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ORAL HEALTH AND KIDNEY DISEASE
with emphasis on diabetic nephropathy

Maarit Vesterinen

Academic dissertation

To be presented and publicly discussed with the permission of the Faculty of Medicine of the University of Helsinki, in the Auditorium XII at University of Helsinki, Unioninkatu 34, Helsinki, on November 18th, 2011, at 12 noon
To Vesa, Amanda, Karoliina and Justus
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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>ADPKD</td>
<td>Autosomal dominant polycystic kidney disease</td>
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<td>BMS</td>
<td>Burning mouth syndrome</td>
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<tr>
<td>CGN</td>
<td>Chronic glomerulonephritis</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence intervals</td>
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<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
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<tr>
<td>CPITN</td>
<td>Community Periodontal Index of Treatment Needs</td>
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<td>CRF</td>
<td>Chronic renal failure</td>
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<tr>
<td>DMFS</td>
<td>Decayed, Missing, Filled Surfaces -index</td>
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<td>DMFT</td>
<td>Decayed, Missing, Filled Teeth -index</td>
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<tr>
<td>DT</td>
<td>Decayed teeth -index</td>
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<td>ESRD</td>
<td>End-stage renal disease</td>
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<td>FT</td>
<td>Filled teeth -index</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>GO</td>
<td>Gingival overgrowth</td>
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<tr>
<td>HbA\textsubscript{1c}</td>
<td>Glycosylated hemoglobin</td>
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<tr>
<td>HPV</td>
<td>Human papilloma virus</td>
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<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
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<tr>
<td>IgA</td>
<td>Immunoglobulin A</td>
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<tr>
<td>IgG</td>
<td>Immunoglobulin G</td>
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<tr>
<td>IgM</td>
<td>Immunoglobulin M</td>
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<tr>
<td>Ns</td>
<td>Not significant</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PM</td>
<td>Painful mouth</td>
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<tr>
<td>PTG</td>
<td>Panoramic tomography</td>
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<td>RRT</td>
<td>Renal replacement therapy</td>
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<td>WHO</td>
<td>World Health Organization</td>
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LIST OF ORIGINAL PUBLICATIONS

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


IV Vesterinen Maarit, Ruokonen Hellevi, Leivo Tomi, Furuholm Jussi, Kari Kirsti, Honkanen Eero, Meurman Jukka H. Oral and salivary parameters of predialysis chronic kidney disease patients. Submitted

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ABSTRACT

A decline in oral health may potentially act as an early marker of systemic disease progression. This series of studies examined oral health in chronic kidney disease (CKD) patients. The hypothesis was that the oral health status, symptoms, sensations, salivary flow rates and salivary composition vary in different renal failure stages and depend on the etiology of the kidney disease.

Altogether 217 patients with chronic renal failure were examined in two studies. The patients were regularly seen at the Department of Medicine, Division of Nephrology, Helsinki University Central Hospital, and further referred for clinical and radiographic oral and dental examination to the Department of Oral and Maxillofacial Diseases of the hospital. Resting and stimulated saliva flow rates were also measured, whilst the biochemical and microbiological composition of saliva was analyzed. Lifestyle and oral symptoms were recorded using a questionnaire, and blood parameters were collected from the hospital records.

Results were analyzed statistically by comparing the disease stages of the various CKD patient groups. This longitudinal 10-year study on 39 patients followed cases from predialysis, to dialysis, to post transplant stage, with no statistically significant difference seen in clinical parameters. However, some saliva parameters after renal transplantation were significantly improved compared to levels at the predialysis stage. For example, levels of immunoglobulin (Ig) A, G and M all decreased significantly after kidney transplantation. Increased concentrations of IgA, IgG and IgM may reflect disintegration of the oral epithelium and are usually markers of poor general condition.

A cross-sectional investigation on 178 CKD patients at the predialysis stage compared diabetic nephropathy patients to those suffering from other kidney diseases. The results showed more dental caries and lower stimulated salivary flow rates in the diabetic patients compared with the other CKD patients. Contrary to our expectation, however, diabetic nephropathy did not seem to affect periodontal health more severely than the other kidney diseases. Although diabetes is known to associate with xerostomia and other oral symptoms, it did not seem to increase the prevalence of oral discomfort.

In summary, this series of studies has provided new information regarding the oral health of CKD patients. As expected, the commencement of renal disease reflects in oral symptoms and signs.
Diabetic nephropathy, in particular, appears to impart a requirement for special attention in the oral health care of patients suffering from this disease.
INTRODUCTION

Chronic kidney disease (CKD) is a worldwide health problem, with adverse outcomes of cardiovascular disease and premature death (Levey et al. 2011). The ageing of populations along with the growing prevalence of chronic diseases such as diabetes and hypertension is leading to worldwide increase in the number of CKD patients (James et al. 2010).

Diabetes is the leading global cause of CKD. According to the World Health Organization (WHO), more than 220 million people worldwide have diabetes and the number is growing. In 2004, an estimated 3.4 million people died from the consequences of high blood sugar and diabetes deaths are predicted to double between 2005 and 2030 (WHO 2011a). In Finland, diabetes is the most common cause for commencing dialysis therapy for end-stage renal disease (ESRD), (Finnish Registry for Kidney Diseases 2009).

Oral changes may be the first sign of systemic disease (Chi et al. 2010). Uraemic patients have more dental problems than healthy controls and the patients seem to develop their problems before they have progressed to dialysis (Thorman et al. 2009b). Greater attention to dental problems should be given during the progression of CKD associated uraemia to not only prevent the worsening of oral health, but also to diminish the risk of infection complications during various phases of CKD and to improve patient survival.

It has become evident that inflammation plays an important role in the pathogenesis of atherosclerosis complications (Huittinen at al. 2003; James et al. 2010). CKD patients also have an increased risk of atherosclerosis complications (including myocardial infarction, sudden death to cardiac arrhythmia, cerebrovascular accidents, and peripheral vascular disease) (Levey et al. 2011). In line with this, oral and dental problems can be an important source of systemic inflammation (Janket et al. 2010). Salivary IgG is an ultrafiltrate of serum IgG (Söderling 1989). Furthermore, increased serum IgG levels against periodontal pathogens have been associated with an increased intima-media thickness (Beck et al. 2006), whilst increased serum IgA levels specific to periodontopathogens has been predictive of future myocardial infarction (Pussinen et al. 2005) and stroke (Pussinen at al. 2004). Salivary IgA may well measure the local inflammation in oral mucosa (Janket et al. 2010).
CKD may cause a variety of systemic symptoms, such as anaemia, platelet disorders, hypertension, development of metabolic acidosis and hyperkalemia. Untreated uremia can affect the central nervous system causing loss of memory, depression, hallucinations, slurred speech, epilepsy, and even coma (Naylor & Frederics 1996; Ferguson & Whyman 1998). Oral manifestations in CKD include xerostomia, gingival bleeding, gingival enlargement secondary to drug therapy namely calcium channel blockers and cyclosporin, fungal infection, bone lesions and tooth mobility, in addition to a wide range of oral mucosal lesions like ulceration, lichen planus, stomatitis, and white patches (Opatry 1997; Kho et al. 1999; Mealey 2000; Klassen & Krasko 2002; Davidovich et al. 2005; Bots et al. 2007; Thorman et al. 2009b). The data is contradictory, however, regarding oral symptoms among the patients with kidney disease: there are conflicting outcomes in recent similar studies (Bots et al. 2006; Sobrado Marinho et al. 2007; Bayraktar et al. 2009).

