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REVIEW ARTICLE

Oral Alterations in Individuals in Pre and Post Heart Transplantation

Sarah Jorge Affonço[1], Luiz Alberto Valente Soares Junior[2], Raquel D'Aquino Garcia Caminha[3], Paulo Sérgio Silva Santos[3]

1. Fundação Bauruense de Estudos Odontológicos, Bauru (SP), Brazil.

2. Universidade de São Paulo – Faculdade de Medicina – Hospital das Clínicas, São Paulo (SP), Brazil.

3. Universidade de São Paulo – Faculdade de Odontologia de Bauru – Departamento de Cirurgia, Estomatologia, Patologia e Radiologia, Bauru (SP), Brazil.

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Correspondence author:
sarah.affonco@gmail.com

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Abstract: Heart failure in advanced stages and unsuccessful alternative treatments can lead the patient to heart transplantation. Patients in pre-heart transplantation who present periodontal alterations can progress to an infectious condition and compromise the success of the transplant. Transplanted patients have intraoral changes associated with immunosuppressive therapy, such as gingival hyperplasia and opportunistic infections that deserve attention, as they result in poor quality of life and worse prognosis. This study searched the literature for oral alterations frequently found in patients with heart failure in a transplant program and heart transplant recipients, highlighting the importance of the dentist in the multidisciplinary team and the long-term follow-up of the transplanted patient. In this review, cohort studies, cross-sectional studies, case-control studies and clinical cases included in the PubMed, Biblioteca Eletrônica Científica Online (SciELO) and *Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs)* databases of the last 11 years (from 2009 to 2020) and in English, Portuguese and Spanish. The search result made available 577 articles, which were screened and selected, so that they included all the information necessary for the statistical analysis. Among the most relevant data regarding the oral condition of pre-heart transplant patients, it was observed that 74.21% of individuals have systemic arterial hypertension as the main comorbidity and 42.69% use immunosuppressants. As for the oral diagnosis, there is a high need for periodontal treatment in 75.57% of the patients. In the profile of transplanted patients, there is a higher prevalence of diabetes mellitus (48.26%), and all patients follow drug therapy, with an association of more than one drug. Of these individuals, 90% need periodontal treatment and 17.34% had gingival hyperplasia. The data obtained allowed us to conclude that both heart transplant and transplant patients need special attention with regard to oral care, as they are susceptible to opportunistic infections and have periodontal care needs, which suggests that oral adequacy prior to transplantation is relevant, as is the control of the secondary effects of immunosuppressive therapy.

Descriptors: Oral Health; Prevention of Diseases; Heart Transplant; Cardiac Insufficiency; Oral Diagnosis.

INTRODUCTION

One of the main causes of mortality, morbidity and low quality of life of an individual is heart failure (HF), which, in advanced stages or without successful treatment, can lead the patient to heart transplantation (HTx).[1] This procedure has shown a subtle growth in Brazil since 2011, with 380 transplants performed in 2019, by 35 teams working in 12 states.[2,3]

The increase in life expectancy of transplant patients is due to surgical improvement, together with advances in immunosuppressive therapy, used to prevent organ rejection.[4] With immunosuppression, patients are more susceptible to opportunistic infections, due to the inability of the immune system to suppress the pathogen.[4,5]

The oral cavity has a symbiotic oral microbiota capable of becoming pathogenic, causing periodontal and dental changes, which can lead to systemic infections, increased length of stay, worsening prognosis of the recipient and compromise of the transplanted organ.[3-7] Poor oral hygiene associated with immunosuppression results in periodontal changes, such as gingival hyperplasia (GH), mainly observed in individuals who use cyclosporine A concomitantly with the use of calcium channel blockers.[4,6-8]

The present narrative review aimed to search the literature for the oral alterations frequently found in patients with HF in a heart transplant and transplant program, emphasizing the importance of dental follow-up in the pre- and post-transplantation periods, providing the transplant doctor and dental surgeon that acts in heart transplants important information for oral adequacy and for the diagnosis and control of oral manifestations resulting from immunosuppressive drugs.

