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ORAL HEALTH IN LIVER TRANSPLANT RECIPIENTS

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ACADEMIC DISSERTATION

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To all the liver transplant patients

Contents

ABSTRACT

Liver transplantation (LT) is the treatment of choice for patients with severe liver disease. Quality of life of patients after LT may be comparable to that of the general population, but permanent immunosuppression poses a high risk for infections. Highly prevalent dental diseases not promptly treated may compromise LT outcome. All possible infectious foci, including dental infections, should thus be treated prior to LT. This thesis aimed to investigate how liver diseases and long-term immunosuppression after LT affect oral health and whether dental infections are associated with liver disease progression or with LT outcome.

The study design was retrospective, cross-sectional, and observational. The study comprised 263 adult recipients of a LT between 2000 and 2006 at the Helsinki University Central Hospital, Finland. Of these patients, 212 (81%) had chronic liver disease, and all underwent dental examinations and treatment prior to LT. The study investigated the effect of differing liver disease etiology and severity on oral health status; the effect of dental infections on the progression of liver cirrhosis was further studied in a subgroup of 116 cirrhotic patients awaiting LT.

Of the study patients, 51 (19%) had acute or subacute liver failure; these were further stratified by whether or not they received pretransplant dental treatment. Post-transplant systemic infectious complications were evaluated from the Finnish Liver Transplant Registry.

After a minimum 2-year follow-up (median follow-up 6 years, range 2-11), all 84 eligible LT recipients were recruited for a new oral health examination according to a fixed protocol. A structured questionnaire was used to assess dry-mouth-related symptoms, with oral *Candida* cultivated, and salivary flow rates measured. The results were compared with those of 252 matched controls from a national health survey. Subjects were grouped according to liver disease etiology and type of immunosuppression.

Dental health status of LT candidates varied depending on the etiology and severity of their liver disease. Alcohol cirrhosis patients (n=37) had significantly more tooth extractions before LT than did primary sclerosing cholangitis patients (n=54) (6 vs. 3, $P<0.005$). Poor liver function, as observed in higher Model for End-Stage Liver Disease (MELD) scores,

associated with fewer teeth (21 vs. 25, 95%CI: -6.7-(-)1.4, P<0.005) and more tooth extractions (5 vs. 2, 95%CI: 1.6-4.2, P<0.001). Tooth extractions were often associated with severe complications such as bleeding. Several dental infections in cirrhotic patients associated with worsening of the liver disease as seen in the shorter time between diagnosis and LT operation. Post-transplant infection risk, especially sepsis, was higher in those acute liver disease patients who received no dental treatment before LT due to their more urgent need for LT compared with that of patients who had received dental treatment (OR=8.54, 95%CI: 1.82–40.1, P<0.05). This risk was independent of age, gender, etiology of acute liver failure, waiting-list time, MELD score, or level of immunosuppression.

Compared with controls, chronic LT recipients had significantly more caries (1.2 vs. 0.5, P<0.005) and a higher prevalence of dysphagia (23% vs. 12%, P<0.05). They also had lower unstimulated salivary flow rates than did the acute LT recipients (0.3 ml/min vs. 0.6 ml/min, P<0.05). Oral mucosal lesions were significantly more frequent in LT recipients than in controls (43% vs. 15%, P<0.001). Drug-induced gingival overgrowth was the most common type of oral lesion, and its prevalence was significantly higher in chronic LT recipients than in their controls (16% vs. 1%, P<0.001). Simultaneous use of cyclosporine-A and calcium-channel blockers increased the overgrowth prevalence even further compared with the tacrolimus group (47% vs. 8%, P<0.05). Precancerous oral mucosal lesions occurred twice as often in chronic LT recipients as in controls (13% vs. 6%, Ns). Oral *Candida* count was positive in more than half the LT patients; use of steroids raised its prevalence to 70%.

The need for dental treatment hence was high before the LT operation with differences in oral health between groups differing in liver disease etiology and severity. Among cirrhotic patients, several dental infections were reflected in the liver disease progression. Those patients who lacked dental treatment before LT showed an 8-fold risk for systemic infections after transplantation. Compared to controls, immunosuppressive and other xerogenic medications predisposed especially the chronic LT recipients to more dry-mouth-related symptoms and caries, and led to a higher risk for oral mucosal lesions, of which some were precancerous. Thus, both pre- and post-transplant dental treatments are highly important for these patients.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to by their Roman numerals I-V in the text.

I Helenius-Hietala J, Meurman JH, Höckerstedt K, Lindqvist C, Isoniemi H. Effect of the aetiology and severity of liver disease on oral health and dental treatment prior to transplantation. Transpl Int 2012;25:158-165.

II Åberg F, Helenius-Hietala J, Meurman JH, Isoniemi H. Association between dental infections and the clinical course of chronic liver disease. Hepatol Res 2013 April 5. doi: 10.1111/hepr.12126.

III Helenius-Hietala J, Åberg F, Meurman JH, Isoniemi H. Increased infection risk postliver transplant without pretransplant dental treatment. Oral Dis 2013;19:271-278.

IV Helenius-Hietala J, Ruokonen H, Grönroos L, Rissanen H, Suominen L, Isoniemi H, Meurman JH. Self-reported oral symptoms and signs in liver transplant recipients and control population. Liver Transpl 2013;19:155-163.

V Helenius-Hietala J, Ruokonen H, Grönroos L, H. Rissanen, Suominen L, Vehkalahti M, Isoniemi H, Meurman JH. Oral mucosal health in liver transplant recipients and controls (submitted).

ABBREVIATIONS

ALF, acute liver failure
BMS, burning mouth syndrome
CD, Crohn’s disease
CI, confidence interval
CLD, chronic liver disease
CMV, cytomegalovirus
CNI, calcineurin inhibitor
CsA, cyclosporine-A
DIGO, drug-induced gingival overgrowth
EBV, Ebstein Barr virus
HBV, hepatitis B virus
HCC, hepatocellular carcinoma
HCV, hepatitis C virus
HPV, human papillomavirus
HSV, herpes simplex virus
HUCH, Helsinki University Central Hospital
IBD, inflammatory bowel disease
IL, interleukin
INR, international normalized ratio
LT, liver transplant(ation)
MARS, Molecular Absorbent Recirculating System
MELD, Model for End-Stage Liver Disease
MMP, matrix metalloprotease
mTOR, mammalian target of rapamycin
Ns, not significant
OLP, oral lichen planus
OML, oral mucosal lesion
PBC, primary biliary cirrhosis
PSC, primary sclerosing cholangitis
PTG, panoramic tomography
SCC, stratified squamous cell carcinoma
SBP, spontaneous bacterial peritonitis
TAC, tacrolimus
UC, ulcerative colitis

INTRODUCTION

Chronic liver disease (CLD) is a growing problem worldwide due to an increased incidence of diabetes, obesity, and lifestyle habits but also for autoimmune causes. Liver transplantation (LT) is a life-saving treatment for patients suffering from end-stage CLD that no longer is curable by conservative treatment. Patients with acute liver failure (ALF) or liver tumor may also be the recipients of a LT.

The first human LT in the world was performed by Thomas Starzle in 1963 in Denver, Colorado; he performed the first successful human LT later, in 1967. The first European LT followed a year later by Sir Roy Calne in Cambridge, UK. The first Scandinavian LT was at the Helsinki University Central Hospital (HUCH) in 1982. Since then, the prognosis has steadily improved with current 5-year survival rates reaching close to 90%, and transplant recipients' quality of life resembles that of the normal population (1). Advances in successful outcomes are mainly due to modern immunosuppressive medication which these patients receive to prevent rejection of the transplanted graft. Today, patient survival is so good, that the main focus in development of more potential immunosuppression has shifted towards reducing complications after LT.

Permanent immunosuppression predisposes to infections which are the leading cause for mortality after LT (2,3). The first post-transplant year is critical; more than half the LT recipients experience infectious complications early on, but the risk for infections remains throughout their lives. To prevent post-transplant systemic infections, it is crucial that before the patient is placed on a waiting list for LT, all potential infection foci are treated (4,5). Among infections, sepsis is one of the most common. An oral pathogen, *Streptococcus viridans,* has been identified as source of septic complication following LT (6), meaning that before LT, elimination of oral infectious foci is essential.

Oral examination for any suspicious oral or dental infection foci has been routine since the start of the LT program in Finland. Most worldwide transplant centers also recommend pre-transplant dental evaluation to prevent bacteremia and sepsis and eventually to improve LT recipients' outcome (7-11). Dental treatment of these immunocompromised patients is carried out in a hospital setting under antibiotic prophylaxis to prevent infection spread; blood transfusions are also available, if necessary, for bleeding (12).

Regular oral examinations are needed also after LT, since organ-transplant recipients are at risk for various orofacial diseases (13). Risk for premalignant oral mucosal lesions is elevated, and therefore the lips and oral mucosal tissues need careful examination for possible neoplasias (14). After LT, osteoporosis and osteopenia are quite common, and alveolar bone loss of the jaws can also occur (15,16).

Studies in this field have not taken place before in Finland, and very few data exist regarding dental treatment of LT recipients. Although empirical knowledge demands pre-transplant dental treatment, clinical recommendations vary greatly, for instance the extent of eradication of oral and dental infectious foci before organ transplantation, or the need for antibiotic prophylaxis in dental procedures afterwards (17,18). Benefits from treatment of infected teeth in reducing septic infections in LT recipients, have been poorly studied.

This thesis focused on the issue of oral infections before and after LT and the systemic infections that oral infections may trigger, while in other fields of medicine the effect of oral infections has been well established in this regard (19,20). Since LT may be done for various reasons, differences in oral health may exist between different etiology- or immunosuppressant groups and may also depend upon the severity of the liver disease. Although liver cirrhosis as such has been well studied, the effect of dental infections on the progression of CLD deserved study in more detail. The main emphasis in this series of studies was to investigate the possible benefits of dental treatment on the outcome of LT and the importance of pre- and post-transplant dental care for the well-being of these patients.

LITERATURE REVIEW

Liver

Anatomy and function of the normal liver

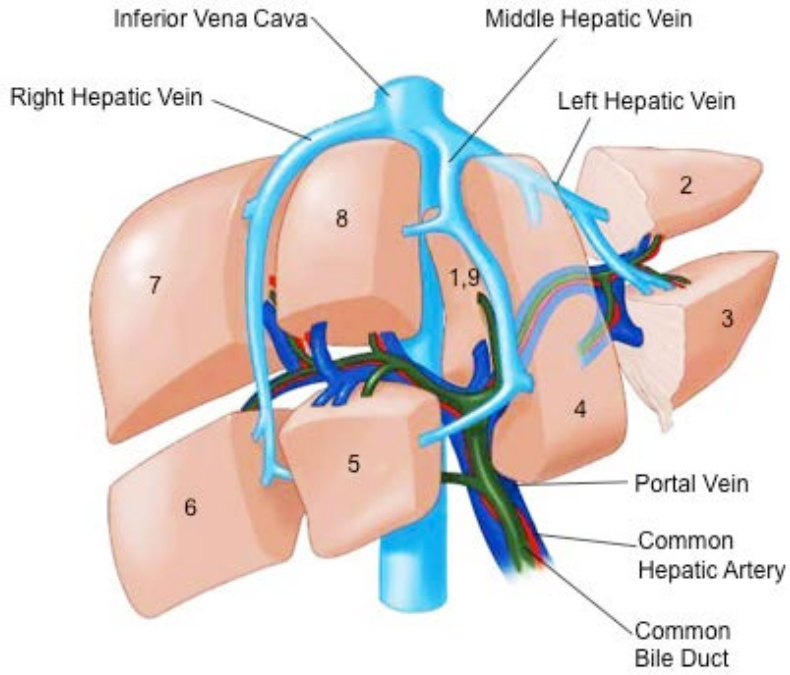
The liver is the largest internal organ and also the largest gland in the human body, weighing about 1.5 kg. No human being can survive without a liver, which can be seen as a large filter or the biochemical factory of the body. It is situated in the right upper abdominal cavity, protected by the rib cage, divided into segments (Fig. 1). It has a dual blood supply; the hepatic artery brings fresh, oxygenated blood from the heart, while the portal vein supplies blood from the intestines and spleen. The liver receives 75% of its blood from the portal vein and the rest from the hepatic artery. Both hepatic artery and portal vein enter the liver at the hilus, along with afferent nerve fibers.

The main cell types are the hepatocytes which are responsible for most functions of this vital organ (21). The functional unit of the liver is the acinus, which is microscopic in size and has a berry-like structure (Fig. 2). Oxygen tension and nutrient level decrease from zone 1 towards zones 2 and 3. Zone 1 hepatic cells are the first to receive oxygenated blood and the last to go into necrosis, in comparison to zone 3, where perfusion is lowest, making this area therefore the most severely affected. The lobule is the histologic unit of the liver with a hexagonal structure. This vascular structure includes a network of sinusoids with a central area that contains the hepatic vein. The outer corners contain the portal triads: hepatic artery, portal vein and the bile duct.

Being part of the gastrointestinal system, the main task of the liver is to help in digestion. The portal vein brings digested food particles to the liver, which then processes and delivers to the inferior vena cava, via the hepatic vein, all the nutrients that the body needs for energy. The liver produces bile that is transported via bile ducts for storage in the nearby gallbladder. To aid in lipid metabolism, this yellow-greenish substance is then secreted to the small intestine. The liver synthesizes proteins (e.g. albumin), several hormones, and coagulation factors and is responsible for the metabolism of glucose and storage of several fat-soluble vitamins. The liver detoxifies harmful substances such as alcohol, drugs, and bacterial toxins from the blood. Other life-supporting functions include the liver's ability to fight against infections by use of its macrophage Kuppfer cells.