The purpose of the present study was to examine the comprehensive oral health of patients in different stages of CKD and to analyze if there are differences in oral health parameters when comparing predialysis patients with diabetic nephropathy with other kidney diseases. The study results were expected to help clinicians to recognize typical oral pathologies associated with renal failure and to allow the clinicians to act on an early reciprocal treatment of both oral and kidney diseases. A proper examination of the oral cavity of patients with renal diseases is an invaluable aid to diagnose potentially life-threatening conditions at a primary stage of multisystemic disease. An early detection of oral pathology potentiates treatment to start sooner and may improve patient health and survival.
LITERATURE REVIEW

Oral health

Definition
Good oral health enhances our ability to speak, smile, smell, taste, touch, chew, swallow and convey our feelings through facial expressions. It is therefore an essential part of our everyday lives. According to the World Health Organization (WHO 2011b), “oral health is a state of being free from chronic mouth and facial pain, oral and throat cancer, oral sores, birth defects such as cleft lip and palate, periodontal (gum) disease, tooth decay and tooth loss, and other diseases and disorders that affect the oral cavity. Risk factors for oral diseases include unhealthy diet, tobacco use, harmful alcohol use, and poor oral hygiene.”

In previous studies, age and sex are referred to as strongly dependent factors for oral health, that is, higher age is associated with more decay, missing, filled teeth and periodontal disease (Hugoson et al. 2005). Furthermore, oral health has been shown to be dependent on socio-economic, behavioral and genetic factors (Hassel & Harris 1995; Gao et al. 2010; Werneck et al. 2010), whilst being of male gender contributes to a worse oral health outcome (Hugoson et al. 1998).

Saliva as a diagnostic fluid
Saliva is produced by the minor salivary glands and three pairs of major salivary glands, the parotid, the submandibular, and the sublingual glands. Saliva ensures stability in the oral cavity environment and plays an important role in oral health. It is essential for the maintenance of the oral ecosystems by providing water, nutrients and antimicrobial factors (Thelin et al. 2008). Saliva is a complex mixture composed of 98% water and 2% of organic and inorganic molecules (Humphrey & Williamson 2001). Salivary glands produce an average of 1000 ml of saliva daily, which serves a whole range of functions. It participates in digestion, taste sensation and maintains the balance of oral microflora. Saliva aids in chewing, swallowing and speech (Sreebny 2000; Lima et al. 2010).

Saliva is a good indicator of the plasma levels of various substances such as hormones and drugs. In recent years salivary biomarkers have been used increasingly to detect and predict disease progression. The immunological contents of saliva include secretory IgA (sIgA), IgG and IgM. Salivary immunoglobulin (Ig) A reflects the functional capacity of the glands, while IgG and IgM
are serum ultrafiltrates as are albumin and urea in saliva. Increased concentration of these components are usually markers of a poor general condition (Marcotte & Lavoie 1998; Bergdahl & Bergdahl 2000; Mellanen et al. 2001; Seemann et al. 2004; Teeuw et al. 2004; Pink et al. 2009; Hopcraft & Tan 2010; Palanisamy & Wong 2010). In the future, nanotechnologic techniques may be applied in the analysis of saliva (Pfaffe et al. 2011).

**Oral mucosa**
The oral cavity represents the entry port to the gastrointestinal tract. The oral mucosa consists of a physical barrier and together with integrated immunological elements it prevents the invasion of pathogenic organisms (Novak et al. 2008). The oral cavity can be affected by a wide range of common disorders that are characterized by acute, recurrent or chronic local inflammation of the oral mucosa and submucosal stroma. The inflammatory component of these disorders can be primary (autoimmune) or secondary to infections (fungal, viral, or bacterial) (Fedele et al. 2011). Oral mucosal lesions appear as a result of both local and systemic influence. Examples of local influences are exposure to food, alcohol, tobacco and oral hygiene habits, whereas systemic influences may include disturbances in the mucosal barrier or the innate immune system (Thorman et al. 2009b).

**Common oral diseases**

**Dental caries**
Dental caries, or tooth decay, is one of the most prevalent chronic diseases of people worldwide and of all ages. It is a multifactorial disease that starts with microbiological shifts within the complex biofilm. Dental caries is affected by salivary flow and composition, exposure to fluoride, consumption of dietary sugars and by preventive behaviours (teeth cleaning) (Selwitz et al. 2007). Fluctuations in the pH (caused by metabolically active bacteria in the biofilm) may cause a loss of mineral from the tooth when the pH is declining, or a gain of mineral when the pH is increasing. This cumulative result of the de- and re-mineralization processes may be a net loss of mineral, leading to dissolution of the dental hard tissues and the formation of a caries lesion (Kidd & Fejerskov 2004).
**Periodontal diseases**

Periodontium is comprised of the enfolding and supporting tissues of the tooth: the gingiva, periodontal ligament, cementum and alveolar bone (Mueller 2005). The main functions of periodontium are to attach the teeth to the jaw bones, resolve the forces generated by mastication, and to act as a defence barrier (see, e.g., Cawson et al 2001).

Periodontal diseases are a group of acute, or chronic, bacterial-induced inflammatory diseases that affect the supporting tissues of the teeth. If left untreated they may lead to tooth loss. The pathogenesis involves immunological responses leading to tissue destruction and bone loss. Periodontopathogenic micro-organisms in dental plaque-biofilm and their products are thought to be the main etiologic agents for initiation and progression of periodontal inflammation (Haffajee & Socransky 1994). The host response to these microbes plays an important part in tissue destruction, which may progress in a “linear” way, or in a “burst” and may even be site-specific (Kinane 2000; Gilthorpe et al. 2003).

Periodontal diseases are mainly categorized into gingivitis and periodontitis (as discussed by Ali et al. 2011). According to the international database (WHO, http://www.whocollab.od.mah.se/index.html), severe periodontitis is found in 5-15% of most populations. In Finland, the prevalence of periodontitis was found to be 72% in men and 57% in women (Kansanterveyslaitos 2004). In addition to pathogenic micro-organisms in the biofilm, environmental and genetic factors, contribute to the cause of these diseases (Pihlstrom et al. 2005). Smoking is associated with a higher risk in terms of periodontitis, whilst diabetic patients seem to more susceptible to gingivitis and periodontitis than their healthy counterparts (Mealey & Oates 2006; Nagasawa et al. 2010).

