Ultrasonography of Salivary Glands — A Highly Specific Imaging Procedure for Diagnosis of Sjögren's Syndrome

DIRK WERNICKE, HEIDEMARIE HESS, ERIKA GROMNICA-IHLE, ANDREAS KRAUSE, and WOLFGANG A. SCHMIDT

ABSTRACT. ***Objective.*** To verify ultrasonographic criteria for examination of the major salivary glands in diagnosis of primary and secondary Sjögren's syndrome (SS).

Methods. Three hundred sixteen consecutive patients with rheumatic diseases were selected according to the European Consensus Study Group diagnostic criteria for SS. Fifty-seven had primary SS, 33 had secondary SS, 78 had Sicca symptoms, and 148 patients served as asymptomatic controls. This cohort was analyzed for size and parenchymal echogenicity of the major salivary glands by ultrasonography.

Results. Evident parenchymal inhomogenicity in 2 or more major salivary glands was detected by ultrasonography in patients with primary and secondary SS with a sensitivity of 63.1% and 63.6%, respectively. The specificity of this imaging approach in our cohort was 98.7%. The volume of submandibular glands was reduced in patients with primary and secondary SS by about 30% compared to patients with sicca symptoms and asymptomatic controls. In receiver-operating characteristic (ROC) curve analysis, the detection of reduced volumes of both submandibular glands in patients with primary and secondary SS had a specificity of 93% and a sensitivity of 48% at the cutoff point of 3.0 ml. Of note, the volume of the parotid glands did not differ between the groups of patients. In patients with primary SS, parenchymal inhomogenicity of the salivary glands was strongly associated with positivity for anti-Ro and/or anti-La antibodies.

Conclusion. Ultrasonographic detection of parenchymal inhomogenicity of the major salivary glands and observation of reduced volume of the submandibular glands resulted in high specificities for diagnosis of primary and secondary SS. The data indicate that ultrasonography of major salivary glands is a noninvasive imaging procedure with high diagnostic value for the diagnosis of primary and secondary SS. (First Release Jan 15 2008; J Rheumatol 2008;35:285–93)

Key Indexing Terms:
PARENCHYMAL INHOMOGENICITY SICCA SYMPTOMS
ANTI-RO ANTIBODY ANTI-LA ANTIBODY SALIVARY GLANDS

Sjögren's syndrome (SS) is a chronic inflammatory autoimmune disease affecting mainly the exocrine glands. While the ocular manifestation of the disease, keratoconjunctivitis sicca, can be well diagnosed by objective tests (Schirmer test, Rose Bengal score), assessment of the manifestation in the salivary glands is more difficult. Besides histopathological examination of the minor salivary glands, parotid sialography, salivary gland scintigraphy, and unstimulated salivary flow examination have been accepted by the American-European Consensus Group as criteria for salivary gland involvement in SS[1]. Sialography is considered to be the most reliable of the imaging methods[2,3]. Salivary gland scintigraphy is very sensitive and especially useful in early stages of the disease[4,5]. Nevertheless, both imaging techniques are used by only a minority of rheumatologists for diagnosis of SS because of the invasive character of sialography and the low specificity of scintigraphy.

Rapid technical development has improved the accuracy of noninvasive methods, including computed tomography[6,7], magnetic resonance (MR) imaging[8-10], MR sialography[11,12], and ultrasonography[13-17]. Among them, ultrasonography of the major salivary glands appears to be the most attractive imaging approach: it is an inexpensive commonly available noninvasive technique that does not cause complications and inconvenience to the patient. The first studies of ultrasonographic abnormalities in SS were performed with a limited number of patients, showing that parenchymal inhomogenicity is the most sensitive ultrasonographic index of salivary gland involvement in SS[6,8,13,15,16]. More recent studies were designed with larger numbers of patients[2,3,17-19]. In these studies most data were obtained from ultrasonographic examination of the parotid glands when ultrasonography was compared with sialography[2,3,19]. In this context, less is known about the ultrasonographic abnormalities of the submandibular glands in SS[20].

From the Clinic for Rheumatology Berlin-Buch, Berlin, Germany.
D. Wernicke, MD, PhD; H. Hess, MD; E. Gromnica-Ihle, MD; A. Krause, MD; W.A. Schmidt, MD.
Address reprint requests to Dr. D. Wernicke, Clinic for Rheumatology Berlin-Buch, Karowerstr. 11, Berlin, 13 125, Germany.
E-mail: dwernic@mdc-berlin.de
Accepted for publication October 2, 2007.

Our objective was to verify the diagnostic value of conventional ultrasonography of the major salivary glands for the diagnosis of primary and secondary SS in a large cohort of consecutive patients with rheumatic diseases.

