Primary Sjögren’s Syndrome
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Chapter 6

General discussion & future perspectives
Chapter 6

The research described in this thesis concerns three different aspects of primary Sjögren’s syndrome (pSS), viz. diagnosis, treatment and patient education. The focus was on the accuracy of ultrasound in diagnosing pSS, the development of markers to personalize treatment in pSS and the value of Internet as a source of information for patients with pSS. Although these three aspects at a first glance are not directly related to each other, they comprise the main interests of both clinicians and patients.

**What is the accuracy of ultrasound in diagnosing pSS?**

In the diagnosis of pSS, the involvement of salivary glands is currently usually assessed by sialometry and histopathology or less frequently by sialography and scintigraphy. Ultrasonography is a non-invasive, inexpensive, widely available, easily accessible and non-irradiating imaging modality [1], which has drawn a lot of attention in the diagnosis of pSS. The meta-analysis described in Chapter 3A demonstrated that major salivary gland ultrasonography has a sensitivity, specificity and diagnostic odds ratio of 69%, 92% and 33.89, respectively, to diagnose SS in the major salivary glands. However, the included studies were characterized by a high risk of bias in ‘patient selection’, ‘index test’ and ‘flow and timing’. Additionally, different ultrasonographic scoring systems and study populations (study and control groups) were used, and publication bias was common.

Furthermore, the majority of included articles analyzed in the study described in Chapter 3A used a case-control design. This means that the difference in ultrasonographic characteristics is large and that ultrasonography can ‘easily’ distinguish healthy controls from pSS patients (Chapter 3A). The patient populations selected so far do not represent the daily practice, as the patients suspected for pSS exhibit a wide range of ultrasonographic characteristics from normal to extremely altered ultrasonographic structure. Consequently, the need of well-designed studies became evident in order to define the reliability and validity of ultrasound.

Moreover, none of the studies included in the meta-analysis (Chapter 3A) recruited as a control group patients with sarcoidosis, amyloidosis, human immunodeficiency virus (HIV) infection and hepatitis C virus (HCV) infection, all being diseases that could mimic a critical aspect of pSS, i.e. affect the major salivary glands, cause dry mouth or have similar histopathological features with pSS. The study described in Chapter 3E assessed these important disease-control groups. This pilot study showed that ultrasound is a potentially accurate imaging technique in diagnosing pSS and in differentiating it from sarcoidosis, amyloidosis, HIV and HCV infection. However, further studies with larger population series in patients with pSS and systemic diseases at different disease stages are required to confirm and elucidate these preliminary findings.

As far as the reproducibility of salivary gland ultrasonography for diagnosing pSS is concerned, the study described in Chapter 3C showed that the intra- and inter-observer reliability ranged from good to excellent. When assessing the individual ultrasonographic parameters, the inter-observer reliability was good for homogeneity and the presence for hypoechogenic areas, moderate for hyperechogenic reflections and salivary gland border and fair for echogenicity. Additionally, we observed that different observers may rather consistently identify in which patients ultrasound of the major salivary glands supports the diagnosis of pSS, but scoring the severity of the ultrasonographic findings is more inconsistent between observers (Chapter 3C). A possible consequence of this phenomenon is that when monitoring patients over time, the observed change by different observers might not be only attributed to the progression of the disease or to the effect of medication used to treat pSS, but might be partly the result of the discrepancy in scoring between different observers. Special attention is needed while following longitudinally an individual patient, i.e. when monitoring the activity or progression of pSS; it is advised that each particular patient is scored by the same ultrasonographer at every time-point.

