in hair, bones, and nails. We should investigate the occurrence of skin diseases such as atopic dermatitis and other systemic manifestations. Early diagnosis may favor the management of dental changes<sup>2,37</sup>.

Teeth affected by enamel defects often present color changes, hypersensitivity, caries disease and progressive loss of dental structure. It is common to observe the need for restorative, endodontic and prosthetic treatments and retreatments in patients with dental enamel defects. The difficulty of adherence and the characteristics of the dental remnant impair adhesive dental procedures and reduce the survival of treatments over time<sup>37,38</sup>.

There are no protocols for patients with generalized dental enamel defects and multidisciplinary dental treatment is essential for a good prognosis and oral health of individuals. However, the first step may be complete dental documentation, including full-mouth radiographic examinations<sup>4,39</sup>.

It is important that dental management prioritizes the dental problems of each patient and outlines a strategy aimed at pain removal, damage reduction and prevention of new injuries. Dental remineralization strategies should be considered to prevent loss of non-carious healthy structure and to decrease dentin hypersensitivity. Prosthetic crowns, laser therapy, fluoride varnishes and, dentifrices that promote obliteration of dentinal tubules can be considered in this process<sup>4</sup>.

## CONCLUSIONS

Tricho-dento-osseous syndrome has oral manifestations relevant to dentistry. Dental enamel defects and severe taurodontism present in patients diagnosed with TDOS deserve attention for diagnostic and therapeutic purposes by the dental surgeon, although there is no clinical protocol or specific recommendations for the dental management of these patients.

## CONFLICT OF INTERESTS

None of the authors of this article claim to have conflicts of interest of any kind.

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