MATERIALS AND METHODS

Patients. Patients included in this consecutive case study came from the Clinic for Rheumatology in Berlin-Buch, a tertiary care institution serving more than 20,000 patients with rheumatic diseases per year. All patients gave informed consent to participate in the study, which was performed according to the criteria of the Helsinki Declaration 1975/1983 and approved by the Ethics Committee of the hospital. Exclusion criteria were a history of sialolithiasis, salivary gland masses, surgery of salivary gland, previous head and neck radiation therapy, hepatitis C and HIV infections, sarcoidosis, and treatment with antidepressants, parasympatholytic drugs or other drugs that may impair salivary gland function. Fifty-seven patients had primary SS based on the revised classification criteria for SS established by the European Consensus Study Group[1]. Thirty-three patients had secondary SS due to inflammatory rheumatic diseases, such as rheumatoid arthritis (RA, n = 9), systemic lupus erythematosus (SLE, n = 8), systemic sclerosis (n = 5), mixed connective tissue disease (n = 4), and other inflammatory rheumatic diseases (n = 7). In the symptomatic control group, 78 patients had sicca symptoms not fulfilling the criteria for SS. Patients in this control group had undifferentiated connective tissue disease (UCTD, n = 21), RA (n = 9), and other inflammatory rheumatic diseases (n = 23). Twenty-five subjects were patients with sicca symptoms who had noninflammatory rheumatic diseases. The asymptomatic control group consisted of 148 patients, who had RA (n = 32), SLE (n = 22), UCTD (n = 17), and other inflammatory rheumatic diseases (n = 40). Thirty-seven members of the asymptomatic control group were patients with noninflammatory rheumatic diseases. Table 1 summarizes the main characteristics of the cohorts, including the diagostic procedures used to verify the diagnosis of SS.

Ultrasonographic examination. All patients were examined with a real-time ultrasonographic system (Ultramark 9 HDI; Advanced Technology Laboratories, Bothell, WA, USA) equipped with a 5–10 MHz linear transducer. Major salivary glands were examined in longitudinal and transverse planes. Volumes of submandibular and parotid glands were calculated according to the formula

$$\text{Volume (ml)} = \text{longitudinal diameter (mm)} \times \text{transverse diameter (mm)} \times \text{sagittal diameter (mm)} \times 0.5$$

Parenchymal echogenicity was determined in comparison with that of the thyroid gland and the surrounding soft tissue. A normal salivary gland has the same echogenicity as the thyroid gland and is hypoechoic compared with the surrounding soft tissue. Parenchymal inhomogenicity was evaluated; 3 grades of parenchymal inhomogenicity were distinguished: Grade 0: normal homogenous parenchyma; Grade I: mild parenchymal inhomogenicity seen as diffuse hypoechoic areolae < 2 mm; Grade II: evident parenchymal inhomogenicity seen as diffuse hypoechoic areolae > 2 mm. Figure 1 illustrates evident parenchymal inhomogenicity of the submandibular gland in comparison with normal homogenous parenchyma.

In 98 of the 316 patients of the cohort the volume and parenchymal echogenicity of major salivary glands were judged independently by 2 observers (WS and HH), who were not aware of the clinical diagnosis or the opinion of the other examiner. The interobserver agreement, analyzed by kappa test, ranged from 0.87 for the volumes of the salivary glands to 0.95 for parenchymal inhomogenicity. Because interobserver agreement was very high for both ultrasonographic indices, we used the grading results obtained from the more experienced examiner (WS) for the analysis of the entire cohort.

Table 1. Main characteristics of patients.

	Primary SS	Secondary SS	Sicca Syndrome	Asymptomatic Controls
No. female/male	50/7	29/4	75/3	120/28
Mean age, yrs	51	53	48	45
Age range	18–77	18–75	23–77	15–77
Ocular symptoms				
Yes	54	28	48	0
No	3	5	30	148
Oral symptoms				
Yes	55	30	61	0
No	2	3	17	148
Keratoconjunctivitis sicca*				
Yes	34	29	0	2
No	19	4	75	76
ND	4	0	3	70
Histopathology of minor salivary gland biopsy**				
Positive	21	11	1	0
Negative	7	2	14	2
ND	29	20	63	146
Sialoscintigraphy				
Positive	46	31	25	15
Negative	6	0	39	12
ND	5	2	14	121
Anti-Ro or anti-La antibodies or both				
Positive	48	15	4	18
Negative	9	18	74	128
ND	0	0	0	3

* Quantitative Rose Bengal score or Schirmer test. ** Determined by focus score > 1[27]. ND: not determined.

