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## Impact of tooth loss due to periodontal disease on the prognosis of rehabilitation

**Abstract:** When periodontal disease is diagnosed, it is difficult to predict the clinical response of treatment of a tooth over time because the result of treatment is affected by several factors and will depend on the maintenance and support of periodontal treatment. Rehabilitation with removable dental prostheses, fixed prostheses, and dental implants makes it possible to restore the function and esthetics of patients with tooth loss due to periodontal disease. The predictive factors of tooth loss in periodontitis patients should be assessed by dentists to inform their clinical decision-making during dental treatment planning. This will provide detailed individualized information and level of risk of patients considered suitable for dental rehabilitation. Therefore, the aim of this article was to review the subject of “Impact of tooth loss due to periodontal disease on the prognosis of rehabilitation” and the effect of fixed, removable, and implant-supported prostheses in periodontal patients.

**Keywords:** Tooth Loss; Periodontal Diseases; Rehabilitation; Prosthesis and Implants; Compliance.

### Introduction

An imbalanced and unhealthy oral microbiota ushers the entry of various cariogenic and periodontal microbes that engender oral biofilm formation and periodontal diseases such as gingivitis and periodontitis. Oral epithelial tissues, mainly the gingival epithelium, play a significant role in resisting the colonization of unfavorable oral pathogens. These tissues readily secrete beta-defensin peptides and histatins, which are the major host defense salivary proteins that maintain the homeostasis of the oral microbiota.<sup>1</sup>

Smoking and calculus are associated with initial disease progression, and calculus, plaque, and gingivitis are associated with loss of attachment and progression to advanced disease. Furthermore, studies have indicated that calculus removal, plaque control, and control of gingivitis are essential procedures in preventing disease progression, further loss of attachment and, ultimately, tooth loss.<sup>2</sup> Therefore, it is difficult to predict the clinical response to treatment of a tooth over time, since the result of treatment is affected by several factors<sup>3</sup> and depends on maintenance and supportive periodontal treatment. Periodic Preventive Maintenance (PPM), a procedure based on regular scheduled visits after active periodontal treatment, is a well-known strategy, essential for preserving the periodontal health of

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treated and rehabilitated patients, and is a preventive strategy for healthy patients.<sup>4</sup>

In patients with a history of periodontitis, rehabilitation with removable dental prostheses<sup>5</sup> and fixed prostheses<sup>6</sup> should be the focus of dentists' attention. Dental implants have become widely recognized as a treatment modality for patients with tooth loss. As an increasing number of patients receive implant therapy to replace teeth lost due to periodontal disease, the question arises as to whether the outcome of dental implants is influenced by a history of periodontitis.<sup>7</sup>

The aim of this study was to carry out a narrative review about the impact on the prognosis of rehabilitation after tooth loss due to periodontal disease and the effect produced by fixed, removable, and implant-supported prostheses in periodontal patients. Therefore, this review was divided into the following sub-headings: host response, incidence and prevalence of losses after rehabilitation and supportive maintenance therapy (SPT), factors that play a pivotal role in or have impact on the longevity of the treatment.

## Host response

During the course of a long and slow process, uncontrolled inflammation in the gingiva may lead to the destruction of periodontal tissue and its attachment to teeth, which is defined as periodontitis.<sup>1</sup> The hallmark of periodontitis, known to be the cause of this disease, are the complex subgingival microbial communities that can comprise about 500 bacterial species.<sup>2</sup> The onset of periodontal disease is caused by a small subset of endogenous gram-negative periodontal bacteria, including *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, and *Treponema denticola*, which trigger innate, inflammatory, and adaptive immune responses.<sup>3,4,5</sup> The continuous loss of gum and bone tissues that support the teeth results in tooth looseness and loss of teeth, which seriously affects patients' quality of life and causes a tremendous social and economic burden.<sup>6</sup> Epithelial surfaces are continuously replaced, however, several of the most pathogenic bacterial species are able to invade the gingival cells and tissues, remain viable, and evade the action of different immune cells.<sup>7</sup>

Innate immunity reflects the host's capacity for rapid defense against infectious insults. The innate response has limited specificity, is responsive to generalizable types of agents, and exhausts without providing long-term protection.<sup>8</sup> The effector mechanisms of the innate immune system are improved by adaptively involving an efficient loop for microbial clearance, in which proper innate mechanisms are triggered to ensure an effective adaptive immune response, which potentiates these innate effector functions against periodontopathic bacteria. The primary response to pathogens in the innate immune system is triggered by Pattern Recognition Receptors (PRRs) that bind to Pathogen-Associated Molecular Patterns (PAMPs) found in a broad range of organisms. These receptor types include toll-like receptors, nucleotide-binding oligomerization domain (NOD) proteins, cluster of differentiation 14 (CD14), complement receptor-3, lectins, and scavenger receptors.<sup>9</sup>

The innate system is activated before an adaptive response. Cellular components of the system consist of phagocytic cells (e.g. monocytes/macrophages), antigen-presenting cells (e.g. monocyte-derived dendritic cells), natural killer cells, a subset of T and B cells participating in innate immunity, as well as epithelial and endothelial cells (natural barriers that synthesize cytokines and chemokines, and recognize danger signals).<sup>10</sup> Toll-like receptors (TLRs) selectively recognize a large number of varied and complex pathogen-associated molecular patterns. Toll-like receptors are evolutionarily conserved proteins that also have a highly conserved intracellular Toll/interleukin-1 receptor (TIR) domain, involved in protein-protein interaction and signaling activation. Among the 10 human toll-like receptors identified so far, toll-like receptor-2 and toll-like receptor-4 are the most defined members. Toll-like receptor-2 is mostly involved in the recognition of a variety of bacterial cell components, such as peptidoglycan and lipoproteins. Toll-like receptor-4 has been shown to specifically recognize the lipopolysaccharide of gram-negative bacteria and act in cooperation with several protein components, such as lipopolysaccharide-binding protein and CD14,<sup>11-16,18,19</sup> and toll-like receptors are expressed in periodontal tissues.<sup>19,20</sup>

The gingiva is constantly exposed to microbes present in dental plaque biofilm, therefore, toll-like receptor signaling plays an important role in the innate immune response and maintenance of periodontal health. However, over-production of pro-inflammatory cytokines due to chronic stimulation of toll-like receptors may lead to tissue destruction.<sup>21,22</sup>

Bacteria and immune cells (neutrophils, macrophages, and lymphocytes) present in the periodontium participate in the maintenance of a healthy equilibrium.<sup>23</sup> Neutrophils continuously transmigrate through the junctional epithelium to the gingival sulcus and release antimicrobial peptides ( $\alpha$ -defensins) against invading bacteria, in addition to stimulating adhesion and spreading keratinocytes on the tooth surface.<sup>24</sup> Resident cells of the periodontium (keratinocytes, fibroblasts, dendritic cells, and osteoblasts) are not passive barriers against bacterial invasion, but initiate the innate immune response and regulate the adaptive immune response.<sup>25,26</sup> An essential component is the complement pathway, which activates, amplifies, and synchronizes the innate immune response by opsonizing and killing bacteria, in addition to activating mast cells, neutrophils, and macrophages of the periodontium.<sup>27</sup>

Keratinocytes, which form the majority of the gingival epithelium, are capable of producing and secreting various immune response mediators, among them human  $\beta$ -defensins (hBDs), cathelicidins, proinflammatory cytokines, chemokines, and angiogenic proteins.<sup>28,29</sup> In healthy gingiva, the innate response is mainly regulated by keratinocytes that secrete hBDs to protect the oral and sulcular epithelium and neutrophils that secrete  $\alpha$ -defensins to protect the junctional epithelium. Gingival keratinocytes recognize pathogen-associated molecular patterns (PAMPs) through their pattern recognition receptors, such as toll-like receptors (TLRs). mRNA expression of TLR 1-9 is detected in the connective tissue and epithelial layers of the gingiva.<sup>30</sup> In addition, bacterial signaling molecules (cyclic dinucleotides and quorum signaling molecules) activate the cytokine response in gingival keratinocytes.<sup>31,32</sup> There is also a reciprocal interaction between innate-immune proteins and keratinocytes. For example, proinflammatory

interleukins (IL-1 $\alpha$ , IL-1 $\beta$ , IL-6) activate protein expression and secretion of hBDs in keratinocytes,<sup>33,34</sup> while keratinocytes can suppress the inflammatory response by secreting monocyte chemotactic protein-induced protein-1.<sup>35</sup>

