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**Paper Accepted\***

**ISSN Online 2406-0895**

**Review Article / Преглед литературе**

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**Oral changes in patients before and after transplantation of solid organs  
and hematopoietic stem cells**

Оралне промене код пацијената пре и после трансплантације солидних  
органа и матичних ћелија хематопоезе

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Serbia

**Received: September 9, 2019**

**Revised: October 3, 2020**

**Accepted: October 30, 2020**

**Online First: November 10, 2020**

**DOI: <https://doi.org/10.2298/SARH190909106J>**

\***Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. *Srp Arh Celok Lek*. Online First, February 2017.

When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

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## Oral changes in patients before and after transplantation of solid organs and hematopoietic stem cells

Оралне промене код пацијената пре и после трансплантације солидних органа и матичних ћелија хематопоезе

### SUMMARY

**Introduction/Objective** The aim of this paper is to point out the prevalence and severity of oral diseases in patients in the period before and after the transplantation of solid organs and hematopoietic stem cells.

**Methods** MEDLINE literature search was done via PubMed.

**Results** The development and improvement of transplantation medicine in specialized centers lead to an increasing number of patients, both adults and children, with transplanted solid organs and hematopoietic stem cells. Despite the success of therapy, numerous changes and complications can be observed on other organs in patients undergoing transplantation of solid organs and hematopoietic stem cells in the pre and post-transplant phase. Systemic diseases and conditions related to organ and cell transplantation, which are accompanied by numerous oral manifestations. The most common oral changes are gingival enlargement, desquamation of the oral epithelium, very painful ulcerations, polypoid and granulomatous changes in the oral mucosa, hard dental tissues with frequent complications, developmental anomalies of teeth in younger children, and in the later stage also the occurrence of oral cancer. After transplantation of solid organs and hematopoietic changes in the oral cavity and other organs occur depending on the patient's post-transplantation period as well as on the applied immunosuppressive therapy.

**Conclusion** Oral changes development pre and post transplantation of solid organ and hematopoietic stem cells points to the importance of timely and good cooperation between the dentist and the doctor who treats the underlying disease.

**Keywords:** organ transplantation; hematopoietic stem cell transplantation; oral diseases

### САЖЕТАК

**Увод/циљ** Сврха овог рада је да се укаже на распрострањеност и тежину оралних обољења код пацијената и у периоду пре и након трансплантације солидних органа и матичних ћелија хематопоезе.

**Метод** Претражена је литература са базама података на *PubMed*.

**Резултати** Развој и унапређење трансплантационе медицине у специјализованим центрима доводи до све већег броја пацијената са трансплантираним солидним органима и матичним ћелијама хематопоезе, како одраслих тако и деце. Код пацијената који су подвргнути процедури трансплантације солидних органа и матичних ћелија хематопоезе се, и поред успешности терапије, могу уочити бројне промене и компликације на другим органима и у фази пре и након трансплантације. Системска обољења и стања везана за трансплантацију органа и ћелија праћена су бројним оралним манифестацијама. Најчешће оралне промене су увећање гингиве, десквамација оралног епитела, веома болне улцерације, полипоидне и грануломатозне промене на оралној слузокожи, обољења тврдих зубних ткива са честим компликацијама, развојне аномалије зуба код деце млађег узраста, а у каснијој фази и појава оралног карцинома. Након трансплантације, промене у усној дупљи и другим органима се јављају у зависности од трансплантационог периода у којем се пацијент налази и од примењене имуносупресивне терапије.

**Закључак** Распрострањене оралне промене пре и након трансплантације солидних органа и матичних ћелија хематопоезе указују на значај правовремене и добре сарадње стоматолога и лекара који лече основно обољење.

**Кључне речи** : трансплантација органа; трансплантација матичних ћелија хематопоезе; орална обољења

## INTRODUCTION

Transplantation of solid organs is a mostly surgical therapeutic method by which, the non-functional organs are replaced with healthy ones. It is applied in treatment of various diseases that lead to permanent damage to the function of certain organs. Transplantation of

hematopoietic stem cells is most frequently carried out in the treatment of the most severe forms of hematological diseases and some forms of malignant tumors. Transplantation of solid organs and hematopoietic stem cells is a demanding and complicated process that requires the engagement of a multidisciplinary team. For the success of this procedure, a comprehensive preoperative and postoperative management of the patient is extremely important. Owing to significant discoveries in the field of transplantation medicine, as well as comprehensive multidisciplinary treatment of patients in the peritransplantation period, years-long survival without symptoms of the basic disease is enabled. Transplantation of solid organs and hematopoietic stem cells significantly influenced the length and quality of life of the patients [1].

