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Dental treatment of organ transplant patients

Organ transplant patients are a growing group of medically compromised patients who must receive life-long immunosuppressant treatment. However, the prognosis for these patients is excellent. For example, 5-year survival of liver transplant patients is 85 % and their quality of life corresponds to that of the normal population. From the standpoint of dental health, it is essential to diagnose and properly treat all potential oral and dental infections in order to avoid systemic complications. Dental treatment of organ transplant patients often calls for hospital dentistry, and special treatment units need to be consulted. Maintaining good oral hygiene daily is extremely important for these patients.

This review examines the problems with oral and dental treatment of organ transplant patients, based mainly on our experiences with kidney and liver transplant patients and on the literature. Knowledge of the oral health problems of other organ transplant recipients, such as heart, lung, pancreas and intestinal transplant patients, is very scarce, so they are only mentioned briefly. There are as yet no evidence based guidelines on dental treatment of organ transplant patients. Bone marrow and stem cell transplants are not within the scope of this article. Virus infections and the possible role of oral health in their onset constitute a category of their own. For example, cytomegalovirus infections may be manifested as oral ulcers, whose prognosis is affected by correct diagnosis and treatment (1). The same is true for *Candida* infections; besides normal *Candida albicans*, virulent non-*albicans* strains, such as *Candida glabrata*, occur in organ transplant patients (2).

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Virus and fungal infections of the mouth are not discussed further in this article.

Up-to-date information on organ transplants in the Nordic countries is found on the Scandiatransplant website (www.scandiatransplant.org). In Finland, more than 7,300 organ transplants were performed between 1964 and 2010. Nearly 300 patients receive a new organ each year. Infection prophylaxis and treatment guidelines for organ transplant patients have been compiled in collaboration with physicians specializing in infectious diseases.

Kidney transplantation

Kidney transplantation is the most common organ transplant procedure. By the end of 2010, a total of 5,807 kidney transplants had been performed in Finland. All transplant patients need immunosuppressive rejection-preventive drugs after surgery, usually a combination of a calcineurin inhibitor (cyclosporine/tacrolimus), glucocorticoid and azathioprine/mycophenolate. Kidney transplant patients often need hypertension and dyslipidaemia drugs as well. Immunosuppressive treatment predisposes these patients to infections, and some of the drugs used are nephrotoxic and also cause osteoporosis. Foci of infection must be diagnosed and treated carefully, both prior to organ transplantation and for the rest of the patients' lives.

Headlines

- Evidence based research data on oral manifestations in organ transplant patients are scarce.
- Oral and dental infections may exacerbate the course of disease and complicate the treatment as well as the prognosis for the transplanted organ and the patient.
- In the event of oral problems in organ transplant patients, the oral and maxillofacial outpatient clinics of central hospitals should be consulted.

Table 1. Diseases leading to kidney transplantation and their significance

Disease	Typical symptoms and findings	Significance
Diabetic nephropathy Glomerulonephritis	Microalbuminurea, hypertension. Acute phase: oedema, general symptoms, proteinuria. Chronic phase: renal insufficiency and nephrotic syndrome.	The most common chronic renal disease IgA nephropathy is the most common glomerulonephritis, usually seen in men >30 yrs.
Congenital nephrosis	Manifest in newborns, fatal without kidney transplantation.	Part of the Finnish Disease Heritage (1, 8,000).
Polycystic kidney disease	A hereditary illness, symptoms include haematuria, hypertension.	Prevalence of adult-type disease is 1, 1,500.
Vascular diseases of the kidney	Symptoms are often severe and dependent on the vasculitis causing the kidney disease.	Several rare syndromes.

The most common cause of chronic kidney disease is type 2 diabetes, which leads to nephropathy in 25–45 % of patients. In Finland, each year diabetes leads to uraemia in about 35 patients per million. Other causes of chronic kidney failure in adults include chronic glomerulonephritis, hereditary polycystic kidney disease and renal problems caused by vascular disturbances (table 1). In Finland, each year about 450 patients are diagnosed with severe renal insufficiency requiring dialysis. The causes of uraemia differ among the Nordic countries, depending on the so-called disease heritage in each country. In Finland, uraemia is typically caused by congenital nephrosis, but structural abnormalities of the urinary tract, cystic renal diseases and glomerulonephritis may also lead to uraemia. Advanced kidney disease is treated with dialysis and, ultimately, with a kidney transplant. Infections are the most important complication of dialysis treatment. At the moment there are more than 1,600 patients undergoing dialysis in Finland (Finnish Registry for Kidney Diseases, 2010, www.musili.fi). Nearly 300 of them are in line for a kidney transplant.