**Candidiasis**

In the majority of adult patients, yeast, mainly Candida albicans, are found to live in the oral cavity (Odds 1988). Other important species are C. tropicalis and C. glabrata (see, e.g., Thorman et al. 2009b). Candidiasis is by far the most common oral fungal infection in humans and has a variety of clinical manifestations. C. albicans may be a component of the normal oral microflora in a small number of people (30-50%), who are carriers without clinical evidence of infection. Candidiasis may exhibit a variety of clinical patterns including pseudomembranous, erythematous, median rhomboid glossitis, chronic multifocal, angular cheilitis, denture stomatitis, hyperplastic, mucocutaneous and endocrine-candidiasis syndromes. Patients who suffer from xerostomia or
hyposalivation for any reason have an increased prevalence of candidiasis (Shimizu et al. 2008; Khovidhunkit et al. 2009; Ergun et al. 2010). Yeast colonization has also been demonstrated in prosthesis (Dorocka-Bobkowska et al. 2010), dental plaque and in periodontal pockets (Pizzo et al. 2002). A main factor associated with yeast overgrowth is a diminished host resistance as a result of some diseases (Rees 2006).

Symptoms of the mouth

**Hyposalivation and xerostomia**

The main factor affecting the composition of saliva is the flow rate (Tenovuo & Lagerlöf 1994). The normal average daily flow of whole saliva in adults is from 1 to 1.5 litres (Edgar 1990; Humphrey & Williamson 2001). Salivary gland hypofunction, hyposalivation, is a condition whereby salivary flow rate (unstimulated or stimulated) is significantly reduced: it is generally defined as an unstimulated whole saliva flow rate less than 0.1-0.2 ml/min and a stimulated whole saliva flow rate less than 0.7 ml/min (Ship et al. 1991; Navazesh et al. 1992; Oxholm & Asmussen 1996). Systemic diseases, such as diabetes or rheumatic diseases (e.g. Sjögren's syndrome) can cause insufficient saliva production (Daniels & Fox 1992; Moore et al. 2001; Habbab et al. 2010). Other influencing factors include the degree of hydration, medication, body position, previous stimulation and circadian rhythm (Dawes 2004). Hyposalivation can be harmful to overall oral health by enhancing oral microbial colonization, yeasts in particular (Pajukoski et al. 2001), but also on the health of the body as a whole (Pink et al. 2009; Montaldo et al. 2010).

Xerostomia is defined as the subjective perception of dry mouth (Fox et al. 1987). It is a subjective symptom which can only be assessed by direct questioning of patients (Hopcraft & Tan 2010). Symptoms of xerostomia include oral burning, halitosis, difficulty to swallow and talk and altered taste sensation. The perception of dry mouth is sometimes, but not necessarily, accompanied by salivary gland hypofunction. Xerostomia and salivary gland hypofunction can increase the risk of dental caries (Dodds et al. 2005) and other oral pathologies, such as oral yeast infection (Pajukoski et al. 2001; Khovidhunkit et al. 2009). Development of xerostomia is associated, for example, with age, certain medications (e.g. antidepressants, antipsychotic medication, antihistamins), radiotherapy, some disease such as Sjögren's syndrome or it may be idiopathic (Bergdahl & Bergdahl 2000; Daniels & Fox 1992; Leal et al. 2010; Pink et al. 2009).
Burning mouth syndrome

It is important to distinguish the terms painful mouth (PM) and burning mouth syndrome (BMS). There has not been consensus concerning the definitions and, until recently, the terms have been confused in the literature. Various conditions of the oral mucosa can give rise to a burning sensation. Candidiasis, erythema migrans, mucocutaneous conditions and stomatitis can all cause mouth burns with visible changes to the oral mucosa. Alternatively, PM has been associated with xerostomia, altered taste sensation and also with hyposalivation (Lamey & Lamb 1988). Other possible causative factors of PM are gingival atrophy and oral ulcerations (Forabosco et al. 1992), candidiasis (Samaranayake et al. 1989) and systemic factors like vitamin B deficiencies (Lamey et al. 1986).

BMS is a fairly rare condition; the prevalence varies in the general population from 0.7% to 4.8% (Lipton et al. 1993; Mott et al. 1993). According to Bergdahl & Bergdahl (1999), BMS affects 3.7% of the general population in Sweden and it is more common in women than men, especially after menopause (5.5%). In Finland, the prevalence of BMS in the adult population has been found to be between 1% and 15% (Tamminen-Salonen et al. 1993).

BMS is an extremely unpleasant condition characterised by a burning sensation of the oral mucosa usually in the absence of clinical and laboratory findings. Frequently-associated symptoms include dry mouth and loss or change of taste. The aetiology of BMS is unknown, even though most of the literature focuses on the role of a possible underlying psychogenic disorder. Conditions that have been reported in association with burning mouth syndrome include chronic anxiety or depression, various nutritional deficiencies, type 2 diabetes and changes in salivary function. Studies have indicated that the dysfunction of several cranial nerves that are associated with taste sensation may be a possible cause of burning mouth syndrome (Grushka et al. 2002). Various conditions of the oral mucosa can give rise to a burning sensation. For example, candidiasis, erythema migrans, mucocutaneous conditions and stomatitis can cause mouth burns with visible changes to the oral mucosa.

The kidneys and chronic kidney disease

The kidneys play a key role in body homeostasis by filtering metabolic waste products from the blood. They are critical in a number of processes including the regulation of electrolyte levels,
blood pressure control and the stimulation of red blood cell production by excreting erythropoietin. A mild decline in kidney function is usually clinically unnoticeable, however serious health problems may occur when people have less than 25% of their kidney function. When this drops below 10%, renal replacement therapy (RRT) is required. When the kidneys are no longer able to remove and regulate water and chemicals, waste products and excess fluid accumulate and cause severe swelling and symptoms of uremia. The associated proteinuria is an important marker in renal disease and independent factor of cardiovascular morbidity and mortality (van der Velde et al. 2011). Common biomarkers of CKD, proteinuria and estimated glomerular filtration rate (GFR), are easy and relatively inexpensive to measure. The associated treatment of patients suffering from renal disease depends on its' nature and severity and differs depending on whether the patient is in the predialysis, dialysis or post transplant stage (Andreoli et al. 2004).

CKD is classified according to GFR (Table 1). Stage 5 includes both patients living with severely impaired renal function and patients on various types of dialysis.