METHODS

This narrative review was carried out by searching for articles included in PubMed, Biblioteca Eletrônica Científica Online (SciELO) and Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) databases, having as a guiding question: what are the oral alterations frequently found in patients undergoing a heart transplant and post-transplantation program? The inclusion criteria were:

- Articles available in full;
- Articles in english, spanish or portuguese;
- Articles that presented the topic addressed;
- Review articles, cohort studies, cross-sectional studies, case-control and clinical cases;
- Articles published in the last 15 years.

The exclusion criteria were:

- Articles that did not have an oral diagnosis in the population studied;
- Articles that did not present specific epidemiological data before or after surgery;
- Population studied under 18 years of age;
- Articles not available online.

The following descriptors and their combination in English, Spanish and Portuguese were used: Dentistry and heart transplantation, Dentistry and transplantation, Oral health and transplantation and Heart transplantation.

RESULTS

In the initial search, 904 articles were found, 327 of which were excluded due to duplicity. Following the inclusion and exclusion criteria established in the methodology, 24 articles were read in full, and the final sample of this narrative review was composed of seven articles from observational studies (Fig. 1), totaling 135 patients in pre-heart transplantation and 274 patients HTx.

Patients undergoing cardiac transplantation

Among the patients in the transplant program, there was a prevalence of males, a mean age of 55 years, and the highest incidence of comorbidities were systemic arterial hypertension (SAH) and diabetes mellitus, found in 74.21 and 34.3% of the individuals, respectively. As for harmful habits, 64% of patients were smokers. Regarding drug therapy, 42.69% of the patients used bisphosphonates and 5.46% used calcium channel blockers.

With regard to oral alterations, only data referring to periodontal alterations and the presence of infections were included in the selected articles, and it was observed that 75.57% of the patients needed periodontal treatment, 75.44% had periodontal disease (being considered of mild, moderate or severe) and 6.25% oral mucosa lesion.