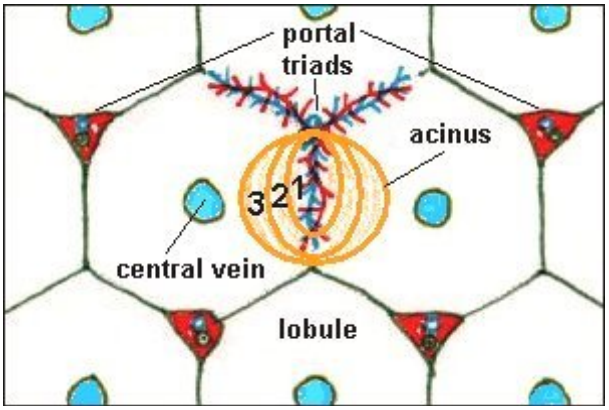
The liver supports almost all organs. Maintaining blood pressure via the renin-angiotensin mechanism is an example of interplay between the liver and the kidneys. Severe liver failure may lead to multiorgan failure with often fatal consequences.

Figure 1. Liver sections and vascular anatomy.



Source: internet, open source (modified).

Figure 2. Acinus and lobule.



Source: with permission from the author (22).

Liver diseases

Liver diseases can be classified by their etiology. This classification includes chronic liver diseases (CLD), acute liver failure (ALF), and liver tumors.

Table 1. Liver diseases.

Chronic liver diseases	Cholestatic liver diseases	Primary biliary cirrhosis (PBC)
		Primary sclerosing cholangitis (PSC)
	Cirrhotic liver diseases	Alcohol cirrhosis
		Autoimmune cirrhosis
		Non-alcohol steatohepatitis (NASH)
		Cryptogenic cirrhosis
		Other cirrhosis
	Metabolic	Wilson's disease
		α1-antitrypsine deficiency
		Hemochromatosis
		Other
	Viral hepatitis	Hepatitis B (HBV)
		Hepatitis C (HCV)
	Other chronic liver diseases	Vascular liver diseases (e.g. Budd-Chiari)
		Polycystic liver disease
Acute or subacute liver disease	Viral hepatitis	HBV
		HCV
	Drugs	Toxic mechanism or idiocynkrasia
	Other toxic substance	e.g. amanita mushroom
	Ischemia	Ischemia
	Other	Pregnancy, trauma etc
	Unknown etiology	
Liver tumors	Primary	Hepatocellular carcinoma (HCC) with cirrhosis
		HCC without cirrhosis
		Hepatoblastoma
		Epitheloid hemangioendothelioma
	Secondary	Neuroendocrine tumor

Chronic liver diseases (CLD)

The most common etiology behind CLD includes viral hepatitis, alcohol liver disease, cholestatic liver disease, autoimmune hepatitis, or metabolic liver disease. All these CLDs usually progress over a long period of time towards cirrhosis of the liver. In Finland, the most common type of CLD are cholestatic liver diseases, primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), whereas viral hepatitis is not as common. Small inner bile ducts get obliterated in PBC, which progresses to fibrosis and finally to biliary cirrhosis. The outer bile ducts may also have strictures in PSC. Bilirubin and bile acids are left circulating in blood due to impaired bile flow. PBC occurs usually in middle-aged women, whereas PSC affects mostly men that are younger. About 80% of PSC patients have inflammatory bowel disease (IBD); either ulcerative colitis (UC) or Crohn's disease (CD) and these intestinal diseases might occur years before the liver disease is diagnosed. Still only about 3 to 8% of colitis patients may have PSC. UC is far more common; 90% of PSC patients with IBD have UC and 10% have CD (23). PSC is also associated with high risk for cholangiocarcinoma. The most common indication for LT in children is biliary atresia.

Acute or subacute liver disease

Acute/subacute liver disease is a rare but very serious condition which can lead to ALF within 8 weeks or sometimes even within just a few hours, or subacute liver failure within 6 months after the first symptoms. These patients are usually generally healthy before sudden liver insufficiency caused by various etiological factors. These factors in ALF include viruses or several toxic substances such as alcohol, drugs such as paracetamol, or other toxins such as from the amanita mushroom, but often the etiology remains unknown. Necrosis of hepatocytes leads to multiorgan failure, and if the own liver does not regenerate, the patient, without LT, dies.

Liver tumors

Tumors of the liver can be benign or malignant. The most common type of malignant liver tumor is the liver metastasis; however, metastatic liver disease is a contraindication for LT except in neuroendocrine tumors in very selected cases. Hepatocellular carcinoma (HCC) is the most common primary liver tumor, in 70 to 80% of HCC cases occuring in a cirrhotic liver. Only in very selected cases is LT possible for HCC with reasonable results.

Clinical evaluation of the patient with liver disease

Clinical symptoms and signs

Early-onset liver diseases may show only a few symptoms, or the symptoms can be aspecific, such as with fatigue, loss of appetite, malaise or mild fever. Patients with a progressive liver disease may experience malnutrition and muscular atrophy resulting from the livers' inability to synthesize albumin and other important nutrients. Patients with a dysfunctional liver disease may suffer from anemia, leukopenia, and thrombocytopenia or decreased synthesis of coagulation factors. Other symptoms are spiders, dilated small capillaries detectable on the skin of the arms, chest or neck. Icterus may occur, a severe itching of the skin caused by increased levels of bile acids. Changed patterns in sleep, cognitive difficulties, and disorientation may be early signs of encephalopathy. Determining whether the symptoms relate to acute or chronic liver disease can be difficult, and symptoms may vary depending on the type of damage to the liver. To find the correct etiology for liver disease, a thorough anamnesis includes family medical history, medications, use of herbal supplements, vitamins, IV drugs, and also information on possible intoxication, blood transfusions, travel to endemic countries, risky sexual behavior, and alcohol use (duration, amounts).

Table 2. Common symptoms and signs in chronic liver diseases.

Severe fatigue
Weight loss/muscle atrophy
Loss of appetite
Abdominal pain/nausea
Pruritus (severe itching)
Fever
Icterus
Hepatomegaly
Splenomegaly
Dark urine, pale stool
Xanthomas (cholesterol)
Ascites, varices (portal hypertension)
Hemorrhage, bruising
Encephalopathy
Recurring infections

Laboratory tests

When doubt exists regarding liver injury with damage to the hepatocytes or the biliary tree, several laboratory tests are necessary (Table 3). The aminotransferases, ALT and AST, are liver enzymes both of which are reliable and sensitive as markers of liver injury representing hepatocellular necrosis. Cholestatic disorders and the presence of biliary obstruction elevate serum bilirubin (Bil), γ-Glutamyltransferase (GT) and alkaline phosphatase (ALP). Bilirubin binds with albumin, and this unconjugated bilirubin is then synthesized into conjugated bilirubin that is secreted into bile. GT has served widely as an index of liver dysfunction and marker of high alcohol intake. Prolonged PT and high INR values are common markers in liver diseases and are warning signs for coagulation problems. Low serum albumin or prealbumin reflects impairment in protein synthesis and may indicate CLD.

Immunological tests may lead to correct diagnosis of the liver disease. Biopsy of the liver is often needed and is the only reliable method in determining the level of liver fibrosis or cirrhosis. The biopsy is done under local anesthesia in conjunction with ultrasound guidance. Radiological tests such as ultrasound (Doppler), CT or MRI are also useful in the diagnosis. Essential for PSC diagnosis is also endoscopic retrograde cholangiography (ERC).

Table 3. Common laboratory tests in liver diseases.

Liver chemistry test	**Clinical implication**
Alanine aminotransferase (S-ALT)	Hepatocellular damage
Aspartate aminotransferase (S-AST)	Hepatocellular damage
Galactose elimination capacity (Gal t½)	Hepatocellular damage
Bilirubin (S-Bil, un/conjugated)	Cholestasis, biliary obstruction
γ-Glutamyltransferase (S-GT)	Cholestasis, biliary obstruction
Alkaline phosphatase (S-ALP)	Cholestasis, biliary obstruction
Prothrombin time (PT)	Synthetic function
International normalized ratio (INR)	Synthetic function
Prealbumin (S-Prealb)	Synthetic function
Albumin (S-Alb)	Synthetic function

Cirrhosis of the liver

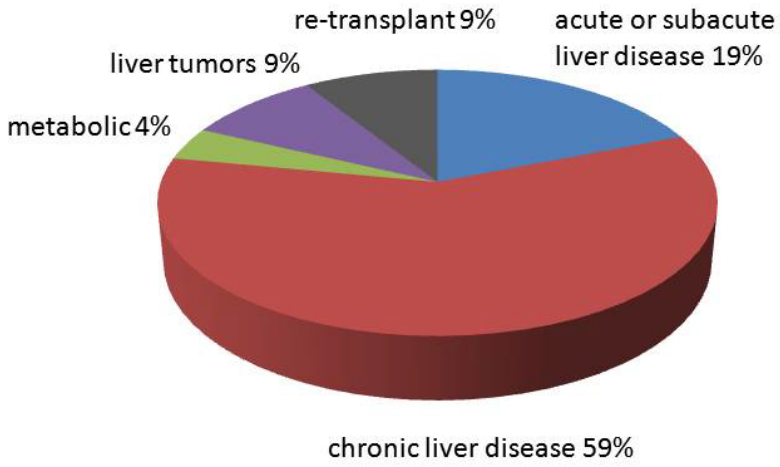
Various pathological conditions of the liver may cause inflammation which results in necrosis of the hepatocytes and finally, over time, leads to fibrosis. Normal liver tissue becomes replaced by scar tissue, and blood flow through the liver is obstructed. This eventually results in cirrhosis, the end-stage of a liver disease. The cirrhotic liver is smaller, darker, and contains fibrotic lumps.

The incidence of cirrhosis continues to rise in Western societies (24). Major etiological factors behind this are obesity, increased alcohol consumption, and an increased incidence of viral hepatitis (especially hepatitis C). Almost all patients with cirrhosis show insulin resistance, and about one-third have diabetes. Increased portal hypertension and decreased synthesis lead to life-threatening complications in cirrhosis which at the decompensated stage include severe ascites, variceal bleeding, hepatorenal and hepatopulmonar syndrome, and hepatic encephalopathy which then may result in coma. Increased suspectibility to infections is a major concern, with spontaneous bacterial peritonitis (SBP) being the most common and life-threatening infection in cirrhosis (25,27). Another severe complication of cirrhosis is risk for HCC (26).

Liver transplantation

LT has established itself as the only curable treatment for end-stage liver disease; it aims to increase life expectancy as well as the quality of life. All transplantations in Finland are centralized to HUCH. Up to the end of 2012, 958 LTs had been done at an annual rate of about 50 to 55 LTs most recently (Figure 3). Most LTs are done for adults, and the gender distribution is almost equal. A potential candidate for LT may be any individual whose liver disease is either life-threatening or no longer is treatable by conservative methods. LT may be considered for a patient with CLD if life expectancy is estimated to be less than a year. The complications and symptoms of endstage CLD, such as ascites, variceal bleeding, hepatorenal syndrome, recurrent infections, or encephalopathy, become more difficult to treat. Severe itching or unbearable fatigue may be devastating to the patient and therefore determine the right time for LT.

Figure 3. Indications for LT in Finland during 1982-2012; total 958 transplantations.



Source: Finnish Liver Transplant Registry.

Since PSC is associated with a high risk for cholangiocarcinoma, the correct timing for transplantation is crucial. PSC and PBC are the most common indications for LT in Finland, whereas, compared to many other countries, viral hepatitis is an infrequent indication. The third most common indication in Finland nowadays is alcohol cirrhosis, although still only about 1% of such alcohol cirrhotic patients may receive LT. Patients with alcohol cirrhosis

must have no other serious organ failures and must observe strict abstinence from alcohol. In the case of ALF, it may be difficult to determine whether the liver will recover without transplantation. Molecular Absorbent Recirculating System (MARS) treatment reduces bilirubin and serum creatinine levels. MARS has been successfully used in Finland and allows a longer waiting time for LT (28). In the case of liver tumors, a contraindication for LT is tumor spread outside the liver. Criteria for LT for tumors follow the Milan criteria: in the liver, one HCC under 5 cm in diameter is accepted, or at maximum 3 HCC nodules if each is under 3 cm.

Pretransplant evaluation

Several medical and social evaluations allow determination as to whether the candidate is suitable for LT and whether timing for LT is appropriate. A wide range of laboratory tests assess liver function and ensure an exact diagnosis of the liver disease. Dental evaluation and eradication of all potential infectious foci has been routine since the early 1980s when the LT program started in Finland. At a multidisciplinary meeting after all the evaluations, a candidate for LT may be placed on a waiting list for a transplant.

The waiting time for LT is among the shortest in Finland but differs between chronic and acute LT candidates. The average wait for CLD is less than 2 months, but for ALF the wait is a mean 4 days with a median of 2 days. Allografts for LT come from cadaveric, brain-dead donors.