In patients with transplanted organs and cells, despite the success of the therapy, numerous changes can be observed on other organs and systems. The risks and adverse effects of transplantation on other organs occur depending on the duration of the underlying disease, general state of the organism, presence of another chronic illness, the applied therapy or age of the patient. These changes can be diagnosed in the pre and post-transplant phase. Changes affecting soft and hard tissues of the oral cavity are among the most widespread changes. The most common oral changes include gingival enlargement, periodontal diseases, desquamation of the oral epithelium, very painful ulcerations, polypoid and granulomatous changes in the oral mucosa and in the later stages, also occurrence of oral cancer [2, 3]. Due to the extensive accumulation of oral biofilm and the presence of mineralized deposits on the teeth, these patients are also suffering from diseases of hard tooth tissues with frequent complications. Changes in the form of obliteration and calcification can occur in the pulp cavity. In children, where the processes of odontogenesis have not yet been completed, developmental anomalies of hard dental tissue may occur. These anomalies are more pronounced and more frequent in younger children in early stages of odontogenesis. Hypoplastic enamel changes, delayed tooth eruption, endogenous changes in tooth color, as well as changes in the development of the roots of primary and permanent teeth are the most commonly occurring anomalies [4–7].

After transplantation of solid organs and hematopoietic stem cells changes in the oral cavity and other organs occur depending on the transplantation period in which the patient is as well as on the applied immunosuppressive therapy. Due to frequent oral diseases in the peri-transplant period, dentists are an important part of the multidisciplinary team

participating in care of patients in all major transplant centers in the world. Dental treatment is an integral part of the transplantation protocol in these centers, both during the preparation period and after transplantation [1, 8].

The most numerous are patients with transplanted cells, that is, hematopoietic stem cells, followed by patients with kidney and liver transplants, when it comes to solid organ transplantation.

## **TRANSPLANTATION OF SOLID ORGANS**

Numerous chronic kidney diseases represent major health problems all over the world. A progressive decrease in renal function or organ failure is usually a consequence of various chronic diseases that lead to nephron damage and glomerular filtration reduction. The therapy of these conditions implies the application of hemodialysis, peritoneal dialysis, and organ transplantation [9]. Also, chronic liver diseases of different etiologies, permanent damage to the function and numerous consequent complications represent indications for liver transplantation.

### **Oral changes before transplantation of solid organs**

Chronic renal diseases are accompanied by frequent clinical manifestations on other organs and systems, or other chronic diseases, among which poorly controlled diabetes and cardiovascular diseases are the most common. In addition, the adverse effects of numerous drugs and therapies have resulted in a wide spectrum of various oral manifestations in about 90% of patients with renal insufficiency [10]. Chronic liver diseases and permanent damage to the functions of this organ often lead to the occurrence of oral diseases affecting oral mucous membrane and salivary glands, gingiva and periodontal tissues, jaw bone and hard dental tissue [8].

In patients with renal and hepatic insufficiency, extensive plaque cumulation is observed, as well as the presence of mineralized deposits on the teeth, gingival inflammation, spontaneous bleeding or bleeding after gingival probing, prolonged and increased bleeding after some dental procedures, gingival recession and loss of the adherent epithelium, as well

as the presence of periodontal pockets [2, 8, 11]. All this leads to an increased risk of developing caries. Non-cariogenic damage and the loss of hard dental tissues in the form of erosion as a consequence of nausea, esophageal regurgitation and vomiting can be also observed. Caries in the neck of the crown of the tooth appears in patients with xerostomia. It often occurs in patients who are on hemodialysis and can also occur due to unwanted effects of drugs, loss of body fluid, reduced fluid intake or breathing through the mouth. Long-standing xerostomia favors the formation of caries and inflammation of the gingiva, complicates speech, chewing and swallowing of food, as well as the retention of prosthetic works. In these patients, caries complications such as pulp disease with periapical lesions, acute and chronic dentogenic infections, and residual roots of decayed teeth often occur. All these local complications may be the cause of systemic infections [2]. Chronic liver diseases in children who have not completed the process of odontogenesis lead to characteristic greenish endogenous dental staining. Developmental anomalies of the teeth can be diagnosed in the form of a delayed emergence of permanent teeth and hypoplastic structural anomalies of the enamel in children with chronic kidney disease [12, 13].

