CHAPTER

9

Summary
This thesis comprehends seven clinical studies related to the oral component of Sjögren’s syndrome (SS), aiming to improve current diagnostics and to obtain clinical outcome parameters.

In chapter 1, it is described that the oral component of SS has been studied in depth in 200 patients by a multidisciplinary research team, in order to improve and simplify the process of diagnosing SS, and to obtain methods to evaluate the effects of drug-therapy. All studied patients were diagnosed in accordance to the revised European classification criteria for SS.

Chapter 2 provides additional background information on SS and its oral component, in order to provide a solid basis of understanding for the topics dealt with in this thesis. Relevant anatomy and physiology of the salivary glands is given for better understanding of the various salivary gland investigations performed in this study. Furthermore, an historical overview is given on the syndrome, in order to explain old nomenclature and to put acquired insights into a proper perspective. Subsequently, current insights on the salivary immunopathology in SS are presented. A summary of clinical symptoms and signs in SS, as observed during the history taking and physical examination, concludes the chapter.

In chapter 3, it is studied and discussed how sialometry and sialochemistry can contribute to the diagnostic process of SS. The frequent occurrence of xerostomia in SS and the easy accessibility of saliva both support the use of sialometry and sialochemistry in the diagnosis. Despite the fact that it is rather inaccurate and impure, collection and analysis of whole saliva is currently in use as the routine technique for sialometry in the diagnostic process of SS. In chapter 3.1, the value of glandular sialometry and sialochemistry was studied as diagnostic instruments in SS. In a group of 100 consecutive patients referred for diagnostics of SS, glandular secretory flow rates and a spectrum of salivary components were assessed. Patients diagnosed with SS differed clearly from the patients tested negative for SS, showing lower flow rates of exclusively the submandibular/sublingual (SM/SL) glands, and a markedly changed composition of parotid- and SM/SL saliva. Besides changes in salivary flow rate and composition, distinct sialometrical profiles were observed, characteristic for either early or late salivary manifestation of SS, or for the xerogenic side effect from medication. It was concluded that glandular sialometry and sialochemistry are not only useful
instruments to differentiate SS from other salivary gland disease in clinical practice, but also have great potential as diagnostic criteria for SS, revealing distinct sialometrical and sialochemical changes as well as profiles. Being simple, safe (noninvasive) and sensitive (early disease detection) glandular sialometry and sialochemistry encompass three major advantages compared to other oral tests for SS.

Since univocal salivary reference values are lacking, it is currently rather difficult to use sialometry and sialochemistry for diagnosing SS, unless major changes have occurred in salivary secretion and composition. In chapter 3.2, cut-off points were selected from Receiver-Operating Characteristic (ROC) curves of gland specific sialometrical and sialochemical variables, which have proven to be potentially relevant for diagnosing SS in the preceding study (chapter 3.1). By combining the most discriminative variables, two different diagnostic approaches for SS were applied in a group of one hundred patients and, subsequently, evaluated in a second group of twenty patients. In the first approach, variables were combined by applying their cut-off points into sets of criteria for a positive diagnosis of SS, in the second approach by including the variables into a logistic regression model that predicts the true state of a patient (SS or non-SS). From both approaches the tests with highest likelihood ratio combined with the smallest number of rejected cases were selected for clinical use. The most accurate test reached a sensitivity of 0.85 and a specificity of 0.96 by combining the stimulated SM/SL-flow rate and parotid sodium and chloride concentration as salivary variables. The selected tests proved equally accurate in the second group of patients. Since the proposed noninvasive diagnostic tools can be easily applied, do not need a laboratory other than for routine blood testing, and are very accurate, we feel that gland-specific sialometry and sialochemistry may eventually replace other, more invasive, diagnostic techniques for diagnosing SS.