MELD score

Several classifications are used to assess the severity of liver disease. The Model for End-Stage Liver Disease (MELD) score predicts the risk of dying without LT (29) and is used for allocation in the USA and in some European countries but not in Finland. It was originally derived in a series of patients undergoing elective transjugular intrahepatic portosystemic shunt **(**TIPS**)** procedures. MELD score is assessed by the values of bilirubin, INR, and creatinine by an equation calculated as

$$9.57 \times \text{Log creatinine (mg/dl)} + 3.78 \times \text{Log bilirubin (mg/dl)} + 11.20 \times \text{Log INR} + 6.43$$

The conversion factor to calculate μmol/l for creatinine is 88.4 and for bilirubin 17.1. The value for MELD score ranges from 6 to 40. For candidates on dialysis, defined as having two

or more dialysis treatments within the preceding week; the MELD score calculator will have their serum creatinine level automatically set to 4.0 mg/dl.

The operation

When a donor is available, selection of the most suitable recipient for LT is based on blood type, size of organ, and medical urgency. To ensure the shortest cold ischemia time, operations for both the donor and the recipient partly overlap. The operation for the LT recipient includes removal of the disfunctioning liver and transplantation of the new liver. The blood vessels and the bile ducts of the recipient and the donor liver are anastomized, and the gall bladders from both the donor and the recipient are removed. The operation takes from 5 to 16 hours.

Post-transplant monitoring

The LT recipient stays from one to 4 days in the ICU and up to 2 or 3 weeks on the ward before discharge. After this, follow-up is organized in cooperation between the specialized health care of the patient's own hospital district and the transplant unit according to protocol. Close monitoring ensures early detection of allograft dysfunction, and possible drug side-effects can also be noticed when follow-up is frequent.

Immunosuppressive and other drugs

Following LT, the recipients' immune system recognizes the transplanted organ as foreign, activating a complex immune response that would result in graft rejection. This immunological response is mainly mediated by T-lymphocytes. The rejection response can be divided into four phases: antigen recognition, lymphocyte activation, lymphocyte proliferation, and graft inflammation (30). To prevent rejection, recipients of LT face lifelong immunosuppression. The cornerstone of immunosuppression is calcineurin inhibitors (CNI); either cyclosporine-A (CsA) or tacrolimus (TAC). Newer immunosuppressants, sirolimus or everolimus, which belong to the drug group mammalian target of rapamycin (mTOR), may serve as a substitute for CNI. Corticosteroids and antimetabolites; azathioprine or mycophenolate mofetil; are often combined with CNI or mTOR.

During longer follow-up, total immunosuppression predisposes to infections and malignancies; the challenge is to find optimal immunosuppressive therapy that prevents rejection with the least number of side-effects (31,32). The most common adverse effects during different types of immunosuppressants are provided in Table 4.

Table 4. Frequent side-effects in different immunosuppressive drug groups. Each drug also possesses specific side-effects in addition to those listed in the table. Modified from the source (33).

Adverse effect	**CsA**	**TAC**	**Cort**	**AZA**	**MMF**	**mTOR**
Alopecia	-	+	-	-	+	-
Bone marrow suppression	+	+	-	+++	++	+
Gastrointestinal toxicity	+	++	++	+	+++	+
Gingival overgrowth	+++	+	-	-	-	(?) *
Hepatotoxicity	+	+	-	++	-	+
Hirsutism	+	-	-	-	-	-
Hyperglycemia/diabetes	+	++	+++	-	-	+ (?)
Hyperlipidemia	++	+	++	-	-	+++
Hypertension	+++	++	+++	-	-	+
Impaired wound healing	-	-	+	-	-	++
Myalgia/arthralgia	-	-	-	-	+	++
Nephrotoxicity	+++	+++	-	-	-	+
Neurotoxicity	++	++	+	-	+	-
Osteoporosis	+	+	+++	-	-	-
Peripheral edema	-	-	++	-	-	++
Pneumonitis	-	-	-	-	-	+
Skin/mucosal lesions	-	+ rash	++	-	+	++acne, oral ulcers

CsA, cyclosporine-A
TAC, tacrolimus
Cort, corticosteroid
AZA, azathioprine
MMF, mycophenolate mofetil
mTOR, mammalian target of rapamycin (sirolimus or everolimus)
-, not reported; +, rarely reported; ++, commonly reported; +++, very frequently reported;
?, data scarce or discordant
* See reference no. (34)

CNIs may cause side-effects which include nephro- and neurotoxicity and infections. Nephrotoxicity may lead to post-transplantation diabetes, and a great concern with CNI and corticosteroids is a risk for cardiovascular diseases (35). Cardiovascular medications are therefore often prescribed to maintain normal blood pressure levels; a selective ß-blocker, diuretics, an ACE-inhibitor, or calcium channel blocker may be used. Statins and other cholesterol-lowering medications are also needed after LT to protect against cardiovascular risk (36).

Bone loss may already be occurring during CLD, especially among post-menopausal women, and risk for osteoporosis rises further by the use of CNIs and corticosteroids (37). Immunosuppression predisposes also to alveolar bone loss (15,16). To prevent osteoporosis and fractures that might follow, vitamin D, calcium derivatives, bisphosphonates, and also new biological drugs are useful (38). Bisphosphonate use increases risk for osteonecrosis of the jaws; therefore before LT, elimination of infected teeth aims to lower risk for serious necrosis of the jaws (39).

Infectious complications

Immunosuppression considerably weakens the host's ability to fight infections. Recipients of LT are therefore at risk for all types of infections (4). A wide range of bacterial, viral (e.g. cytomegalovirus (CMV) infection), or fungal infections such as *Candida* and *Aspergillus* can be life-threatening among immunocompromised hosts (5). The most common cause for mortality after LT is infectious complications. Risk is highest during the early stages after LT when immunosuppression is the strongest. To minimize risk for post-transplant infection, all potential infection foci should be eradicated before transplantation. This includes eradication of infectious dental foci.

Quality of life after transplantation

Liver transplantation aims to improve quality of life. LT recipients' quality of life is equal to that of the general population (1). Younger LT recipients often, a mere 6 months after transplantation, have returned to work or to their studies.

Oral cavity

The oral cavity is covered by a moist lining called the oral mucosa over the palate, the palatine arches, the uvula, the inner cheeks, and the floor of the mouth as well as the lips. Inside the oral cavity are the tongue and the teeth with their supporting structures. Food enters this uppermost part of the gastrointestinal tract, and digestion begins with the effect of the salivary enzymes.

Mucosal integrity

The normal oral mucosa consists of an outer stratified squamous epithelial layer and an inner *lamina propria* made mainly of fibroblasts. The basement membrane is situated between these two structures. Oral mucosal health is dependent on iron, folic acid, and vitamin B_{12}. Depletion of these nutrients may compromise mucosal integrity and leave the oral cavity vulnerable to becoming a port of entry for diseases.

Saliva

Saliva is fundamental to the well-being of the oral cavity. This oral fluid is secreted from the salivary glands that include the parotid, submandibular, sublingual, and the minor labial salivary glands. Every day we swallow approximately one liter of saliva. The submandibular glands are mainly responsible for the secretion of unstimulated whole saliva, whereas the parotid gland secretes most of the stimulated saliva. Oral stimuli, both masticatory and olfactory, trigger both the sympathetic and parasympathetic nerves that affect the salivary glands. Different stimuli result in different flow rates and a different composition of saliva; 2% citric acid causes the maximum stimulus, and it is often used in salivary clinical research (40). Salivary flow rate has huge individual and gender variation, and the time of day can also affect salivary flow. Our daily saliva follows circadian rhythms, and even minor temperature changes seem to affect salivary flow rates (41). Aging as such does not affect saliva secretion, but in older individuals lowered salivary flow rates are mainly due to various anticholinergic and xerogenic drugs.

Saliva composition is very complex. It contains water, electrolytes, various cells and micro-organisms, proteins, amino acids, enzymes, lipids, and DNA/RNA. Digestion starts already

in the mouth during mastication via salivary enzymes. When chewing has stimulated the salivary flow, then also more enzymes such as amylase and peroxidase are secreted.

Saliva has many functions and properties. Saliva lubricates the oral surfaces, and a sufficient volume is necessary for cleansing the oral mucosa and tooth surfaces of oral microbes. In addition to the clearance of microbes, saliva also has antimicrobial properties to fight oral diseases. Ability to neutralize acids, or buffering capacity, is an important function of the saliva and correlates with the salivary flow. Saliva is supersaturated with phosphate, calcium, and fluoride ions, enabling remineralization of the enamel. The normal pH of saliva is around 7, and whenever the pH falls below 5.5, demineralization occurs on the enamel surface. Most fuzzy drinks are very acidic, and if consumed on a daily basis, can cause severe erosion of the teeth (42).

A sufficient amount of saliva is important in speaking and in wearing dentures. Saliva also protects the taste receptors within the taste buds in the tongue, and normal salivary flow is required for the sense of taste. Salivary hypofunction thus helps explain why food tastes different to different people.

Oral microbiota

The warm and moist environment of the oral cavity favors the existence of many different oral microbes. Distinct oral habitats, such as the teeth, gingival crevice (the space between the tooth and the gingiva), tongue, cheek, hard and soft palate, the tonsils, and the pharynx, may harbor site-specific bacteria, viruses, and fungi that form the oral microbiota or oral microbiome.

Bacteria

One estimate is that the total number of bacteria in the mouth is around 6 billion. Thus far, hundreds of species of oral bacteria are known (43), but novel species are continually discovered by 16S rDNA gene sequencing (44). The pellicle – consisting of a thin layer of protective salivary glycoproteins interacting with the enamel – also acts as a substrate on which bacteria attach. The ability of bacteria to stick onto hard or soft oral surfaces then creates a perfect environment for the plaque bacteria to mature. Dental plaque is referred to

as dental biofilm (45), and this rich, complex network of bacteria forms microbial communities which divide into smaller micro-niches (46).

Most oral bacteria are commensal, benefiting both the host and the organism itself, and in small numbers, the bacteria are harmless. A shift from health to disease occurs when the equilibrium of the ecological balance between the host and oral micro-organisms is disturbed. This change in population dynamics may result from poor oral hygiene, aging, diet, genetic factors, or underlying systemic conditions in the host which in turn can predispose the host to oral diseases (47).

Although normal oral flora is difficult to define (Table 5), between healthy and diseased oral cavities are distinct differences. The primary colonizers in the oral cavity are gram-positive aerobes or facultative anaerobes such as *Streptococcus* and *Actinomyces* species. Mature plaque contains mainly gram-negative anaerobes like *Fusobacterium* and *Treponema*. Various bacteria possess various virulence factors and geographical variations. *Streptococcus viridans* is part of the normal oral flora and can also occur on intestinal mucosa and on the skin. These α-hemolytic bacteria cause about 40% of endocarditis cases, and they may also cause bacteremia or meningitis in immunocompromised hosts. Recently, research has linked *S. viridans* to SBP infections in CLD patients (48).

Fungi

Oral fungi, also part of the normal oral microbiota, are usually harmless and superficial in healthy individuals with an innate immune response. The most typical are *Candida albicans,* which accounts for about 50% of cases. *C. albicans* grows mainly on mucosal surfaces: the inner cheeks, tongue, and the floor of the mouth, but can be cultivated from porous denture surfaces. Interest is increasing in research on non-*albicans* strains which are highly resistant to common antifungal therapies (49). *C.glabrata* produces the highest mortality rate due to its hemolytic activity that allows for tissue invasion and increased risk for bloodstream infections in immunocompromised hosts (50,51).

Viruses

The following viruses belonging to the Herpes virus family can occur in the oral cavity: herpes simplex virus types 1 and 2 (HSV1, HSV2), Varicella Zoster virus, Epstein Barr virus (EBV), and CMV. EBV and CMV are common in organ-transplant recipients and also occur in the oral cavity (Table 6). They may be associated with oral ulcers, oral hairy leukoplakia, and other infectious oral mucosal lesions (52). HSV-1 and HSV-2, however, are still most common viruses affecting oral health; they cause recurrent herpetiform ulcerations or cold sores (53). Human papilloma virus (HPV), specifically HPV type 16, has been linked to head and neck squamous cell carcinoma (SCC) (54).

Table 5. Characteristic species of oral microbiota.

Micro-organism	Examples of species
Bacteria	
Cariogenic	*Streptococcus viridans* group: *S. mutans, S. mitis, S. sobrinus, S. salivarius, S. oralis, S. sanguis* *Lactobacillus, Actinomyces*
Periodontal	*Porphyromonas gingivalis, Prevotella intermedia, Treponema denticola, Fusobacterium nucleatum, Aggregatibacter actinomycetemcomitans, Tannerella forsythia*
Fungi	*Candida albicans*
	Non-*albicans Candida: C. glabrata, C. parapsilosis, C. krusei, C. tropicalis*
Viruses	CMV, EBV, HBV, HCV, HIV, HPV, HSV

CMV, cytomagalovirus
EBV, Ebstein Barr virus
HBV, hepatitis B virus
HCV, hepatitis C virus
HIV, human immunodeficiency virus
HPV, human papillomavirus
HSV1, herpes simplex virus type 1
HSV2, herpes simplex virus type 2

Signs and symptoms involving the mouth

Caries

Caries or tooth decay is the most common and widespread infectious dental disease worldwide, and the risk for dental diseases, especially caries and periodontitis, increases as people live longer and retain their teeth for a longer period of time.