Patients with renal insufficiency have a characteristic uremic fetor. They complain of metal taste in the mouth and pain caused by the appearance of uremic stomatitis. Uremic stomatitis is manifested in the form of erythematous-membranous changes, ulcerations, hemorrhagic and hyper-parakeratotic changes of the oral mucosa [14, 15]. The changes are prone to secondary fungal, viral and bacterial infections. Fungal infections of the *Candida albicans* genus are often the cause of opportunistic infections and occur in the form of pseudomembranous, erythematous and atrophic lesions at the oral mucosa. More frequent presence of fungal infections has been identified in patients with diabetic nephropathy [2, 4]. Viral infections in patients with renal insufficiency are most commonly caused by Herpes simplex type 1 virus (HSV1). Poor oral hygiene, decreased secretion and change in pH of the saliva, altered oral microflora composition, reactivation of the virus, as well as the disturbed integrity of oral mucous membranes favor the occurrence of oral bacterial, viral and fungal infections, their dissemination and the appearance of systemic infections in patients with renal and liver insufficiency [16]. In addition to the above-described, other mucosal lesions such as leukoplakia and lichenoid changes are also frequent in these patients. Patients undergoing dialysis program are also on anticoagulant therapy, which increases the risk of enhanced bleeding in the oral cavity. Chronic renal diseases are often accompanied by anemia due to the reduction of erythropoietin synthesis, as well as hemostatic disorders

resulting from altered platelet aggregation, which is manifested by spontaneous bleeding or increased and prolonged bleeding after dental interventions, followed by pallor of oral mucosa and the appearance of petechiae and ecchymosis [14].

Metabolic disorders, acidosis, hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism occurring in 92% of hemodialyzed patients lead to the occurrence of renal osteodystrophy. Demineralization, reduction in the number of trabecula and the thickness of the bone cortex are noticed on the jaw bones and temporomandibular joint. On the tooth-supporting apparatus, these disorders lead to the loss of the lamina dura, to the expansion of the periodontal membrane and to the large destruction of parodontium, causing pathological teeth mobility and their loss [6, 13, 17].

### **Oral changes after solid organ transplantation**

The occurrence of oral changes in patients after transplantation of solid organs is mainly caused by the adverse effects of various drugs and the presence of infection in the mouth. Patients with transplanted organs are on long-term immunosuppressive therapy that reduces the risk of organ rejection. Immunosuppressants often exhibit adverse effects such as nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension, and enlargement of the gingiva. Gingival enlargement is at the same time the most frequent change in soft tissue of the oral cavity, which, in addition to the effects of immunosuppressive therapy, is also favored by combination of immunosuppressants and some drugs used for reduction of blood pressure, as well as extensive dental plaque cumulation. Children and adolescents are particularly prone to these gingival changes [18, 19, 20]. The greatest tendency to gingival enlargement is evidenced immediately after transplantation and after three months. Long-term immunosuppressive therapy, most often after two years, caused appearance of granulomatous changes in the oral mucosa and dorsal surface of the tongue, enlargement of the lips, the appearance of angular cheilitis and fissures on the lips, pigmentation on the oral mucosa and erythroplakia. Patients complain of dry mouth, mouth sores, bad odor from mouth, and bleeding gums during tooth washing [21]. An unusual proliferation of lymphocytes in the post-transplant period leads to lymphoproliferative changes in the paranasal cavities, in the oral cavity, on the larynx and salivary glands [22].