Fibroblasts are responsible for the synthesis of new collagen bundles and for removing the old collagen by secreting matrix metalloproteinases (MMPs). Overexpression of MMPs by gingival fibroblasts may either induce the release of cytokines and chemokines from the extracellular matrix or cleave cytokines and interrupt immune response-signaling cascades.<sup>36</sup>

In a healthy environment, dendritic cells have high phagocytic capacity against invading microorganisms, but during infection they initiate a maturation process that involves their migration to lymph nodes to activate CD4+ T cells<sup>37</sup> and promote the polarization of T-helper (Th)1, Th2, Th17, and B cells.<sup>38</sup> Uncontrolled upregulation of Th1 and Th17 cell pathways enhances alveolar bone loss via induction of osteoclastogenesis.<sup>39</sup> There is also evidence that dendritic cells can differentiate into osteoclasts.<sup>40</sup>

Neutrophils form the primary defense system in periodontal tissues. Notably, they migrate through the junctional epithelium into the gingival sulcus in a continuous process, which may differ from other organs, in which transmigration is a hallmark of infection.<sup>41</sup> In a healthy oral cavity, neutrophil populations tend to be parainflammatory, whereas in periodontal disease there is presence of proinflammatory neutrophil phenotypes.<sup>42</sup>

Tissue macrophages are derived either from circulating monocytes or from embryo-derived precursors.<sup>43</sup> Phenotyping them as inflammatory and resolving macrophages will define their roles in disease and health. Inflammatory macrophages produce and secrete a large group of cytokines (IL-1 $\beta$ , IL-23, IL-6, tumor necrosis factor (TNF)- $\alpha$ ) and enzymes (MMPs) that participate in osteoclastogenesis and collagen degradation in periodontitis.<sup>44</sup>

Although the host defense system is fundamental to oral health, there are situations in which the challenge is greater and may lead to the progression of periodontal disease, loss of teeth, and thus require rehabilitation initiatives to restore oral function and esthetics.

## Reasons for tooth loss

In this sense, recent data of tooth loss in the Brazilian population have shown that over half (53.7%) of the elderly population (> 65 years old) had tooth loss. This was of one of the highest rates of prevalence of tooth loss in the world, second only to Portugal (70%) and Turkey (67%). Teenagers (15-19 years old) have shown a prevalence of tooth loss of 17.4%, and adults (35-44 years old), of 22.4%.<sup>45</sup> These data highlighted the important fact that socioeconomic conditions were directly associated with tooth loss in the Brazilian population studied. This has shown that the less schooling these individuals had, the higher was the rate of tooth loss in this population.<sup>45,46</sup> One of the reasons for this association in this population could be the presence of higher caries index, which is one of the most frequent causes of tooth loss. To reduce the caries index in the population, fluoridation of public water supply was suggested and recognized as one of the most important public health achievements in the 20<sup>th</sup> century.<sup>47</sup> In contrast, according to a study conducted by the IBGE (Brazilian Institute of Geography and Statistics) Foundation in 2000, up to this time, only 45% of the Brazilian municipalities and 37% of the Brazilian districts had adopted the fluoridation system, with possible exclusion of more rural districts and peripheral regions.<sup>48</sup> This fact and the difficult access to dental care by this population can explain the socioeconomic correlation with a higher rate of tooth loss in the Brazilian population.<sup>49</sup>

Furthermore, a recent multilevel study designed by Roberto et al.<sup>50</sup> evaluated tooth loss in Brazilian adults (33-44 years old) according to their individual and contextual social characteristics. The authors used the Municipal Human Development Index (MHDI), which is an index that evaluates information about income, educational level, and longevity in each municipality. They demonstrated that tooth loss in adults was associated with the contextual variables of MHDI and public water fluoridation.

In addition, age and gender were suggested to be risk indicators of tooth loss in the Brazilian population. In a study by Corraini et al.,<sup>51</sup> the authors have shown that in an isolated population of Brazil, 90% of the subjects had lost at least one tooth and 39% had lost

more than eight teeth. This higher tooth loss was associated with adult age and female gender. Another risk indicator was that the most frequently missing teeth in individuals were the permanent first molars. This could be explained by the fact that these are the first permanent teeth to erupt, so they are more susceptible to the development of caries.<sup>51, 52, 53</sup>

## Fixed dental prostheses and removable partial dentures in periodontal patients

Severe periodontal disease is a common cause of tooth loss worldwide<sup>54</sup> and may have an impact on mastication, food choices, psychological issues, and occlusal stability.<sup>55,56</sup> Raval and Johansson<sup>57</sup> have shown that patients treated for periodontal disease continued to lose teeth even during maintenance therapy, and that periodontal disease was the main reason for these losses (73%) in association with smoking and periodontal pockets with a depth of 4-6 mm.

Moreover, periodontal parameters are frequently used to determine whether teeth will be rehabilitated or extracted. During periodontal examination, it is difficult to establish the prognosis of teeth because several variables are involved<sup>58,59</sup> including prosthetic and restorative factors.<sup>60</sup> According to Walter et al.,<sup>61</sup> tooth loss is a reliable and easy-to-measure variable in long-term clinical outcomes through the comparison of different rehabilitation treatments.

Faggion et al.<sup>62</sup> proposed a prognostic model for tooth survival in patients treated for periodontitis and found that diabetes mellitus, teeth with alveolar bone loss, increased tooth mobility, multirooted teeth, and non-vital pulp were significant predictors for tooth loss during supportive periodontal therapy (SPT). In addition, Helal et al.<sup>63</sup> recently reported that some others predictive factors were also associated with tooth loss in patients with periodontitis and patients at higher risk, like older patients, non-compliant patients, smokers, and those with higher values of pocket probing depth.

In many patients, missing teeth may require replacement in order to restore oral function, esthetics and quality of life. However, the process of adaptation

to tooth loss varies among individuals, and not all of them need to replace every lost tooth.<sup>64</sup> When rehabilitation is indicated, several options between fixed and removable dentures are available.<sup>61,65,66</sup> There are even protocols for each type of dental rehabilitation; and decision-making depends on professional ability, treatment philosophy, countries, age groups, oral and financial conditions of the patients, and maintenance of the rehabilitation.

Fixed rehabilitations are considered the treatment of choice for partially edentulous patients,<sup>67</sup> however, removable prostheses are still frequently provided, especially because of their lower cost and less complex treatment involved.<sup>68,69</sup> At present, the literature is heterogeneous and limited in showing the main reasons for tooth loss and the type of rehabilitation used, especially in long-term studies with missing data and those with inconclusive data. Survival and success rates, number of teeth lost, reasons for loss, and complications of the treatment are important pieces of information that need to be reported in long-term studies to enable analysts to determine which factors are associated with the prognosis of rehabilitation.

## Fixed dental prostheses

Changes in the profile of patients from totally to partially edentulous due to socioeconomic factors, better plaque control, and compliance with PPM (Periodic Preventive Maintenance) and Supportive Periodontal Therapy (SPT) over the years have resulted in a larger number of single or multiple interdental gaps that can be rehabilitated with fixed dental prostheses (FDPs).<sup>69,70</sup>

FDPs are good alternatives for rehabilitating minor gaps, especially in the anterior region, due to the lower risk of developing injuries in the periodontal tissues, less demanding maintenance, higher survival rates, in addition to greater patient satisfaction and improved oral health-related quality of life (OHRQoL).<sup>68</sup> Provided that adequate periodontal and prosthetic treatments and maintenance care over time are implemented, it would be possible to provide patients who have advanced loss of periodontal support with rehabilitation treatments that can have a higher rate of success in the long term.<sup>71</sup>

The main biological complications associated with the survival rates of FDPs are secondary caries, loss of vitality, abutment tooth fracture, and periodontal disease.<sup>60,61,63,64</sup> Among these, according to Bergenholtz and Nyman,<sup>71</sup> biological complications of endodontic origin are more common, especially among teeth used as abutments for FDPs when compared with non-abutment teeth (*e.g.* 15% vs. 3%). In the cited study, abutment and non-abutment teeth showed a comparable degree of periodontal destruction and were treated with similar periodontal therapies. According to the authors, the highest proportion of endodontic complications in abutment teeth was strongly associated with traumas caused during the procedures of preparation to receive an FDP.<sup>72</sup> In addition, Valderhaug et al.<sup>73</sup> estimated that the pulp vitality in teeth with crowns, which remained free of signs and symptoms of pulp deterioration, showed proportions of 98%, 92%, 87% and 83% after 5, 10, 20, and 25 years, respectively.