Nutrition, tooth anatomy, quantity and quality of saliva, host response, and typical cariogenic bacteria all play a role in the multifactorial etiopathogenesis of caries (55,56). Hyposalivation associates with systemic diseases, like diabetes, rheumatic diseases, and asthma, which are considerable risk factors for caries. *Streptococcus mutans*, belonging to the *S.viridans* group, is an acidogenic plaque pathogen that initiates caries formation by fermenting carbohydrates into acids. Frequent consumption of sugars (especially sticky sweets) lowers the salivary pH and favors *Lactobacillus* species involved in caries progression. An "acid attack" occurs every time we eat or drink, and this may cause demineralization of the enamel, leading to tooth decay. Initial carious lesions limited to the enamel surface can be reversed by remineralization under normal salivary conditions; phosphate, calcium, and fluoride ions in the saliva "rebuild" the unique structure of the enamel, and the pH rises. High *S.mutans* and *Lactobacillus* counts, low salivary flow, and poor buffering capacity of the saliva elevate the risk for demineralization, and cavitation may extend into the dentinal layer. Untreated carious lesions may progress deeper into the tooth structure. If the carious pathogens reach the inner pulp containing the blood vessels and nerves, an endodontic infection - infection of the root canal system - occurs.

Gingivitis

If the biofilm formation is not disturbed, bacterial plaque accumulates on teeth. Gingivitis or gum disease refers to the inflammation of the gingiva that surrounds the tooth; it manifests as swollen, red gums that easily bleed. Gingivitis prevalence is estimated to be around 90%, but as with caries, gingivitis can be prevented with good oral hygiene that includes brushing and cleaning in between the teeth in order to limit the bacteria to small amounts.

Periodontitis

Gingivitis may lead to periodontitis when the tooth-supporting structures produce a more serious form of cellular inflammatory response to the bacterial deposits on teeth. The

pathogenesis of periodontitis is a complex cascade involving periodontal pathogens that trigger the secretion of matrix metalloproteases (MMPs), IL-1, TNF-α, and other proinflammatory cytokines that result in destruction of the collagen attachment between the tooth and the alveolar bone (57). MMPs have long been recognized as the key inflammatory markers found in saliva or in the gingival crevicular fluid, resulting in periodontitis when periodontal pathogens are also present (58). Elevated levels of MMPs, especially MMP-8, thus cause deterioration of the tooth-supporting structures, which may result in tooth loss. A host response in periodontitis is crucial, since genetic mutations in the host may result in a more aggressive form of periodontal disease. Significant attachment loss appears clinically as deepened (≥ 4 mm) periodontal probing depth, and radiographically as severe alveolar bone loss. Typical periodontal pathogens are gram-negative anaerobic bacteria found in subgingival crevices (see Table 5). In deeper periodontal pockets, the number of bacteria are higher.

Untreated caries lesions or periodontal disease may cause abscesses that, in a healthy individual, remain local, due to the normal immunological function of the lymphocytes. In contrast, in immunocompromised hosts, the oral infections may spread through inflamed gums to the general circulatory system, causing sepsis or lung or brain abscesses which can be fatal. Periodontal disease is linked to many systemic diseases, such as diabetes, low birth weight, and atherosclerosis (19,20,59-61).

Oral mucosal lesions (OML)

When mucosal integrity is compromised, a risk arises for oral mucosal lesions (OML), grouped by color into red, white and pigmented (62). OMLs are often associated with systemic conditions or diseases; Table 6 shows one practicable way of classifying these lesions.

An oral mucosal **ulcer** penetrates the mucosal epithelium, reaching the inner connective tissue containing the blood vessels. Differential diagnosis of oral ulcers is crucial. If an ulcer does not heal within two weeks, the possibility exists that it may be malignant, since oral cancer and other malignant tumors in the oral region may manifest as ulcers. The most common type of oral lesion is the recurrent aphtous ulcer, which can be classified into idiopathic or secondary. The secondary form is associated with CD, UC, certain medications (metotrexan, non-steroidal anti-inflammatory drugs [NSAID], ß-blockers), or deficiency of

iron, folic acid, or vitamin B_{12}. Predisposing factors include stress, trauma, infections, and food allergies. Recurrent aftous ulcers occur both in health and in disease, but the ulcers associated with systemic diseases can be more resistant to treatment.

Table 6. Classification of oral mucosal lesions. Modified from the source (63).

Drug or allergy induced	Drug induced gingival overgrowth, galvanic reactions (e.g. rough amalgam filling)
Hyperplasia	*Candida* infections, ill-fitting denture, poor oral hygiene, trauma
Infectious lesions	CMV, EBV, HCV, HPV, HSV
Lesions of the tongue	Atrophic tongue, fissured tongue, geographic tongue, hairy leukoplakia, median rhomboid glossitis
Manifestations of derma-tological diseases	Discoid lupus erythematosus, Erythema multiforme, oral lichen planus, pemfigoid
Precancerous and malignant lesions	Atrophic/erosive lichen, erythroplakia, leukoplakia, oral cancer/SCC
Ulcers	Atrophic *Candida*, CMV, dermatitis herpetiformis, discoid lupus erythematosus, EBV, Erythema multiforme, HSV, IBD, oral lichen planus, pemfigoid, pemfigus, recurrent aphtous ulcer, SCC, syphilis, trauma/radiation, Wegener's granulomatosis

CMV, cytomegalovirus
EBV, Ebstein Barr virus
HCV, hepatitis C virus
HPV, human papillomavirus
HSV, herpex simplex virus
IBD, inflammatory bowel disease
SCC, squamous cell carcinoma

Atrophic tongue is often a consequence of nutritional deficiencies such as avitaminosis of B_{12}, or folic acid, or depletion of iron. The tongue is bright red and it has a smooth surface due to disappearance of filiform papillae. Predisposing factors, like spicy foods and irritating oral health products such as toothpastes containing natrium layryl sulfate should be avoided if they cause symptoms.

Fissured tongue is a common, usually symptomless lesion of the dorsal surface of the tongue that is associated with dry mouth. The fissures can be several millimeters deep, and may harbor *Candida* and other microbes. Careful cleaning of the tongue surface is necessary. **Geographic tongue** is a benign condition that may exist together with fissured tongue, psoriasis, or Reiter's syndrome. It is characterized by reddish, atrophic patches that alternate between the dorsal and lateral tongue surfaces. Its etiology is unknown, but possible triggers are stress, infections, genetic predisposition, or allergies. **Hairy tongue** consists of long papillae on the dorsum of the tongue. Predisposing factors include smoking, poor oral hygiene, hyposalivation, or candidosis. **Median rhomboid glossitis** is characterized by a red area on the midline of the dorsal surface of the tongue as a result of papillary atrophy.

Candida species are evidently true opportunistic pathogens, since they cause oral infection when the host has an underlying predisposing systemic condition, as in HIV infection, endocrine disorders, nutritional deficiencies, or treatment with broad-spectrum antibiotics, or during immunosuppression (64). In immunocompromised patients, fungal infections are associated with high mortality (65). Local predisposing factors include poor oral hygiene, lowered salivary flow, and inhaled glucocorticoids. Stinging, burning sensation in the mouth, and also malodor are typical clinical symptoms of **oral candidosis**. Four primary forms can be detected clinically: (a) acute pseudomembranous candidosis, (b) chronic erythematous candidosis, (c) acute erythematous candidosis, and (d) chronic hyperplastic candidosis. A secondary form includes denture stomatitis, angular cheilitis, and median rhomboid glossitis; these often occur if dentures need repair**.** Inflamed palatal mucosa under an upper full denture is characteristic of **denture stomatitis** and the corners of the mouth are involved in **angular cheilitis.** Treatment includes topical antifungals, repair of dentures or new dentures, and proper oral hygiene.

Early detection of **precancerous oral lesions** is important since oral cancer is associated with high mortality, making regular follow-up of these lesions vital. Precancerous or potentially malignant OMLs include oral lichen planus (OLP), leukoplakia, erythroplakia, and ulcers (66). Lichen ruber planus is a chronic, inflammatory, autoimmune disease of the skin, scalp, nails, and mucous membranes with its etiology unknown (67). **Oral lichen planus** (OLP) is 5 to 10 times as common and complex as the skin form of the disease. Other recognized forms of OLP are striated, papular, plaque, atrophic/erosive, ulcerative, or bullous (68). Regular follow-up of these lesions is important, since the atrophic/ulcerative/erosive form of

OLP may become malignant (69). A definite diagnosis requires a biopsy from the lesion. OLP is an idiopathic condition, whereas a lichenoid reaction may be triggered as a reaction to an outside source such as allergy to restorative tooth material, a rough tooth filling, a drug reaction, HCV, or graft-vs-host disease (70-72). These similar entities are sometimes hard to differentiate from each other. Topical ointments containing steroids, calcineurin inhibitors, and 0.1% triamcinolone acetonide have ameliorated symptoms and expedited recovery (68,73). OLP has been associated with liver disease (67).

Leukoplakia is defined as a white patch, either verrucous or nodular, that will not wipe away from the surface it adheres to and cannot be characterized clinically or pathologically as any other definable disease (74). Differential diagnosis includes burns, frictional or tobacco (hyper) keratosis, linea alba, OLP, lichenoid reactions, *Candida* infection, or hairy leukoplakia. Smoking is a strong risk factor for this lesion; concomitant use with alcohol increases the risk even more (75). Candidosis and human papillomavirus (HPV) associate with leukoplakia, and at risk sites (floor of mouth, ventrum of tongue, lower lip), up to 30% of these heterogenous group of lesions can be malignant (76).

Erythroplakia is a rare lesion that appears more red than its surroundings. It is usually located on the floor of the mouth or on the tongue, and 90% of erythroplasias are dysplastic, so risk for SCC is high. The etiology behind it is unclear, but smoking and heavy alcohol use increase risk. Atrophic *Candida* infection or contact allergy can be mistaken for erythroplasia, and diagnosis is by biopsy.

The most common type of **oral cancer** is SCC, derived from the stratified squamous epithelial layer of the oral mucosa. Its prognosis is still very poor (77). Healthy and pathological sites harbor different types of microbiota, and recent evidence has emerged that the pathogenesis of cancer in the oropharyngeal cavity is associated with oral microbes (78). Oral microbes like *S. mutans* have the ability to degrade ethanol into acetaldehyde, a strong carcinogen. Poor oral hygiene, candidosis, and smoking and alcohol use together therefore increase the risk for oral cancer (79). Other risk factors include the erosive or atrophic form of OLP, HPV (types 16,18), sunburn, and immune deficiencies (54,69).

Xerostomia and hyposalivation

Xerostomia refers to a subjective feeling of dry mouth in contrast to objectively measured hyposalivation which by definition (80) is diagnosed when both unstimulated and stimulated salivary flow rates are significantly reduced. The thresholds for hyposalivation are: unstimulated saliva <0.1 ml/min and stimulated saliva <0.7 ml/min. A feeling of dry mouth can exist without hyposalivation's being objectively assessed (81).

Systemic diseases affect salivary flow by differing mechanisms (82). Diabetes causes disturbance of the electrolyte balance, resulting in dehydration (83). Physiological and hormonal changes during menopause can also affect salivary flow (84). Diseases of the salivary glands such as sialoadenitis, sarcoidosis, and Sjögren's syndrome cause salivary hypofunction (85,86). Irradiation to the head and neck region may cause permanent destruction of the salivary glands, resulting in total oral dryness (87).

Drugs are the main cause of xerostomia, with most medications and drug types found to be xerogenic. These include antihypertensives, antidepressants, anxiolytics, appetite suppressants, decongestants, and antihistamines (82,88,89). Emotion, neurosis, systemic diseases, infections, and tumors may also be responsible for xerostomia, which can be devastating to a patient (81). Eating, talking, and wearing dentures all become difficult when saliva is insufficient (90,91), and in a dry mouth, risks for all oral diseases increase. New biological drugs, such as rituximab and anti-TNF-α are promising new drugs in the treatment of hyposalivation (92,93).

Burning mouth syndrome (BMS)

This condition, BMS, is also dry-mouth-related with population prevalences between 1 and 10% (94). It is characterized as an oral burning sensation in the absence of any organic disorders of the oral cavity (95). As it is most often found in middle-aged women (96), hormonal changes may predispose to oral burning (84,97). A variety of other conditions such as nutritional deficiencies, diabetes, and medication side-effects contribute to a secondary form of BMS (98); this is the most common type of BMS. In the primary or idiopathic form of BMS, no local or systemic causes can be identified, so neuropathological mechanism may be the underlying cause. BMS has a strong association with psychological disorders.

Dysphagia

Difficulty in swallowing, or dysphagia, is often accompanied by xerostomia or hyposalivation, but the cause may be esophageal motility disorder (99). Talking, eating, and taking medications may become difficult with this unpleasant symptom. Esophageal overgrowth of *Candida* may also cause dysphagia, which can result in nutritional problems (100). In such cases, treatment of candidosis by antifungals is necessary.

Dysgeusia

Altered taste sensation or dysgeusia is not as common as the other dry-mouth-related subjective oral symptoms, but this clinical taste phantom has been associated with BMS (101). Taste perception is centralized to the tongue and its papillae. In a dry mouth, function of the papillae is lessened, and the sensation of taste diminishes. Some medications may alter taste, and denture wearers may also face a risk for dysgeusia which can lessen quality of life (89). Candidosis has also been associated with this disorder (100).

Liver diseases and the mouth

Patients with CLD have generally poor oral health (Table 7). In end-stage liver disease, cirrhotic patients are susceptible to infections which can be fatal. Impairment of coagulation causes a significantly increased tendency for bleeding (12,102). Professional cleaning of teeth or tooth extraction may follow, with extensive bleeding that can be life-threatening if not treated properly (103). In this setting, dental treatment of these medically compromised patients is often complicated, and the most severe liver disease patients should thus be referred to a local hospital that includes hospital dentistry.

