

# Dental Approach in Individuals with Loeys-Dietz Syndrome: A Mini Review



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Received: June 3, 2018; Published: June 12, 2018

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## Abstract

Loeys-Dietz syndrome (LDS) is a connective tissue disease which develops due to the mutations in the genes synthesizing TGF-beta receptors. Hypertelorism, cleft palate with bifid uvula and arterial/aortic aneurysms are the 3 basic elements of the disease forming a triad. Considering oral and maxillofacial findings in individuals with Loeys-Dietz syndrome, the responsibility of dentist is very important both in diagnosis of syndrome and in treatment. In the literature, there has been no publication of a dental approach to LDS and it is expected that this publication may be a guide to dentists for the syndrome.

## Introduction

Loeys-Dietz syndrome is a rare disease with autosomal dominant inheritance. The disease results from a heterozygous mutation in the TGFBR1 and TGFBR2 genes affecting the connective tissues [1,2]. It was described by Loeys and Dietz in 2005 for the first time [1]. The classical triad of the syndrome consists of

- a. Hypertelorism,
- b. Cleft palate or bifid uvula and
- c. Arterial/aortic aneurysms and/or arterial tortuosity [3-5].

The skeletal abnormalities of LDS include pectus deformity, scoliosis, joint hypermobility, cervical spine malformations and/or instabilities, arachnodactylia, and talipes equinovarus [6,7]. The craniofacial findings of LDS include widely spaced eyes, blue sclerae, bifid uvula/cleft palate, and craniosynostosis [8,9]. Accompanying cutaneous findings may include a translucent skin, a soft and velvety skin, milia, easy bruising, and atrophic scars [10,11]. The patients with LDS are susceptible to allergic and inflammatory diseases such as food allergies, eczema, asthma, and chronic sinusitis [11,12]. Six different types of LDS has been defined based on the presence of mutations. Type 1 includes TGFBR1 (20-25%), Type 2 includes TGFBR2 (55-60%), Type 3 includes SMAD3 (5-10%), Type 4 includes TGFBR2 (5-10%), Type 5 includes TGFBR3 (1-5%), and Type 6 includes SMAD2 (1-5%) mutations [7].

The disease displays similarities with other connective tissue disorders, like Marfan and Ehlers Danlos syndrome, because of the presence of arterial and aortic aneurysms/dissections. Loeys-Dietz syndrome is differentiated from Marfan syndrome by hypertelorism, bifid uvula or cleft palate, diffuse aortic and arterial aneurysms and tortuosity [13,14]. Furthermore, ectopia lentis, a distinctive finding for the Marfan syndrome, is not seen in Loeys-Dietz syndrome [15]. Due to the aggressive arterial diseases and ruptures, the mean survival in LDS (37 years) is significantly lower compared to Ehlers Danlos (48 years) and Marfan (70 years) syndromes [4,16,17]. Compared with Marfan's syndrome, dissections and ruptures occur in younger ages and in smaller diameters in LDS [18]. Craniosynostosis is seen in 50% of the patients with LDS. Craniosynostosis can be evaluated by a three-dimensional tomography. The sagittal suture is found to be prematurely closed and this premature closing can also be observed with the coronal, metopic and squamous sutures [19].

Respiratory distress and obstructive sleep apnea may occur due to the micrognathia and cleft palate of the disease. Obstructive sleep apnea can also be seen in Marfan syndrome [20]. Beta-adrenergic receptor blockers or angiotensin receptor blockers and anticoagulants are used in the treatment of LDS. Angiotensin receptor blocker losartan has been shown to slow down the development process of aneurysms [21]. Patients should be warned that they should avoid challenging exercises and exercises which

may cause joint injuries. Congenital heart diseases including the bicuspid aortic valve, atrial septal defect or patent ductus arteriosus in LDS patients are more common compared to those seen in the general population [22,23]. In addition, a mitral valve prolapse and/or mitral valve insufficiency is also seen in LDS [23-25]. In these patients, oral hygiene should be kept at the highest levels to prevent bacteremia. It should be remembered that prophylaxis may be required before surgery. In addition, hemorrhages may emerge in patients using anticoagulant medications, therefore, rearrangements of the drug regime might be changed by consulting the patient's physician before the surgery.

In patients with LDS, joint hypermobilities are common, including congenital hip dislocations and recurrent and multiple joint subluxations [19]. However, in some patients, there may be a decrease in the joint mobility as well, especially in the hands and feet. In the literature, there are not any studies available demonstrating the relationship between LDS and TME disorders, however, there are studies reporting that there are increases in the subluxation of TME and increases in the signs and symptoms of temporomandibular disease in Marfan syndrome, which is a similar syndrome [26,27]. We are of the opinion that LDS may also be associated with TME diseases. Erkula et al. in their study evaluating the musculoskeletal findings in patients with LDS, reported the rates of the high-arched palate, cleft palate, and dolichocephaly as 76%, 36%, and 20%, respectively [28]. Malocclusions may require orthodontic treatment due to the high and narrow structure of the palate.

The orthodontic evaluation must definitely be performed in patients with LDS to identify any requirements for treatment. H. Dietz and B. Loeys observed dental damages due to the hypoplasia of the enamel, requiring extractions of the deciduous teeth [19]. Other abnormal findings like a bifid uvula, uvula with raphe, large or long uvula may be observed in LDS patients, however, there are numerous patients with LDS as well, who do not develop these abnormalities. When a dentist observes any abnormalities of the uvula during the oral examination, she or he must evaluate the patient for LDS. LDS has been reported to be associated with osteoporosis and bone fragility in younger ages [4,29,30]. Amor et al. have clarified those findings in LDS patients reporting that the TGF- $\beta$  overexpression in osteoblasts results in a lower bone mass, a thin cortical bone, a high bone turnover, and an increased bone matrix mineralization [3]. These changes in the bone structure must be taken into consideration during the dental implant therapy because there are studies in the literature reporting that the rate of bone turnover or osteoporosis affects the success of the implanting [31-33].

## Conclusion

Although Loeys-Dietz syndrome is quite rare, it should be well-recognized as a syndrome involving many aspects of dentistry. Patients with LDS require a special procedure for the surgical procedures due to the medications they receive and the risk of infective endocarditis. Dentists are involved in the diagnosis of the disease and in the treatment of craniofacial anomalies of the

syndrome. From a dentist's aspect, the most important goal is to keep the oral hygiene at the highest level in patients with LDS.

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