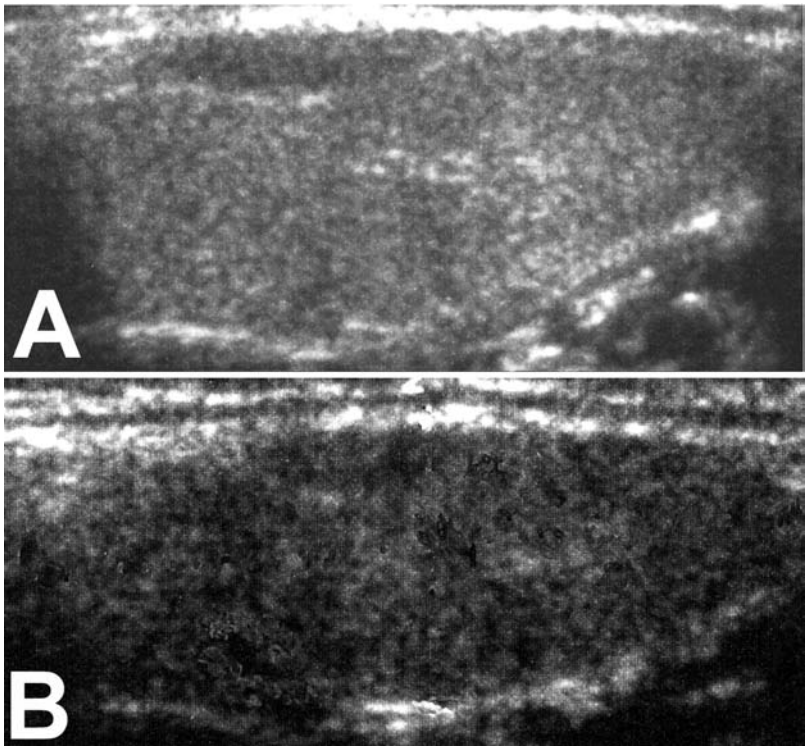

Figure 1. Parenchymal inhomogenicity in primary SS revealed by ultrasonography. Image shows a normal submandibular gland (A) and a submandibular gland with evident parenchymal inhomogenicity (grade II) in a patient with primary SS (B).

Laboratory investigations. Routine laboratory and immunoserological examinations were carried out on all patients: antinuclear antibodies (ANA; positive if titer > 1:80 by indirect immunofluorescence on HEp-2 cells), IgM rheumatoid factor (RF; positive if > 20 IU/ml by nephelometry), and anti-extractable nuclear antigen antibodies anti-Ro/SSA and anti-La/SSB (positive if titer > 7 IU/ml by ELISA).

Statistical analysis. SPSS 14.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analyses. $P < 0.05$ was considered statistically significant. Data are expressed as means ± SE. Mann-Whitney U-test was used to analyze differences between the groups of patients. Receiver-operating characteristic (ROC) curves were employed to describe how well various sizes of the salivary glands determined by ultrasonography distinguish patients with SS from controls. Reproducibility of the data between the 2 observers was assessed by kappa coefficient.

RESULTS

Analysis of volume of salivary glands. In asymptomatic controls, women had smaller submandibular and parotid glands compared with men ($p < 0.025$). The analysis of both submandibular glands revealed a mean volume of 4.8 ± 1.5 ml in women and 6.1 ± 1.7 ml in men. The mean volume of the parotid glands was 14.4 ± 5.2 ml in women and 18.2 ± 5.1 ml in men. The volume of the major salivary glands did not depend on the age of the patients or their size or weight (data not shown). In the female controls, the volume of the right submandibular gland was larger (4.9 ± 1.7 ml) than the left (4.6 ± 1.6 ml; $p < 0.025$). In parallel, the right parotid gland was also larger (15.4 ± 5.6 ml) in comparison with the left (13.3 ± 4.5 ml; $p < 0.01$). The number of male controls in the cohort was too small to determine differences in volumes between left and right salivary glands.

In comparison with asymptomatic controls, the mean volume of the submandibular glands in female patients with primary and secondary SS was reduced by 33% and 40%, respectively (Table 2). In parallel, in male patients with primary SS the mean volume of the submandibular glands was reduced by 28% compared with asymptomatic controls. The mean volume of submandibular glands in men with secondary SS was also markedly reduced, but was not significantly different from controls, probably due to the small number of male patients in our cohort. At the same time, the mean volume of parotid glands did not differ between the groups of patients in the cohort (data not shown).

The distribution of average volumes of the submandibular glands of female patients was studied in more detail. As shown in Figure 2, the volumes of submandibular glands in the asymptomatic control group was normally distributed. The curve of patients with primary SS follows a nearly normal distribution, with a certain bias toward smaller volumes of the submandibular glands. The curve for patients with secondary SS shows 2 peaks, both located below the mean volume of the asymptomatic control group. The curve for patients with sicca symptoms has 2 peaks, one below and the other above the mean volume of the asymptomatic control group, in a nearly symmetrical expression. Distribution of volumes of the sub-

Table 2. Mean volumes of the submandibular glands. The volumes of both submandibular glands were measured to calculate average volume for each patient. Mean volumes of patient groups were calculated from the subjects' average volumes.

	Women		Men	
	Volume, ml	n	Volume, ml	n
Primary SS	3.2 ± 1.7*	48	4.4 ± 1.4**	7
Secondary SS	2.9 ± 1.8*	27	5.0 ± 1.5	4
Sicca symptoms	4.7 ± 2.0	69	5.4 ± 1.6	3
Asymptomatic controls	4.8 ± 1.5	102	6.1 ± 1.7	22

* $p < 0.001$ compared with female asymptomatic controls; ** $p < 0.025$ compared with male asymptomatic controls.

mandibular glands in men could not be calculated because of the small number of male patients.

Figure 3 illustrates how frequently enlarged or reduced volumes of the submandibular glands were detected unilaterally and bilaterally in patients with SS. The mean volume of the submandibular glands in the asymptomatic control group ± 1 SD was defined as the "normal" volume and was calculated separately for women and men.

ROC curves were employed to assess the diagnostic accuracy of bilaterally reduced volumes of submandibular glands for the diagnosis of SS. Figure 4A shows the relation between sensitivity and specificity for female patients with primary and secondary SS in comparison with symptomatic and asymptomatic controls. As further shown in Figures 4B and 4C, the relations between sensitivity and specificity are very similar for patients with primary and secondary SS. Table 3 summarizes the values of sensitivity and specificity for different cutoff points calculated from the ROC curve of Figure 4A. The cutoff point of 3 ml yielded 93% specificity and 48% sensitivity, with a positive predictive value of 77% and negative predictive value of 80%.