In a systematic review that evaluated 5-year survival of metal-ceramic and all-ceramic tooth-supported FDPs, Pjetursson et al.<sup>69</sup> found an incidence of FDP failures and losses associated with recurrence of periodontal disease reported in 37 studies. Among them, 2,096 FDPs were evaluated, with a loss of 29 dental prostheses, an overall annual failure rate of 0.23% and a failure rate of 1.2% over 5 years. The authors also evaluated the annual failure rates according to the different types of FDPs and found results that ranged from 0.06% to 1.59%. The highest failure rates reported were 0.60% and 1.59% for reinforced glass ceramic and glass-infiltrated alumina, respectively. In addition, metal-ceramic FDPs were used as a reference for the relative complication rates of different types of FDPs, with significantly more glass-infiltrated alumina FDPs and reinforced glass ceramic FDPs lost due to periodontal diseases.

The literature also points out that patients with severe bone loss, but healthy nevertheless, who were rehabilitated with cantilevered pontics FDPs had failure rates of approximately 8% after 5 and 10 years of follow-up.<sup>74,75</sup> This long-term success was only possible because the fundamental principles of correct occlusal design and manufacturing of extensive FDPs were respected.<sup>75</sup>

## Removable partial dentures

Removable partial dentures (RPDs) are in great demand as a common method of rehabilitation used to restore the dental function, comfort, and esthetic appearance of partially edentulous patients. Moreover, they are a feasible and lower cost option when compared with FDPs, although RPDs can also cause some biological complications in patients, especially in the absence of programmed return visits.<sup>68,76,77,78</sup>

Prosthetic rehabilitation increases the risk of tooth loss; however, there was no difference between the different types of prosthetic treatments relative to abutment tooth loss.<sup>79</sup> Higher rates of abutment loss have been reported among the studies. Studer et al.<sup>80</sup> have shown that partially edentulous free-end condition and dentate opposing jaw were considered risk factors for prosthetic complications. They reported 73 teeth lost in a period of up to 6 years, of which 29 (40%) were lost due to fractures, 21 (29%) due to untreatable caries, 18 (25%) due to abutment extractions, and 5 (6%) due to endodontic complications, although no periodontal reasons were detected as primary reasons for failure in combined fixed-removable rehabilitations. Tada et al. (2014)<sup>81</sup> have shown that 42% (68/162) of abutment teeth were lost because of periodontal disease, 29.6% (48/162) were extracted due to caries, and in patients with RPDs, 26.5% (43/162) were found to have fractures.

Other previous studies have also shown biological complications in patients with RPDs or a rapid deterioration of the dentures when compared with FDP or even with non-treatment.<sup>79,80,82</sup> In the study of Muller et al.,<sup>79</sup> in 90 patients, 1,937 teeth had been submitted to periodontal treatment 5–17 years earlier and rehabilitated with fixed dental prostheses (FDP; n = 29) and/or removable partial dentures anchored with clips (RPDC; n = 25) or double crowns (RPDD; n = 25). In addition, 25 patients had undergone periodontal treatment without prosthetic treatment. A total of 317 teeth and 70 abutment teeth were lost during approximately 10 years of follow-up. Of these, the majority of teeth, 273 (86%), and 48 (68.5%) abutment teeth were lost for periodontal reasons (generalized, moderate-to-severe aggressive or chronic periodontitis); a mean loss of 3.5 teeth per

patient. Patients with partial dentures showed a tooth loss rate of 4.4 and those without prostheses, a rate of 1.2. In addition, prosthodontic treatment, age, socioeconomic status, diabetes mellitus, mean initial bone loss, and aggressive periodontitis were factors significantly associated with tooth loss in patients with prosthodontic rehabilitation undergoing long-term supportive periodontal therapy when compared with patients without prostheses.

When the biological complications related to removable prostheses were analyzed in the literature, their survival rates were limited.<sup>68,78</sup> Moldovan et al. (2018)<sup>68</sup> recommended that dentists evaluate some biological parameters like tooth loss, caries, endodontic treatment, tooth fracture, tooth mobility, pocket probing depth, radiographic bone loss, gingival recession, plaque and gingival indices, as well as experience with supportive care, to reduce complication rates after the treatment with RPDs. These authors have also shown that, depending on the observation period, tooth loss varied between 0 and 18.1% for clasp-retained RPDs; 5.5 and 29% for attachment-retained, and between 5.5 and 51.7% for double crown-retained RPDs. The authors also reported that suitable pre-treatment and supportive care could reduce these complication rates.

When shortened dental arches are rehabilitated with fixed and removable dentures, higher tooth loss rates were found for RPDs,<sup>79,82</sup> although other authors have shown no significant differences.<sup>60,83,84</sup> However, limited information was found on the reasons for tooth loss. In a 5-year longitudinal study, Budtz-Jorgensen et al.<sup>82</sup> investigated a cantilevered FDP compared with RPDs. The authors observed that caries, occlusal and functional impairments were present more frequently in the RPD group. Nineteen percent of FDPs failed, while 38% of failures occurred in the RPD group over the 5-year period. The RPD group had higher numbers of dental and prosthodontic procedures performed during the follow-up period, for example, amalgam or composite fillings, endodontic treatment, repairs, and relining. Eleven teeth were extracted in the RPD group, while one extraction occurred in the FDP group. The main reasons were endodontic problems, caries, complications, and fractures. The authors suggested

that denture wearers developed more caries lesions and that RPDs promoted more biofilm accumulation than the FDPs.

In a recent systematic review, McAllister et al.<sup>86</sup> analyzed the survival rates of different rehabilitation interventions (removable partial dentures, conventional or resin bonded bridgework, implant supported crowns or bridgework) and the risk of tooth loss with and without these interventions in patients with shortened dental arches, in a period of five years or longer. The authors concluded that there was not enough evidence to recommend one replacement strategy over another in patients with 4 to 10 remaining functional teeth in occlusion.

Preshaw et al.<sup>77</sup> reported that there was no clear evidence that RPDs increased the risk of periodontitis, but minor deleterious effects of RPDs were found in periodontally healthy patients. Other previous studies have shown increased levels of plaque and gingivitis, particularly on abutment teeth, and these results may reflect the less hygienic and more complex design used. Almeida et al.<sup>65,66</sup> have also shown worse periodontal conditions in teeth used as direct abutments, as well as in their distal aspects<sup>66</sup> compared with indirect abutments in bilateral end-free dental prostheses. Tada et al.<sup>81</sup> also reported that prostheses were more prone to fracture if the abutment teeth were extensively restored or affected by root caries.

In a systematic review, Moldovan et al.<sup>78</sup> demonstrated that RPDs were capable of providing satisfactory solutions as long as suitable previous treatments and programmed return appointments were followed right from the early stages of dental rehabilitation. In a short-term study of 18 months, Almeida et al.<sup>65</sup> showed that removable prostheses in bilateral end-free prostheses did not impair the periodontal condition during periodically supportive periodontal therapy. However, in the absence of periodontal maintenance, after 4 years of follow-up, most clinical parameters had values similar to those of the baseline situation of the study.<sup>66</sup> Other authors reported that periodic revision by the dentist and adequate oral hygiene procedures by the patients played key roles in the success of the rehabilitation.<sup>65,66,71,86,87</sup> Tada et al.<sup>81</sup> have shown that 6-monthly periodontal maintenance visits

had a positive impact on the survival rate of direct abutment teeth. Furthermore, constant review of the periodontal treatment results allows reevaluation of the prognosis of rehabilitation.<sup>58</sup>

Irrespective of the data collection instrument and the location of the study, scientific literature has reported a significant association between unfavorable OHRQoL (Oral Health-related Quality of Life) scores and tooth loss, with increased compromise according to the location and distribution of this loss.<sup>56</sup> Rehabilitation with FDPs or RPDs can improve this association. However, patients with missing teeth have recently shown preference for rehabilitation with FDPs, and up to approximately 40% of RPDs are rejected by patients at an early stage after insertion.<sup>67</sup> Although well performed, these procedures require acceptance by patients for a successful treatment.

Special attention should be paid to the elderly due to their impaired ability to perform their own oral hygiene and the complexity of rehabilitation in association with limitations in performing personal health care. Moreover, their reduced host response can increase the risk of root caries, periodontal and peri-implant diseases, and other oral diseases. Individualized preventive measures and regular maintenance visits should be scheduled for the elderly, irrespective of the design of their prosthetic habilitation, in order to assure that adequate oral hygiene procedures will routinely be performed. Tada et al.<sup>81</sup> indicated that periodontal maintenance at 3- or 6-monthly time intervals had favorable outcomes and could prevent further tooth loss.

