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Oral Manifestations in Patients with Down's Syndrome and Management in Prosthodontics

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ABSTRACT

Down syndrome is an autosomal disorder associated with involving mental and physical changes. The types of craniofacial phenotypes and dental anomalies in individuals with Down syndrome have been described extensively, but further elaboration of their impact of oral and craniofacial conditions still needs to be understood. In addition, in prosthodontic, oral rehabilitation with complete dentures and implants in patients with Down's syndrome still needs to be studied. The aim of this review is to describe that the oral and craniofacial manifestations may occur in patients with Down syndrome, and determine the effectiveness of oral rehabilitation treatments in patients with Down syndrome. The article was conducted of two databases and were limited to the period from January 2016 to February 2022 with a combination of the following keywords: “Down Syndrome”, “oral manifestation”, “implant”, “prosthodontic treatment”. The results obtained were 194 articles found at the beginning of the search in both databases, and the 16 full text articles were selected for further review and discussion. The results of this study shows that Down syndrome causes several oral and craniofacial manifestations, dental caries risk, higher periodontal disease, dental abnormalities, soft and occlusal tissue, and the presence of a craniofacial complex. In prosthodontics, the choice of using removable dentures or implants must be adjusted to each patient's condition. Down syndrome is an autosomal disorder that has oral and craniofacial manifestations that must be a concern for health practitioners, especially dentists. In prosthodontics, oral rehabilitation with either complete dentures or implants in patients with Down's syndrome is the right choice, but it is necessary to consider the complications that may occur.

1. INTRODUCTION

Down syndrome is an autosomal disorder associated with involving mental and physical changes. The types of craniofacial phenotypes and dental anomalies in individuals with Down syndrome have been described extensively, but further elaboration of their impact of oral and craniofacial conditions still needs to be understood. In prosthodontic, oral rehabilitation with complete dentures and implants in patients with Down's syndrome still needs to be studied. The aim of this review is to describe that the oral and craniofacial manifestations may occur in patients with Down syndrome, and determine the effectiveness of oral rehabilitation treatments in patients with Down syndrome.[1] Individuals with Down Syndrome have symptoms of intellectual disability from mild to severe, growth retardation and heart defects, and more susceptible to developing hypertension, leukemia, digestive problems and early Alzheimer's disease. Down syndrome is also responsible for respiratory, blood, muscular, neurological and endocrine disorders. In the oral cavity, patients with Down syndrome are more likely to experience dental agenesis, macroglossia, reverse articulation, cheilitis, geographic and fissured tongue, candidiasis and also periodontal disease. [1,2] Patients with Down's Syndrome have poor oral hygiene and poor body defense mechanisms. The prevalence of periodontal disease in patients with Down's Syndrome is very high. This can eventually lead to tooth loss, resulting in the edentulous state requiring

prosthetic rehabilitation. Dental rehabilitation treatment is very complex due to intellectual limitations that limit Down Syndrome patients to communicate and adapt to the environment. Behavioral management is sometimes necessary for patients with Down syndrome. [3]

Most of patients with Down's syndrome successfully wear removable prostheses, but because some patients have intellectual limitations, rehabilitation with removable prostheses can be complex, with difficulties in cleaning, handling, and adapting. Thus, fixed dental prostheses are a rehabilitation alternative for these patients, provided the treatment is accompanied by good oral hygiene and supportive therapy. However, in some patients, the use of dental implants is the only option for anchoring a fixed dental prosthesis.[2] Rehabilitation with dental implants has a high success rate. However, several risk factors can cause failure in the Osseo integration process. Patients with Down syndrome may present with parafunctional habits, poor oral hygiene, macroglossia with limited articulation, and a tendency to suffer from periodontal disease. Macroglossia, associated with mechanical factors, leads to unstable and unfavorable occlusions, poor hygiene, and genetic characteristics that can affect the Osseo integration process and success of implant therapy.[2] Patients with Down syndrome have a high probability of suffering from periodontal and peri-implant disease. The success rate of implants in patients with Down's Syndrome is lower than in patients without any abnormalities.[2] Although periodontal changes are common in patients with Down syndrome, the relationship between this syndrome and loss or failure of the Osseo integration process is unclear. Several studies have evaluated this rehabilitation therapy in a group of patients, and most of them could not find an explanation for the reason for this occurrence. Thus, leaving uncertainty about the link between dental implant rehabilitation therapy and Down Syndrome. [2]