Parenchymal inhomogenicity of the salivary glands. Parenchymal inhomogenicity, the most important ultrasonographic change seen in patients with SS[6,8,13,15,16], was evaluated in patients with primary and secondary SS, patients with sicca symptoms, and in asymptomatic controls. Based on the ultrasonographic scoring system we employed, our findings were regarded as typical for SS when at least 2 major salivary glands showed parenchymal inhomogenicity grade II. As shown in Table 4, such findings were noted in patients with primary and secondary SS of our cohort with a sensitivity of 63.1% and 63.6%, respectively. The specificity of this imaging approach was 96.1% for patients with sicca symptoms and 100% for asymptomatic controls. For the entire group of patients with primary and secondary SS the positive predictive value of the procedure was 95%, and the negative predictive value was 87%.

Parenchymal inhomogenicity of salivary glands in association with clinical and laboratory findings in primary SS. Table 5 shows frequent clinical manifestations and laboratory findings in the group of patients with primary SS in association with parenchymal inhomogenicity in at least 2 major salivary glands. As indicated, immunological findings but not extraglandular manifestations of primary SS correlated with parenchymal inhomogenicity observed with ultrasonography. In patients with parenchymal inhomogenicity, ANA and anti-Ro and/or anti-La antibody positivities were the most frequent immunological changes, with an occurrence of 97%. IgM RF positivity and hypergammaglobulinemia were detected in patients with parenchymal inhomogenicity grade II with frequencies of 88.9% and 69.4%, respectively.

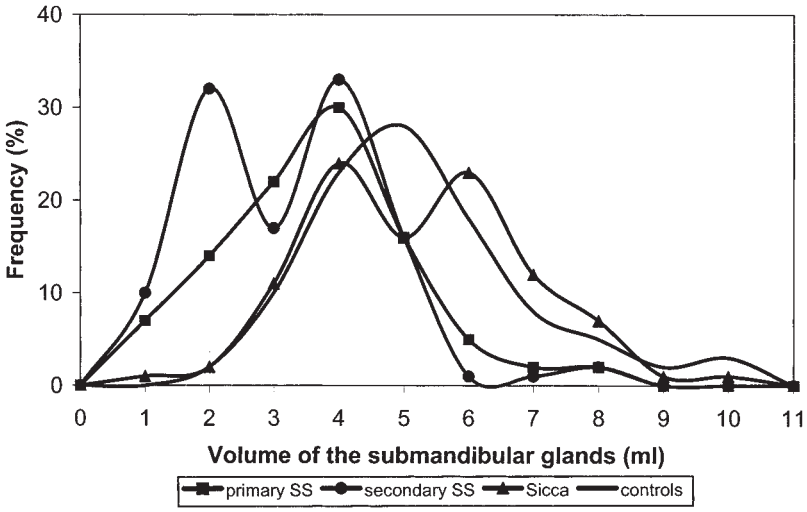

Figure 2. Distribution of volumes of submandibular glands in patients with primary and secondary SS and sicca symptoms and in asymptomatic controls. The volumes of both submandibular glands were measured to calculate the average for each patient. The figure shows the average volumes of submandibular glands of female patients: 50 with primary SS, 29 with secondary SS, and 75 with sicca symptoms, and 120 asymptomatic controls.

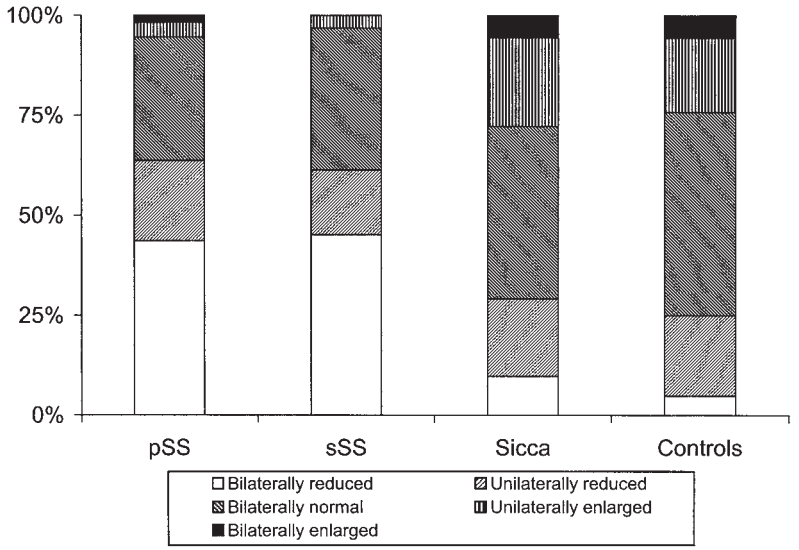

Figure 3. Unilateral and bilateral involvement of submandibular glands. The percentage of reduced or enlarged submandibular glands is shown for 57 patients with primary SS, 33 with secondary SS, and 78 with sicca symptoms, and 148 asymptomatic controls. The mean volume of submandibular glands in the asymptomatic control group ± 1 SD was selected as the normal volume and calculated separately for female and male patients.