In general, tooth loss is a multifactorial outcome that is difficult to predict. Apart from periodontal diseases, caries, and endodontic complications, fractures are other reasons for tooth extraction and should be considered as clinical indicators for assessing the success of treatment outcomes.<sup>69, 78, 87</sup> Bone and tooth preservation are the principles on which saving healthy and/or periodontally compromised teeth is based. Furthermore, predictive factors of tooth loss in periodontitis patients should be evaluated by dentists for purposes of clinical decision-making during dental treatment planning in order to have detailed individualized information about patients considered suitable for dental rehabilitation and know

the risks to which they may be exposed.<sup>54</sup> There are increasing indications for the use of dental implants to replace missing teeth, and this possibility has changed the perception of prosthodontic therapy with the expansion of fixed and removable implant-supported treatments in the last decades.

## **Implant-supported prostheses in periodontal patients**

As mentioned earlier, due to the high prevalence of tooth loss in the population, the demand for rehabilitation has increased in the last decades driven by the pursuit of better quality of life. One of the options for treating these patients is implant-supported restoration. Increasing numbers of dental implants are being placed every year. However, the effects of implant placements in patients with a history of periodontal disease continue to be actively researched.

Correia et al.<sup>88</sup> conducted a retrospective cohort study to evaluate the survival rates of implants in patients with and without a history of periodontal disease. They found no statistically significant difference between the survival rates of implants in these subjects and confirmed the safety of placing implants in patients with a history of periodontal disease. Corroborating this study, Gianserra et al.,<sup>89</sup> in a 5-year follow-up of dental implants placed in patients who had undergone previous treatment for periodontal disease, found that a history with the disease was not associated with implant failures. A case series study comparing 1- and 2-stage implants placed in periodontally compromised patients demonstrated that the survival rate of implants, after a follow-up period of 5 years of patients with previous history of periodontal disease, was similar to that observed in periodontally healthy patients for both implant stages (97% and 94% respectively). After 10 years, the survival rate remained 97% for 2-stage and dropped to 78% for 1-stage implants. Although the survival rate of 1-stage implants was reduced after 10 years, the authors affirmed that dental implants continued to be a good treatment for patients with a history of periodontal disease.<sup>90</sup> A systematic review with short-term (< 5 years) and long-term follow-up (> 5 years) has shown that there was no difference

in the survival rates of implants between patients with previous periodontal disease and periodontally healthy patients.<sup>91</sup>

Schou et al.<sup>92</sup> conducted a systematic review covering 5- and 10-year periods of follow-up to compare the risk of loss of implants, risk of peri-implantitis, peri-implant marginal bone loss, and loss of supra structures between patients who had lost teeth due to previous periodontal disease and patients who had lost teeth for reasons other than periodontitis. The authors suggested that the survival rate of implants and supra structures did not differ between these subjects. However, an increase in the incidence of peri-implantitis and marginal bone loss was associated with patients with a history of previous periodontitis. This could affect the long-term survival of the implants. Nevertheless, it is important to emphasize that the small sample size and the methodological quality assessment of the studies have to be interpreted with caution.<sup>92</sup>

In a recent meta-analysis, Dank et al.<sup>93</sup> evaluated the effect of dental implant surface roughness on the implant survival rate and other risk factors, such as mean marginal bone loss and incidence of bleeding on probing in patients with a history of periodontal disease. They concluded that there is a lack of long-term data (> 5 years) for analyzing these factors. Therefore, the influence of surface roughness of dental implants placed in patients with previously compromised periodontal conditions cannot be established yet.

There is contradictory evidence showing that it is not recommendable for patients with a history of periodontal disease to receive rehabilitation with dental implants. Van der Weijden et al.<sup>94</sup> conducted a systematic review to evaluate the survival rate of implants and supporting bone loss in periodontally compromised patients in a long-term follow-up period (> 5 years). The authors concluded that the placement of implants in these patients was different when compared with periodontally healthy patients. These findings have to be analyzed with caution due to the limited scope of the data. Another systematic review demonstrated that patients with a history of periodontal disease achieved lower implant survival rates and had more complications around implants

when compared with patients without any history of periodontal disease.<sup>95</sup> In a meta-analysis, Wen et al.<sup>96</sup> demonstrated that history of periodontal disease could be a risk factor for the long-term survival rate of implants.

Hypotheses relative to lower implant survival rates in periodontally compromised patients have suggested that the pathogens present in the periodontal pockets could be transmitted from adjacent teeth to implants.<sup>97,98</sup> Another hypothesis is related to the host response of the patients.<sup>99,100</sup>

Data comparing the implant survival rate in patients with previously compromised periodontal conditions seem to be unclear. Studies have indicated confounding factors that had influence on the local and systemic response of patients, such as diabetes mellitus and cigarette smoking.<sup>101</sup> Other facts, such as supportive periodontal therapy, seem to be important factors that influence the prevalence of tooth loss. Moreira et al.,<sup>46</sup> in a study with Brazilian middle-aged adults, evaluated the link between tooth loss and multilevel factors. They have shown that the risk of tooth loss in a population that had never visited a dentist or had not visited a dentist in three or more years was increased by 33.5% and 21.3% respectively.

## Supportive periodontal therapy in prosthetically rehabilitated subjects with history of periodontitis

Supportive Periodontal Therapy (SPT) plays a pivotal role in the maintenance of the remaining teeth in patients with periodontitis. SPT is the main phase of periodontal treatment that aims not only to avoid the recurrence but also to control the periodontal disease. The adherence to SPT depends on the severity and extension of the periodontal destruction as well as on the patients' compliance with this therapy. Although dental biofilm is a direct cause, even an optimal plaque control is not enough to prevent the return of these diseases, since the best oral hygiene performed by the patient does not affect subgingival biofilm at the bottom of the periodontal pocket, and recolonization can occur in a few weeks.<sup>102</sup>

Implant- and tooth-supported restorations are cause for concern in patients with a history

of periodontitis. Several studies<sup>102-108</sup> have shown that non-compliers with SPT exhibited the worst clinical periodontal parameters when compared with compliers. Although it seems logical that compliers with SPT would show better longitudinal results, professionals struggle to maintain patients under strict periodontal control. A recent systematic review<sup>102</sup> has shown that compliance with SPT was found to be unsatisfactory. The compliance of patients ranged between 3 to 86% and smokers were more prone to not adhering to the SPT program.

In addition, risk factors such as diabetes and smoking, associated with a pathogenic biofilm and local factors, might jeopardize the effect of and adherence to the supportive maintenance, and this must, therefore, be taken into account during the treatment planning of the periodontal therapy and SPT. Supportive therapy for orally rehabilitated patients includes procedures such as frequent appointments to monitor the progression or possible recurrence of the disease, particularly in patients who have had previous treatment for periodontal and peri-implant diseases;<sup>109</sup> radiographic analyses of the affected sites and restorative margin contours;<sup>110</sup> recording of clinical periodontal parameters and occlusal adjustments;<sup>109</sup> removing biofilm and calculus;<sup>110</sup> motivating and ensuring that patients perform excellent oral hygiene, according to their skills and considering the complexity of the restoration,<sup>110</sup> and raising the odds of finding and treating – in advance – any condition or disease found in the oral cavity.<sup>109</sup>

An earlier study<sup>106</sup> evaluated 68 patients with moderate to severe periodontitis who received active periodontal treatment. Afterward, these patients received a fixed or removable dental prosthesis and SPT for at least 10 years. The study has shown that both fixed and removable prostheses had high survival rates when combined with an active periodontal therapy previous to the rehabilitation and regular SPT maintenance after it. This idea has been ratified by other studies<sup>102,107</sup> that say that patients' compliance with the SPT treatment is *sine-qua-non* to achieving good results in the long term. Lack of compliance, specially from patients with a history of periodontitis or peri-implantitis, may result in

a faster progression of the disease and increase the chances of losing teeth or dental implants. The value of SPT has been emphasized in a plethora of studies, but systematic reviews<sup>102,111</sup> have reported that many studies did not report their maintenance programs in detail, making it difficult to analyze and compare the results of SPT.