2. METHOD

This review was carried out by following several stages, namely determining the PICO analysis (Patient/Population, Intervention, Comparison, Outcome) and searching for data sources. Research articles was conducted on Google Scholar and Pubmed using a combination of the following keywords: "Down Syndrome", "oral manifestation", "implant" and "prosthodontic treatment" and the articles published from January 2016 to February 2022.

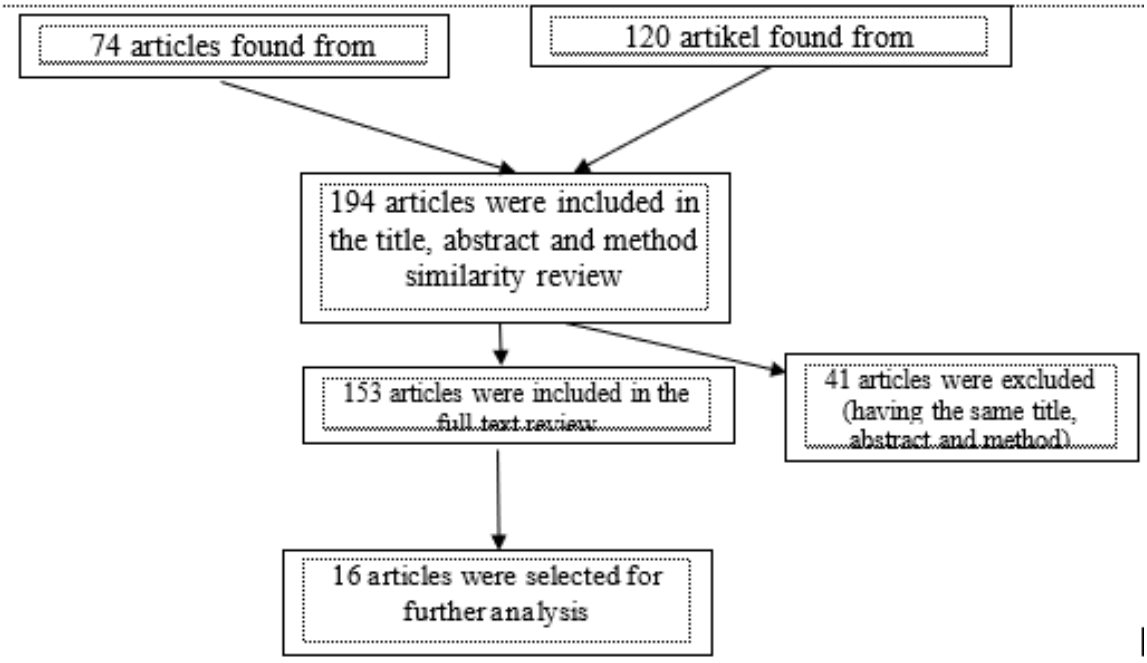

Figure 1 Research Methodology

3. RESULTS AND DISCUSSION

Etiology

The etiology of Down syndrome is a failure of chromosome division during meiosis or meiotic nondisjunction. Another etiology of trisomy 21 is the result of isochromosomes which cause structural abnormalities of chromosomes that should have long and short arms to become completely long arms. This process can occur during the process of egg or sperm cell development. In addition, trisomy 21 can also arise as a result of a Robertsonian translocation where the long arm of chromosome 21 attaches to another chromosome.[4]

The three most common types of Down syndrome are:

1. Trisomy 21 Classic

Classic trisomy 21 consists of 3 complete copies of chromosome 21, so this type of Down syndrome patient has 47 chromosomes. Classic trisomy 21 is the most common abnormality found in Down syndrome patients (95%). Classic trisomy 21 is the result of meiotic chromosome 21 nondisjunction which can occur during egg (90%) or sperm (10%) formation. [4,5]