Long-term immunosuppressive therapy, poor oral hygiene and untreated oral diseases can be the cause of numerous infections. In patients on immunosuppressive therapy, even microorganisms that form a normal oral flora can be the cause of common infections. Various bacterial and fungal infections caused by *Candida* species are commonly seen in patients following kidney transplantation. Also, a greater presence of Herpes simplex virus type 1, Epstein-Barr virus, and Cytomegalovirus was evidenced in sputum in these patients. In addition to the fact that these microorganisms are causes of numerous oral changes and disruption of the integrity of the oral mucous membranes, there is the possibility of their dissemination, onset of systemic infection and the risk of rejection of the transplanted organ [21, 23, 24, 25].

The tendency to epithelial dysplasia, occurrence of premalignant and malignant lesions in oral mucosa after organ transplantation, was also observed. The predisposing localization of malignant lesions is the skin of the head and neck as well as mouth and lips, with squamous and basocellular carcinomas being the most common. Several factors lead to the emergence of oral cancer, with long-term application of immunosuppressive therapy, inadequate immune response of the organism to the activation of malignant cells, and the presence of papillomas and other oncogenic viruses being most commonly implied [26].

## **TRANSPLANTATION OF HEMATOPOIETIC STEM CELLS**

Transplantation of cells, that is, hematopoietic stem cells, can be allogeneic and autologous. Standard indications for the hematopoietic stem cell transplantation are inborn and acquired diseases of the lymphohematopoietic system and some solid tumors [27, 28].

### **Oral changes before transplantation of hematopoietic stem cell**

In this period, changes in oral tissues arise as part of the adverse effects of very aggressive chemotherapy or combined chemotherapy and radiotherapy, which are applied under various protocols for treatment of the most severe malignancies. The oral cavity is very sensitive to the direct and indirect effects of cytotoxic therapy. Direct stomatotoxicity of cytostatics is a consequence of the non-specific effect of drugs on cells in the process of

division, when in the addition to malignant cells, healthy cells are also involved [29, 30]. The tissues with faster cellular cycle are more extensively affected, including oral tissues with a cellular division cycle of 7 to 14 days. Cytostatic drugs result in reduction of basal layer regeneration of the oral epithelium and occurrence of mucositis most often a week after application of the therapy. Buccal mucosa, lips, soft palate, and the ventral side of the tongue as well as floor of the oral cavity are usually affected [31]. According to the World Health Organization (WHO) criteria for the assessment of toxic effects of cytostatics on oral tissues, mucositis is defined from individual painless ulceration to highly prominent erythema and edema of oral mucosa with multiple, extremely painful ulcerations that require the application of enteral or total parenteral nutrition [27, 32, 33]. Mucositis is more common in young people due to increased mitotic activity of oral epithelial cells in younger age. The intensity of mucositis depends on the type and dose of cytostatics, the length of treatment, the individual sensitivity of the patient, and the condition of the oral cavity before initiation of the therapy [34, 35]. The onset of mucositis is directly related to the degree of neutropenia resulting from the effects of cytostatics on the bone marrow and their indirect stomatotoxic effect. Owing to their myelosuppressive action, cytostatics lead to thrombocytopenia and granulocytopenia. Thrombocytopenia results in onset of petechiae in oral mucosa and frequent bleeding in the oral cavity, and granulocytopenia leads to an increased risk of the occurrence of oral infections [36]. Due to changes in oral mucous membrane and parenchyma of the salivary glands after the application of therapy for hematologic malignancies, as well as stress, in the period prior to the tissue and cell transplantation, reduction in the secretion of stimulated saliva may be observed. Poor oral hygiene and decreased salivary secretion lead to a greater number of diseased teeth and the higher prevalence of periodontal disease [10].

### **Oral changes after hematopoietic stem cell transplantation**

The application of high-dose chemotherapy or a combination of high-dose chemotherapy and radiation of the body in the conditioning regimen prior to hematopoietic stem cell transplantation, as well as bone marrow aplasia within the first 3-4 weeks following transplantation are the causes of early complications in the form of febrile neutropenia and mucositis [28, 37]. Pain and bleeding, xerostomia due to transient dysfunction of the salivary glands, taste disturbance and hypersensitivity of dentin may appear. Saliva becomes viscous, resulting in reduced lubrication of the oral mucosa. The accumulation of dental plaque is



increased, which influences the change in the qualitative and quantitative composition of the oral microflora. Loss of antibodies and other antibacterial proteins, changes in the salivary glycoprotein concentration can compromise the barrier function of oral mucous membranes and increase the risk of developing infections. Poor oral hygiene, untreated caries and caries complications, extensive periodontal disease, and dental infections can be the cause of streptococcal bacteremia in the period immediately following the hematopoietic stem cell transplantation [29, 37, 38].