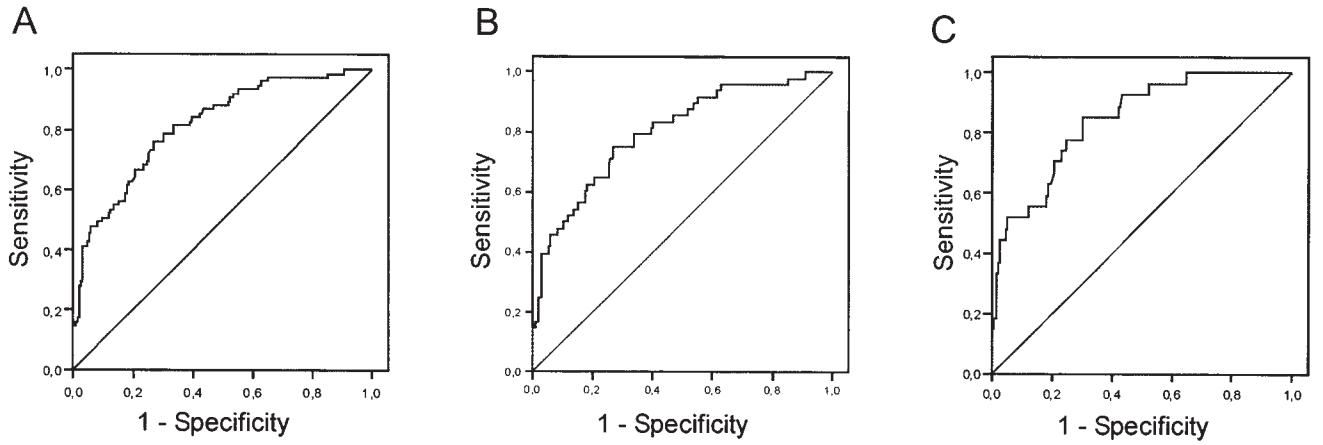

Figure 4. Diagnostic accuracy of reduced volume of submandibular glands by ultrasonography. ROC curves illustrate relations between sensitivity and specificity for detection of bilaterally reduced volumes of submandibular glands of female patients with primary and secondary SS (A), primary SS (B), and secondary SS (C) compared with symptomatic and asymptomatic female controls. The area under curve A is 0.815 ± 0.029 (95% CI 0.758 to 0.873), that of curve B is 0.800 ± 0.037 (95% CI 0.728 to 0.872), and that of curve C is 0.842 ± 0.038 (95% CI 0.768 to 0.916).

The average disease duration in patients with primary SS demonstrating grade II parenchymal inhomogenicity was 7.8 years, while the average disease duration in patients without ultrasonographic changes was 4.2 years ($p < 0.05$). In secondary SS, the average duration of sicca symptoms was 8 years in patients with grade II parenchymal inhomogenicity and 6 years in patients without ultrasonographic abnormalities within the major salivary glands ($p < 0.1$).

We found 14% of patients with primary SS (n = 8) and 9% of patients with secondary SS (n = 3) had extraglandular cervical lymph nodes that were suspicious for lymphoproliferative disease, demonstrating a significant difference between primary and secondary SS.

DISCUSSION

Ultrasonography of the major salivary glands represents an informative imaging procedure for detection of parenchymal abnormalities in SS. In order to optimize the sensitivity and specificity of this imaging approach, several ultrasonographic scoring systems have been developed[2,3,6,15-19]. In this context, our study was performed with a large cohort of consecutive patients with rheumatic diseases to evaluate simple and prac-

Table 3. Sensitivity and specificity of reduced volumes of the submandibular glands in female patients with primary and secondary SS by ultrasonography, in comparison with symptomatic and asymptomatic controls; calculated from the ROC curve shown in Figure 4A.

Volume, ml	Sensitivity ($\times 10^{-2}$ %)	Specificity ($\times 10^{-2}$ %)
1.50	0.120	1.000
2.00	0.240	0.982
2.50	0.333	0.971
3.00	0.480	0.930
3.10	0.493	0.906
3.20	0.520	0.883
3.30	0.560	0.830
3.40	0.613	0.819
3.50	0.627	0.807
3.60	0.680	0.766
3.70	0.733	0.743
3.80	0.760	0.719
3.90	0.787	0.673
4.00	0.813	0.632
4.50	0.880	0.503
5.00	0.947	0.380
5.50	0.973	0.287
6.00	0.973	0.222
6.50	0.987	0.117
7.00	1.000	0.058

tical ultrasonographic criteria for the characterization of structural abnormalities in SS.