2. Translocation

About 5% of Down syndrome patients are caused by chromosomal translocation abnormalities. Chromosomal translocations result in 2 normal copies of chromosome 21 and chromosome 21 material attached to other chromosome arms, for example chromosomes 13, 14, 15, and 22. This type of Down syndrome patient still has 46 chromosomes. Translocations can occur de novo (new) or in one parent (mostly the mother) with a normal phenotype but only 45 chromosomes.[4,5]

3. Mosaic

In the mosaic type of Down syndrome, nondisjunction occurs after the fertilization process, so that trisomy 21 only occurs in a few body cells. Clinical symptoms and medical disorders that arise are generally milder than the other 2 types of Down syndrome. [4,5]

Risk Factors

The risk factors for Down syndrome involve host factors and environmental factors as follows:

1. Host Factors

The physiological factor that greatly influences the incidence of Down syndrome is the age of the pregnant woman. Increasing maternal age increases the risk of forming aneuploid oocytes which may be due to aging which makes egg cells more vulnerable. The aging effects of the egg coupled with the accumulation of toxic factors from the environment lead to interruptions in the meiotic process or genetic changes such as mitochondrial deletion.[6]

Aging can also disrupt chromosome segregation due to reduced chiasma, defects in chiasm arrangement, and disturbance of chiasm frequency. Aging of the ovaries is associated with a decrease in the number of oocytes, a decrease in the number of mature follicles in each cycle, and changes in the balance of reproductive hormones. Ovarian aging is also associated with inadequate levels of hormone signaling and a higher error rate in meiosis. The correlation between maternal age at conception and classic trisomy 21 cases has been shown in several studies with different populations and time periods. The risk of conceiving a baby with Down syndrome is 1 per 1,400 in women aged <25 years, which can then increase to 1 per 350 in women who are pregnant at age >35 years. This figure continues to increase as the mother ages, reaching 1 per 85 births to mothers aged >40 years.[6]

Genetic recombination disorder on chromosome 21 is a risk factor that affects the incidence of Down syndrome. Genetic recombination is the exchange of genetic information between two DNA molecules that results in a new combination of alleles. Disturbances in the recombination process for chromosome 21 are associated with an increased proportion of errors resulting in maternal nondisjunction (maternal chromosome). Studies on recombination on chromosome 21 show that no exchange of genetic material or only a single telomere that undergoes exchange will increase the risk of errors in meiosis I. Meanwhile, pericentromeric exchange will increase the risk of errors in meiosis

II. Increasing maternal age triggers an exchange process that is not optimal, thereby increasing the possibility of nondisjunction.[6]

Genetic factors are also influenced by paternal factors (father's chromosomes). About 10% of trisomy 21 is caused by paternal nondisjunction. Older father's age, >49 years, has a correlation with an increased risk of having a Down syndrome baby due to a greater number of aneuploid sperm. Mothers who have children with Down syndrome have a higher risk of getting pregnant again with a fetus with Down syndrome, this risk is even higher for mothers aged <35 years. [6]

2. Environmental Factors

Environmental factors that affect the birth of a baby with Down syndrome include:[6]

- Exposure to secondhand smoke: increased incidence of Down syndrome in women <35 years
- Exposure to ionizing radiation: increased incidence of Down syndrome births after Chernobyl in radiation-exposed areas of Europe
- Exposure to toxic chemicals: triggers the occurrence of chromosomal nondisjunction which causes trisomy
- Folate deficiency
- History of use of hormonal contraception
- Socioeconomic status of parents

Pathophisiology

The pathophysiology of Down Syndrome begins with the presence of an additional chromosome on autosomal chromosome 21. This extra chromosome can appear due to failure of chromosome separation during gametogenesis (nondisjunction), due to translocation, or mosaicism. In very rare cases, trisomy 21 can arise due to isochromosomes, namely a condition in which there is a duplication of one arm of chromosome 21 along with a deletion of that chromosome arm. The extra chromosome on chromosome 21 causes gene expression abnormalities with various manifestations in several organ systems and causes phenotypic variations in Down syndrome patients. [4,5]

There are several hypotheses in the molecular pathogenesis of Down syndrome, namely gene dosage effect, amplified developmental instability, and critical region. [4,5]