Teeth

Early childhood liver disease, typically biliary atresia, can cause **discoloration** of the developing permanent teeth (104,105). Increased bilirubin levels in cholestasis color the dentinal layer greyish-green, although microscopic analysis has shown that the outer enamel maintains its translucency (106). The teeth appear to be green in color. Developmental disturbances may also cause enamel **hypoplasias** in the teeth, which appear as white or yellow patches.

The gastric reflux common in liver diseases may have harmful effects on the teeth due to acidic regurgitation. Gastric fluid is very acidic, its pH is around 2 and **tooth erosion** occurs when the surface pH falls below 5.5. Hyposalivation caused by several medications can make erosive wear even greater (42). Dental erosion can also be caused by extrinsic factors; it is a common manifestation in alcoholic liver disease, since the pH of most alcoholic beverages is low (107). **Attrition** has been reported in liver disease patients, this being another condition that wears down the teeth and may cause sensitivity due to exposed nerve endings in the dentin. Its cause is bruxism or grinding of the teeth, and lowered salivary flow causes more depletion of the dental material. Sometimes it is difficult to differentiate between attrition and erosion, since these disorders may exist simultaneously.

Table 7. Oral symptoms and signs in chronic liver diseases.

Oral manifestation	Examples of etiology/cause	Reference
Petechiae, hematoma, gingival bleeding, reduced wound healing	Hemorrhagic changes/coagulation disturbances	(12,102,103,108-113)
Discolorations of teeth	Biliary atresia	(104-106)
Periodontal disease	Anemia, neutropenia, IBD	(114-117)
Tooth decay (caries)	Hyposalivation/xerostomia, alcoholic liver disease	(118-120)
Erosion	Alcohol cirrhosis	(107)
Oral lichen planus	HCV, PBC	(13,73,121-123)
Leukoplakia	HCV	(121)
Mucosal ulcers	IBD, PBC, Bechet's disease	(110,124-126)
Candidosis	Xerostomia	(110,121,127)
Angular cheilitis	Cirrhosis of the liver	(110,127)
Pyostomatitis vegetans	IBD	(128)
Herpetic ulcerations	CMV, HCV	(110)
Glossitis, smooth tongue, atrophic tongue	Alcohol liver disease, nutritional deficiencies	(129,130)
Fissured tongue	HCV, IBD, hyposalivation/ xerostomia	(124,159)
Xerostomia	HCV, PBC, IBD	(11,85,131-133)
Halitosis	Xerostomia, IBD	(134)
Sjögren's syndrome	HCV, PBC	(131-133)
Parotid gland enlargement/ sialoadenitis	Alcohol cirrhosis, HCV	(85)

CMV, cytomegalovirus
HCV, hepatitis C virus
IBD, inflammatory bowel disease (associated with primary sclerosing cholangitis)
PBC, primary biliary cirrhosis

Oral mucosa

CLD patients often suffer from malnutrition and anemia. Depletion of iron and avitaminosis of B12 and folic acid promote susceptibility to OMLs (135,136) of which, several kinds occur in patients with liver diseases. Elevation in bilirubin manifests also in the oral cavity, making the oral mucosa yellow-brownish in color. The lowered immune response in these patients also predisposes to candidosis (119,121). Chronic, active hepatitis or PBC has a strong correlation with OLP (123). Especially the erosive form of OLP has been associated with CLD (122). Because the oral mucosal membrane is very similar to the inner lining of the intestines, similar lesions may be found in the oral cavity and in the other parts of the gastrointestinal tract.

Oral lesions associated with IBD

Both IBDs share similar oral manifestations, but the oral lesions occur more frequently with CD with varying prevalences ranging from 0.5 to 80% (137). Certain typical lesions such as recurrent aphtous ulcers, may appear months or even years before IBD is diagnosed since the early symptoms of this disease are often mild. Therefore, recognition of these lesions is crucial since the dentist may be the first clinician to suspect UC or CD. Consultation with a gastroenterologist is indispensable in the overall treatment of these patients (134).

Periodontitis, which is also a chronic inflammatory disease, has been associated with both UC and CD (117). CD patients may experience disease-specific oral lesions such as diffuse buccal mucosal swelling, typical cobbler-stone-like oral mucosa, deep linear ulcerations in the buccal sulci, mucosal tags, or candidosis (138). Other common features include swollen lips or facial skin. The mouth can be sore from inflamed gums that appear granulomatotous. Sometimes changes in the anemic profile as often manifested in periodontal disease, could lead to the right diagnosis of CD (114).

Pyostomatitis vegetans manifests as painful ulcerations or multiple erythematous pustules in the oral mucosa and it is considered a highly specific marker of IBD; these erosive changes in the oral mucosa can be early signs of UC (128).

Several medications may affect salivary flow, and CLD patients may therefore suffer from xerostomia and from many other dry-mouth-related symptoms and signs (85,131).

The liver transplant patient and the mouth

Pretransplant dental evaluation

Infections of the oral cavity are usually frequent among patients waiting for an LT (9,18,139). The main purpose of dental evaluation is to prevent bacteremia and sepsis that could arise from untreated oral or dental sources, because in these immunosuppressed patients the leading cause for morbidity and mortality is infection (140). When planning dental treatment, consultation with the treating physician is most important.

Infectious dental foci

The focal theory in dentistry was first introduced by WD Miller in the 1890's (141). By definition, "a focal infection is a localized or generalized infection caused by the dissemination of microorganisms or toxic products from a focus of infection in various organic districts, including the oral district". Oral bacterial flora may be transferred to the blood stream by invasive dental procedures, tooth brushing, or chewing, but poor oral health and frequent dental infections clearly worsen the development of bacteremia (142). In healthy individuals, the host's reticuloendothelial system clears the pathogens from the blood, but in immunocompromised hosts, risk for focal infections is higher.

Systemic diseases and conditions such as diabetes, cardiovascular diseases, infectious endocarditis, cerebral abscesses, lung infections, premature birth, and several other conditions have been linked to oral infections, specifically to periodontal disease, although this theory is still controversial (19,20,59-61,143). Oral infections seem to worsen the progression of several systemic diseases, but the relationship is bidirectional in that systemic diseases also aggravate oral health status.

Any infections of the oral cavity can be regarded as potential infection foci. Infectious oral and dental foci include the oral mucosa, teeth with their supporting structures, and the jaws. Panoramic tomography (PTG) is necessary, since symptomless, chronic infections may hide far back in the jaws.

Current guidelines

Most of the world's transplant centers recommend pretransplant dental evaluation and treatment of infectious dental foci before LT to prevent sepsis and bacteremia of oral origin (9,10,18). Their guidelines rely mostly on empirical knowledge and can differ greatly among transplant centers and countries (17,144). No uniform guidelines thus exist for the dental management of LT candidates. Still, the general consensus is that eliminating active and chronic sources of infection from the oral cavity is essential before LT (7-9). Sometimes full-mouth, total extractions are advisable if the patient has advanced periodontal disease and shows no interest in oral self-care (7). The LT candidate should always have his or her oral hygiene reinforced with proper home-care instructions. Current guidelines at HUCH are in Table 10.

Post-transplant dental treatment

Infections

All dental treatment should be avoided until 6 months after transplantation. Immunosuppression is strongest during the first months, so patients are extremely prone to bacterial, viral, and fungal infections despite prophylaxis to prevent infectious complications. Opportunistic oral infections by *C.albicans* are common at this time, and HSV1 may also reactivate and manifest as painful and slow-healing oral ulcers (9). Removal of plaque deposits by toothbrushing is extremely important, and chlorhexidine mouth rinses may be beneficial in lessening bacterial inflammation of the oral cavity (145). Tooth brushing should be done carefully because, if the gums are inflamed due to poor oral hygiene, too vigorous brushing may result in bacteremia (146). A hospital dentistry department must be consulted if any severe dental problems emerge during the first 6 months, and only emergency dental care should be given at this time (9).

After 6 to 12 months the graft should be stabilized, and the patient's dental care be provided by his/her own dentist. Dental treatment in LT recipients does not differ to any great extent from that of the normal population. Since oral diseases are caused by oral pathogens, plaque control is most important to avoid oral and dental diseases and to prevent possible infectious complications. A recent study of pediatric LT recipients revealed a need to improve utilization of preventive dental care for these patients (147). Consultation with the patient's physician concerning possible drug interactions is necessary to avoid too low/too high

concentrations of immunosuppressive medications (148). Referral to a special dental unit of a hospital is recommended in complicated cases. Regular oral examinations are essential every 6 months to detect early signs of infection of teeth or the oral mucosa. Even edentulous patients are in need of regular dental visits in order to treat possible precancerous or other OMLs. Removable dentures need to be checked regularly for their fit, and possible candidosis requires treatment. Otherwise, patients can receive normal dental care, even implants, if the patient's medical condition is stable, and jaw bone structure is sufficiently strong (149). Effective oral hygiene habits are still the cornerstone of a healthy oral cavity.

Antibiotic prophylaxis

Invasive dental treatments such as periodontal and restorative treatments in particular are associated with some bleeding; in order to avoid infection's spreading from the oral source, antibiotic prophylaxis is recommended for high-risk, immunocompromised LT recipients (142,150). Recommendations follow the guidelines for the prevention of infectious endocarditis by the American Heart Association. The issue of antibiotic prophylaxis is controversial, however, and the benefits of antibiotic use should always outweigh the risks (151,152). A current recommendation includes 2 g amoxicillin, or 600 mg clindamycin for patients with penicillin allergy, given one hour before dental treatment.

Drug-induced gingival overgrowth (DIGO)

Drug-induced gingival overgrowth (DIGO) is commonly associated with CsA (153,154); simultaneous use of calcium-channel blockers increases its prevalence (34,155). DIGO can be very unpleasant for the patient, and the treatment often involves surgical removal. Proper oral hygiene and periodontal treatment may lower the risk for DIGO (156), but replacing CsA with TAC or changing calcium channel-blocker to another antihypertensive may reverse this condition (157,158).

Several other oral mucosal lesions afflict LT recipients. These include OLP, stomatitis, fissured tongue, candidosis, leukoplakia, and oral cancer; maxillofacial tumors also occur (13,14,159-161). Corticosteroids lead to increased prevalence of candidosis and more bone loss (15), but some of these conditions may have existed even before LT, so it is difficult to point out which of these specifically relate to immunosuppressive medications. Several medications may be xerogenic, and xerostomia has been frequently evident in LT recipients (9,159,162).

AIMS OF THE STUDY

This study focuses on the association between oral conditions and systemic diseases in patients receiving a LT. Since the relationship is bidirectional, we first aimed to study how liver disease affects oral health. Further, the aim was to study how oral health status may affect liver disease or LT outcome. In addition, a further aim was to investigate how the immunosuppression which is a direct consequence of the LT may affect these patients' oral health. The main hypotheses of the study were that treatment of oral infections before LT is beneficial for LT prognosis, and, in addition that life-long immunosuppression necessitated by LT affects oral health.

The specific aims were to investigate:

1. How liver disease etiology or severity affects oral health (**Study I**).
2. How dental infections affect the progression of liver cirrhosis (**Study II**).
3. What effect pretransplant dental treatment has on the development of systemic infections after LT (**Study III**).
4. How immunosuppression affects oral health of LT recipients in comparison to a control population (**Study IV**).
5. How immunosuppression affects specifically oral mucosal health of the LT recipients when compared with the control population (**Study V**).

PATIENTS AND METHODS

This study was conducted at the Institute of Dentistry, University of Helsinki, and at the Department of Oral and Maxillofacial Diseases and the Transplant and Liver Surgery Clinic, Helsinki University Central Hospital (HUCH), Helsinki, Finland. The study had the approval of the HUCH Research Committee, and Studies IV and V had the ethical approval (192/13/03/02/2008, 16.8.2008) of the ethics committee of the Helsinki and Uusimaa Hospital district. Permission for the Health 2000 Health Examination Survey in Finland was given by the ethics committees of the University Hospital Region of Helsinki and Surroundings and the National Public Health Institute. Each of the patients as well as all the Health 2000 Health Examination Survey participants signed an informed consent form which was available in both Finnish and Swedish.

Patients

Features of the study design and patient characteristics are presented in Tables 8 and 9 and in Figure 4. The study population comprised all 263 adult recipients of a LT between 2000 and 2006 at the Transplant and Liver Surgery Clinic, HUCH, Helsinki, Finland. The follow-up of these patients also took place in the same hospital.

Of the study patients, 212 (80.6%) (all chronic liver disease) had dental examinations and treatment prior to the LT. In this examination, oral health status was evaluated and need for dental extraction served as the dependent variable (outcome) to study the impact of the different liver pathologies (by etiology) and severity (MELD) on oral health status. Etiology groups included PSC, PBC, alcohol cirrhosis, cryptogenic cirrhosis, other cirrhosis, liver tumors, and other chronic liver diseases (**Study I**).

Of the chronic patients, 116 (54.7%) had end-stage liver cirrhosis. Their tooth extractions were used as evidence of the progression of liver cirrhosis as seen in MELD score change during one year before dental examination. Episodes of spontaneous bacterial peritonitis (SBP) cases were compared between two groups formed by the median number of tooth extractions during pretransplant dental evaluation (**Study II**).

Of the study patients, (51) 19.4% had LT due to acute or subacute liver failure. They were subsequently stratified by whether they had had pretransplant dental treatment (n=16), or none (n=35). The occurrence of systemic infectious complications and their related microbiota after LT was assessed from the Finnish LT Registry (**Study III**).