Regarding the validity of ultrasound, we learned from the study described in Chapter 3D that the agreement between ultrasound and parotid or labial gland biopsy outcome was good and moderate, respectively. Specificity of ultrasound was higher when a parotid gland biopsy instead of labial biopsy was used as ‘gold standard’, which might be explained by the fact that the parotid gland is included in the ultrasonographic evaluation, whereas the labial gland is not. One of the most important findings is that negative ultrasound was a strong predictor of having also a parotid gland biopsy with focus score <1, while positive ultrasound was a strong predictor of having positive labial biopsy. Additionally, when ultrasound and serology were both negative, 94% of the patients had a negative parotid gland biopsy and 78% had a negative labial gland biopsy. Overall, ultrasound had high negative predictive value (NPV) for parotid gland biopsy and high positive predictive value (PPV) for labial gland biopsy (Chapter 3D), possibly, because patients with a positive parotid gland biopsy might have a distinct clinical profile from patients with a positive labial biopsy. There is still a need for larger studies focusing on the inherent differences in the histopathological characteristics of parotid and minor salivary gland tissue in both pSS patients and healthy controls. The ‘NIH Salivary biomarkers for SS detection’ study, currently running in the UMCG, will hopefully soon address this issue.

When combining positive ultrasound with presence of anti-SSA antibodies 94, 97 and 97% of the patients fulfilled the AECG, ACR and ACR-EULAR criteria, respectively. When combining negative ultrasound with absence of anti-SSA antibodies 98, 100 and 98% of the patients did not fulfill the AECG, ACR and ACR-EULAR criteria, respectively, if a parotid gland biopsy is amongst the items of the classification criteria. In case that a labial gland biopsy was considered as an item of the classification criteria, the combination of negative ultrasound with absence of anti-SSA
antibodies could not sufficiently exclude the classification of patients according to the AECG, ACR and ACR-EULAR criteria (Chapter 3D). Further research is needed to elucidate the accuracy of the classification criteria if ultrasound is added or if ultrasound replaces one of the existing items.

When interpreting the results, it should be kept in mind that the classification criteria are developed for research purposes to define homogenous study groups instead of diagnostic purposes, because of lack of sensitivity [2]. However, in clinical practice, classification criteria are often used for diagnostic purposes. This study showed that ultrasound is not able to replace salivary gland biopsy at group level. However, at individual patient level, and for diagnostic purposes, positive ultrasound may predict classification according to the AECG, ACR and ACR-EULAR classification criteria. Furthermore, ultrasound in combination with anti-SSA antibodies highly predicts classification according to the AECG, ACR and ACR-EULAR criteria, if parotid gland biopsy is performed as part of the diagnostic work-up.

Implications and future perspectives in ultrasound of the major salivary glands for diagnosing SS

We recommend that future diagnostic studies on ultrasound of the major salivary glands in pSS should comply with the QUADAS-2 guidelines in order to ensure high diagnostic quality [3]. Specifically, the following points from the guidelines should be followed:

1. a consecutive or random sample of patients should be used; a case control design and inappropriate exclusion of patients should be avoided;
2. ultrasonography results should be interpreted by observers blinded to each other as well as for the results of the reference test (diagnostic criteria, histology, sialography, scintigraphy, etc.). Ideally, the applied threshold scoring should be pre-specified;
3. an appropriate and rather short interval should elapse between the application of ultrasonography and the reference test, the whole study population should receive the reference test (which should be always the same) and the whole study population should be included in the analysis.

The aforementioned features should be clearly stated by authors of future studies to avoid potential misunderstanding and underestimation of the study design.

The development of validated automatic software has the potential to improve the reliability of salivary gland ultrasonography applied for pSS diagnostics [4]. Furthermore, so far static images have been analyzed instead of live ones for study purposes. Therefore, it is worth comparing the scoring of live images to static ones, since in daily practice live images are scored. Whether ultrasound can assess ‘true’ changes over time, e.g., when monitoring the activity or progression of pSS, remains also a burning question. That is why the next logical step should be to identify the minimal clinically relevant change, in other words, the smallest difference in score in the domain of interest, perceived as important change by the patient or the clinician, which could potentially mandate a change in patient management [5]. Last but not least, the development of a consensus and widely accepted ultrasonographic scoring system, by e.g., the EULAR US-pSS Study Group, for evaluating the major salivary glands of patients with pSS will allow better comparison between studies.

Is personalized treatment realistic in SS?