### Table 1. Stages of chronic kidney disease.

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<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR ml/min/1.73m²</th>
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<tr>
<td>1</td>
<td>Slight kidney damage with normal or increased filtration</td>
<td>&gt;90</td>
</tr>
<tr>
<td>2</td>
<td>Mild decrease in kidney function</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate decrease in kidney function</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe decrease in kidney function</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
</tr>
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### Etiologic factors of CKD

ESRD, a condition of severe renal disease requiring RRT, results from the progressive and irreversible destruction of nephron mass, regardless of cause. This leads initially to structural and functional hypertrophy of surviving nephrons (compensatory hypertrophy due to adaptive hyperfiltration) and eventually to loss of glomerular filtration capacity. Several laboratory abnormalities are seen in CKD 3-5, such as anaemia, hyperphosphatemia and hypocalcemia.
Glomerulonephritis has been regarded as the leading global cause of ESRD in the past, however a collection of new primary causes encompasses changes in environment, life style, improved control of infections, advances in the treatment of glomerulonephritis, diabetes mellitus and hypertensive renal disease. The Finnish Registry for Kidney Diseases provides up-to-date information on dialysis and kidney transplantation patients in Finland: the coverage of the registry is estimated at 97-99%. According to the latest report (2009), glomerulonephritis is the most common, and type 1 diabetes the second most common, diagnosis for prevalent patients receiving RRT, whilst it is the most common diagnosis in patients receiving peritoneal dialysis. In addition, the number of patients with type 2 diabetes is growing and it is the leading diagnosis of patients receiving hemodialysis treatment.

**Diabetic nephropathy** is the leading cause of ESRD in western countries: it may be associated both with type 1 and type 2 diabetes. Diabetic nephropathy is characterized clinically by proteinuria and progressive renal insufficiency. The typical glomerular lesion is glomerulosclerosis. Medication that lowers intraglomerular pressure, dramatically slows the progression of diabetic nephropathy, even in normotensive patients (Andreoli et al. 2004).

**Chronic glomerulonephritis** is a group of renal diseases that are clinically characterized by persistent proteinuria and/or hematuria and renal insufficiency. Most cases of chronic glomerulonephritis typically progress slowly over years. The course of the disease depends on the type of chronic glomerulonephritis and often includes a variable combination of proliferative, membranous and sclerotic changes.

**Polycystic kidney disease** of adult type (ADPKD) is a hereditary renal tubular disorder. The kidneys are enlarged with multiple cysts often studding the surface of the kidney. Between 1% and 5% of nephrons develop cysts and the remaining renal parenchyma reveals varying degrees of tubular atrophy, intestinal fibrosis and nephrosclerosis. A progressive decline in renal function is common, with approximately 50% of PKD patients developing end-stage renal disease by age 60 (Andreoli et al. 2004).

**Other CKD diagnoses** include several diseases with renal manifestations, such as hypertensive nephrosclerosis, arteriosclerotic nephropathy, urinary tract obstruction, tubulointerstitial nephritis,
renal amyloidosis, and congenital or hereditary diseases such as Finnish type congenital nephrosis and Alport’s syndrome, in addition to other undefined kidney diseases.

**Therapeutic considerations of CKD**

Medical and dietary therapy are imposed early in order to control symptoms, minimize complications, and to slow the progression of renal insufficiency. Effective, usually multidrug, treatment of hypertension is essential and restriction of dietary sodium intake is important. Preventive measures include the avoidance of nephrotoxic agents such as non-steroidal anti-inflammatory drugs. As renal insufficiency progresses (stage 3, see Table 1), phosphate and potassium rich food should also be restricted. In advanced CKD (stage 4 and 5, see Table 1), it is usually necessary to correct the observed metabolic acidosis and hyperkalemia. Consequently, when the degree of uremia worsens, dialysis and/or transplantation should be considered (Shaver 2004).

CKD patients are at an increased risk of developing infections due to their decreased immune system response and incompetent cell-mediated immune response, in addition to malnutrition and lack of vitamin D.

**Dialysis (haemodialysis and peritoneal dialysis).** The principle of haemodialysis involves the diffusion of solutes across a semipermeable membrane to dialysate according to a concentration gradient. For this purpose, the blood is allowed to flow through a special filter that removes extra fluid in addition to toxic solutes. The clean blood is then returned to the body after filtration over the membrane during a 4-5 hour session three times a week. Low-molecular weight heparin is administered to the blood circulation in the dialysis machine to avoid clotting. Alternatively, in peritoneal dialysis, a catheter is used to fill the abdomen with 2-3 litres of dialysis solution. The peritoneum allows waste products and extra fluid to pass from the blood into the dialysis solution. The solution also contains glucose that causes an osmotic gradient and thus extra fluid also moves into the abdominal cavity.

**Kidney transplantation.** Transplantation is the best way of correcting renal failure whenever it can be performed safely and there are no contraindications to the procedure. Renal allograft can be transplanted from a dead or a living donor. The probability of survival and cost-effectiveness is superior to dialysis. After transplantation the patient requires permanent immunosuppressive therapy to prevent rejection.
Oral health in diabetic nephropathy and other patients with chronic kidney disease

CKD patients may be predisposed to different oral symptoms due to the disease affecting the kidneys, the drugs used for treating the CKD and due to dialysis treatment. For example, diabetic patients often present a higher frequency of oral and dental diseases, including oral yeast infections, especially if their diabetes is poorly controlled (Tekeli et al. 2004; López et al. 2006). When the oral health of CKD patients has been studied, however, data have been contradictory regarding oral symptoms.

Dental caries
Several studies have shown a significantly worse dental health in uremic patients compared to healthy controls regarding the DMFT index (decayed, missing, filled teeth; Bayraktar et al. 2007; Borawski et al. 2007; Bayraktar et al. 2009; Thorman et al. 2009a). On the other hand, no significant differences in DMFT index have been found among CKD patients in some studies (Bots et al. 2006; Bots et al. 2007; Sobrado Marinho et al. 2007).

Periodontal diseases
ESRD is also associated with worse oral health with regard to periodontal loss attachment, periapical lesions, plaque index, gingival index and calculus surface index (Bayraktar et al. 2007; Borawski et al. 2007; Bayraktar et al. 2008; Thorman et al. 2009a). However, many studies have shown no differences in dental plaque, gingival bleeding, or periodontal indices in patients with less severe CKD compared to healthy controls (Bots et al. 2006; Bots et al. 2007; Sobrado Marinho et al. 2007). The prevalence of severe periodontitis was not significantly different between transplant patients and control subjects (Shaqman et al. 2010). Diabetes seems to increase the risk of periodontal diseases (Mealey & Oates 2006; Nagasawa et al. 2010).

Saliva
In a study by Tomás et al. (2008), the whole saliva flow was similar in CKD patients and controls but salivary creatinine, urea, sodium, potassium, chloride and alpha-amylase were significantly higher in ESRD patients than controls. Bayraktar et al. (2009) found a salivary flow rate significantly lower in dialysis patients compared to controls. Renal transplantation has been found to enhance salivary flow and decrease symptoms of xerostomia and thirst (Bots et al. 2007). Total protein and albumin levels in saliva are found to be lower in dialysis patients than in patients in
predialysis stage (Bibi et al. 2008). Importantly, diabetes per se is known to affect saliva secretion and render the patients liable for a variety of oral symptoms such as xerostomia and burning mouth (Lamey & Lamb 1988; Lamey 1996; Moore et al. 2001; Borges et al. 2010; Habbab et al. 2010).