Initial studies of ultrasonographic abnormalities in SS revealed that parenchymal inhomogenicity is the most reliable sonographic index for salivary gland involvement in SS[6,13,15,16]. At the same time, it was shown that only evident parenchymal inhomogenicity is of true diagnostic value[8,13,16]. Therefore, in our study, an ultrasonographic diagnosis of SS was only given when at least 2 major salivary glands showed evident grade II parenchymal inhomogenicity. Based on this strong assumption, the specificity of ultrasonography was 96.1% for patients with sicca symptoms and 100% for asymptomatic controls. SS was diagnosed in our cohort with a sensitivity of 63%. Our results are in agreement with investigations showing a specificity of ultrasonography between 92% and 100%[2,13,15,20,21]. The specificity of ultrasonography was lower in only 2 reports, about 84%[13,16]. At the same time, the sensitivity of ultrasonography ranged from 43% to 90% in different studies[2,13,15,18-21]. This wide range of sensitivities may be due to differences between the patient groups or the different methodological approaches, or both. Giuseppetti, *et al*[22] described a rather high sensitivity of 87.5% using ultrasonography with a contrast-enhanced technique. But only minor alterations of blood flow in the major salivary glands were detected by Doppler sonography, indicating that this ultrasonographic technique is not appropriate for characterization of chronic inflammatory changes in SS[23]. Further, development of methods for quantitative analysis of ultrasonographic data did not improve the overall sensitivity of ultrasonography[18,19]. Even more differentiated ultrasonographic scoring systems were not able to enhance the sensitivity of the procedure[3,9,13,16-19]. For example, Hocevar, *et al*[17] investigated several ultrasonographic variables in a large cohort of consecutive patients with rheumatic diseases. The detailed ultrasonographic scoring system of that study had a sensitivity of 58.8% and a specificity of 98.7%. The positive and negative predictive values were 95.2% and 84.0%, respectively. The data obtained by Hocevar, *et al*[17] are very similar to the results of our study, which were, however, solely based on the investigation of evident parenchymal inhomogenicity.

While parenchymal inhomogenicity is the most reliable ultrasonographic measure for salivary gland involvement in SS, less is known about the expression of parenchymal inhomogenicity. Sialographic findings suggest that hypoechoic areas represent enlarged glandular lobules that have been replaced by lymphocyte infiltration[21]. On the other hand, MR sialography revealed that in advanced stages of the disease the number and size of sialoectatic foci are reduced and replaced by fat tissue[10]. In this context, hyperechogenic findings in ultrasonography might represent fibroses and fat accumulation. Interestingly, parenchymal inhomogenicity seen by ultrasonography was well confirmed by MR imaging[8].

In our cohort, patients with primary and secondary SS were detected with similar sensitivities. In contrast, De Vita, *et al*[13] described milder salivary involvement in patients with secondary SS compared with primary SS. Most likely, the sensitivity of ultrasonography for diagnosis of secondary SS depends on the severity of salivary gland involvement in these

Table 4. Sensitivity and specificity of parenchymal inhomogenicity of the major salivary glands. Number of patients is shown with distinct grades of parenchymal inhomogenicity as described in Materials and Methods. Diagnosis of primary or secondary SS was made when at least 2 major salivary glands showed parenchymal inhomogenicity grade II.

Ultrasonographic Score	Primary SS	Secondary SS	Sicca Symptoms	Asymptomatic Controls
Grade 0	18	10	69	141
Grade I	3	2	6	7
Grade II	36	21	3	0
Total number	57	33	78	148
Sensitivity, %	63.1	63.6	—	—
Specificity, %	—	—	96.1	100

Table 5. Extraglandular manifestations and laboratory findings in patients with primary SS in association with parenchymal inhomogenicity.

Manifestation/ Laboratory Findings	Positive on Ultrasonography, n = 36 Frequency of Occurrence, n (%)	Negative on ultrasonography, n = 21 Frequency of Occurrence, n (%)
Arthritis	7 (19)	6 (28.6)
Arthralgia	29 (80.5)	19 (90.5)
Xeroderma	22 (61.0)	11 (52.4)
Raynaud's phenomenon	11 (30.6)	4 (19.0)
IgM RF	32 (88.9)	7 (33.3)
Anti-Ro or anti-La antibodies, or both	35 (97.2)	13 (61.9)
ANA	35 (97.2)	12 (57.1)
Hypergammaglobulinemia	25 (69.4)	4 (19.0)

RF: rheumatoid factor; ANA: antinuclear antibody.

patients. Accordingly, in our study the degree of parenchymal inhomogenicity was positively correlated with the duration of disease in patients with primary and secondary SS.

Although several studies were performed to analyze the echogenicity of major salivary glands in SS, less is known about their sizes. In the past, exact determination of the posterior border of parotid glands was hampered by the low resolution of the ultrasonographic equipment[6,13,15,16]. In addition, most data were obtained from ultrasonographic examination of the parotid glands when ultrasonography was compared with other imaging procedures, such as sialography, MR imaging, and MR sialography[2,3,8,17-19]. As a result, little is known about the size of the submandibular glands[13,20].

Our data show that the volume of the submandibular glands, but not parotid glands, was reduced in patients with primary and secondary SS. Similar data were published from small cohorts of patients with primary SS[13,20]. Analysis of the distribution of average volumes of both submandibular glands in the subgroup of female patients with primary SS revealed a nearly normal distribution (Figure 2). In contrast, the curve for patients with secondary SS shows 2 peaks located below the mean volume of the submandibular glands in asymptomatic controls. These data indicate differences in the expression or progression of the pathologic processes in the submandibular glands in secondary SS. Interestingly, the curve for patients with sicca symptoms has 2 peaks, one below and the other above the mean volume of submandibular glands in asymptomatic controls. These data suggest that some of the patients with sicca symptoms are going to develop true SS. The peak above the mean volume of the asymptomatic controls is most likely caused by inflammation and edema in the submandibular glands in some of these patients. The peak below the mean volume of the asymptomatic controls might be caused by existing atrophic changes in the submandibular glands in a number of subjects. At least 2 observations might explain why the volume of the submandibular glands, but not that of parotid glands, is reduced in SS. First, histologic differences between parotid and submandibular glands (serous parotid glands versus mixed serous and mucous submandibular glands) might affect the expression and/or progression of the pathogenetic changes. Second, more severe functional impairment of the submandibular glands compared with the parotid glands was reported in SS and sialadenitis, suggesting more significant morphological changes in the submandibular glands[24,25]. Therefore our findings suggest that determination of the volume of the submandibular glands is an informative approach for evaluation of patients with sicca symptoms. Although the sensitivity of this imaging technique for diagosis of primary and secondary SS was low (48%), the specificity reached a remarkable 93%, even in consecutive patients with rheumatic disorders (Table 3).