The estimated high incidence of SS and the variety of conditions that often mimic SS prompt for a simple screening test for SS, which can also be used by dentists and general practitioners. Based upon a noninvasive diagnostic technique, which was proposed in the previous study to assess the oral component of SS, a test-strip is designed (chapter 3.3) that can be used for screening for SS using a drop of saliva. Changes in the composition of saliva characteristic for SS (altered chloride, phosphate and sodium concentration) can be visualised within a few minutes. These changes proved to have a sensitivity of 92 percent, and a specificity of 62 percent or higher depending on the type of saliva used. The manufacturing and subsequent clinical evaluation of the test-strip is subject of current studies. Appropriate and early
referral, resulting from proper use, will benefit patients as well as clinicians confronted with SS.

Organ damage that directly results from an autoimmune attack in SS can hypothetically be demonstrated by measuring an increase of organ-specific enzymes in serum, as an alternative to currently practised techniques that demonstrate loss of organ-function or change in architecture. This assumption could be true for the salivary glands, containing large amounts of amylase, and almost invariably involved in SS. In chapter 4, the clinical value of measurement of serum isoamylase activity as a clinical parameter in SS is determined. In a group of 100 consecutive patients referred for diagnostics of SS serum activity of salivary (S) and pancreatic (P) isoamylase were assessed. SS patients showed significantly higher serum activities for salivary- and total (salivary and pancreatic) amylase compared to non-SS patients. The optimum threshold of S-isoamylase for detecting SS (105U/L), selected from a Receiver-Operating Characteristic (ROC) curve, had a specificity of 89%, but a limited sensitivity of 35%. Further data analysis explained this low sensitivity by disclosing a biphasic course of S-type isoamylase serum activity in SS patients (increase-decrease), related to the duration of oral complaints. In addition, data analysis revealed that S-type isoamylase serum activity correlated positively with the sialochemical variables sodium and chloride concentration, which both are known to be related to inflammation of the salivary glands. This prospective clinical study shows that measurement of isoamylases in serum has limited diagnostic value for SS, but does have potential use for assessing disease progression.

In chapter 5, characteristics of sialography are studied with regard to its use as diagnostic instrument in SS. Sialography is commonly used for the purpose of diagnosing SS, though its invasive nature is often regarded as a drawback for routine usage. The aim of this study was to evaluate the morbidity and acceptability of parotid sialography using oil-based contrast fluid (chapter 5.1). Twenty-four consecutive sialographic procedures were evaluated by assessing the morbidity and the patient's acceptance of the procedure with a standardised questionnaire, and by recording relevant physical parameters during the procedure. There was good acceptance of the sialographical procedure, and the morbidity was low. No signs of overfilling or fausse route were observed in any of the sialograms. On average, 0.74 ±0.08 ml contrast fluid was infused at a velocity of 0.01 ml/s. The whole procedure was completed within 12 minutes. From this study, it appears that parotid sialography appears less invasive than is often thought, given its low morbidity and its good acceptance by the patients.
Despite the availability of many new imaging procedures, sialography has, after decades of use, maintained its status as the imaging procedure of choice for evaluating the oral component of SS. In chapter 5.2, the clinical value of sialography as a diagnostic tool in SS was explored by assessing its diagnostic accuracy, observer bias and staging potential. One hundred parotid sialograms were interpreted independently in a blind fashion by two trained- and two expert-observers. Sialograms were derived from a group of consecutive patients, referred for diagnostics of SS. Patients were categorised as SS and non-SS by the revised European classification criteria. Trained observers reached a sensitivity of 95 and a specificity of 33 percent, whereas expert-observers reached a sensitivity of 87 and a specificity of 84 percent. There was only ‘fair’ inter-observer agreement between trained- and expert-observers, whereas both expert-observers showed ‘good’ agreement with one another, according to Cohen’s kappa. Intra-observer agreement was ‘good’ to ‘very good’ for all observers. Furthermore, the four different gradations of sialectasia, i.e. punctate, globular, cavitary and destructive, showed a weak but significant correlation with the duration of oral symptoms. This study markedly shows that the diagnostic value of parotid sialography for diagnosing SS greatly depends upon the skills of the observer. This implies that sialography lacks general applicability as a diagnostic tool in SS and requires specific expertise, especially for doubtful cases. Nevertheless, given its potentially high sensitivity and specificity in diagnosing SS as well as its useful staging potential for SS, sialography still has its use in the evaluation of its oral component.