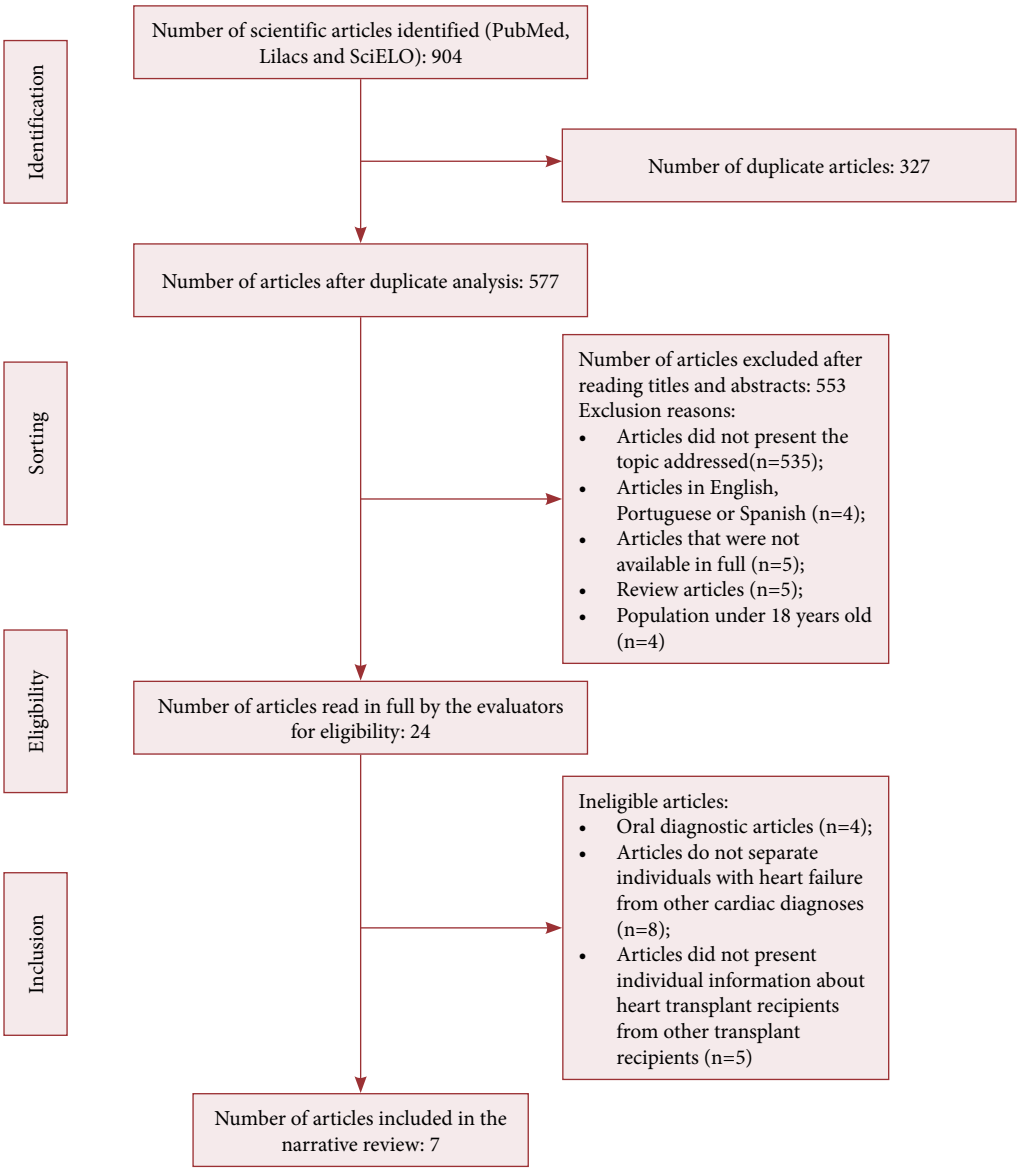

Figure 1. Process of identification and selection of studies for inclusion.

The percentages cited were calculated by including only the total number of patients who presented information, covering all data from this population in Table 1.

Heart transplant patients

Among transplanted patients, there was a prevalence of males, a mean age of 55 years, and the highest incidence of comorbidities were diabetes mellitus and SAH, found in 48.29 and 42.15%, respectively. As for harmful habits, 45.49% of patients were smokers. Regarding drug therapy in these patients, more drugs were used than among patients with HF, with the highest prevalence being antimetabolites (70.99%) and glucocorticoids (65.64%), followed by channel blockers. calcium (65.64%), bisphosphonates (31.25%) and antiproliferatives (10.63%).

Regarding oral alterations, only the data referring to periodontal alterations and the presence of infections were included in the selected articles, and it was observed that 89.84% of the patients needed periodontal treatment, 90% had periodontal disease (considering mild, moderate or severe), 17.34% had GH and 11% had a diagnosis of fungal infection by Candida albicans.

The percentages mentioned were counted, including only the total number of patients who presented this information, encompassing all data from this population in Table 2.

Table 1. Characteristics of patients in a transplant program.

Authors	Kind of study	Average age	Male (n)	Comorbidities (n) / harmful habits (n)	Drug therapy (n)	Oral diagnosis
Cunha et al.[7]	Cohort	not informed	8 (16)	NR	NR	PD (11) Oral mucosal injury(1)
Binner et al.[34]	Cross-sectional	56	85 (89)	HAS (66) DM (32) Obesity (38) KD (40) Osteoporosis (4) Smokers (54)	Calcium channel (5) Bisphosphonates (38) NR (5)	PD (89) Need periodontal treatment (77)
Schulze-Spätee et al.[35]	Cross-sectional	55	29 (39)	HAS (29) DM (12) Hypercholesterolemia (26) IR (13) Liver failure (2)	Calcium channel blockers (2)	PD (26)
Ziebolz et al.[36]	Cohort	55	13 (14)	NR Smokers (3)	NR	Need periodontal treatment (11)

SAH: systemic arterial hypertension; DM: diabetes *mellitus*; KF: kidney failure; NR: not reported; PD: periodontal disease

Tabela 2. Characteristics of heart transplant patients.