It is a common observation that in primary SS high anti-Ro and/or anti-La antibody titers are associated with parenchymal inhomogenicity in ultrasonography[2,8,9,17,18]. Accordingly, in our patients with primary SS, grade II parenchymal inhomogenicity showed a strong association with ANA and anti-Ro or anti-La antibody positivity (Table 5). These data suggest that patients with ANA and anti-Ro or anti-La positivity develop evident structural changes in the major salivary glands via specific autoimmune mechanisms. Accordingly, parenchymal inhomogenicity of the parotid glands was more frequently detected in those patients who were positive for anti-Ro and anti-La antibodies at the same time[8]. Further, we observed that parenchymal inhomogenicity was also associated with IgM RF positivity and hypergammaglobulinemia, confirming data from other studies[8,18]. It is known that specific (anti-Ro and/or anti-La antibodies) and unspecific (IgM RF) antibody production and hypergammaglobulinemia represent humoral markers of B cell hyperactivity, and that oligoclonal B cell proliferation and the formation of ectopic lymphoid tissue are characteristic pathogenetic features of SS[26]. On the other hand, clinical manifestations have a poor association with parenchymal inhomogenicity in ultrasonography. In our study, the best association found was for arthralgia, confirming observations reported by Makula, *et al*[8].

Our ultrasonographic findings indicate that parenchymal inhomogenicity of 2 or more salivary glands is highly specific, 98.7%, for the diagnosis of SS. A comparable high speci-

ficity for diagnosis of SS was reported for MR imaging, ranging from 97.8% to 100%[8,9,18], and for sialography, 98%[2,3]. At the same time, high sensitivity for diagnosis of SS was shown for MR imaging, ranging from 81% to 93.9%[8,9,18], sialography (87% to 96%)[2,3], minor salivary gland biopsy (72% to 83%)[16], and for anti-Ro and/or anti-La antibody positivity (95%)[2]. Although the sensitivity of ultrasonographic detection of parenchymal inhomogenicity is low, this ultrasonographic measurement might contribute to the diagnosis of SS in combination with other diagnostic criteria. In particular, detection of anti-Ro and/or anti-La antibody titers was shown to be highly sensitive for the diagnosis of primary SS[2]. As discussed above, our data, and those of previous studies, reveal that anti-Ro and/or anti-La antibody positivity is strongly associated with parenchymal inhomogenicity (Table 5)[2,8,9,17,18]. Therefore, ultrasonography of the major salivary glands in combination with a laboratory test for anti-Ro and anti-La antibody positivity might effectively predict the presence of primary SS.

In order to confirm these ultrasonographic results, the major salivary glands, and the submandibular glands in particular, should be investigated for their size by a second imaging technique (MR imaging or computer assisted tomography). Due to the low number of male patients, possible sex-related differences could not be determined in our investigation and should be analyzed in consecutive studies.

Substantial efforts were made in recent years to establish noninvasive imaging procedures for the diagnosis of SS. Ultrasonography is a good candidate for a first-line imaging examination, because it is more widely available and cheaper than MR techniques. Ultrasonography provides the opportunity to evaluate all salivary glands at the same time and it is the most suitable for followup of patients with SS. It would be of interest to complete the classification criteria for SS established by the American-European Consensus Group[1] by noninvasive imaging procedures, particularly by ultrasonography. In this context, subsequent studies should be designed to test the data obtained by ultrasonography about the sizes of the major salivary glands by MR imaging, and to determine the properties of the parenchymal inhomogenicity in SS.

ACKNOWLEDGMENT

The authors thank Bernd Schicke, PhD, for performing the statistical analysis.