Figure 4. Patient profile among different studies.

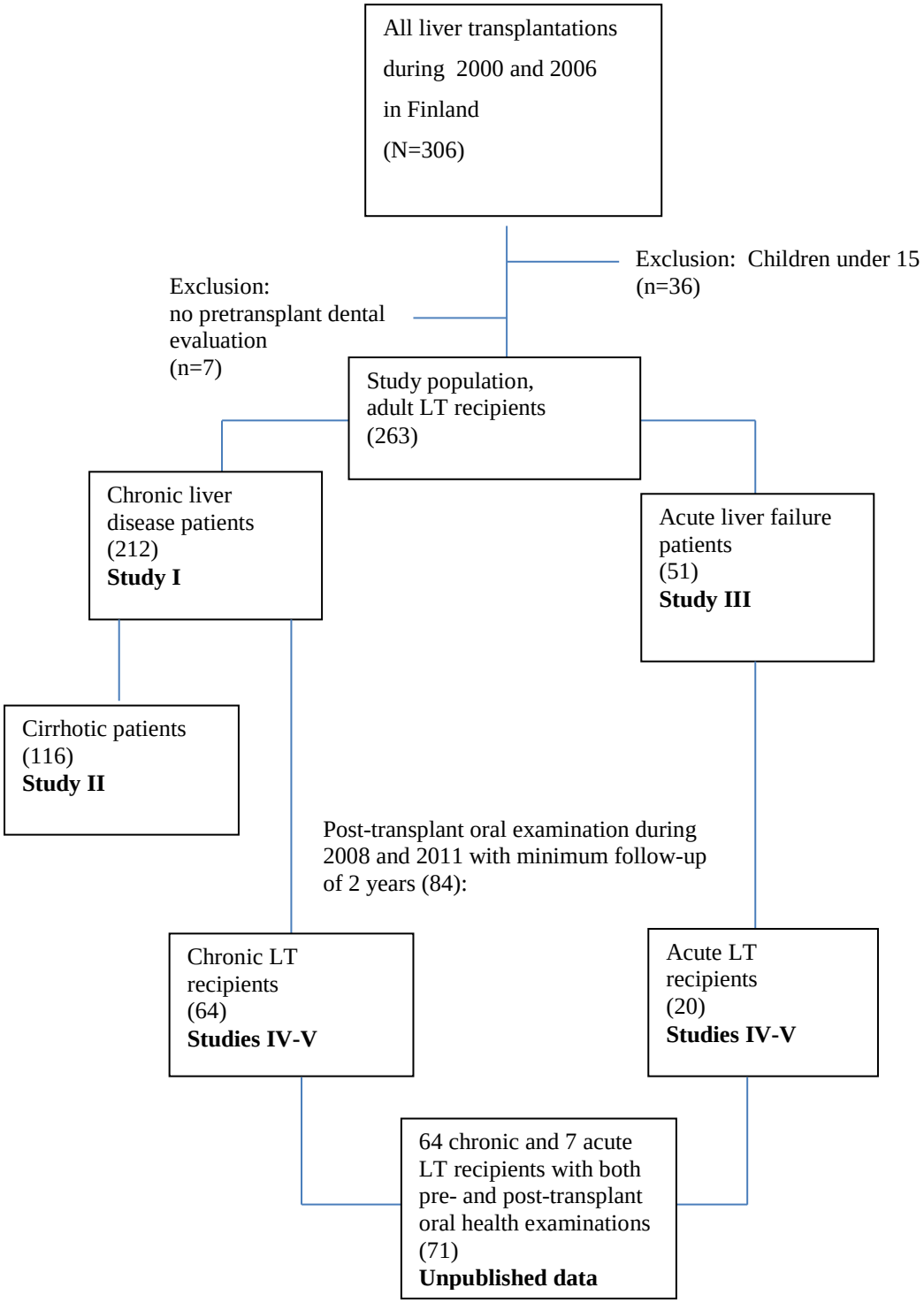


Table 8. Features of study design and patient characteristics.

Study number	**I**	**II**	**III**	**IV**	**V**
Number of patients	212	116	51	84	84
Inclusion	Chronic pre-transplant patients	Cirrhotic pretransplant patients	Acute pre-transplant patients	Post-transplant patients	Post-transplant patients
Study design	Retrospective, cross-sectional	Retrospective, cross-sectional	Retrospective, cross-sectional	Prospective, cross-sectional, case-control	Prospective, cross-sectional, case-control
Control group	No	No	No	Yes §	Yes§
Data collection	Patient records	Patient records, LT Registry	Patient records, LT Registry	Patient records, protocol oral examination, questionnaire	Patient records, protocol oral examination, questionnaire
Age at LT, median (range)	51 (15-74)	49 (39-66)	48 (19-68)	55 (25-71)	55 (25-71)
Gender, men %	57	54	35	61	61
LT diagnosis, all %					
Chronic	89	100		71	71
PBC	15	27		7	7
PSC	25			27	27
ALCI	17	32		14	14
CRCI	7	13		7	7
OTCI*	16	28		11	11
OTHER ¶	9			5	5
Acute			100	24	24
Unknown			59		
Drug-related			18		
AIH			12		
Acute Budd-Chiari			8		
Other			3		
Liver tumors	11			5	5

AIH, autoimmune hepatitis; ALCI, alcohol cirrhosis; CRCI, cryptogenic cirrhosis; OTCI, other cirrhosis; OTHER, other chronic liver diseases; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis

* including autoimmune hepatitis and viral hepatitis

¶ including Budd-Chiari and metabolic liver diseases

§ Health 2000 Health Examination Survey in Finland; matched for age, gender, and residence area

A subset population of 84 eligible LT recipients were recruited for a clinical oral health examination with a minimum follow-up of 2 years (median follow-up 6 years, range 2-11) after LT. A questionnaire (Appendix) allowed assessment of dry-mouth-related symptoms, *Candida* was cultivated and salivary flow rates were measured. Complete oral health status according to a fixed protocol and subjective oral symptoms were evaluated and compared with those of a matched control group of 252 from a national health survey. Groups were formed by LT etiology or by difference in immunosuppression (**Studies IV-V**).

Table 9. Oral health status among studies and in controls.

	Study I	**Study II**	**Study III**	**Study IV**	**Study V**	**Controls**
Number of teeth, mean (SD)	23 (8)	22 (9)	21 (11)	22 (9)	22 (9)	20 (10)
Number of carious teeth, mean (SD)	2 (3)			1.1 (1.4)	1.1 (1.4)	0.5 (0.9)
Number of extractions, mean (SD)	3 (4)	4 (4)	4 (7)	0 (1)	0 (1)	
Percentage of oral mucosal lesions	19			43	43	15

Oral examination

Pretransplant oral health status **(Studies I-III)**

In LT candidates PTG had been performed before a clinical oral examination which included assessment of oral infectious foci. A radiologist's written statement was available for diagnosis. Number of teeth was calculated from PTG. Oral mucosal status was recorded, number of carious teeth (teeth to be filled) was assessed, and the quality of possible dentures was recorded as well. Differing dental infectious foci were reported separately in Study I; they included all non-restorable teeth as presented in Table 10 according to HUCH guidelines for the dental management of LT candidates before their acceptance on a waiting list for LT.

Table 10. Current guidelines for LT candidates at HUCH.

Oral source of infection	**Procedure**
Cysts, abscesses of the jaws	Surgical operation
Infectious dental foci:	
Periapical osteitis/apical periodontitis	extraction of teeth
Advanced periodontitis; ≥6 mm periodontal probing depth / severe alveolar bone loss	
Vertical, bony pockets	
Deep carious lesions reaching the pulp (devital teeth)	
Root remnants	
Wisdom teeth with pericoronitis	
Carious lesions (vital teeth)	Temporary or permanent fillings
Dental calculus	Removal, scaling and root planing
Plaque deposits	Removal and guidance in oral self-care
Oral mucosal lesions	Treatment of candidosis and other oral mucosal pathologies
Dry mouth	Information, recommendation of saliva substitutes

A liver surgeon was the consultant, regarding the current status of the patient, drug selection and dosage, and need for possible replacement therapy to prevent any bleeding associated with the dental procedures. Tooth extractions were done in a hospital operating room with necessary antibiotic prophylaxis to prevent systemic infections. Restorative treatments were done by placement of either temporary or permanent fillings into teeth, and dental calculus was removed. Periodontal treatments were often carried out in an operating room, in case of bleeding. Oral hygiene was emphasized to the patients waiting for a LT. Some patients may have been so ill that dental treatment had to be postponed due to rapidly progressing liver failure without the possibility of an oral examination.

Post-transplant oral health status **(Studies IV-V)**

A new PTG was performed to discover any signs of infection in the jaws. Two experienced hospital dentists examined patients during antibiotic prophylaxis according to a standard protocol. Oral health status was recorded, including oral mucosal status, periodontal status, and cariological status as well as assessment of occlusion and possible temporomandibular joint dysfunction. Saliva secretion was measured for both unstimulated and stimulated whole saliva and mucosal samples taken for possible *Candida* infection. Quality of possible dentures was recorded. In addition to oral health data, background demographic and clinical data for all studies included age, gender, time of LT, etiology for LT (liver disease diagnosis), waiting time for LT, other diseases, medications, and MELD score. The data were assessed from patient medical and dental records, radiographs, the Finnish LT registry, and HUCH laboratory database.

Questionnaire

For Studies IV-V, LT recipients filled in a questionnaire before the clinical oral examination (Appendix). A similar questionnaire has been used in our clinic in several previous and also in ongoing studies (163). The questionnaire was available in the two official languages of Finland: Finnish and Swedish. It inquired about educational level, working status, last dental visit, smoking, alcohol use, and self-assessment of oral health, and several questions were aimed at assessment of dry-mouth-related oral symptoms.

Control population

Control data for Studies IV and V came from the Health 2000 Health Examination Survey in Finland in which a total of 6335 individuals participated both in a clinical oral health examination and in a home interview during 2000-2001 (164). This nationwide survey sought information on the most important public national health problems, their causes, and treatment, as well as on the population's functional capacity and working capacity (165). Liver disease was an exclusion criterion in control-subject selection, but not other systemic diseases, like cardiovascular disease and diabetes. Three control subjects for each LT recipient were matched with respect to age, gender, and area of residence, and the matching was done separately for chronic and acute LT recipients.

The oral examination included PTG and thorough examination of the oral mucosa, teeth, and gingival tissue (164). The oral examination was performed in a similar manner as for the LT recipients, except that no salivary flow was measured and no *Candida* cultivation took place. The questionnaire for the controls covered educational level, working status, dysphagia, burning mouth, and dysgeusia, as well as questions on self-assessment of one's own oral health. Information regarding smoking and alcohol use of the controls came either from the questionnaire or home interiew.

Statistical analysis

The statistical software was PASW (IBM Co., Armonk, NY, USA) versions 17.0 and 18.0. In general, the Chi-Square (Fischer's exact test, two-tailed) test served for categorical variables and the Mann-Whitney U-test for continuous variables. All CIs were calculated at the 95% level, and P-values <0.05 were considered significant.

One-way ANOVA served to analyze differences in means between the liver disease etiology groups. Student's t-test or the non-parametric Mann-Whitney U-test served for study of statistical associations between liver disease etiology groups and MELD score groups in relation to oral health. Uni- and multivariate logistic regression analysis was performed to study risk factors associated with worse oral health (**Study I**).

Associations between number of days from diagnosis of liver disease to LT and number of tooth extractions were tested by uni- and multivariate linear regression. Correlations between number of tooth extractions (median tooth extractions) and change in MELD score during the preceding year before LT were evaluated by Spearman test (**Study II**). Infection risk was assessed by two methods: by incidence rates, which takes into account multiple infections in the same patient and by Cox regression analysis, which allows for multivariate analysis. Multivariate analysis included both pre- and post-transplant variables such as age, gender, etiology of acute liver failure, waiting time for LT, MELD score, and immunosuppression. The Kaplan–Meier method with the log-rank test served for survival analysis to compare infection incidences between groups (**Study III**).

Multivariable binary logistic regression analysis (backward Wald) allowed assessment of possible risk factors for the subjective oral symptoms in LT recipients. Variables entered into the model were: age, gender, follow-up time, diabetes, current alcohol use, current smoking, number of medications, central nervous system medications, cardiovascular medications, pulmonary medications, working status, and removable dentures (**Study IV).** Logistic regression analysis involved risk factors for OML both in LT recipients and in controls. Variables entered into the same model: case/control, age, dysphagia, presence of removable dentures, number of teeth, alcohol use, current smoking, and total number of daily medications and cardiovascular medications (**Study V**).

RESULTS

Pretransplant dental evaluation of chronic LT candidates (Study I)

Among 212 chronic LT candidates, mean number of teeth was 23 (including 11 edentulous patients). The 31 PBC patients had significantly fewer teeth than did the 54 PSC patients (20 vs. 26, P<0.005); 11% of the patients had removable dentures. Of the CLD patients, 133 (63%) required tooth extractions, and 14 (11%) of them needed hospital treatment for complications associated with tooth extraction. 10 had episodes of excessive bleeding, and 4 had fever, and these complications occurred only among the cirrhotic patients: ones with alcohol cirrhosis, PBC, or other cirrhosis. On average, 3 teeth each were extracted, among all patients. The highest number of tooth extractions had occurred in alcohol cirrhosis patients, a difference significant when compared to PSC patients (6 vs. 3, P<0.005). LT candidates with a higher MELD score (11-18) associated significantly with older age, fewer teeth, and more tooth extractions when compared with those patients with a lower MELD score (1-10), as shown below.