**Oral mucosal diseases**

Renal transplant recipients are at an increased risk of developing oral mucosal disease and cancer due to immunosuppressive medication. Compared with the general population the risk to develop non-cutaneous malignancies is 1.6 times increased in renal transplant patients (Wisgerhof et al. 2011). They have a significantly elevated risk for cancers of the lip and the oral cavity (Mäkitie et al. 2008). Increased oral candidiasis is found in the transplant population: ESRD patients have significantly more oral fungal infections than controls and those experiencing mouth dryness and dental plaque formation also seem to be at risk of developing oral fungal infections (Thorman et al. 2009b). The majority of transplant patients are colonized by C. albicans but C. glabrata appears to emerge as the second most prevalent species (Dongari-Bagtzoglou et al. 2009). Common oral pathologies found in kidney transplant patients are infective and neoplastic lesions, such as fungal infection and viral infections (HSV, HPV, CMV). Oral candidiasis and diffuse gingival enlargement are increased after renal transplantation mainly as a result of the immunosuppressive therapy or drug side effects. Gingival overgrowth secondary to drug therapy in renal transplant patients has been reported unambiguously and it is mainly associated with cyclosporine, the most commonly used calcineurin inhibitor in Finland. The risk of infection is further increased if the patient simultaneously uses calcium channel blocking drugs for hypertension (Grassi et al. 2006; Al-Mohaya et al. 2009). The incidence of gingival overgrowth in transplant patients receiving tacrolimus is less than in those reported for cyclosporine (Ellis et al. 2004; Spolidorio et al. 2006).
AIMS OF THE STUDY

The aim of this study was to investigate the oral health of CKD patients. The study hypothesis was that the patients’ oral health status, symptoms, sensations and the biochemical composition of saliva varies in different stages of renal failure and according to different causes of the kidney diseases. The specific goals of the study were:

1. To follow-up oral health parameters of patients from predialysis, to dialysis and kidney transplantation (study I),
2. To investigate oral health clinically, by using WHO criteria, in the predialysis stage of kidney disease (study II),
3. To evaluate self-assessed oral symptoms in predialysis patients by using a structured questionnaire (study III),
4. To analyze salivary composition (total proteins, albumin, immunoglobulins A, G and M, urea) in predialysis patients (study IV).
SUBJECTS 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 Department of Medicine, Division of Nephrology, Helsinki University Central Hospital (HUCH), Helsinki, Finland. The project was approved by the Ethics committee of the Helsinki and Uusimaa District (HUS99/E6/2000). Informed consent to participate in the study was obtained from all the patients.

Subjects

Study 1 (Study I) Thirty-nine patients with CKD were examined from 1992 to 1994. Fifteen out of these 39 predialysis patients were invited to participate in re-examination at the post transplantation stage about 10 years after the beginning of the study. Nine of these patients (8 men, 1 woman; mean age 50.8 years) participated and were re-examined in 2001-2002. Four patients had diabetic nephropathy, 3 PKD and 2 had CGN. Ten patients dropped out from the study by own choice.

Study 2 (Studies II-IV) was a cross-sectional study of 178 chronic kidney disease patients at the predialysis stage. The patients were examined during the years 2000-2005. Thirty patients were excluded due to GFR level more than 20 ml/min/1.73m². The remaining 148 patients with a lower GFR (≤20 ml/min/1.73m²) were finally included in this study. Of these patients, 53 had diabetic nephropathy (29 with diabetes type 1 and 24 with diabetes type 2), 29 had CGN, 32 had PKD, 19 had other defined diagnosis and 15 had undefined kidney disease.
Figure 1. Studies II, III and IV patient profile.
Oral examination

Dental examination
The clinical oral examination took place in a normally equipped dental unit of the hospital. The same periodontist performed the re-examination of the patients in study 1 and examined all the patients in study 2. Dental recordings were made according to WHO criteria (WHO 1997) and by using the Decayed, Missing, Filled Teeth-index (DMFT). Decayed teeth (DT) and filled teeth (FT) indices were separately recorded. If a tooth had both a caries lesion and a filling it was calculated as “D” only. All the missing teeth, whether extracted or congenitally missing, were calculated as “M”. Following the WHO criteria for DMFT index, the third molars were not taken into account in M-score, however we included third molars into the DT or FT counts and in the scores of the total number of the teeth. Panoramic tomography x-ray (PTG) was taken from all patients and additional periapical and bite-wing radiographs were taken when indicated. The number of teeth with signs of dental erosion were recorded (by yes/no based on clinical evaluation).

Periodontal examination
Periodontal clinical examination involved evaluations of all surfaces of all the teeth. It included a measurement of the gingival margin (gingival recessions), probing pocket depths, signs of inflammation, signs of gingival overgrowth (GO) and other oral mucosal lesions, spacing and diastemas and mobility of teeth. To describe periodontal status the WHO Community Periodontal Index for treatment Needs (CPITN) index was used. The highest score per sextant was recorded and used in the analyses.

According to the WHO (WHO, 1987) CPITN is defined as follows:

Codes in descending order of severity are:

4: pocket depth > 6mm
3: pocket depth 4 or 5mm
2: calculus felt during probing
1: bleeding observed, directly or by using a mouth mirror, after probing
0: healthy
A PTG was taken from every patient, in addition to supplementary periapical x-rays when indicated (from teeth previously endodontically treated or suspicion of periapical pathology), and analyzed by a hospital radiologist specialized in dental and oral radiology.

**Salivary analyses**

Saliva samples were collected during the clinical oral and dental examination. Unstimulated saliva was collected for 5 min using the free-flow method (Meurman & Rantonen 1994). Stimulated saliva samples were collected for 5 min by giving the patients a standard piece (1 g) of paraffin wax to chew, and the chewing rate was approximately once per second. Salivary flow rate was measured as milliliter per minute. The saliva samples were collected for at least 60 min after a meal and/or smoking and in the afternoon to avoid diurnal variation. The remaining saliva samples were centrifuged for 4 min at 8000 g at 4 ºC and the supernatants were stored at -75 ºC until further analysis.

Further analyses were conducted from stimulated saliva samples. Salivary total protein was measured with the colorimetric Lowry method. Albumin was analyzed according to Webster (1977). Immunoglobulins A, G and M were analyzed by an enzyme immunoassay (Lehtonen et al. 1984). Urea was analyzed with routine photometric and enzymatic methods of clinical chemistry. All analyses were made immediately after thawing. All analyses were made at least in duplicates. Urea (U) was analyzed at the hospital laboratory. The Transpocult® dip-slide method was used for cultivation for yeast infection (Orion Diagnostica, Espoo, Finland). The samples for the yeast analyses were taken with a sterile spatula from the tongue surface.

**Medical records**

Medical records of all patients were available, and blood samples were taken in the hospital and analyzed using routine methods. The diagnosis of the type of kidney disease by the nephrologist was, if possible, based on histological findings in renal biopsy or verified diabetes with concomitant retinopathy associated with proteinuric renal disease (diabetic nephropathy), or typical radiological findings (ADPKD).