1. Gene Dosage Effect

Excess chromosome 21 causes gene expression 1.5-fold due to the effect of gene dose. Overproduction of certain proteins encoded by genes on extra chromosome 21 disturbs the biochemical balance and cellular functions which are important for the development and physiology of certain organs. The phenotype of Down syndrome patients is thought to be a direct result of the dose effect of this gene. 4,5

In cases of congenital heart defects in Down syndrome, overexpression of the DSCAM (Down syndrome cell adhesion molecule) and COL6A2 (collagen type VI alpha 2 chain) genes was found that correlated with the incidence of atrial septal defects. Down syndrome patients who have leukemia show abnormalities in the GATA1 hematopoietic gene. Leukemia in Down syndrome patients shows 3 abnormalities, there are namely trisomy 21, GATA1 mutations, and other genetic disorders that cannot be determined. Other genes related to the pathogenesis of Down syndrome are DOPEY and DYRK1A (learning and memory processes), TTC3 and PREP1 (neurological development), as well as amyloid beta precursor protein/APP, dual specificity tyrosine-Y-phosphorylation regulated kinase 1A/DYRK1A, RCAN1 (risk of Alzheimer's disease in Down syndrome). 4,5

2. Amplified Developmental Instability

The amplified developmental instability hypothesis reveals that the extra chromosome in Down syndrome results in a genetic imbalance that causes disturbances in homeostatic regulation and expression of several other genes. [4,5]

3. Critical Regions

The critical region hypothesis reveals that only certain chromosomal regions on the long arm of chromosome 21 cause the Down syndrome phenotype. This region is called the DSCR (Down syndrome critical region), measuring 3.8-6.5 Mb located at 21q21.22 and consisting of ±30 genes. Molecular analysis in other studies shows that the 21q22.1-q22.3 regions is a critical region of Down syndrome, and has genes that correlate with congenital heart defects in Down syndrome patients. A new gene, namely DSCR1, which was identified in the 21q22.1-q22.2 regions is believed to be highly involved in the pathogenesis of Down syndrome because it is widely expressed in brain and heart cells, so it is associated with intellectual disability and heart defects. Extra genes in the proximal 21q22.3 give a distinctive physical phenotype including intellectual impairment, distinctive facial deformities, hand deformities, and congenital heart disease which can be found in almost half of Down syndrome patients. [4,5]

Oral and Craniofacial Manifestations

Contaldo et al and Mubayrik et al made observations through a meta-analysis regarding conditions that are often found in intraoral and extraoral examinations of patients with Down's Syndrome, and present the results as follows. [1,7]

1. Dental caries

Mubayrik et al suggested that patients with Down syndrome have lower caries potential. This is due to delayed eruption, diastema of the teeth, congenital oligodontia and some salivary characteristics. The relatively smaller size of the teeth may also have an effect on this. But there are several other risk factors such as sugar intake, fluoridation, poor oral hygiene, frequency of visits to the dentist, deficiency of health education, lack of prevention programs and the role of parents. [7]

2. Periodontal disease

Patients with Down syndrome have an increased prevalence of early aggressive periodontitis and edentulism compared with normal individuals or other mentally retarded individuals. Severe periodontitis usually appears in patients in their teens, with greater bone loss, which is around 0.03 mm/year, so that at the age of 35 years, bone loss reaches 65%. Usually this occurs in the anterior area of the mandible. Both local and systemic factors influence this such as poor oral hygiene, calculus deposits, macroglossia, tooth morphology, gingival tissue abnormalities, and salivary characteristics. Another factor is the differences in subgingival microbiota in patients with Down syndrome. For example, there are increased levels of *Propionibacterium acnes* (associated with persistent apical periodontal infection), Treponema socranskii (associated with tissue destruction), and *Streptococcus constellatus* (refractory periodontitis). [1]

Associated systemic factors include intense oxidative bursts from granulocytes and monocytes, depressed chemotaxis, impaired oxidative metabolism, and immunity. Another possible cause is a reduction in the CD4+/CD8+ ratio thereby interfering with immune regulation and function. Poor periodontal tissue health and its prognosis are closely related to an individual's age, IQ level and parental education. However, supervised brushing, good dental care and prevention can improve periodontal status. [7]