Allogeneic hematopoietic stem cell transplantation is often accompanied by the onset of Graft-Versus-Host disease. This disease is a multisystemic immune phenomenon that occurs due to the immune response of donor immunocompetent T-lymphocytes and recipient cells, and may have an acute and chronic form. Oral lesions in acute form are most commonly localized in buccal mucosa, mucous membranes of lips, in the tongue, hard and soft palate and mouth floor in the form of painful, erythematous ulcerations and desquamations. These oral changes may be the initial manifestations of the acute form of the graft-versus-host disease [6, 38, 39]. The chronic form of this disease occurs after one hundred days of transplantation of hematopoietic stem cells. It is associated with painful diffuse erythema, lichenoid changes, painful ulcerations, and desquamations of irregular shape, the appearance of papules and mucocele on the oral mucous membrane. Oral mucous atrophy with a feeling of burning and sticking and limited opening of the mouth is also common [40]. Progressive atrophy of the salivary glands leads to xerostomia, dysphagia and dysgeusia, and opportunistic viral, bacterial and fungal infections can also occur. Numerous oral changes can be followed by multiple systemic changes primarily on the skin, eyes, gastrointestinal tract and liver. Oral mucosal lesions were accompanied by erythematous changes in the skin, atrophy of the salivary glands, atrophy of the lacrimal glands, that is, xerostomia while limited mouth opening was accompanied by sclerotic changes on the skin. Chronic graft-versus-host disease is in approximately one half of allogeneic tissue and cell transplantation the leading cause of non-relapse mortality [39, 41].

In addition to numerous systemic diseases, several years after hematopoietic stem cell transplantation a greater distribution of oral diseases is observed: gingival inflammation due to the presence of dental plaque, gingival enlargement in patients on immunosuppressive therapy and as a consequence of vascular and fibrotic gingival changes, increased incidence of caries and significantly higher colonization of *Streptococcus* mutants and *Lactobacilli* in

saliva compared to healthy population. The occurrence of oral squamous carcinoma is also a late complication of hematopoietic stem cell transplantation. The etiology of these malignancies is not fully understood, but it is thought to be found in long-term immunosuppressive therapy, the presence of oral lesions in chronic graft-versus-host disease, and in the presence of oncogenic viruses [26]. In children subjected to high doses of chemotherapy and radiation therapy during treatment of malignant diseases more frequent occurrence of developmental dental anomalies is observed several years after the hematopoietic stem cell transplantation. Structural irregularities in the teeth, mineralization disorders of hard dental tissues, irregularities in the length and shape of the teeth roots, reduced tooth crown size, as well as the lack of a smaller or greater number of teeth may occur [36, 41].

## CONCLUSION

Oral changes are widely distributed both in the period before and after transplantation of solid organs and hematopoietic stem cells, i.e., numerous systemic diseases are accompanied by pronounced oral manifestations. These changes with frequent local symptoms impair the quality of life of patients, aggravate the underlying disease as well as the general condition of patients before transplantation and can significantly disturb the course and outcome of the transplant itself. It is therefore necessary to point out the importance and distribution of oral diseases, as well as the measures that have to be taken to reduce the risk of these diseases. Good cooperation is needed between dentists and doctors of other specialties, and adequate dental treatment should be an integral part of the protocol for the treatment of patients at each stage before and after transplantation. The former contributes to the success of the transplant itself, reduces the negative impact of oral diseases on the course and outcome of the underlying disease and significantly improves the quality of life in the peritransplant period.

## **ACKNOWLEDGMENT**

Olivera Jovičić reported a similar topic (oral presentation, paper not printed) at the Second Congress of Preventive Dentistry, November 2–3, 2018, Sava Center, Belgrade, Serbia.

The oral presentation was titled “Prevention of oral diseases in children with organ transplants.”

**Conflict of interest:** None declared.

Paper accepted

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