Liver transplantation

The first liver transplantation in the Nordic countries was performed in 1982 at the Surgical Hospital in Helsinki. Today, liver transplantation is an established procedure as curative treatment for severe liver disease. The reasons behind this include advanced surgical and anaesthesiological know-how, patient selection and improved immunosuppressive medication. In Finland, the 5-year survival rate for liver transplant patients is 85 %, and their post-operative quality of life is similar to that of the general population (3).

The most common reasons for liver transplants in Finland are primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), acute liver disease and alcoholic cirrhosis (table 2). Liver transplantation is normally performed when the patient's end-stage liver disease becomes life-threatening and no other possibilities for cure exist.

The role of the liver as the body's most important "factory" affects nearly all-vital functions. Liver insufficiency is manifested in a wide variety of symptoms and findings. From the standpoint of dental treatment, the most important of these are coagulation disorders and increased tendency to bleed. This means that patients

with liver insufficiency should be treated in a hospital setting, so that if necessary, clotting factor replacement therapy can be administered.

Sheehy et al. examined 27 children prior to and after liver transplantation and a corresponding number of control patients, finding no differences in dental health between the two groups (4). However, cyclosporine treatment started after transplant surgery caused gingival hyperplasia in 41 % of the transplant children (regardless of whether or not nifedipine was administered simultaneously). Lin and Yang confirmed this finding; however, they pointed out that the plaque index (poor oral hygiene) of children who had received a liver transplant showed a strong correlation with gingival hyperplasia similar to that of serum cyclosporine level (5). Nifedipine has been shown to be strongly associated with development of gingival hyperplasia after liver transplantation (6).

Intensified periodontal treatment aimed at keeping cyclosporine treatment-related gingival hyperplasia under control helped 22 Italian liver transplant patients in a one-year open follow-up study (7). In a set of Spanish data (n=53, follow-up time 3 years 9 months), 22 % of liver transplant recipients developed gingival hyperplasia and nearly 40 % had mucous membrane lesions of the tongue as a result of cyclosporine and tacrolimus treatment (8). According to the most recent research, tacrolimus-induced gingival hyperplasia manifests later than does gingival hyperplasia caused by cyclosporine (9). In adult patients, vitamin D insufficiency after liver transplantation has been shown to be associated with alveolar osteoporosis, which also correlates with patient's age, parathormone level and duration of systemic cortisone treatment (10).

Infections are the most important cause of death among organ transplant patients. In Finland, right from the early days liver transplant patients have undergone short antibiotic and antifungal prophylaxis in connection with surgery; in the 1990s, pre-emptive CMV infection prophylaxis was added to the regimen. Before liver patients are accepted to the transplant list, their mouths and teeth have to be examined and loci of infection treated (11). This practice has been followed in Finland since 1982 because at that time it was revealed that the reason for the severe infection that destroyed a kidney transplant was a *Streptococcus* strain of oral origin (observation made by KH).

The role of odontogenic infections has not, however, been studied in more detail. Complications caused by eradication of dental infections were discussed in a set of material comprising 39 patients prior to liver transplant surgery (12). If patients had alcoholic cirrhosis, complications after dental procedures were seen in as many as 43.8%. Bleeding complications occurred in 15.4% of the patients, regardless of the reason for their liver disease, even though clotting factors had been administered during treatment. In a Finnish set of data in which infections appearing more than one year after transplant surgery were studied in 501 liver transplant patients, cholangitis (20%), pneumonia (19%) and sepsis (14%) were the most common infections; the spectrum of microbes was wide, including one viridans-group *Streptococcus* infection (13). However, commonly accepted clinical guidelines on dental treatment of liver transplant patients are still lacking, despite attempts to draw attention to the issue (14).