3. Dental and occlusal anomalies

The most common occlusal abnormality, caused by variations in vertical and horizontal dimensions such as open bite, crossbite, and extreme overjet, with a higher prevalence of class III tendencies. Congenital tooth loss and delayed tooth eruption are common in patients with Down syndrome. The most common tooth agenesis was the third molar, then the maxillary lateral incisor and second premolar. In some cases supernumerary teeth can be found. [7]

Morphological diversity such as microdontia and lateral pegs are often found in patients with Down syndrome. Overall, all teeth except mandibular incisors and maxillary first molars, were smaller than normal. In many cases, the maxillary canines and premolars are frequently impacted. Another abnormality reported is taurodonsia.[7]

4. Craniofacial Complex

In general, these patients are craniofacially smaller than normal individuals, with a brachicephalic, flat cranial base, small sella turcica, and a prominent forehead. The cranial bones are thin and no diploe is found. The paranasal sinuses and supraorbital ridges are missing or underdeveloped. The nasal bones are shorter with the frontal processes of the maxilla undeveloped giving an impression of retrusion in the middle of the face. Growth of both jaws decreased. The ramus and body of the mandible are short. The vertical dimension of the maxillary and mandibular alveolar heights is reduced

5. Soft tissue and orofacial abnormalities

According to Mubayrik et al, soft tissue characteristics including a fissured, protrusive and scalloped tongue were found in these patients. In the observations made by Contaldo et al, fissured tongue is a benign, usually asymptomatic condition characterized by deep grooves on the dorsal surface and edges of the tongue. The prevalence of fissured tongue increases with age. The existence of fissured tongue can become a place for debris and bacterial and fungal plaque, resulting in poor oral hygiene conditions for patients and can cause infection in the oral cavity. 1,7

Meanwhile, geographic tongue is a harmless condition of uncertain etiology that affects the dorsal tongue, edges of the tongue and at other locations in the oral cavity, although this is rare. Geographic tongue is reported to occur in approximately 1-3% of the healthy population with no difference between males or females or age. The prevalence of geographic tongue was found to be higher in patients with Down's syndrome, which is around 14% at the age of 0-5 years. 1

Macroglossia and dry tongue dorsum caused by breathing through the mouth. Slanted lower lip, inadequate lip, drooling, bivid uvula, submucous cleft lip and palate are also common in these patients. These things can trigger the occurrence of oral candidiasis in children with Down syndrome patients or young adults than normal individuals. These lesions usually appear in the area around the lips. 1,7

Management in prosthodontics

Down syndrome is a congenital pathological condition that can cause a series of disorders of the stomatognathic system, including oligodontia, macroglossia, periodontal disease, and caries. Dental implant placement provides an option for rehabilitation of edentulous areas. Although there is no definitive explanation for the lower success rate, these patients have been reported to be more prone to the development of periodontal disease and to have a higher risk of developing nonosseointegrated implants, as well as the development of peri-implantitis. 3

Wen et al observed that patients who had periodontal disease prior to implant placement, despite treatment, had a higher risk of implant failure. Genetic alterations in patients with Down syndrome predispose them to be more prone to developing periodontal disease, which explains their low implant success rate. 8

Recently, Baus-Dominguesz et al conducted that a genetic study in patients with Down syndrome, evaluating possible genetic causes of implant failure associated with peri-implant disease. They observed that patients with peri-implant disease and implant failure had low expression of the MT1 and MT2 genes, which are involved in metalloprotein metabolic pathways, molecules with important influences on bone metabolism. They concluded that patients with Down syndrome accompanied by low expression of MT1 and MT2 genes are more prone to developing periodontal disease and failure in the osseointegration process. 9

Implant failure during osseointegration before prosthetic placement appears to be more common in patients with Down's syndrome. In the present review, it was observed that 21 implants failed during osseointegration and 1 implant failed after prosthetic placement, which is a clear indication of osseointegration failure. In addition, 17 implants also failed, the cause or timing was not explained. The exact cause of this failure in osseointegration remains unclear, but low gene levels are associated with high metalloprotein and osteoclastogenesis gene expression, inflammatory responses, and high defense responses, some of which are specifically associated with patients with Down syndrome. This may help explain why some patients with Down syndrome are more susceptible to periodontal and peri-implant disease, as well as failure of dental implants to osseointegrate. 9,10