Table 11. Dental health status of CLD patients by MELD group.

	MELD 1-10 n=80	MELD 11-18 n=74	MELD 19-40 n=58
Age, mean (SD)	47 (12) *	51 (12)	50 (12)
Number of teeth, mean (SD)	25 (7) ¶	21 (10)	23 (7)
Number of extractions, mean (SD)	2 (3) §	5 (5)	3 (4) **

* P<0.05, CI: 0.4-8.1
¶ P<0.005, CI: -6.7-(-)1.4 between middle and lower MELD groups
§ P<0.001, CI: 1.6-4.2
** P<0.05, CI: 0.4-2.6 between upper and lower MELD groups

By univariate analysis, a higher MELD score (OR=0.6, CI: 0.5-1.0, P<0.05) and certain etiologies such as alcohol cirrhosis (OR=0.2, CI: 0.0-0.5, P<0.005) correlated with need for tooth extractions but after adjusting for several confounders, age remained the only significant factor for tooth extractions (OR=1.0, CI: 0.9-1.0, P<0.005).

Association between dental infections and clinical course of chronic liver disease (Study II)

In univariate linear regression analysis, multiple tooth extractions in liver cirrhosis patients were associated with worsening of liver cirrhosis as indicated by a shorter duration from diagnosis of liver disease to need for LT ($P<0.05$). After adjusting for various confounders, as seen in Table 12, the association between multiple dental infections and progression of liver cirrhosis remained significant ($P<0.05$). Liver cirrhosis patients with 6 or more tooth extractions (= dental infectious foci) had their LT approximately 3 months earlier than those patients who had less than 5 extractions.

Among a subgroup of patients residing within the transplant center's hospital district (n=38) and with accurate laboratory follow-up data, the MELD score increased by roughly 4 units on average during the year preceding the dental examination, and it correlated with the number of tooth extractions ($r=0.43$, $P<0.05$). Among 38 patients, 10 had 13 episodes of SBP. *Streptococcus viridans* occurred only among patients with multiple tooth extractions.

Table 12. Association between number of tooth extractions and time in days from diagnosis to LT among patients with liver cirrhosis.

	Univariate			**Multivariate**		
	Beta	95% CI	P	Beta	95% CI	Significance
Tooth extractions	-147	-269-(-25.5)	0.02	-96.2	-196-(-5.80)	<0.05
Age	30.8	-22.8-84.5	0.24	38.0	-12.3-88.2	Ns
Alcohol cirrhosis	-2733	-3819-(-1647)	<0.001	-1872	-3443-(-302)	<0.05
MELD score	-3.73	-75.6-68.1	0.92	47.2	-26.7-121	Ns

Oral infections and post-transplant infectious complications among acute or subacute LT recipients (Study III)

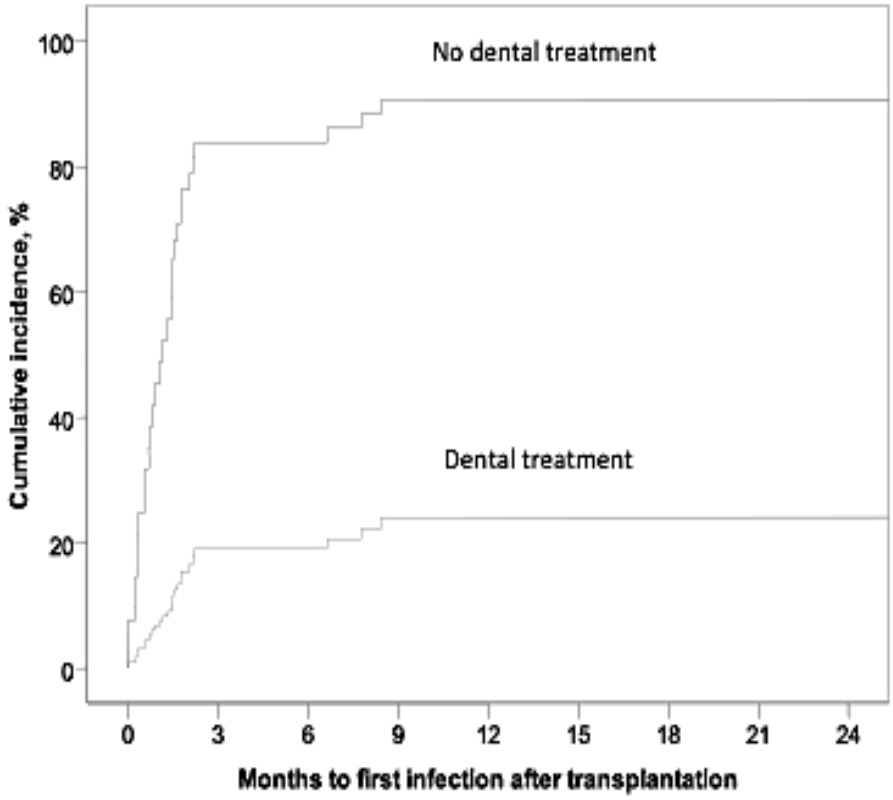
Among acute LT recipients, lack of dental treatment before LT elevated their risk for post-transplant infectious complications by 8-fold in the multivariate Cox regression analysis (OR=8.54, 95%CI:1.82–40.1, P<0.05), taking into account several pre- and post-transplant factors: age, gender, etiology of acute liver failure, waiting time for LT, MELD score, and level of immunosuppression. Both early (<6 months) and late (>6 months) post-transplant infections occurred significantly more often in the group without dental treatment. Nine cases of septic infections occurred in the group without dental treatment but only one septic episode in the group with dental treatment. Pathogens occurring in the groups are shown below.

Table 13. Pathogens isolated from the septic complications after LT by group.

	No dental treatment n=16	**Dental treatment** n=35
Klebsiella spp.	3	
Escherichia coli	2	
Staphylococcus epidermidis	1	1
Pseudomonas aeruginosa (tobramycin resistant)	1	
Enterococcus faecalis	1	
Candida albicans	1	
Total number of septic episodes	9	1

The cumulative infection incidence (number of patients with at least one infection episode) reached over 80% at 9 months post-transplant in the group without dental treatment, but remained under 30% in the group with pretransplant dental treatment as shown in Figure 5. This difference between the groups emerged mainly during the first 3 months after transplantation.

Figure 5. Cumulative infection incidence.



Effect of immunosuppression on oral health in LT recipients compared to a control population (Study IV)

Median follow-up time after LT was approximately 6 years (range 2-11) among both chronic (n=64) and acute (n=20) LT recipients. Between chronic and acute LT recipients, immunosuppressive medication did not differ. About half of all patients used CsA and the other half TAC. Only 4 chronic LT recipients used mTOR. Table 14 shows number of medications, salivary flow rates, oral health data, as well as subjective oral symptoms and other data obtained from the questionnaire in LT recipients and controls. Of all LT recipients, 24% wore removable dentures.

Dysphagia was significantly more common in chronic LT recipients than in controls (23% vs. 12%, $P<0.05$). Neither burning mouth syndrome (BMS) nor dysgeusia was more common in LT recipients.

Taking 8 or more different daily medications, including immunosuppression and concomitant disease medication, when compared with 4 or fewer, raised risk for xerostomia significantly in the chronic LT recipients ($P<0.01$). The same trend was evident in acute LT recipients. For controls, taking 8 or more daily medications led to significantly increased risk for BMS when compared to 4 or fewer ($P<0.05$).

Working correlated with xerostomia (OR=0.3, 95%CI: 0.1-0.8, $P<0.05$). Risk factors for BMS included older age and shorter follow-up after LT (OR=1.1, 95%CI: 1.0-1.2, $P<0.05$; OR=0.5, 95%CI: 0.3-0.9, $P<0.01$, respectively). Medications to treat disorders in the central nervous system increased risk for dysphagia (OR=2.9, 95%CI: 1.3-6.6, $P<0.05$) and having dentures correlated with dysgeusia (OR=23.4, 95%CI: 1.1-511, $P<0.05$).

Table 14. Oral health data in LT recipients and controls.

	Chronic LT recipients n=64	**Controls for chronic n=192**	**Acute LT recipients n=20**	**Controls for acute n=60**
Number of medications, mean (SD)	7 (2) †	2 (2)	6 (2)	2 (2)
Cardiovascular medications, %	86 †	35	95 †	25
Unstimulated salivary flow, ml/min, mean (SD)	0.3 (0.3) ‡	NK	0.6 (0.5)	NK
Stimulated salivary flow, ml/min, mean (SD)	1.7 (1.1)	NK	1.8 (0.9)	NK
Reduced unstimulated salivary flow (≤0.1 ml/min), %	31	NK	10	NK
Reduced stimulated salivary flow (≤0.7 ml/min), %	20	NK	10	NK
Xerostomia, %	48	NK	42	NK
Dysphagia, %	23 ¶	12	5	15
Burning mouth syndrome, %	19	12	5	23
Dysgeusia, %	5	8	0	13
Number of teeth, mean (SD)	21.2 (8.5)	20.5 (9.8)	23.1 (8.5)	19.5 (10.4)
Number of carious teeth, mean (SD)	1.1 (1.5) *	0.5 (1.0)	0.9 (1.1) ¶	0.5 (1.1)
Self-assessment of oral health, good, %	38 *	61	47 ¶	65
Alcohol use, %	38 †	82	20 †	78
Current smoking, %	14	24	20	30

NK, not known
† P<0.001 between LT recipients and their controls
‡ P<0.01 between chronic and acute LT recipients
* P<0.005 between LT recipients and their controls
¶ P<0.05 between LT recipients and their controls

Effect of immunosuppression on oral mucosal health in LT recipients compared to control population (Study V)

OMLs were significantly more frequent in LT recipients (43%) than in controls (15%) (P<0.001). Different types of OMLs could have occurred simultaneously in the same patient (Table 15). Precancerous OMLs were twice as common in chronic LT recipients as in controls (12.5% vs. 5.7%, Ns). DIGO was significantly more common in the CsA (29%) than in the TAC group (5%) (P<0.01), and simultaneous use of calcium-channel blockers led to increased risk when a calcium-channel blocker was added either to CsA (47%) or TAC (8%) (P<0.05). Use of steroids increased the risk for any OML (53%) and for *Candida* (68%) (Ns).

Table 15. Oral mucosal lesions in LT recipients and in controls

	Chronic LT recipients n=64	**Controls for chronic n=192**	**Acute LT recipients n=20**	**Controls for acute n=60**
Any oral mucosal lesion, (%) *	43.8 *	14.1	40.0	16.7
DIGO	16.1 *	1.0	20.0	0.0
Mucosal hyperplasy	4.7	2.6	10.0	3.3
Denture stomatitis	1.6	5.7	10.0	8.3
Tongue lesions ¶	9.4	NK	5.0	NK
Precancerous lesions §	12.5	5.7	5.0	10.0
Other oral mucosal lesions †	9.4	9.9	10.0	10.0
Candida infection, %	57	NK	55	NK

NK, not known
* P<0.001 between LT recipients and their controls
¶ hairy tongue, atrophic tongue, fissured tongue, geographic tongue
§ OLP, leukoplakia, erythroplakia, ulcers (excluding frictional keratosis)
† angular cheilitis, echymoses (bruise), petechiae, fistula, tumor-like structures (e.g. fibromas, hemangiomas, mucoceles), and other inflammatory oral mucosal lesions

Risk factors for OMLs were investigated in the same regression model for both the 84 LT recipients and 252 controls. Risk was highest for LT recipients (OR=9.2, 95%CI: 4.5-19.0, P<0.001). Other significant risk factors were number of teeth, current alcohol use, and smoking (OR=0.9, 95%CI: 0.9-1.0, P<0.001; OR=2.4, 95%CI: 1.2-5.0, P<0.05; OR=2.0, 95%CI: 1.0-3.8, P<0.05).

Comparison of oral health data before and after LT (unpublished data)

Both pre- and post-transplant oral health data were available for 71 LT recipients. Changes in their oral health data are presented in Table 16. Although the mean number of teeth was significantly lower (from 25 to 21 teeth), a significant improvement had occurred in prevalence of oral infection foci and caries lesions. Oral mucosal health seemed also to have improved but not significantly.

Table 16. Comparison of pre- and post-transplant oral health data.

Oral health status	Before LT	After LT	Significance
Oral mucosal pathologies, %	52	45	Ns
Number of teeth, mean (SD)	25 (8)	21 (9)	P<0.001
Number of carious teeth, mean (SD)	2 (2)	1 (1)	P<0.01
Infectious dental foci, mean (SD)	3 (3)	0 (0)	P<0.001

DISCUSSION

Infection risk

In the group of ALF patients who had no dental treatment before LT, risk for infectious post-transplant complications was higher, and this significantly elevated risk emerged even after adjustment for various confounding factors. Two fatal septic complications occurred only in the group lacking dental treatment. Most infection episodes occurred very early, within the first 3 months post-transplant when the level of immunosuppression was highest. These findings stress the importance of eliminating – whenever possible – all potential sources of infectious oral and dental foci before LT (4), taking into consideration the patient's medical condition.

Oral bacteria were not, in this study, cultivated from mouth samples, but two possible oral-derived microbes were isolated in the systemic infections: *E. faecalis and C.albicans.* LT candidates generally had poor oral health before transplantation, and it may be assumed that the group that had no dental treatment may have had several untreated dental infections. Inflammation caused by gingivitis or periodontitis possibly led to the increased levels of proinflammatory cytokines, ones such as TNF-α, IL-1, and MMPs, which then triggered such systemic infections.