Other organ transplantations

Apart from a few isolated reports, there are no references in the literature to oral and dental treatment of organ transplant patients. The following is therefore merely a short presentation of general features based on the Nordic organ transplant registry (www.scandiatransplant.org).

Heart transplantation

Heart transplantation is the last treatment option in severe heart failure. The most common indication for heart transplantation is end-stage dilated or ischaemic cardiomyopathy. Other indications for surgery include syndromes leading to heart failure, cardiac sarcoidosis, aortic valve periprosthetic leakage and massive myocardial infarction during valvular surgery. By the end of 2010, a total of 471 heart transplants had been performed in Finland. The five-year survival rate for heart transplant patients is about 80%, both internationally and in Finland. The annual rate of mortality after that is about 4%.

Lung transplantation

The main indications of lung transplantation include chronic pulmonary fibrosis, alpha 1-antitrypsin deficiency, pulmonary hypertension and chronic obstructive pulmonary disease. By the end of 2010, a total of 138 lung transplants had been performed in Finland. The majority of patients recover from lung transplant surgery, attaining nearly normal pulmonary function and quality of life during the year following surgery. The 5-year survival rate in Finland is about 80%.

Joint heart and lung transplantation

Joint heart and lung transplantations are rare; only 35 have been performed in Finland, *e.g.* on patients whose pulmonary circulation has been irreparably damaged by a congenital heart defect, or in cases where lung disease is associated with a heart condition that cannot be repaired or that will not be reversed by a lung transplant alone. The 5-year survival rate for lung-heart transplants is around 60%.

Pancreas transplantation

More than 30,000 pancreas transplantations have been performed globally. About 800 are performed annually in Europe, nearly 40 in Sweden and Norway combined. In Finland, pancreas transplantations started in 2010. Pancreas transplantation is often combined with kidney transplantation. About 80% of pancreas transplants function after 5 years; the corresponding figure for kidney transplants can be over 90%. Pancreas transplantation is the only way of ensuring long-term normoglycaemia and with the possibility of preventing vascular complications in patients with diabetes.

Points to be observed in dental treatment

Table 3 shows a number of points that should be considered in dental treatment of organ transplant patients. Oral and maxillofacial departments should be consulted on oral health problems of organ transplant patients. The most difficult cases should be referred to these clinics for treatment. Organ transplant patients are susceptible to infections, and common symptoms of infection are masked by medication that prevents rejection, which is why odontogenic

Table 2. The most common diseases leading to liver transplantation in Finland

Disease	Symptoms and findings	Significance
Primary biliary cirrhosis	Symptoms unspecific at first; itching, fatigue; jaundice, hepatomegalia, elevated alkaline phosphatase and bilirubin levels.	10–50: 100,000, most commonly in women
Primary sclerosing cholangitis	Cholangitis gamma glutamyl transferase and alkaline phosphatase levels at first elevated. Most patients have inflammatory bowel disease;	Significantly elevated risk of cholangiocarcinoma.
Alcoholic cirrhosis	Symptoms at first unspecific; fatigue, nausea, jaundice, severe bleeding.	Most common indication for liver transplant in the US and Europe.
Acute fulminant liver failure in 1–12 weeks in a previously healthy person	Fatigue, confusion, rapid deterioration of liver synthesis (thrombin time, prealbumin), liver coma, cessation of kidney function Aetiology unknown in 50%.	Requires immediate treatment in intensive care unit. About 10 cases leading to liver transplantation each year.

Table 3. Things to be considered in dental treatment of organ transplant patients.

General

- As infections may exacerbate the underlying disease and/or complicate treatment, all foci of infection in the mouth and teeth must be diagnosed and treated in time. X-ray of the jaws is necessary to diagnose hidden infections
- Patients may suffer from dry mouth and burning mouth syndrome, and their risk of dental and oral mucosal diseases may increase
- Maintenance of good daily oral hygiene (electric toothbrush) is of utmost importance in prevention of infections of dental and oral origin