**Questionnaire**

The structured questionnaire for Study III consisted of 12 questions. The patients were questioned by the same dentist who also performed the clinical oral examinations. The questions concerned
background characteristics (smoking habits, education, working status), oral symptoms (BMS, dry mouth, dysphagia, dysgeusia) and as well as self-assessed oral health. The questions were either multiple-choice or the choice of answers was given by alternatives yes/no when appropriate.

Statistical analyses
Data from each patient was grouped according to the different phases of the renal disease (predialysis, dialysis and post transplant). The Friedman test was used to analyze the changes within the subjects at different time points. Means, medians and standard deviations were calculated (Study I).

The patients were grouped into 2 groups depending on the origin of the kidney disease. The data was analyzed by comparing the patients with diabetic nephropathy with the non-diabetic patients. Patients were also divided into groups of smokers and non-smokers. T-test was used for parameters normally distributed while binomial data were analyzed with cross tabulations and chi-square test (Studies II, III).

Student’s t-test was used for parameters normally distributed while binomial data were analyzed with cross tabulations and chi-square test. Logistic regression analysis was performed to estimate odds ratios (OR) and 95% confidence intervals (CI) on selected variables (Study IV).

The results were analyzed using the SPSS program version 11.0, 15.0 and 18.0 statistical package for Windows (SPSS inc. Chicago, USA). The level of significance was set at probability-value (p) less than 0.05.
RESULTS

The follow-up time for **Study I** was 10 years; 15 patients were asked for re-examination and nine of these patients participated in the study. Their mean duration of kidney disease was 25 (±8.6) years.

No significant changes were observed for either the DMFT-index or the CPITN-index during the follow-up period (Table 2). The mean stimulated salivary flow rate was lowest at the post transplant stage, with no statistically significant changes during the follow-up time. After kidney transplantation, decreased concentrations of the total proteins in saliva were observed (Ns). The IgA and IgM concentrations were highest in the dialysis stage, while IgG was highest in the predialysis stage. The urea concentration of saliva was high in all stages. The salivary and plasma urea concentrations followed a similar trend, showing the lowest values in kidney transplant patients. The results are given in Table 3.

**Table 2.** Results of DMFT and CPI index, means with SD, of **Study I** patients.

<table>
<thead>
<tr>
<th></th>
<th>Predialysis stage</th>
<th>Dialysis stage</th>
<th>Post transplant stage</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMFT</td>
<td>24.9 (7.1)</td>
<td>25.1 (7.2)</td>
<td>25.7 (6.4)</td>
<td>Ns</td>
</tr>
<tr>
<td>CPI</td>
<td>2.4 (0.9)</td>
<td>2.1 (0.8)</td>
<td>2.3 (0.5)</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Ns; Not significant

**Table 3.** Results of salivary and plasma urea analyses, median with range, of **Study I** patients.

<table>
<thead>
<tr>
<th></th>
<th>Predialysis stage</th>
<th>Dialysis stage</th>
<th>Post transplant stage</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow rate (ml/min)</td>
<td>2.2 (1.0-3.2)</td>
<td>2.0 (0.8-7.0)</td>
<td>1.6 (0.4-3.2)</td>
<td>Ns</td>
</tr>
<tr>
<td>IgA (µg/ml)</td>
<td>43.7 (21.6-65.1)</td>
<td>59.7 (31.7-110.7)</td>
<td>23.8 (18.0-46.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IgG (µg/ml)</td>
<td>17.7 (3.7-47.7)</td>
<td>13.2 (1.8-55.6)</td>
<td>5.1 (1.9-12.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IgM (µg/ml)</td>
<td>2.7 (0.6-5.5)</td>
<td>3.2 (0.3-7.0)</td>
<td>0.6 (0.3-1.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total protein (µg/ml)</td>
<td>1185.0 (724.0-2311.9)</td>
<td>1670.0 (890.0-865.0)</td>
<td>935.0 (660.0-1690.0)</td>
<td>Ns</td>
</tr>
<tr>
<td>Albumin (µg/ml)</td>
<td>399.0 (152.0-682.0)</td>
<td>353.0 (151.0-1962.0)</td>
<td>181.0 (143.0-228.0)</td>
<td>Ns</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>19.1 (11.6-26.5)</td>
<td>16.0 (8.0-35.2)</td>
<td>12.0 (6.2-17.6)</td>
<td>Ns</td>
</tr>
<tr>
<td>Plasma urea (mmol/l)</td>
<td>26.3 (23.6-37.1)</td>
<td>17.4 (16.0-37.6)</td>
<td>12.4 (9.7-19.2)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Ns; Not significant
Studies II, III and IV consist of 178 CKD patients in the predialysis stage.

Oral health findings are given in Table 4. Diabetic nephropathy patients had more carious teeth per patient and the number of carious teeth per patient was also significantly higher ($p<0.01$). No statistically significant difference was observed in the periodontal status. Yeast counts were more often positive in the diabetic group than with the other kidney disease patients, but the difference was not statistically significant. Dental erosion was detected more often in the diabetic nephropathy patients (Ns). No difference in the prevalence of oral mucosal pathology between the groups was observed. Stimulated salivary flow was significantly lower in the diabetic nephropathy group: $1.2 \text{ ml} \pm 0.4 \text{ ml/min}$ and $1.6 \pm 0.5 \text{ ml/min}$, respectively ($p<0.05$) (study II).

As expected, the HbA$_{1C}$ values of the diabetic patients were significantly higher than those in the other kidney disease group. No difference was observed in the other blood analyses of the patients. A statistically significant difference was observed in the number of drugs used daily in the diabetic nephropathy group than in the other kidney disease group ($p<0.05$). No differences were found in the background variables (gender, age, smoking habits, concomitant diseases) analyzed.

**Table 4.** Oral health findings, means with SD, of Study II.

<table>
<thead>
<tr>
<th></th>
<th>Diabetic nephropathy</th>
<th>Other kidney disease</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of teeth (SD)</td>
<td>21.5 (7.2)</td>
<td>22.9 (8.3)</td>
<td>Ns</td>
</tr>
<tr>
<td>Number of patients with dental caries</td>
<td>52</td>
<td>79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean number of carious teeth</td>
<td>5.1 (4.6)</td>
<td>3.1 (3.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Number of patients with gingivitis</td>
<td>7</td>
<td>18</td>
<td>Ns</td>
</tr>
<tr>
<td>Number of patients with &gt;5-mm deep periodontal pockets</td>
<td>23</td>
<td>33</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Ns: Not significant

No difference was seen in the frequency of oral discomfort between the diabetic nephropathy and other kidney disease groups (study III, Table 5).
Table 5. Oral symptoms (%) of Study III.