Patients with pSS have different genetic backgrounds, demographic features and prognosis and exhibit a broad variety of clinical manifestations, involving a number of pathophysiological pathways [6]. Personalized treatment, i.e. providing ‘the right patient with the right drug at the right dose at the right time’ [7] will therefore contribute to treating pSS. In previous studies it has been shown that rituximab (B cell depletion therapy) has beneficial objective and subjective clinical effects on patients with pSS [8-16]. However, not all patients seem to benefit from this treatment. An important finding of the study described in Chapter 4A was, therefore, that clinical responders to treatment with rituximab (RTX) had a higher number of CD20+ B-cells/mm² of parenchyma of parotid gland tissue at pre-treatment (baseline) compared to non-responders. Moreover, this study also observed a correlation between the change in the number of CD20+ cells/mm² of parenchyma and the change in ESSDAI. When higher numbers of B-cells are present in parotid gland parenchyma, it is presumed that RTX may result in depletion of more absolute numbers of B-cells responsible for the disease activity (measured by ESSDAI) than when lower numbers of B-cells are present in the tissue. The baseline number of B-cells/mm² of parenchyma of parotid gland may thus predict the patients’ response to RTX and may be considered as a biomarker for a more personalized treatment approach to pSS patients. We arrived at the same conclusion when we tested the baseline proportions (and not only absolute numbers) of B-cells in the parotid gland tissue (Chapter 4B) of responders compared to non-responders. The nature of these disease-associated B-cells, which are reduced after RTX, needs to be elucidated.

The study described in Chapter 4A revealed also that RTX significantly reduced the overall lymphocytic infiltrate with a major loss of the B-cell component and number of germinal centers (GC)/mm² of parotid gland parenchyma in pSS patients. In addition, a major reduction of the quantity and severity of lymphoepithelial lesions (LEL) was apparent, reflecting significant restoration of the striated ducts. To explain this, we have hypothesized that the trigger for LEL formation is diminished, and as a result less epithelial reaction takes place leading to reduced proliferation and finally anatomical restoration of the striated ducts. The trigger for LEL forma-
Implications and future perspectives in the treatment of pSS

A major aim of the treatment of pSS should be the restoration of the glandular tissue. To the best of our knowledge, RTX is the only medication that leads to restoration of the salivary gland ductal lesions [18]. The study described in Chapter 4A showed that pre-treatment histopathological evaluation of parotid gland biopsy in pSS patients may provide biomarkers to predict responsiveness to RTX treatment. However, there is lack of consensus guidelines to standardize the histopathological evaluation of salivary gland biopsies. Consensus guidelines will assist the pathologist to correctly identify and quantify histopathological parameters in pSS and contribute to a more accurate prediction of disease progression and personalized treatment, as well as to allow the comparison between study cohorts and different clinical trials. Chapter 4C points towards the urgent need for consensus guidelines. In particular, histological definition of germinal centers (GCs) in salivary gland tissue is warranted, since these structures can be difficult to detect in diagnostic hematoxylin & eosin (H&E)-stained tissue sections. Detection of GCs in the periductal lymphoid infiltrates of the salivary glands is clinically relevant, not only for assessing the responsiveness to treatment but also because the presence of these structures is associated with more severe disease [19]. Furthermore, the presence of GCs in minor salivary gland biopsies has been postulated to be a predictor of patients at risk for lymphoma development [20,21]. To confirm and elucidate the latter and to facilitate proper and easy detection of GCs, also by less trained persons, supplemental immunohistochemical staining might be helpful. Therefore, we recommend staining for B-cell lymphoma 6 (Bcl-6), a transcription factor expressed at high levels by GC B-cells (Chapter 4C).

Are Internet sites and YouTube reliable sources of information for patients with pSS?