Oral hygiene, an important factor for implant success and a peri-implant clinical assessment parameter, was not well reported by the studies analyzed. Only 2 studies reported oral health status, and both described “poor” oral hygiene. This fact alone raises the question of what type of rehabilitation therapy should be used in this patient. Patients with Down syndrome may have motor and cognitive difficulties coupled with parafunctional habits, making oral hygiene difficult to maintain, factors that must be considered before dental implants are given to patients. Oral hygiene must be properly monitored by dentists and oral hygienists, it is necessary to control dental biofilm and periodontal and peri-implant health, so as to reduce the risk of implant failure. 11

Peri-implant clinical parameters, such as marginal bone loss and probe depth were inconsistently evaluated in these studies. Three studies described marginal bone loss, two of which described a loss of approximately 1.8 mm. Corcuera-Flores et al explained proportionally that only 6 of 31 implant samples showed bone loss of less than a third of the implant. Only Posse et al described the probe depth of the implants, ie with an average depth of 2.2 mm. A detailed description of the clinical parameters of a healthy peri-implant is essential to determine implant success, which cannot be characterized by osseointegrated implants alone. Further studies with good clinical parameters should be carried out in patients with Down syndrome. 12,13

Although tin his systematic review determined that the success rate of dental implants in patients with Down syndrome and peri-implant parameters was lower compared to patients without these conditions, the authors consider that implant therapy may still be indicated because not only dental factors must be considered. Many patients have physical and mental deficiencies, but still require rehabilitation of removable prostheses and rehabilitation with dental implants, because psychological, social, masticatory function, and patient's quality of life are the top priority.

Post-Implant Care

The implant that enters is actually responded to as a foreign object by the body. The body's acceptance of foreign objects depends on the tissue's acceptance of these foreign objects or known as biocompatibility. Biocompatibility is the ability of a material to cooperate with the host's response, or the ability of a material to accept a suitable host response and not harm the host. Biomaterials that are able to be accepted by the body are materials that can function and are accepted biologically or by living tissue with reactions that are not harmful or with minimal losses.14 The body's reaction when there is intolerance to an object that is considered foreign, responds sequentially in the form of injury reactions, blood-material interactions, accumulation of inflammatory matrix, acute inflammation, chronic inflammation, formation of granulation tissue, and ends with the formation of fibrous tissue.15 Post-implant care can be supported by using a mouthwash that has an anti-plaque agent, chlorhexidine, and can be combined with anti-microbial, anti-oxidant and anti-inflammatory substances. It can also include ingredients containing hyaluronic acid to support optimal formation of new tissue and speed up the healing process.16

Implant Treatment If Inflammation Occurs

Recently there is greater awareness of the biological complications associated with dental implants. Peri-implantitis was defined as an inflamed mucosa with bleeding on probing and/or suppuration, a probing depth of >4 mm, and no bone loss. Peri-implantitis as the initial phase of an inflammatory process (swelling and redness) limited to the peri-implant soft tissue with indications of no loss of peri-implant bone. It is not known what factors determine the development of peri-implantitis, but the length of time the exposure of the functioning implant and the ongoing microbial exposure appear to play a role. Therefore, it is recommended to carry out a basic evaluation, such as a radiographic assessment, to assess the health of the peri-implant area after removal of the causative factor (biofilm accumulation). Regular control needs to be carried out by the dentist on the patient's oral hygiene.[15]

4. CONCLUSION

Based on the findings of this review, it can be concluded that Down syndrome is an autosomal disorder that has oral and craniofacial manifestations including: dental caries, periodontal disease,

dental and occlusal anomalies, craniofacial complex, and soft tissue and orofacial abnormalities. Oral rehabilitation with dental implants in patients with Down syndrome is the right choice but it is necessary to consider the complications that may occur. The control studies with better methodological designs are needed to increase scientific evidence regarding treatment in patients with Down syndrome.

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