<table>
<thead>
<tr>
<th></th>
<th>Diabetic nephropathy</th>
<th>Other kidney disease</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS</td>
<td>6.0</td>
<td>5.7</td>
<td>Ns</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>41.7</td>
<td>48.2</td>
<td>Ns</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>37.3</td>
<td>23.3</td>
<td>Ns</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3.9</td>
<td>4.6</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Ns; Not significant

Approximately 23.5% of the diabetic nephropathy patients were working full-time, compared to 50% of the patients suffering from other kidney diseases (p<0.01). In contrast, diabetic nephropathy patients used significantly more drugs daily than patients suffering from other kidney disease (p<0.05).

The salivary composition of CKD patients was analyzed in Study IV (Table 6). Again, the study design was to compare diabetic nephropathy patients to those suffering from other kidney diseases. The diabetic patients had significantly higher salivary IgA levels (p<0.05). In the logistic regression analyses, age was the principal explanatory factor for high salivary total protein concentration (OR 1.059, 95% CI 1.013-1.108; p<0.05) and for low unstimulated salivary flow (OR 1.086, 95% CI 1.014-1.163; p<0.05). Poor dental health (number of decayed teeth OR 1.202, 95% CI 0.997-1.448; p=0.054, severity of periodontal disease OR 2.234, 95% CI 0.997-5.105; p=0.057) seemed to be an explanatory factor for high salivary albumin concentrations. Salivary urea levels were significantly linked with diabetic nephropathy (OR 7.608, 95% CI 1.833-31.578; p<0.01) and with serum urea concentrations (OR 1.277, 95% CI 1.130-1.443; p<0.01).
Table 6. Biochemical profile of blood and saliva of the patients, means with SD, of Studies II and IV.

<table>
<thead>
<tr>
<th></th>
<th>Diabetic nephropathy</th>
<th>Other kidney disease</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>457 (126.4)</td>
<td>530 (158.9)</td>
<td>Ns</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>8.0 (1.7)</td>
<td>5.9 (1.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>24.4 (6.4)</td>
<td>24.3 (7.8)</td>
<td>Ns</td>
</tr>
<tr>
<td><strong>Salivary parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (µmol/l)</td>
<td>20.0 (6.6)</td>
<td>18.9 (7.1)</td>
<td>Ns</td>
</tr>
<tr>
<td>Total protein (µg/l)</td>
<td>1822.6 (930.9)</td>
<td>1783.9 (880.1)</td>
<td>Ns</td>
</tr>
<tr>
<td>Albumin (µg/l)</td>
<td>101.5 (126.4)</td>
<td>90.4 (157.8)</td>
<td>Ns</td>
</tr>
<tr>
<td>IgA (µmol/l)</td>
<td>71.7 (81.1)</td>
<td>51.5 (50.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IgG (µmol/l)</td>
<td>38.9 (47.1)</td>
<td>35.6 (60.7)</td>
<td>Ns</td>
</tr>
<tr>
<td>IgM (µmol/l)</td>
<td>4.1 (4.4)</td>
<td>3.1 (5.3)</td>
<td>Ns</td>
</tr>
</tbody>
</table>

Ns; Not significant
DISCUSSION

This series of studies was designed to obtain new information about oral health, its impact, and oral health habits of patients with chronic kidney disease. It was of particularly interest to establish whether oral health parameters differ in patients with kidney diseases of different etiologies, with comparison to patients suffering from diabetic nephropathy or other causes of nephropathy.

In the follow-up study (Study I), where the patients’ oral health was assessed from the predialysis stage through to the dialysis and post transplantation stages, hardly any changes were observed in oral health parameters. However, salivary analyses indicated that the patients’ oral health improved after kidney transplantation. Therefore, it was not unexpected to find salivary protein concentration decreased after transplantation. In particular, the observation of a decrease in salivary immunoglobulin concentrations was logical and probably due to the immunosuppressant medication taken permanently after transplantation. Similarly, the decrease in plasma urea concentration most likely reflected the patients’ improved health after kidney transplantation. The validity of the results needs to be discussed further, however, because the number of patients was unexpectedly small at the 10-year follow-up. This could not be avoided since the re-examination was, naturally, on a voluntary basis. However, there are no previous follow-up studies of oral health in CKD patients from predialysis to dialysis and post transplantation stages. Hence, the present data gives a solid basis for further hypothesis generation and future investigations with larger patient numbers.

The second series of the present study (II-IV) was the first comprehensive investigation of oral health and salivary flow rates in patients suffering from different renal diseases at the predialysis stage (CKD 4 or 5, see Table 1), with special emphasis on diabetes mellitus. The results showed that diabetic nephropathy patients had worse dental health than the patients with other kidney diseases in the predialysis stage. Diabetic nephropathy patients had significantly more carious teeth per patient, suggesting that diabetes poses a potentially high risk for the development of dental caries. Furthermore, an association between dental caries and increased HbA1c level has been reported (Karjalainen et al. 1997, Miralles et al. 2006), however, this association was not investigated in our studies; although the diabetic patients studied here demonstrated a mean HbA1c value of 8.0 %, which is generally considered to indicate poor metabolic control. Thus, the observed difference in caries prevalence between diabetic and non-diabetic patients is in agreement with
those reported by Miralles et al. (2006). Siudikiene et al. (2008) have found higher DMFS increments in children with diabetes versus controls in a 2-year follow-up study. Similarly, in the studies by Miralles et al. (2006) and Jawed et al. (2010) the diabetic group showed a higher incidence of caries than in the control group. On the other hand, Arrieta-Blanco et al. (2003) found no difference in the number of caries teeth in a diabetic population compared to a control population. In a study of Tagelsir et al. (2011) no significant differences were observed regarding caries experience between diabetic children and healthy controls. Hence, the effect of diabetes on caries remains controversial and not conclusive.

Deep periodontal pockets indicating periodontitis were evident for 45% of the diabetic nephropathy patients and 34% with other kidney diseases. However, the difference was not statistically significant and the result was therefore contrary to the study hypothesis as it has been suggested that diabetic patients have an increased risk of periodontitis (Bascones-Martinez et al. 2011; Ioannidou & Swede 2011). The reason for the lack of statistical difference in periodontal status when comparing the diabetic with non-diabetic patients may be due to the relatively small number of patients in the groups of the present study. Furthermore, the use of CPITN to describe periodontal disease may be criticized; it is a practical tool for population studies and the index was originally developed for the purpose of assessing periodontal treatment needs in a population (Ainamo et al. 1982; Ainamo & Ainamo 1994; Unell et al. 2000). However, the index has been recommended for prevalence studies in populations and not for the assessments of the severity of periodontal disease (Cutress et al. 1987). For practical reasons, the CPITN-index was used in this study’s protocol even though the full periodontal status was recorded from every patient due to the fact that they were referred for treatment of dental infection foci.