Nowadays, patients are increasingly turning to Internet and video-sharing Web platforms, like YouTube, to make informed healthcare decisions for themselves and to rate the information provided by professionals or others. Internet is believed to have the power to modify patient-doctor relationship, by encouraging patients in the management of their health through a more shared decision making approach [22]. However, the diversity of authorship and the lack of peer-review process have led to dissemination of inaccurate and misleading information [23]. Practically speaking, any Internet user without exception regarding his/her background, medical qualifications, professionalism and intentions is authorized to create a site and upload video clips.

It was found that the bulk of the Web information regarding xerostomia was written in a fairly difficult to very difficult understandable mode and language (Chapter 5A). As a result, readers may fail to broaden their understanding of this symptom or may even misinterpret crucial information on healthcare decisions. Misperception may be further aggravated in stressful conditions [24,25]. Additionally, the Web pages were rated with medium accessibility and a considerably low reliability was detected for the sites under investigation, with implications for site transparency, expertise authorship, review procedures and update frequency (Chapter 5A). These findings have raised concerns about the susceptibility of patients to misinformation.

We also showed that approximately 50% of YouTube videos relevant to pSS were deemed useful (Chapter 5B), a finding lying close to the range of 54.9-63.0% reported by studies with similar methodology, which investigated the role of YouTube in the e-education of patients regarding H1N1 influenza pandemic, cardiovascular resuscitation, nephrolithiasis, rheumatoid arthritis and hypertension [26-30]. Incomplete information on the etiology of pSS and drugs of unknown ingredients were posted by the misleading videos of the study (Chapter 5B). This observation confirms previously expressed safety concerns in retrieving YouTube information for healthcare decision making; promotion of unscientific therapies without authority approval, and dissemination of contradicting information to reference guidelines [31]. The substantial proportion of YouTube video material related to personal experiences is also calling for attention. It has been previously demonstrated that patient testimonials may be driven by financial motives [32]. In terms of global quality score (GQS), reliability and comprehensiveness of information, government/news agencies appeared to be the most creditable contributors. On the other hand, university channels/professional organizations presented as high GQS as government/news agencies, while none video was classified as misleading. Therefore, to increase the chances of accessing high quality information on pSS, YouTube users should seek for videos of reliable origin.

Implications and future perspectives in e-education of pSS patients

The writing style of the e-material intended for patients preferably should be revised to a more favorable comprehensive level. Sentences should be kept short, while uniform and plain language should be maintained throughout the text. Long lists should preferably be avoided and bullet points as well as graphics are advised to be used with caution [33]. Administrators of Web sites should be advised by search engine optimization (SEO) experts to ensure that their sites are easily accessible. Patients and their intimates as well as patient organizations should be encouraged to use verified Web sites, generated by specialists, with structured interactive educational programs.

The results of our study underline also the need for quality filtering of YouTube videos displaying health information on pSS (Chapter 5B). YouTube encourages its
users to ‘flag’ videos of inappropriate content. Such an option may be intentionally misused by users with conflict of interest, however [34]. The social networking approach could offer the benefits of collective intelligence in assessing the trustworthiness of YouTube videos. Peer reviews by the crowd, like patient support groups, have been found capable of identifying and fixing incorrect information [35]. University and governmental institutions should be represented in these examination bodies. Interfaces that enable coupling of YouTube with evidence-based references could enhance the dissemination of accurate information [31]. In agreement with other researchers, we also suggest modification of YouTube’s ranking search algorithm to extract first the health related videos of trustworthy origin when a medical term is entered in YouTube’s video search engine [36].

Epilogue

The research described in this thesis has shown that:

i. ultrasound of the major salivary glands is a reliable imaging technique in the diagnostic process of patients suspected with pSS and has good and moderate agreement with parotid and labial gland biopsy, respectively. The combination of ultrasound with anti-SSA antibodies is highly predictive for fulfilling the classification criteria, when the outcome of the parotid gland biopsy is considered as an item of the classification criteria.

ii. baseline histopathological characteristics of parotid gland biopsy may strongly contribute to a more personalized treatment approach to pSS patients with RTX.

iii. online information on xerostomia and pSS exhibits currently variable quality and therefore should be approached with caution.

References