Dysfunction of exocrine glands manifests itself clinically predominantly in the lacrimal and salivary glands (chapter 6). Little is known, however, about the relationship between lacrimal and salivary gland involvement in SS. Furthermore, it is of interest which tear test contributes the most to the diagnosis of SS. Therefore, the aim of this study was to determine the performance of different tear tests and to disclose how these tests relate to common serologic and salivary tests in SS, as used in the revised European classification criteria. In patients suspected of SS, the tear break-up time (BUT), and a possible new test, the tear mucus score, were evaluated in addition to the routine tests, Rose Bengal score and Schirmer test. Eighty consecutive patients were included in this study, categorised into primary SS (pSS), secondary SS (sSS), and negative for SS (non-SS). A corresponding change of tear- and saliva quality and secretion rate was noted in both pSS and sSS patients. Also a clear correlation was found in SS patients, between the Rose Bengal score and observations with parotid sialography. Hyperglobulinemia and presence of SS-B antibodies in serum of SS patients both correlated significantly to increased Rose
Bengal scores of the eyes. The Rose Bengal score was also significantly increased with longer duration of subjective eye-dryness, and with a decreased tear-gland function as estimated by the Schirmer test. The BUT and mucus score both performed insufficiently in diagnosing SS. From the observed relationship between the ocular and the oral component, we conclude that, theoretically, a positive evaluation of one of these components (either ocular or oral), in addition to positive serology or histopathology for SS, could be sufficient to diagnose the syndrome for clinical purposes. Furthermore, it is concluded that hyperglobulinemia and especially positive SS-B serology may warrant close monitoring of the eyes since these serum findings appear to relate to the severity of ocular surface damage. Of all tear tests, the Rose Bengal score still remains the test of choice having the highest specificity for SS. It also appears applicable for monitoring disease progression of SS, relating to duration of subjective complaints and to tear-gland dysfunction.

In chapter 7, two unusual cases are described that stress the importance of accurate diagnostic procedures in SS. A case of primary sialoangiectasia, which in this case was initially misdiagnosed as SS, is described in chapter 7.1. Other diseases, including HIV-infection, psoriatic arthritis and acute parotitis, may cause glandular changes similar to the changes found in the syndrome. Therefore, sialography always must be combined with other methods of assessment of the oral cavity when suspicion is high for SS. A patient is demonstrated (chapter 7.2) who presented with sarcoidosis and SS. Diagnoses of both diseases were based on current internationally accepted criteria. Furthermore, histopathological findings characteristic for both diseases were present in salivary gland biopsies. As sarcoidosis is considered an exclusion criterion for SS in current sets of diagnostic criteria we propose that these criteria should be reconsidered with respect to the exclusion of sarcoidosis.

In chapter 8, general conclusions are drawn. The diagnostic process of SS can be optimised by modification of current diagnostic procedures, by first-echelon screening with tear- or saliva-strips (latter not yet available), and perhaps, in near future by reducing the diagnostic process by one component if proven to be justified. After establishment of the diagnosis, it appears SS can be subdivided into two or three different sequential stages of disease progression according to the type of sialectasia and/or to the Rose Bengal score, with a corresponding degree of oral and ocular dryness, respectively. Such sequential stages may consist of an early- (<1 year), an intermediate- (1-4 years) and a progressed stage of SS (>4 years). Furthermore, it appears that glandular disease activity could be estimated by
measuring serum salivary isoamylase activity, which might even predict the rate of exocrine function-loss. In addition to these transversal prospective studies, it is required to validate all retrospectively acquired ‘time relations’, to differentiate reversible processes, i.e. disease activity, from irreversible processes, i.e. disease progression, and to further define the different disease stages with long-term prospective studies. If validated markers of disease progression and -activity could eventually be agreed upon they would constitute important tools for disease monitoring and clinical trials.

Follow-up and ongoing studies in our clinic encompass a histopathology- and morbidity study on salivary gland biopsies, long-term prospective studies on clinical disease course, and randomised clinical trials with new therapeutic agents in SS patients.