Nowadays, with the increasing number of dental implants placed worldwide<sup>112</sup> to restore missing teeth, the use of SPT has raised important and relevant questions. The SPT is mandatory for the success rate of implant-supported restorations in the long term, since the prevalence of peri-implantitis is two times greater in patients who did not attend any appointments in the first 5 years after conclusion of the implant treatment when compared with patients who attended control appointments once a year.<sup>113</sup>

In this sense, a recent cohort study evaluated the prevalence of mucositis, peri-implantitis, bone loss, and implant survival of 126 dental implants installed in 20 partially edentulous patients who had previously been treated for periodontitis, with 10 to 20 years of long-term follow-up results. The patients were followed up every 3 months and received SPT. The results demonstrated a moderate rate of peri-implant mucositis (< 30%) and peri-implantitis (< 25%), and the authors concluded that patients with periodontal history could be rehabilitated with dental implants in the long term, provided there was a tight control schedule.<sup>104</sup> Although the long-term survival rates of dental implants seem to be the same in patients with previous history of periodontitis associated with tooth loss and patients without periodontitis associated with tooth loss who received SPT, the peri-implant marginal bone loss is greater in patients with previous tooth loss due to periodontitis. Although patients susceptible to periodontitis may be indicated to receive rehabilitation with dental implants, the higher prevalence of peri-implantitis may jeopardize the lifespan of the implant.<sup>111</sup> Patients with a history of peri-implantitis who have had their lost teeth replaced with dental implants must frequently attend SPT appointments right after loading the implant-supported restoration. This is because there is a significant prevalence of peri-implantitis

over the course of time and, with regular SPT, the problem can be diagnosed while the lesion is still at the stage of peri-implant mucositis, thereby raising the odds of a successful treatment.<sup>101, 114.</sup>

Furthermore, a retrospective study<sup>103</sup> on peri-implant complications after 10 years of functional loading in periodontally compromised patients detected a cumulative incidence of 24.4% of peri-implantitis. The study also reported that peri-implantitis appeared more frequently after 5 years and the peak rate of incidence of the diseases occurred in the seventh year, demonstrating the importance of SPT in implant-supported restorations in the long term.

Finally, the active periodontal therapy combined with SPT of teeth and dental implants has delivered good results in the long term and should be the first-choice treatment for patients with periodontitis if there is any hope of maintaining the teeth, since there is no evidence of the dental implants exceeding the time of survival of teeth correctly treated for periodontitis.<sup>108, 111</sup>

## Conclusion

Predicting a tooth's clinical response to treatment over time is difficult, despite our knowledge of the mechanism of the host defense system against periodontitis, conditions in which biofilm may be retained in the dentures. The rehabilitative treatment performed with fixed or removable dental prostheses or dental implants will always be a challenge. This is because the inadequate design and infrastructure of removable partial dentures, marginal adaptation with overlapping of the fixed partial dentures, and implant-supported dental prostheses all favor greater biofilm retention. Therefore, the oral health of these patients will also depend on changes in their behavior, both relative to compliance with periodontal treatment and in their control at home. Moreover, patients will require professional plaque control with Periodic Preventive Maintenance performed during regular scheduled visits, and this will be an essential strategy to preserve the periodontal health of rehabilitated patients.

## References

1. Khurshid Z, Naseem M, Sheikh Z, Najeeb S, Shahab S, Zafar MS. Oral antimicrobial peptides: types and role in the oral cavity. *Saudi Pharm J*. 2016 Sep;24(5):515-24. <https://doi.org/10.1016/j.jsps.2015.02.015>
2. Ramseier CA, Anerud A, Dulac M, Lulic M, Cullinan MP, Seymour GJ, et al. Natural history of periodontitis: disease progression and tooth loss over 40 years. *J Clin Periodontol*. 2017 Dec;44(12):1182-91. <https://doi.org/10.1111/jcpe.12782>
3. McLeod DE, Lainson PA, Spivey JD. The predictability of periodontal treatment as measured by tooth loss: a retrospective study. *Quintessence Int*. 1998 Oct;29(10):631-5.
4. Chambrone L, Chambrone D, Lima LA, Chambrone LA. Predictors of tooth loss during long-term periodontal maintenance: a systematic review of observational studies. *J Clin Periodontol*. 2010 Jul;37(7):675-84. <https://doi.org/10.1111/j.1600-051X.2010.01587.x>
5. Tuominen R, Ranta K, Paunio I. Wearing of removable partial dentures in relation to periodontal pockets. *J Oral Rehabil*. 1989 Mar;16(2):119-26. <https://doi.org/10.1111/j.1365-2842.1989.tb01325.x>
6. Livingstone D, Murthy V, Reddy VK, Pillai A. Prosthodontic rehabilitation of a patient with aggressive periodontitis. *BMJ Case Rep*. 2015 Mar;2015 mar05 1:bcr2014204588. <https://doi.org/10.1136/bcr-2014-204588>
7. Heitz-Mayfield LJ, Huynh-Ba G. History of treated periodontitis and smoking as risks for implant therapy. *Int J Oral Maxillofac Implants*. 2009;24 Suppl:39-68.
8. Hajishengallis G, Korostoff JM. Revisiting the Page & Schroeder model: the good, the bad and the unknowns in the periodontal host response 40 years later. *Periodontol 2000*. 2017 Oct;75(1):116-51. <https://doi.org/10.1111/prd.12181>
9. Paster BJ, Boches SK, Galvin JL, Ericson RE, Lau CN, Levanos VA, et al. Bacterial diversity in human subgingival plaque. *J Bacteriol*. 2001 Jun;183(12):3770-83. <https://doi.org/10.1128/JB.183.12.3770-3783.2001>
10. Amano A. Bacterial adhesins to host components in periodontitis. *Periodontol 2000*. 2010 Feb;52(1):12-37. <https://doi.org/10.1111/j.1600-0757.2009.00307.x>
11. Kinane DF, Demuth DR, Gorr SU, Hajishengallis GN, Martin MH. Human variability in innate immunity. *Periodontol 2000*. 2007;45(1):14-34. <https://doi.org/10.1111/j.1600-0757.2007.00220.x>
12. Liang S, Krauss JL, Domon H, McIntosh ML, Hosur KB, Qu H, et al. The C5a receptor impairs IL-12-dependent clearance of *Porphyromonas gingivalis* and is required for induction of periodontal bone loss. *J Immunol*. 2011 Jan;186(2):869-77. <https://doi.org/10.4049/jimmunol.1003252>
13. Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, et al. Update on Prevalence of Periodontitis in Adults in the United States: NHANES 2009 to 2012. *J Periodontol*. 2015 May;86(5):611-22. <https://doi.org/10.1902/jop.2015.140520>
14. Tribble GD, Lamont RJ. Bacterial invasion of epithelial cells and spreading in periodontal tissue. *Periodontol 2000*. 2010 Feb;52(1):68-83. <https://doi.org/10.1111/j.1600-0757.2009.00323.x>
15. Meyle J, Dommisch H, Groeger S, Giacaman RA, Costalonga M, Herzberg M. The innate host response in caries and periodontitis. *J Clin Periodontol*. 2017 Dec;44(12):1215-25. <https://doi.org/10.1111/jcpe.12781>
16. Arancibia SA, Beltrán CJ, Aguirre IM, Silva P, Peralta AL, Malinarich F, et al. Toll-like receptors are key participants in innate immune responses. *Biol Res*. 2007;40(2):97-112. <https://doi.org/10.4067/S0716-97602007000200001>
17. Hato T, Dagher PC. How the innate immune system senses trouble and causes trouble. *Clin J Am Soc Nephrol*. 2015 Aug;10(8):1459-69. <https://doi.org/10.2215/CJN.04680514>
18. Kikkert R, Laine ML, Aarden LA, van Winkelhoff AJ. Activation of toll-like receptors 2 and 4 by gram-negative periodontal bacteria. *Oral Microbiol Immunol*. 2007 Jun;22(3):145-51. <https://doi.org/10.1111/j.1399-302X.2007.00335.x>
19. Mori Y, Yoshimura A, Ukai T, Lien E, Espevik T, Hara Y. Immunohistochemical localization of Toll-like receptors 2 and 4 in gingival tissue from patients with periodontitis. *Oral Microbiol Immunol*. 2003 Feb;18(1):54-8. <https://doi.org/10.1034/j.1399-302X.2003.180109.x>
20. Sugawara Y, Uehara A, Fujimoto Y, Kusumoto S, Fukase K, Shibata K, et al. Toll-like receptors, NOD1, and NOD2 in oral epithelial cells. *J Dent Res*. 2006 Jun;85(6):524-9. <https://doi.org/10.1177/154405910608500609>
21. Beklen A, Hukkanen M, Richardson R, Konttinen YT. Immunohistochemical localization of Toll-like receptors 1-10 in periodontitis. *Oral Microbiol Immunol*. 2008 Oct;23(5):425-31. <https://doi.org/10.1111/j.1399-302X.2008.00448.x>
22. Watanabe K, Iizuka T, Adeleke A, Pham L, Shlomon AE, Yasin M, et al. Involvement of toll-like receptor 4 in alveolar bone loss and glucose homeostasis in experimental periodontitis. *J Periodontol Res*. 2011 Feb;46(1):21-30. <https://doi.org/10.1111/j.1600-0765.2010.01304.x>
23. Könönen E, Gursoy M, Gursoy UK. Periodontitis: A multifaceted disease of tooth-supporting tissues. *J Clin Med*. 2019 Jul;8(8):1135. <https://doi.org/10.3390/jcm8081135>
24. Gursoy UK, Könönen E, Luukkonen N, Uitto VJ. Human neutrophil defensins and their effect on epithelial cells. *J Periodontol*. 2013 Jan;84(1):126-33. <https://doi.org/10.1902/jop.2012.120017>
25. Benakanakere M, Kinane DF. Innate cellular responses to the periodontal biofilm. *Front Oral Biol*. 2012;15:41-55. <https://doi.org/10.1159/000329670>

26. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontol*. 2014 Feb;64(1):57-80. <https://doi.org/10.1111/prd.12002>
27. Damgaard C, Holmstrup P, Van Dyke TE, Nielsen CH. The complement system and its role in the pathogenesis of periodontitis: current concepts. *J Periodontol Res*. 2015 Jun;50(3):283-93. <https://doi.org/10.1111/jre.12209>
28. Liu J, Du X, Chen J, Hu L, Chen L. The induction expression of human  $\beta$ -defensins in gingival epithelial cells and fibroblasts. *Arch Oral Biol*. 2013 Oct;58(10):1415-21. <https://doi.org/10.1016/j.archoralbio.2013.04.013>
29. Kasnak G, Könönen E, Syrjänen S, Gürsoy M, Zeidán-Chulíá F, Firatli E, et al. NFE2L2/NRF2, OGG1, and cytokine responses of human gingival keratinocytes against oxidative insults of various origin. *Mol Cell Biochem*. 2019 Feb;452(1-2):63-70. <https://doi.org/10.1007/s11010-018-3412-y>
30. Song B, Zhang YL, Chen LJ, Zhou T, Huang WK, Zhou X, et al. The role of Toll-like receptors in periodontitis. *Oral Dis*. 2017 Mar;23(2):168-80. <https://doi.org/10.1111/odi.12468>
31. Elmanfi S, Zhou J, Sintim HO, Könönen E, Gürsoy M, Gürsoy UK. Regulation of gingival epithelial cytokine response by bacterial cyclic dinucleotides. *J Oral Microbiol*. 2018 Nov;11(1):1538927. <https://doi.org/10.1080/20002297.2018.1538927>
32. Freita D, Könönen E, Gürsoy M, Ma X, Sintim HO, Gürsoy UK. Quorum sensing molecules regulate epithelial cytokine response and biofilm-related virulence of three *Prevotella* species. *Anaerobe*. 2018 Dec;54:128-35. <https://doi.org/10.1016/j.anaerobe.2018.09.001>
33. Hiroshima Y, Bando M, Kataoka M, Inagaki Y, Herzberg MC, Ross KF, et al. Regulation of antimicrobial peptide expression in human gingival keratinocytes by interleukin-1 $\alpha$ . *Arch Oral Biol*. 2011 Aug;56(8):761-7. <https://doi.org/10.1016/j.archoralbio.2011.01.004>
34. Jura J, Skalniak L, Koj A. Monocyte chemoattractant protein-1-induced protein-1 (MCP1) is a novel multifunctional modulator of inflammatory reactions. *Biochim Biophys Acta*. 2012 Oct;1823(10):1905-13. <https://doi.org/10.1016/j.bbamcr.2012.06.029>
35. Franco C, Patricia HR, Timo S, Claudia B, Marcela H. Matrix metalloproteinases as regulators of periodontal inflammation. *Int J Mol Sci*. 2017 Feb;18(2):440. <https://doi.org/10.3390/ijms18020440>
36. Wilensky A, Segev H, Mizraji G, Shaul Y, Capucha T, Shacham M, et al. Dendritic cells and their role in periodontal disease. *Oral Dis*. 2014 Mar;20(2):119-26. <https://doi.org/10.1111/odi.12122>
37. Song L, Dong G, Guo L, Graves DT. The function of dendritic cells in modulating the host response. *Mol Oral Microbiol*. 2018 Feb;33(1):13-21. <https://doi.org/10.1111/omi.12195>
38. Cheng WC, Hughes FJ, Taams LS. The presence, function and regulation of IL-17 and Th17 cells in periodontitis. *J Clin Periodontol*. 2014 Jun;41(6):541-9. <https://doi.org/10.1111/jcpe.12238>
39. Alnaeeli M, Penninger JM, Teng YT. Immune interactions with CD4+ T cells promote the development of functional osteoclasts from murine CD11c+ dendritic cells. *J Immunol*. 2006 Sep;177(5):3314-26. <https://doi.org/10.4049/jimmunol.177.5.3314>
40. Parkos CA. Neutrophil-epithelial interactions: A double-edged sword. *Am J Pathol*. 2016 Jun;186(6):1404-16. <https://doi.org/10.1016/j.ajpath.2016.02.001>
41. Fine N, Hassanpour S, Borenstein A, Sima C, Oveisi M, Scholey J, et al. Distinct oral neutrophil subsets define health and periodontal disease states. *J Dent Res*. 2016 Jul;95(8):931-8. <https://doi.org/10.1177/0022034516645564>
42. Davies LC, Rosas M, Jenkins SJ, Liao CT, Scurr MJ, Brombacher F, et al. Distinct bone marrow-derived and tissue-resident macrophage lineages proliferate at key stages during inflammation. *Nat Commun*. 2013;4(1):1886. <https://doi.org/10.1038/ncomms2877>
43. Hajishengallis G, Sahingur SE. Novel inflammatory pathways in periodontitis. *Adv Dent Res*. 2014 May;26(1):23-9. <https://doi.org/10.1177/0022034514526240>
44. Dutzan N, Konkel JE, Greenwell-Wild T, Moutsopoulos NM. Characterization of the human immune cell network at the gingival barrier. *Mucosal Immunol*. 2016 Sep;9(5):1163-72. <https://doi.org/10.1038/mi.2015.136>
45. Peres MA, Barbato PR, Reis SC, Freitas CH, Antunes JL. [Tooth loss in Brazil: analysis of the 2010 Brazilian Oral Health Survey]. *Rev Saude Publica*. 2013 Dec;47 Suppl 3:78-89. Portuguese. <https://doi.org/10.1590/S0034-8910.2013047004226>
46. Moreira RS, Nico LS, Barrozo LV, Pereira JC. Tooth loss in Brazilian middle-aged adults: multilevel effects. *Acta Odontol Scand*. 2010 Sep;68(5):269-77. <https://doi.org/10.3109/00016357.2010.494617>
47. Centers for Diseases Control and Prevention. Achievements in public health, 1900-1999. Fluoridation of drinking water to prevent dental caries. *MMWR Morb Mortal Wkly Rep*. 1999;44 RR-13:1-40.
48. Ministério da Saúde (BR). Secretaria de Atenção à Saúde. Departamento de Atenção Básica. A fluoretação das águas de abastecimento público como uma medida de garantia ao acesso a água tratada. *Rev Bras Saude Fam*. 2006;12(1):4-8.
49. Rebelo Vieira JM, Rebelo MA, Martins NM, Gomes JF, Vettore MV. Contextual and individual determinants of non-utilization of dental services among Brazilian adults. *J Public Health Dent*. 2019 Dec;79(1):60-70. <https://doi.org/10.1111/jphd.12295>
50. Roberto LL, Silveira MF, Paula AMB, Ferreira EF, Martins AMEBL, Haikal DS. Contextual and individual determinants of tooth loss in adults: a multilevel study. *BMC Oral Health*. 2020 Mar;20(1):73. <https://doi.org/10.1186/s12903-020-1057-1>
51. Corraini P, Baelum V, Pannuti CM, Pustiglioni AN, Romito GA, Pustiglioni FE. Tooth loss prevalence and risk indicators in an isolated population of Brazil. *Acta Odontol Scand*. 2009;67(5):297-303. <https://doi.org/10.1080/00016350903029107>