REFERENCES

1. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
2. Yonetsu K, Takagi Y, Sumi M, Nakamura T, Eguchi K. Sonography as a replacement for sialography for the diagnosis of salivary glands affected by Sjogren's syndrome. Ann Rheum Dis 2002;61:276-7.
3. Shimizu M, Okamura K, Yoshiura K, Ohyama Y, Nakamura S, Kinukawa N. Sonographic diagnostic criteria for screening Sjogren's syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:85-93.
4. Decuzzi M, Tatulli F, Giampaolo M, et al. Sialocintigraphy versus ultrasonography of the salivary glands in patients first diagnosed with Sjogren's syndrome. Hell J Nucl Med 2006;9:103-5.
5. Nishiyama S, Miyawaki S, Yoshinaga Y. A study to standardize quantitative evaluation of parotid gland scintigraphy in patients with Sjogren's syndrome. J Rheumatol 2006;33:2470-4.
6. de Clerck LS, Corthouts R, Francx L, et al. Ultrasonography and computer tomography of the salivary glands in the evaluation of Sjogren's syndrome. Comparison with parotid sialography. J Rheumatol 1988;15:1777-81.
7. Tonami H, Matoba M, Yokota H, Higashi K, Yamamoto I, Sugai S. CT and MR findings of bilateral lacrimal gland enlargement in Sjogren syndrome. Clin Imaging 2002;26:392-6.
8. Makula E, Pokorny G, Kiss M, et al. The place of magnetic resonance and ultrasonographic examinations of the parotid gland in the diagnosis and follow-up of primary Sjogren's syndrome. Rheumatology Oxford 2000;39:97-104.
9. Niemela RK, Takalo R, Paakko E, et al. Ultrasonography of salivary glands in primary Sjogren's syndrome. A comparison with magnetic resonance imaging and magnetic resonance sialography of parotid glands. Rheumatology Oxford 2004;43:875-9.
10. Takagi Y, Sumi M, Sumi T, Ichikawa Y, Nakamura T. MR microscopy of the parotid glands in patients with Sjogren's syndrome: quantitative MR diagnostic criteria. AJNR Am J Neuroradiol 2005;26:1207-14.
11. Niemela RK, Paakko E, Suramo I, Takalo R, Hakala M. Magnetic resonance imaging and magnetic resonance sialography of parotid glands in primary Sjogren's syndrome. Arthritis Rheum 2001;45:512-8.
12. Tomiita M, Ueda T, Nagata H, et al. Usefulness of magnetic resonance sialography in patients with juvenile Sjogren's syndrome. Clin Exp Rheumatol 2005;23:540-4.
13. De Vita S, Lorenzon G, Rossi G, Sabella M, Fossaluzza V. Salivary gland echography in primary and secondary Sjogren's syndrome. Clin Exp Rheumatol 1992;10:351-6.
14. Ariji Y, Ohki M, Eguchi K, et al. Texture analysis of sonographic features of the parotid gland in Sjogren's syndrome. AJR Am J Roentgenol 1996;166:935-41.
15. Makula E, Pokorny G, Rajtar M, Kiss I, Kovacs A, Kovacs L. Parotid gland ultrasonography as a diagnostic tool in primary Sjogren's syndrome. Br J Rheumatol 1996;35:972-7.
16. Salaffi F, Argalia G, Carotti M, Giannini FB, Palombi C. Salivary gland ultrasonography in the evaluation of primary Sjogren's syndrome. Comparison with minor salivary gland biopsy. J Rheumatol 2000;27:1229-36.
17. Hocevar A, Ambrozic A, Rozman B, Kveder T, Tomsic M. Ultrasonographic changes of major salivary glands in primary Sjogren's syndrome. Diagnostic value of a novel scoring system. Rheumatology Oxford 2005;44:768-72.
18. El Miedany YM, Ahmed I, Mourad HG, et al. Quantitative ultrasonography and magnetic resonance imaging of the parotid gland: can they replace the histopathologic studies in patients with Sjogren's syndrome? Joint Bone Spine 2004;71:29-38.
19. Chikui T, Okamura K, Tokumori K, et al. Quantitative analyses of sonographic images of the parotid gland in patients with Sjogren's syndrome. Ultrasound Med Biol 2006;32:617-22.
20. Kawamura H, Taniguchi N, Itoh K, Kano S. Salivary gland echography in patients with Sjogren's syndrome. Arthritis Rheum 1990;33:505-10.
21. Takashima S, Morimoto S, Tomiyama N, Takeuchi N, Ikezoe J, Kozuka T. Sjogren syndrome: comparison of sialography and ultrasonography. J Clin Ultrasound 1992;20:99-109.
22. Giuseppetti GM, Argalia G, Salera D, Ranaldi R, Danieli G, Cappelli M. Ultrasonographic contrast-enhanced study of sicca

syndrome. Eur J Radiol 2005;54:225-32.
23. Carotti M, Salaffi F, Manganelli P, Argalia G. Ultrasonography and colour doppler sonography of salivary glands in primary Sjogren's syndrome. Clin Rheumatol 2001;20:213-9.
24. Aung W, Murata Y, Ishida R, Takahashi Y, Okada N, Shibuya H. Study of quantitative oral radioactivity in salivary gland scintigraphy and determination of the clinical stage of Sjogren's syndrome. J Nucl Med 2001;42:38-43.
25. Tighe JV, Bailey BM, Khan MZ, Stavrou M, Todd CE. Relation of preoperative sialographic findings with histopathological diagnosis in cases of obstructive sialadenitis of the parotid and submandibular glands: retrospective study. Br J Oral Maxillofac Surg 1999; 37:290-3.
26. Hansen A, Lipsky PE, Dorner T. B cells in Sjogren's syndrome: indications for disturbed selection and differentiation in ectopic lymphoid tissue. Arthritis Res Ther 2007;9:218-25.
27. Daniels TE, Whitcher JP. Association of patterns of labial salivary gland inflammation with keratoconjunctivitis sicca. Analysis of 618 patients with suspected Sjogren's syndrome. Arthritis Rheum 1994;37:869-77.