SBP is a very serious complication with high mortality in cirrhotic patients, and these infections may be caused by various pathogens. Different *viridans* group streptococci such as *S.mitis, S.mutans, S. salivarius*, and *S. oralis*, have been reported in SBP episodes among CLD patients (48), and all these microbes can occur in the oral cavity. Our results showed that *S. viridans* cases emerged only among those LT patients who had undergone multiple tooth extractions and therefore had worse dental health. Although oral pathogens were not cultivated in this retrospective study, we can still speculate that since *S.viridans* is abundant in the oral cavity, those peritonitis cases associated with *S.viridans* may have originated from dental infections. Poor oral hygiene and carious lesions are associated with *viridans* group streptococci, of which, *S.mutans* is the caries pathogen. Even among healthy individuals, if they have poor oral hygiene and untreated dental infections, they may have *S. mutans* spreading through inflamed gums into their general circulatory system and leading to

bacteremia and sepsis. The consequences of *S. viridans*-derived bacteremia in patients with immune deficiency can, however, be fatal (166). In infective endocarditis, *S. viridans* is the most common causative pathogen, with especially the serotype k *S. mutans* highly virulent in systemic diseases (167).

Interest has increased in the relationship between periodontal disease and liver disease. A recent study showed periodontal disease to have an effect on lipid levels and therefore to impact the progression of liver disease (115). Similar findings came from another study that found effects of inflammatory mechanisms of proatherogenic pathogens upon lipid metabolism in an animal model (168). In yet another study, HCC patients with chronic periodontitis showed a more severe form of HCC (116). We assume that the circulating periodontal and other oral cytokines in our cirrhotic patients added to the overall inflammation in the body, triggering the progression of chronic liver disease. This is a novel finding, since the possibility of oral-derived bacteremia in the course of chronic liver disease has been poorly studied, but prospective studies are necessary to confirm the causative relationship between dental infections and CLD progression.

Oral health data

LT candidates experienced frequent dental and oral infections in general but the differing etiologies of CLD affected their oral health differently. Our results are in line with others' that have shown generally poor oral health among LT candidates (119), but our study is the first to report on oral health status between etiology groups and especially according to MELD score. The MELD score of PBC and alcohol cirrhosis patients was considerably higher than that of PSC patients, and seemed to associate with worse oral health. PBC patients had the least number of teeth, and the alcohol cirrhosis patients had the most tooth extractions in comparison with PSC patients.

Not all PSC patients had developed end-stage CLD, and their indications for LT included recurrent cholangitis episodes or progressive changes in the bile ducts that could develop into cholangiocarcinoma. The better general health, and younger age among PSC patients most likely also affected their oral health status as seen in their higher number of teeth. PBC and alcohol cirrhosis patients, on the other hand, often were in end-stage liver insufficiency during pre-transplant dental evaluation. Smoking and alcohol are significant risk factors for

periodontitis (169,170), and the alcohol cirrhosis patients often also smoked or had been heavy smokers. Ours is in agreement with a previous study that showed differences in oral health between alcohol cirrhosis or other cirrhotic patients and healthy controls (171). Alcohol cirrhosis patients were also presumed to neglect their oral health care, which may have led to the full-mouth extractions evident among several of our alcohol cirrhosis patients. These risk factors as well as basic differences in the etiologies of liver disease and also CLD severity may have affected oral health between CLD groups.

Because liver cirrhosis is associated with high risk for bleeding and infections, dental treatments in these patients also proved to be risky according to our own investigation. Some of the bleeding complications were still occurring several days post-operatively and required hospital treatment. The cases of fever needed strong iv-antibiotics. These complications occurred only in those patients with end-stage CLD, so a worse general health condition among cirrhotic patients was also reflected by their dental-treatment history. Although studies in this field report bleeding complications during dental procedures among CLD patients (102,109,111), one recent study found no episodes of postoperative bleeding in CLD patients following invasive dental procedures (172). The patients in that study differed with ours, however. That study by Hong et al. included CLD patients who had no end-stage liver insufficiency and had a mean INR of less than 2; they needed no replacement therapy, whereas we frequently used replacement therapy for our end-stage CLD patients. Patients with CLD should be reminded of the importance of regular dental visits and good oral hygiene during the course of their liver disease and well before planned LT. This may result in fewer tooth extractions and possibly also lead to a more favorable outcome regarding high-risk dental treatments (173). This in turn could also contribute to less expense in treating these immunocompromised patients for complications that may develop and may require specialized health care.

Oral findings in LT compared to those in controls

LT recipients' oral health data was compared to that of a general Finnish population by our forming control groups matched with the LT recipients by age, gender, and residence area. The LT recipients were followed on average for 6 years after transplantation. Several significant differences emerged in oral health, especially between the chronic LT patients and

controls. Those chronic LT patients presenting with significantly more caries also suffered from dysphagia significantly more often.

The largest difference in oral health data between LT patients and controls was in the frequency of OMLs. In Study V, these occurred in 43% of the LT recipients and were most likely attributable to immunosuppressive medications, since DIGO was the single most common type of lesion. Our results support previous research in that respect (154-159). Compared to a study by Diaz-Ortiz et al (159), fissured tongue was less common among our patients, a difference perhaps explained by differing etiologies in LT. Viral hepatitis is not a common indication for LT in our country, in contrast to the situation in many other countries.

Our chronic LT patients showed a marked risk for precancerous lesions such as leukoplakia. Alcohol use and smoking are common risk factors for such potentially malignant oral lesions (75). Here, these risks correlated with OMLs, but it is noteworthy that LT patients used alcohol and smoked far less than did the population controls. We therefore assume that the effect of immunosuppressive medications on potentially malignant lesions remains strong. Transplant recipients in general experience a roughly 2 to 4-fold elevated risk for de-novo cancers (174). Especially skin cancers have been reported in this population (175). In addition, persistent infection with oncogenic viruses – those such as Kaposi sarcoma EBV, high-risk HPVs, and EBV in general - are associated with an up to 100-fold increased risk for malignancies (176).

Assessment of their own oral health was also investigated between the LT patients and controls. The chronic LT patients felt that their oral health was significantly less good. An earlier study from our own center investigating health-related quality of life and employment status in LT recipients (1) included most of the same patients as in the present study. Younger patients often returned to work in less than 6 months after LT. Being active and younger may therefore also reflect the way that these patients perceive their oral health status. Missing teeth and impaired chewing function could also account for worse perception of oral health. A large number of teeth were extracted before LT, and prosthetic rehabilitation was not always done. Only one patient had a dental implant replacing a missing molar; most patients' molars were not replaced if they still retained premolars.

Medications

LT recipients used on average 7 different daily medications, a difference highly significant with respect to the control population's. In addition to immunosuppressive medications, among which CsA and TAC were used equally between the patient groups, were other medications, most commonly cardiovascular ones. CNIs and corticosteroids elevate the risk for hypertension. This in turn can lead to cardiovascular disease, one of the leading causes of late mortality among LT recipients (174). For blood pressure, drugs of choice are selective ß-blockers, diuretics, ACE-inhibitors, calcium channel blockers, and other cardiovascular medications. Cardiovascular medications are xerogenic, and diuretics in particular reduce salivary flow (177).

Indeed, the high number of daily medications may have caused hyposalivation and xerostomia which led to increased susceptibility to caries and dry-mouth-related symptoms (178). The increasing number of medications seemed to be linked to increases in all the dry-mouth-related symptoms, both among patients and controls; although significant differences between number of drugs emerged only in relation to xerostomia in the chronic LT patients, whereas burning mouth syndrome was frequent among the control population.

When our immunosuppressant groups among the LT patients were compared in relation to OML, DIGO was the single most common type of OML in LT recipients and to no one's surprise, CsA and concomitant use of calcium-channel blocker increased its prevalence significantly over that of TAC supporting previous research (34,153-155). Systemic corticosteroid use promoted the prevalence of all OMLs. Risk for oral candidosis in particular increased considerably, with more than half of all LT patients being positive for *Candida*. In addition to steroids and other immunosuppressants, another risk factor that may have added to risk for *Candida* may have been the dentures often showing a need for repair. The porous surface of a denture is an ideal habitat for oral microbes. Our finding agrees with findings also of a high prevalence of candidosis among transplant populations (52,179).

Dry mouth

Among all LT patients, xerostomia was highly prevalent. Dysphagia, a term which might describe the feeling of dry mouth even better, was a significantly more frequent complaint among chronic LT patients than among population-based controls. Similar findings with respect to dry mouth were found by Guggenheimer and coworkers but their study included LT candidates (11). Patients responded that dry mouth was felt mainly at night-time, unsurprisingly, because salivary secretion follows circadian rhythms (41). A subjective feeling of dry mouth in LT patients did not always correlate with objectively measured hyposalivation, since only 46% of the patients diagnosed with hyposalivation reported xerostomia. Similar findings have also been reported (180).

Our chronic LT patients reported all dry-mouth-related symptoms more frequently than did the acute LT patients, who in turn showed even fewer symptoms than did the population-based controls. Immunological variations by liver disease etiology may explain these differences. Chronic LT recipients included many with autoimmune liver disease such as autoimmune hepatitis or PBC, which may share similar characteristics with Sjögren's syndrome. These patients are known to suffer from sicca syndrome (99,132,181). One-third of the chronic LT patients also had diabetes, which predisposes to reduced salivary flow (83). PBC patients also commonly used cardiovascular and psychiatric medications, known to affect salivary flow (81). Therefore, immunological differences, other concomitant diseases, and medications affecting salivary flow may explain why the chronic LT patients had significantly lower salivary flow rates than did the acute patients.

Hyposalivation is a considerable risk factor for all oral and dental diseases, so the significantly lower unstimulated salivary flow may be the cause of the higher incidence of caries in the chronic than in the acute patients or in controls. Dental caries progresses rapidly in a dry mouth; especially root caries is a challenge dentists face when treating patients who retain their teeth until old age (182,183). In addition, dry mouth is very unpleasant for the patient, causing difficulties in speaking, eating, tasting, or wearing removable dentures, and the possible oral mucosal lesions can be extremely painful in a dry mouth. Dry mouth is a real challenge in immunocompromised LT patients taking several medications. Regular dental appointments are extremely important for them since undetected oral infections can cause systemic complications. Good oral hygiene is most important in minimizing risk for

oral-derived inflammation that could compromise general health. Edentulous patients also need reminders of regular oral examinations since potentially malignant lesions are usually more common in denture wearers and dentures also need regular checking for fit and condition. All clinicians treating such patients should encourage them to quit smoking and use alcohol moderately; these factors, together with xerogenic medications, pose a real threat of oral cancer as well.

Does liver transplantation worsen or improve oral health?

Our oral health data were available both before and after LT in a subgroup of 71 patients. A large number of oral infection foci were prevalent before LT, but after LT only a few sporadic cases included severe dental infections that resulted in tooth extractions. Although LT recipients are at risk for caries, after LT ours showed significantly fewer caries. Their oral mucosal status also seemed to improve slightly after LT, although a high prevalence of drug-induced oral mucosal lesions occurred. Those lesions that were associated with the underlying liver disease, for instance, petechias present in the oral mucosa of cirrhotic patients had disappeared due to their now-functioning liver. It is noteworthy that the patients were examined differently in Study I than in Studies IV and V; the latter studies included a fixed protocol. We can therefore assume that some OMLs may have been overlooked during pretransplant dental evaluation, and the true prevalence of OMLs before LT may have been even greater. Overall oral health status, indeed, thus seemed to improve due to LT.

KEY FINDINGS AND CONCLUSIONS

Good oral and dental health is of utmost important for LT patients both in the pre- and the post-transplant stages. The following conclusions can be drawn from the present series of studies:

1. Chronic liver disease affected oral health differently depending on the underlying etiology and severity of the disease. PBC patients had on average 20 teeth in comparison to PSC patients' mean number of 26 teeth. Alcohol cirrhosis patients had the most teeth extracted, and their dental treatments were often linked with serious complications such as bleeding problems and post-operative infections. More severe liver disease condition seemed to correlate with worse oral health status (**Study I**).

2. Dental infections were associated with the progression of chronic liver disease. Cirrhotic patients with the most teeth extracted had a shorter time from their diagnosis of liver disease to their need for LT (**Study II**).

3. In the acute LT recipients, treatment of dental infections before LT was associated with fewer systemic infections after the operation. For those patients who lacked pre-transplant dental treatment, risk for post-transplant systemic infections was 8-fold higher. (**Study III**).

4. Compared to population controls, chronic LT recipients had twice as many caries lesions and reported almost twice as often dysphagia. They also had lower salivary flow rates than did acute LT recipients. These differences may have been due to the differing etiology of their liver disease and also due to immunosuppressive and other xerogenic medications (**Study IV**).

5. Compared with those among population controls, oral mucosal lesions in chronic LT recipients were 3-fold-, and precancerous lesions twice as common. The most common type of oral lesion was drug-induced gingival overgrowth; simultaneous use of cyclosporine-A and calcium-channel blockers increased its prevalence. Furthermore, use of steroids led to increased risk for *Candida.* Frequent oral mucosal lesions may be explained not only by immunosuppression but also by the high number of other medications used by LT recipients. Since these lesions may offer a risk of becoming malignant, regular oral examinations are indicated (**Study V**).

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