52. Fure S. Ten-year incidence of tooth loss and dental caries in elderly Swedish individuals. *Caries Res.* 2003 Nov-Dec;37(6):462-9. <https://doi.org/10.1159/000073401>
53. Batista MJ, Rihs LB, Sousa ML. Risk indicators for tooth loss in adult workers. *Braz Oral Res.* 2012 Sep-Oct;26(5):390-6. <https://doi.org/10.1590/S1806-83242012000500003>
54. Hugoson A, Sjödin B, Norderyd O. Trends over 30 years, 1973-2003, in the prevalence and severity of periodontal disease. *J Clin Periodontol.* 2008 May;35(5):405-14. <https://doi.org/10.1111/j.1600-051X.2008.01225.x>
55. Gotfredsen K, Walls AW. What dentition assures oral function? *Clin Oral Implants Res.* 2007 Jun;18 Suppl 3:34-45. <https://doi.org/10.1111/j.1600-0501.2007.01436.x>
56. Gerritsen AE, Allen PF, Witter DJ, Bronkhorst EM, Creugers NH. Tooth loss and oral health-related quality of life: a systematic review and meta-analysis. *Health Qual Life Outcomes.* 2010 Nov;8(1):126. <https://doi.org/10.1186/1477-7525-8-126>
57. Ravald N, Johansson CS. Tooth loss in periodontally treated patients: a long-term study of periodontal disease and root caries. *J Clin Periodontol.* 2012 Jan;39(1):73-9. <https://doi.org/10.1111/j.1600-051X.2011.01811.x>
58. Becker W, Becker BE, Berg LE. Periodontal treatment without maintenance. A retrospective study in 44 patients. *J Periodontol.* 1984 Sep;55(9):505-9. <https://doi.org/10.1902/jop.1984.55.9.505>
59. McGuire MK. Prognosis versus actual outcome: a long-term survey of 100 treated periodontal patients under maintenance care. *J Periodontol.* 1991 Jan;62(1):51-8. <https://doi.org/10.1902/jop.1991.62.1.51>
60. McGuire MK, Nunn ME; The effectiveness of clinical parameters in accurately predicting tooth survival. prognosis versus actual outcome. III. The effectiveness of clinical parameters in accurately predicting tooth survival. *J Periodontol.* 1996 Jul;67(7):666-74. <https://doi.org/10.1902/jop.1996.67.7.666>
61. Walter MH, Dreyhaupt J, Hannak W, Wolfart S, Luthardt RG, Stark H, et al. The randomized shortened dental arch study: tooth loss over 10 years. *Int J Prosthodont.* 2018 Jan/Feb;31(1):77-84. <https://doi.org/10.11607/ijp.5368>
62. Faggion CM Jr, Petersilka G, Lange DE, Gerss J, Flemmig TF. Prognostic model for tooth survival in patients treated for periodontitis. *J Clin Periodontol.* 2007 Mar;34(3):226-31. <https://doi.org/10.1111/j.1600-051X.2006.01045.x>
63. Helal O, Göstemeyer G, Krois J, Fawzy El Sayed K, Graetz C, Schwendicke F. Predictors for tooth loss in periodontitis patients: systematic review and meta-analysis. *J Clin Periodontol.* 2019 Jul;46(7):699-712. <https://doi.org/10.1111/jcpe.13118>
64. Carlsson GE. Critical review of some dogmas in prosthodontics. *J Prosthodont Res.* 2009 Jan;53(1):3-10. <https://doi.org/10.1016/j.jpor.2008.08.003>
65. Almeida ML, Tôrres AC, Oliveira KC, Calderon PD, Carreiro AD, Gurgel BC. Longitudinal improvement in periodontal parameters between RPD abutment teeth with direct and indirect retainers, after periodontal therapy. *J Prosthodont.* 2019 Jan;28(1):e440-4. <https://doi.org/10.1111/jopr.12774>
66. Almeida ML, Oliveira EP, Tôrres CS, Calderon PD, Carreiro AD, Gurgel BC. Evaluation of periodontal parameters on Removable Partial Denture abutment teeth with direct and indirect retainers: A 48-month follow-up. *J Int Acad Periodontol.* 2020 Apr;22(2):10-7.
67. Berg E, Isidor F, Öwall B. Prosthodontics for the elderly patient - a Scandinavian approach. *Protet Stomatol.* 2018;68(3):255-66. <https://doi.org/10.5604/01.3001.0012.2556>
68. Moldovan O, Rudolph H, Luthardt RG. Biological complications of removable dental prostheses in the moderately reduced dentition: a systematic literature review. *Clin Oral Investig.* 2018 Sep;22(7):2439-61. <https://doi.org/10.1007/s00784-018-2522-y>
69. Pjetursson BE, Sailer I, Makarov NA, Zwahlen M, Thoma DS. All-ceramic or metal-ceramic tooth-supported fixed dental prostheses (FDPs)? A systematic review of the survival and complication rates. Part II: multiple-unit FDPs [published correction appears in *Dent Mater.* 2017 Jan;33(1):e48-e51]. *Dent Mater.* 2015 Jun;31(6):624-39. <https://doi.org/10.1016/j.dental.2015.02.013>
70. Teichmann M, Göckler F, Weber V, Yildirim M, Wolfart S, Edelhoff D. Ten-year survival and complication rates of lithium-disilicate (Empress 2) tooth-supported crowns, implant-supported crowns, and fixed dental prostheses. *J Dent.* 2017 Jan;56:65-77. <https://doi.org/10.1016/j.jdent.2016.10.017>
71. Yi SW, Ericsson I, Carlsson GE, Wennström JL. Long-term follow-up of cross-arch fixed partial dentures in patients with advanced periodontal destruction. Evaluation of the supporting tissues. *Acta Odontol Scand.* 1995 Aug;53(4):242-8. <https://doi.org/10.3109/00016359509005980>
72. Bergenholtz G, Nyman S. Endodontic complications following periodontal and prosthetic treatment of patients with advanced periodontal disease. *J Periodontol.* 1984 Feb;55(2):63-8. <https://doi.org/10.1902/jop.1984.55.2.63>
73. Valderhaug J, Jokstad A, Ambjørnsen E, Norheim PW. Assessment of the periapical and clinical status of crowned teeth over 25 years. *J Dent.* 1997 Mar;25(2):97-105. [https://doi.org/10.1016/S0300-5712\(96\)00008-5](https://doi.org/10.1016/S0300-5712(96)00008-5)
74. Valderhaug J, Ellingsen JE, Jokstad A. Oral hygiene, periodontal conditions and carious lesions in patients treated with dental bridges. A 15-year clinical and radiographic follow-up study. *J Clin Periodontol.* 1993 Aug;20(7):482-9. <https://doi.org/10.1111/j.1600-051X.1993.tb00395.x>
75. Lulic M, Brägger U, Lang NP, Zwahlen M, Salvi GE. Anté's (1926) law revisited: a systematic review on survival rates and complications of fixed dental prostheses (FDPs) on severely reduced periodontal tissue support [published correction appears in *Clin Oral Implants Res.* 2008 Mar;19(3):326-8]. *Clin Oral Implants Res.* 2007 Jun;18 Suppl 3:63-72. <https://doi.org/10.1111/j.1600-0501.2007.01438.x>