Organ transplant patients

- Potential organ transplant recipients should undergo careful oral and dental examination before they are put on an organ transplant list
- Any odontogenic infection foci must be treated before transplantation
- The risk of bleeding in liver insufficiency patients must be taken into account when procedures are performed
- Immunosuppressive medication given after transplantation may also mask infection symptoms in the mouth
- Antibiotic prophylaxis is needed with dental procedures that cause bleeding. Postoperative antibiotic treatment for a few days is often needed as well
- Corticosteroids diminish the patient's own corticosteroid production, which must be kept in mind in connection with more extensive surgical procedures. Demanding procedures should be concentrated in oral and maxillofacial outpatient clinics
- Medication used to prevent rejection (cyclosporine, tacrolimus) cause gingival hyperplasia in many patients (especially children); the worse the patient's oral hygiene, the more complicated the hyperplasia. Gingival hyperplasia is also promoted by simultaneous calcium-channel blocker use (particularly nifedipine). The foundation of prevention and treatment of gingival hyperplasia is maintenance of good oral hygiene by the patient and regular periodontal treatment
- It is often necessary to consult the oral and maxillofacial outpatient clinics

infections should be diagnosed and treated carefully even prior to putting patients on organ waiting lists. Smoking increases oral and dental diseases in organ transplant patients (11). Patients should be guided to manage their daily oral hygiene as well as possible. However, teeth should not be brushed so vigorously that this causes gingival bleeding, which releases large amounts of oral bacteria into the bloodstream where they can cause infection (15).

A large number of symptoms and findings associated with failure of vital organs, such as anaemia and increased tendency toward bleeding, must be taken into account when invasive procedures are performed. In practice, eradication of dental infection means extraction of teeth that cause problems with root canal treatment, periodontal teeth and unerupted teeth that have penetrated the mandibular cortex. Teeth with cavities are filled, infection in dental periodontal tissue is treated, and patients are instructed about home care that prevents oral and dental illness and motivates them to maintain good oral hygiene, if this has not been done previously. Only necessary dental treatment is given during the first 6 months following organ transplantation. These patients should be referred for treatment at oral and maxillofacial clinics in hospitals.

Medications and dosages used should be adjusted according to the patient's underlying disease and immunosuppressive treatment. Dental treatment often involves prescribing antimicrobials as well as analgesics and NSAIDs; their suitability for individual patients must be checked carefully. There are no obstacles to the use of local anaesthetics.

There is conflicting information in the literature concerning the necessity of antibiotic prophylaxis in dental treatment of organ transplant patients. The use of prophylaxis is dependent on the treating unit, country and selection of patients. Dental procedures undoubtedly give rise to bacteraemia, but this is in any case caused by normal daily activities, such as tooth brushing. However, anti-

biotic prophylaxis is recommended in connection with procedures that cause copious bleeding which are likely to cause bacteraemia. According to the American Heart Association, the general guideline for antibiotic prophylaxis is 2g amoxicillin one hour prior to the procedure. For patients who are allergic to penicillin, clindamycin 600 mg one hour before the procedure is recommended.

Gingival hyperplasia, caused by medication intended to prevent rejection, in particular, cyclosporine, which is seen in 25% – 81% of organ transplant patients, was discussed above (16). The extent and severity of gingival hyperplasia correlates significantly with the plasma concentration of the drug in question. The risk of gingival hyperplasia is increased by nifedipine, which is used to treat hypertension (17). Good oral hygiene and regular periodontal treatment are the foundation for prevention and treatment of gingival hyperplasia (5). Macrolide antibiotics may be of benefit in connection with clinical treatment procedures (18).

In conclusion

Evidence-based research data on oral manifestations in organ transplant patients are scarce. Most of what is known is based on experience from a small number of patients and on case reports. However, the most important thing to bear in mind with organ transplant patients is that oral and dental infections may exacerbate the course of disease and complicate the treatment as well as the prognosis for the transplanted organ and the patient. Even hidden foci of infection in the teeth and jaws should be carefully diagnosed and treated before patients are put on an organ transplant list. Panoramic tomography of the jaws is necessary. The patient's underlying disease and its treatment may cause oral symptoms and complicate treatment of the mouth and teeth. Gingival hyperplasia caused by medication intended to prevent rejection often requires surgical treatment. In the event of oral problems in organ trans-

plant patients, the oral and maxillofacial outpatient clinics of central hospitals should be consulted, and the most difficult cases should be referred for treatment.