Authors	Kind of study	Average age	Male n (total)	Transplant time (years)	Comorbidities (n) / harmful habits (n)	Drug therapy (n)	Oral diagnosis (n)
Ying et al.[8]	Cross-sectional	47	47 (81)	3 to 4 years	SAH (34) DM (25) Smokers (14)	Calcium channel blockers (81) Glucocorticoids (43) Antimetabolites (79)	Need periodontal treatment (60) Gingival hyperplasia (24)
Santos et al.[10]	Clinical case	59	1 (3)	8 to 14	SAH (1) Smokers (3)	Calcium channel blockers (3) Glucocorticoids (1) Antimetabolites (2)	PD (3) Gingival hyperplasia(3) dental abscess (1) Periapical lesion (1)
Dongari-Bagtzoglou e Fidel Jr.[31]	Case control	56	6 (9)	5 to 8	DM (6) Smokers (6)	Calcium channel blockers (7) Glucocorticoids (8) Antimetabolites (9) Antiproliferatives(1)	Erythematous candidiasis(1)
Binner et al [34]	Cross-sectional	56	86 (112)	5 to 70	SAH (62) DM (39) Obesity (58) KF (95) Osteoporosis (6) Smokers (83)	Calcium channel blockers (28) Bisphosphonates (35) NR (49)	PD (112) Need periodontal treatment (89) Gingival hyperplasia (7)
Schulze-Spätee et al. [35]	Cross-sectional	55	30 (38)	3 to 4	SAH (16) DM (16) Hypercholesterolemia (8) KF (8)	Calcium channel blockers (37) Glucocorticoids (34) Antiproliferatives (4) Antimetabolites (3)	NR
Ziebolz et al. [36]	Cohort	55	23 (31)	NR	NR Smokers (3)	NR	Need periodontal treatment (28)

SAH: systemic arterial hypertension; DM: diabetes *mellitus*; KF: kidney failure; NR: not reported; PD: periodontal disease.

DISCUSSION

In both pre-transplant and transplant patients, a high prevalence of the need for periodontal treatment, presence of periodontal disease and secondary effects of immunosuppressive therapy were observed, resulting in opportunistic infections, with oral

candidiasis being more common.[9-11] Therefore, it is necessary to monitor the dental team not only for the treatment, but for the early diagnosis of oral infections, so that the quality of life of the recipients is not compromised.[2,12]

Periodontal changes

Periodontal diseases are of inflammatory origin and are associated with resident oral microflora and the presence of biofilm, and can be divided into two large groups: gingivitis and periodontitis. Gingivitis is characterized by spontaneous bleeding or by touch and by change in color and volume of the marginal gingiva, usually self-limiting, while periodontitis is progressive, characterized by the formation of periodontal pockets and loss of alveolar bone, which can lead to the formation of abscesses, resulting in pain, purulent discharge, and swelling.[5,11]

As shown in the results, most pre-transplantation and HTx patients need treatment for periodontal diseases. Some studies present the products synthesized by gram-negative bacteria (which cause periodontitis) as triggers for the production and release of pro-inflammatory cytokines, which induce a response from the host itself, increasing C-reactive protein levels and increasing the risk of cardiovascular diseases. , as well as gingival bacteria, which are linked to the formation of atheromatous plaques, resulting in ischemic diseases, bacteremia, sepsis and endocarditis.[12-15]

Another periodontal alteration is drug GH, present in transplant patients. It is a multifactorial condition, but some studies have shown a relationship with the incidence and severity associated with the use of tacrolimus and especially cyclosporine A.[3,10]

Drug GH is characterized by an increase in connective tissue, caused by an increase in collagen and fibroblasts deposits in the gingival tissue, which can range from small to large extensions. As a consequence of this gingival enlargement, alterations in occlusion, speech and mastication (leading the patient to a nutritional deficiency) and difficulty in cleaning can be observed in large proportions, which results in inflammation, greater susceptibility to infections and hemorrhagic foci, which may generate bacteremia and sepsis.[12,16-18]