Reduced salivary flow is a well-known risk for dental health. It is known from previous studies that diabetes is a disease that causes reduced saliva flow and xerostomia (Sreebny et al. 1992; Quirino et al. 1995; Moore et al. 2001; Habbab et al. 2010). Thorman et al. (2010) reported evidence of chronic inflammatory onset and signs of down-regulation of acute-phase inflammation in the CKD subjects with hyposalivation. In this study, the diabetic patients had lower stimulated salivary secretion rate when compared with the other kidney disease group. Drug-induced hyposalivation is a side-effect of the drug’s intended action (Guggenheimer & Moore 2003). The more drugs a patient takes daily, the greater is the effect on salivary secretion (Närhi et al. 1996). All the diabetic
patients required cardiovascular medication and the number of drugs used daily was significantly greater among the diabetic patients than in the non-diabetic patients.

The prevalence of dry mouth sensation was 42% of diabetic nephropathy patients and 48% of non-diabetic patients. Murtagh et al. (2010) reported xerostomia symptom prevalence and severity in the last month of life of patients with stage 5 CKD. Of these patients, 69% complained of having a dry mouth. Borges et al. (2010) reported a 25% prevalence of xerostomia in elderly type 2 diabetic individuals, while decreased salivary flow rate was found in 48% of unstimulated and 46% of stimulated salivary flow rates. Chronic diseases and use of drugs together with aging may decrease salivary flow as much as 40% (Gutman & Ben-Aryeh 1974; Ben-Aryeh et al. 1984; Leal et al. 2010). This may link with xerostomia. In order to manage these different conditions appropriately it is important to recognize and distinguish between patients with subjective complaints from those with evidence of true salivary hypofunction, or those who are suspected of having a systemic disease (Napeñas et al. 2009).

Yeast count was positive in 36% of the diabetic and 23% of the non-diabetic patients, however this difference did not reach statistical significance. Several authors have reported that end-stage renal disease patients (Schander et al. 2009; Thorman et al. 2009b; Gülec & Haberal 2010) and diabetic patients (Guggenheimer et al. 2000; Al-Attas & Amro 2010; Sashikumar & Kannan 2010) have an increased predisposition to manifestations of oral candidiasis. This study’s findings seem to be in line with other studies on patients with CKD in this respect.

Burning mouth syndrome is an unpleasant condition characterized by a burning sensation of the oral mucosa usually in the absence of clinical and laboratory findings. The prevalence of BMS varies 0.7 - 4.8% in the general population (Mott et al. 1993; Ship et al. 1995). In this study, 6% of the diabetic nephropathy patients, and 5.7% of the non-diabetic patients, reported BMS. The association between diabetes and BMS has also been reported previously (Lamey & Lamb 1988; Negrato & Tarzia 2010). Hence the current findings did not differ from those of previous studies. Nevertheless, the present study is the first investigation to evaluate BMS in CKD patients.

Diabetes is associated with problems in oesophageal motility and these may thus also reflect in problems with swallowing (Kinekawa et al. 2008). The two types of dysphagia, oropharyngeal and esophageal, involve different phases of swallowing, and have different etiologies (Marshall 1985).
Dysphagia particularly links with diabetic neuropathy. In this study, the diabetic nephropathy patients reported dysphagia slightly more often than the non-diabetic patients but the difference was not statistically significant. As neurological and neuromuscular disorders are known to lead frequently to dysphagia, thus the findings reported here are in agreement with the results of previous studies (Hüppe et al. 1992).

The prevalence of smoking in this study group was in agreement with that of general populations. The overall prevalence of smokers in the adult population in Finland is 23%, in the UK 26% (Health 2000 Report 2002; WHO 2004) and among US adults 20.8%, to give a few examples (US Centers for Disease Control and Prevention 2007). In concordance, no effect of smoking on the prevalence of oral symptoms was observed here.

Approximately 65% of the diabetic nephropathy patients and 49% of the non-diabetic patients were retired. Subsequently, less diabetic patients were working full time when compared with the non-diabetic group. Poor sleep is also common in type 2 diabetes and may adversely impact quality of life (Luyster & Dunbar-Jacob 2011). These findings emphasize the impact of diabetes on the overall morbidity and well being of the patients.

Study IV investigated salivary aspects among the diabetic versus non-diabetic CKD patients. It was of special interest to analyze certain salivary proteins to assess whether or not their concentrations might reflect the patients’ general disease status. Salivary immunoglobulins may be used as a marker of general oral inflammatory state (Janket et al. 2010). Salivary IgA is considered to belong to the first line of defense of the host against pathogens. In the present study, salivary IgA concentration was significantly higher in diabetic patients. High salivary IgA levels have also previously been reported in diabetic patients (Anil et al. 1995; Twetman et al. 2002; Javed et al. 2009). The logistic regression analysis identified the patient age, the number of concomitant diseases and the low salivary flow rate values as explaining variables for the highest tertiles of salivary protein concentrations. Similarly, diabetic nephropathy emerged as risk for high salivary urea concentrations. These results are in agreement with the concept of impaired epithelial integrity caused by disease, namely the saliva proteins analyzed reflect serum ultrafiltrates into the mouth (Meurman et al. 2002; Helenius et al. 2005). The results thus confirmed the study IV hypothesis.

The final conclusions from the results of this series of studies are presented in the next chapter.
KEY FINDINGS AND CONCLUSIONS

Study I

- There were no statistically significant differences in clinical oral symptoms investigated during the 10-year follow-up period of the patients undergoing treatment from predialysis and dialysis to the post transplant stage.
- Salivary flow rate did not change significantly during the 10-year follow-up period. The lowest value was at the transplantation stage and this finding might be a consequence of immunosuppressive therapy. Also, all the patients were taking antihypertensive medication known to reduce saliva secretion.
- Salivary immunoglobulin (IgA, IgG, IgM) concentrations decreased after kidney transplantation. The finding is in concordance with normalization of uremic milieu after successful transplantation.
- Salivary urea levels were high in all the 3 stages, which is an expected finding in uremic patients.
- Plasma urea concentration followed a similar trend as salivary urea, showing the lowest value after kidney transplantation, as expected.

Studies II-IV

- The diabetic nephropathy patients had more dental caries than the other CKD patients.
- The diabetic nephropathy patients had a lower stimulated salivary flow rate than the other CKD patients.
- No statistically significant difference was found in the periodontal health comparing the two patient groups.
- The diabetic nephropathy patients took more drugs daily than the other CKD patients.
- The diabetic nephropathy patients had more concomitant diseases than the other CKD patients.
- Other kidney disease patients were more often working fulltime when compared with those with diabetic nephropathy.
- No statistically significant differences were found in the oral symptoms investigated in the predialysis patients when comparing the two groups.

- In the salivary analyses, predialysis diabetic nephropathy patients had higher IgA level than the other CKD patients.

- In the logistic regression analyses, the salivary IgA concentrations reflected the overall disease state of the predialysis patients. Age was the principal explanatory factor for high salivary total protein concentrations and for low unstimulated salivary flow rate. Salivary urea levels linked significantly with diabetic nephropathy and with serum urea concentrations.
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