Literature

1. Olczak-Kowalczyk D, Pawłowska J, Cukrowska B, Kluge P, Witkowska-Vogt E, Dzierzanowska-Fangrat K, Wrzeńska D, Smirska E, Grenda R. Local presence of cytomegalovirus and *Candida* species vs oral lesions in liver and kidney transplant recipients. *Ann Transplant.* 2008; 13: 28–33.
2. Dongari-Bagtzoglou A, Dwivedi P, Ioannidou E, Shaqman M, Hull D, Bureson J. Oral *Candida* infection and colonization in solid organ transplant recipients. *Oral Microbiol Immunol.* 2009; 24: 249–54.
3. Åberg F, Rissanen AM, Sintonen H, Roine RP, Höckerstedt K, Isoniemi H. Health-related quality of life and employment status of liver transplant patients. *Liver Transpl.* 2009; 15: 64–72.
4. Sheehy EC, Roberts GJ, Beighton D, O'Brien G. Oral health in children undergoing liver transplantation. *Int J Paediatr Dent.* 2000; 10: 109–19.
5. Lin YT, Yang FT. Gingival enlargement in children administered cyclosporine after liver transplantation. *J Periodontol.* 2010; 81: 1250–5.
6. Hosey MT, Gordon G, Kelly DA, Shaw L. Oral findings in children with liver transplants. *Int J Paediatr Dent.* 1995; 5: 29–34.
7. Aimetti M, Romano F, Priotto P, Debernardi C. Non-surgical periodontal therapy of cyclosporin A gingival overgrowth in organ transplant patients. Clinical results at 12 months. *Minerva Stomatol.* 2005; 54: 311–9.
8. Díaz-Ortiz ML, Micó-Llorens JM, Gargallo-Albiol J, Baliellas-Comellas C, Berini-Aytés L, Gay-Escoda C. Dental health in liver transplant patients. *Med Oral Patol Oral Cir Bucal.* 2005; 10: 66–76.
9. Paix O CG, Sekiguchi RT, Saraiva L, Pannuti CU, Silva HL, Medina-Pestana JO, Romito GA. Gingival overgrowth among patients medicated with cyclosporin a and tacrolimus undergoing renal transplantation: a prospective study. *J Periodontol.* 2011; 82: 251–8.
10. Oettinger-Barak O, Segal E, Machtei EE, Barak S, Baruch Y, Ish-Shalom S. Alveolar bone loss in liver transplantation patients: relationship with prolonged steroid treatment and parathyroid hormone levels. *J Clin Periodontol.* 2007; 34: 1039–45.
11. Guggenheimer J, Eghtesad B, Close JM, Shay C, Fung JJ. Dental Health Status of Liver Transplant Candidates. *Liver Transpl.* 2007; 13: 280–86.
12. Niederhagen B, Wolff M, Appel T, von Lindern JJ, Bergé S. Location and sanitation of dental foci in liver transplantation. *Transpl Int.* 2003; 16: 173–8.
13. Åberg F, Mäkisalo H, Höckerstedt K, Isoniemi H. Infectious complications more than 1 year after liver transplantation: A 3-decade nationwide experience. *Am J Transplant.* 2011; 11: 287–95.
14. Firriolo FJ. Dental management of patients with end-stage liver disease. *Dent Clin North Am.* 2006; 50: 563–90.
15. Lucas VS, Gafan G, Dewhurst S, Roberts GJ. Prevalence, intensity and nature of bacteraemia after toothbrushing. *J Dent Res.* 2008; 36: 481–7.
16. Seymour RA, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. *J Clin Periodontol.* 2000; 27: 217–23.
17. O'Valle F, Mesa F, Aneiros J, Gomez-Morales M, Lucena MA, Ramirez C, et al. Gingival overgrowth induced by nifedipine and cyclosporin A. Clinical and morphometric study with image analysis. *J Clin Periodontol.* 1995; 22: 591–7.
18. Condé SA, Aarestrup FM, Viera BJ, Bastos MG. Roxithromycin reduces cyclosporine-induced gingival hyperplasia in renal transplant patients. *Transplant Proc.* 2008; 40: 1435–8.

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