In order to prevent drug-induced GH, adequate oral hygiene is important and, for treatment purposes, the following may be necessary: surgical intervention, prescription of antibiotics, mouthwash with chlorhexidine. In persistent lesions, replacement of cyclosporine with tacrolimus may be necessary.[12-17]

Maxillary osteonecrosis associated with medication use

Osteoporosis and the increase in the prevalence of bone fractures have been observed in patients before and after solid organ transplantation, being considered predisposing factors for bone disorders in these individuals: use of loop diuretics, heparin, vitamin D deficiency and secondary hyperparathyroidism, hypogonadism, renal failure, and adverse effects of glucocorticoids and calcineurin inhibitors. Bisphosphonates are widely used to prevent and treat mineral density loss, as these drugs decrease bone turnover through inhibition and apoptosis of osteoclasts.[19-22]

Maxillary osteonecrosis associated with the use of medications, as updated by the American Association of Oral and Maxillofacial Surgeons in 2014, is characterized by an area of bone exposure that is not repaired within eight weeks and affects patients who use antiresorptive or antiangiogenic drugs and in patients who have not undergone irradiation or who have metastatic disease in the maxillomandibular complex. Its association with bisphosphonates has been discussed in the literature due to its ability to alter bone remodeling, inhibition of angiogenesis (especially the use of zoledronic acid) and soft tissue toxicity (associated with the use of denosumab), resulting in inadequate tissue repair. in the face of trauma or infection.[21,23-26] In this study, it was observed that 42.69% of pre-heart transplant patients and 31.25% of transplant patients use bisphosphonates. Therefore, they must undergo periodic dental evaluation to control risk factors for maxillary osteonecrosis associated with medication use.

Infections in immunosuppressed patients

In addition to periodontal changes, this profile of patients is more prone to opportunistic infections of fungal, viral or bacterial origin, due to altered immune defense. In general, infections during the first month after transplantation may be due to preexisting microbial agents in the patient, surgical complications or nosocomial infections, with fungal infections being more frequent at this first moment.[27] Some studies show a high incidence of infection by the Epstein-Barr virus, *Candida albicans*, and herpes virus in individuals with altered immunity, as a consequence of the immunosuppressive regimen used in patients in a transplant program and after heart transplantation.[12,28]

The oral cavity is a site commonly affected by fungal infections such as candidiasis, and some studies show the prevalence of pseudomembranous and erythematous types in immunosuppressed patients. Some drugs, in addition to corticosteroids, are related to candidal conditions, such as mycophenolate and azathioprine, as they lead to neutropenia.[29-31] Cases of oropharyngeal candidiasis occur mainly in the first year after transplantation and can progress to a condition of disseminated infection, causing morbidity and mortality in patients.[29-33]

CONCLUSION

The high prevalence of periodontal disease and the need for dental treatment in patients to be transplanted denote the importance of the dentist in the multidisciplinary team, since oral hygiene instruction is an effective strategy to reduce microorganisms that act as etiological agents of the disease. periodontal disease, as this can compromise the individual's health, as well as the elimination of infectious foci prior to transplantation. Likewise, the follow-up of the transplanted patient is of great value for the treatment of periodontal disease and control of the secondary effects of immunosuppressants, effectively reducing comorbidities and providing a better prognosis and quality of life for patients. In pre- and post-transplant individuals, the prevalence of maxillary osteonecrosis associated with medication use can also be observed. Such a condition directly implies the low quality of life of these patients and must be controlled by the dentist in regular consultations.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Affonço SJ, Soares Junior LAV, Caminha RDG and Santos PSS; **Conception and design:** Affonço SJ and Santos PSS; **Technical procedures:** Affonço SJ and Santos PSS; **Data analysis and interpretation:** Affonço SJ, Soares Junior LAV, Caminha RDG and Santos PSS; **Critical review:** Affonço SJ, Soares Junior LAV, Caminha RDG and Santos PSS; **Final approval:** Affonço SJ, Soares Junior LAV, Caminha RDG and Santos PSS.

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Not applicable.

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