76. Amaral BA, Barreto AO, Seabra EG, Roncalli AG, Carreiro AFP, Almeida EO. A clinical follow-up study of the periodontal conditions of RPD abutment and non-abutment teeth. *J Oral Rehabil.* 2010 Jul;37(7):545-52. <https://doi.org/10.1111/j.1365-2842.2010.02069.x>
77. Preshaw PM, Walls AW, Jakubovics NS, Moynihan PJ, Jepson NJ, Loewy Z. Association of removable partial denture use with oral and systemic health. *J Dent.* 2011 Nov;39(11):711-9. <https://doi.org/10.1016/j.jdent.2011.08.018>
78. Moldovan O, Rudolph H, Luthardt RG. Clinical performance of removable dental prostheses in the moderately reduced dentition: a systematic literature review. *Clin Oral Investig.* 2016 Sep;20(7):1435-47. <https://doi.org/10.1007/s00784-016-1873-5>
79. Müller S, Eickholz P, Reitmeir P, Eger T. Long-term tooth loss in periodontally compromised but treated patients according to the type of prosthodontic treatment. A retrospective study. *J Oral Rehabil.* 2013 May;40(5):358-67. <https://doi.org/10.1111/joor.12035>
80. Studer SP, Mäder C, Stahel W, Schärer P. A retrospective study of combined fixed-removable reconstructions with their analysis of failures. *J Oral Rehabil.* 1998 Jul;25(7):513-26. <https://doi.org/10.1046/j.1365-2842.1998.00294.x>
81. Tada S, Ikebe K, Matsuda K, Maeda Y. Multifactorial risk assessment for survival of abutments of removable partial dentures based on practice-based longitudinal study. *J Dent.* 2013 Dec;41(12):1175-80. <https://doi.org/10.1016/j.jdent.2013.07.018>
82. Budtz-Jørgensen E, Isidor F. A 5-year longitudinal study of cantilevered fixed partial dentures compared with removable partial dentures in a geriatric population. *J Prosthet Dent.* 1990 Jul;64(1):42-7. [https://doi.org/10.1016/0022-3913\(90\)90151-2](https://doi.org/10.1016/0022-3913(90)90151-2)
83. Gerritsen AE, Witter DJ, Bronkhorst EM, Creugers NH. An observational cohort study on shortened dental arches: clinical course during a period of 27-35 years. *Clin Oral Investig.* 2013 Apr;17(3):859-66. <https://doi.org/10.1007/s00784-012-0765-6>
84. Walter MH, Hannak W, Kern M, Mundt T, Gernet W, Weber A, et al. The randomized shortened dental arch study: tooth loss over five years. *Clin Oral Investig.* 2013 Apr;17(3):877-86. <https://doi.org/10.1007/s00784-012-0761-x>
85. McLister C, Donnelly M, Cardwell CR, Moore C, O'Neill C, Brocklehurst P, et al. Effectiveness of prosthodontic interventions and survival of remaining teeth in adult patients with shortened dental arches-A systematic review. *J Dent.* 2018 Nov;78:31-9. <https://doi.org/10.1016/j.jdent.2018.02.003>
86. Carreiro AFP, Dias KC, Lopes ALC, Resende CMBM, Martins ARLA. Periodontal conditions of abutments and non-abutments in removable partial dentures over 7 years of use. *J Prosthodont.* 2017 Dec;26(8):644-9. <https://doi.org/10.1111/jopr.12449>
87. Ercoli C, Caton JG. Dental prostheses and tooth-related factors. *J Clin Periodontol.* 2018 Jun;45 Suppl 20:S207-18. <https://doi.org/10.1111/jcpe.12950>
88. Correia F, Gouveia S, Felino AC, Costa AL, Almeida RF. Survival rate of dental implants in patients with history of periodontal disease: a retrospective cohort study. *Int J Oral Maxillofac Implants.* 2017 Jul/Aug;32(4):927-34. <https://doi.org/10.11607/jomi.3732>
89. Gianserra R, Cavalcanti R, Oreglia F, Manfredonia MF, Esposito M. Outcome of dental implants in patients with and without a history of periodontitis: a 5-year pragmatic multicentre retrospective cohort study of 1727 patients. *Eur J Oral Implantol.* 2010;3(4):307-14.
90. Baelum V, Ellegaard B. Implant survival in periodontally compromised patients. *J Periodontol.* 2004 Oct;75(10):1404-12. <https://doi.org/10.1902/jop.2004.75.10.1404>
91. Karoussis IK, Kotsovilis S, Fourmouis I. A comprehensive and critical review of dental implant prognosis in periodontally compromised partially edentulous patients. *Clin Oral Implants Res.* 2007 Dec;18(6):669-79. <https://doi.org/10.1111/j.1600-0501.2007.01406.x>
92. Schou S, Holmstrup P, Worthington HV, Esposito M. Outcome of implant therapy in patients with previous tooth loss due to periodontitis. *Clin Oral Implants Res.* 2006 Oct;17(2 Suppl 2):104-23. <https://doi.org/10.1111/j.1600-0501.2006.01347.x>
93. Dank A, Aartman IH, Wismeijer D, Tahmaseb A. Effect of dental implant surface roughness in patients with a history of periodontal disease: a systematic review and meta-analysis. *Int J Implant Dent.* 2019 Feb;5(1):12. <https://doi.org/10.1186/s40729-019-0156-8>
94. Van der Weijden GA, Bemmels KM, Renvert S. Implant therapy in partially edentulous, periodontally compromised patients: a review. *J Clin Periodontol.* 2005;32:506-11.
95. Ong CT, Ivanovski S, Needleman IG, Retzepi M, Moles DR, Tonetti MS, et al. Systematic review of implant outcomes in treated periodontitis subjects. *J Clin Periodontol.* 2008 May;35(5):438-62. <https://doi.org/10.1111/j.1600-051X.2008.01207.x>
96. Wen X, Liu R, Li G, Deng M, Liu L, Zeng XT, et al. History of periodontitis as a risk factor for long-term survival of dental implants: a meta-analysis. *Int J Oral Maxillofac Implants.* 2014 Nov-Dec;29(6):1271-80. <https://doi.org/10.11607/jomi.3544>
97. Karoussis IK, Kotsovilis S, Fourmouis I. A comprehensive and critical review of dental implant prognosis in periodontally compromised partially edentulous patients. *Clin Oral Implants Res.* 2007 Dec;18(6):669-79. <https://doi.org/10.1111/j.1600-0501.2007.01406.x>
98. Quirynen M, Vogels R, Peeters W, et al. Dynamics of initial subgingival colonization of 'pristine' peri-implant pockets. *Clin Oral Implants Res.* 2006; 17: 25-37.
99. Quirynen M, Vogels R, Peeters W, et al. Dynamics of initial subgingival colonization of 'pristine' peri-implant pockets. *Clin Oral Implants Res.* 2006; 17: 25-37.
100. Costa FR Jr, Alvim-Pereira CC, Alvim-Pereira F, et al. Influence of MMP-8 promoter polymorphism in early osseointegrated implant failure. *Clin Oral Investig.* 2013; 17: 311-6.
101. Anner R, Grossmann Y, Anner Y, et al. Smoking, diabetes mellitus, periodontitis, and supportive periodontal treatment as factors associated with dental implant survival: A long-term retrospective evaluation of patients followed for up to 10 years. *Implant Dent.* 2010; 19: 57-64.

102. Amerio E, Mainas G, Petrova D, Giner Tarrida L, Nart J, Monje A. Compliance with supportive periodontal/peri-implant therapy: A systematic review. *J Clin Periodontol*. 2020;47(1):81–100.
103. Pandolfi A, Rinaldo F, Pasqualotto D, Sorrentino F, La Torre G, Guerra F. A retrospective cohort study on peri-implant complications in implants up to 10 years of functional loading in periodontally compromised patients. *J Periodontol*. 2020;91(8):995–1002.
104. Thöne-Mühling M, Pricope L, Mogk M, Mengel R. Turned surface implants in patients treated for periodontitis: Preliminary 10- to 20-year results of a long-term cohort study. *Int J oral Implantol (New Malden, London, England)*. 2020;13(2):173–84.
105. Heschl A, Haas M, Haas J, Payer M, Wegscheider W, Polansky R. Maxillary rehabilitation of periodontally compromised patients with extensive one-piece fixed prostheses supported by natural teeth: A retrospective longitudinal study. *Clin Oral Investig*. 2013;17(1):45–53.
106. Graetz C, Schwendicke F, Kahl M, Dörfer CE, Sälzer S, Springer C, et al. Prosthetic rehabilitation of patients with history of moderate to severe periodontitis: A long-term evaluation. *J Clin Periodontol*. 2013;40(8):799–806.
107. Lee CT, Huang HY, Sun TC, Karimbux N. Impact of patient compliance on tooth loss during supportive periodontal therapy: A systematic review and meta-analysis. *J Dent Res*. 2015;94(6):777–86.
108. Tomasi C, Wennström JL, Berglundh T. Longevity of teeth and implants - A systematic review. *J Oral Rehabil*. 2008;35(S1):23–32.
109. Schwarz F, Derks J, Monje A, Wang HL. Peri-implantitis. *J Periodontol*. 2018;89(September 2017):S267–90.
110. Manresa C, Ec S, Twigg J, Bravo M. Supportif Periodontal Therapy in adults treated for periodontitis ( Review ). 2018;(1).
111. Schou S. Implant treatment in periodontitis-susceptible patients: A systematic review. *J Oral Rehabil*. 2008;35(S1):9–22.
112. Marcantonio Junior E, Romito GA, Shibli JA. Peri-implantitis as a “burden” disease. *Braz Oral Res*. 2019;33(suppl 1):e087. Published 2019 Sep 30. doi:10.1590/1807-3107bor-2019.vol33.0087
113. Jepsen S, Berglundh T, Genco R, Aass AM, Demirel K, Derks J, et al. Primary prevention of peri-implantitis: Managing peri-implant mucositis. *J Clin Periodontol*. 2015;42(S16):S152–7.
114. Figuro E, Graziani F, Sanz I, Herrera D, Sanz M. Management of peri-implant mucositis and peri-implantitis. *Periodontol 2000*. 2014;66(1):255–73.