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Dental implants in dentate primary and secondary Sjögren's syndrome patients: A multicenter prospective cohort study

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Abstract

Objectives: To prospectively assess the clinical performance and patient-reported outcomes of dental implants in dentate patients with primary and secondary Sjögren's syndrome (pSS and sSS, respectively) compared to patients without SS.

Materials and Methods: Thirty-seven implants were placed in 17 patients with pSS/sSS and 26 implants in 17 non-SS patients to replace missing (pre)molars. Clinical performance, marginal bone-level changes, patient satisfaction, and oral health-related quality of life (OHRQoL) were assessed at 1 (T1), 6 (T6), 12 (T12), and 18 (T18) months after placement of the superstructure. Marginal bone-level changes were measured on standardized dental radiographs. Clinical parameters included implant and crown survival, plaque, bleeding and gingival indices, and probing depth. Patient satisfaction and OHRQoL were assessed with validated questionnaires.

Results: Implant survival at T18 was 100% in the patients with pSS/sSS and 96.2% in the non-SS group. Mean marginal bone loss at T18 did not differ between patients with pSS/sSS and non-SS patients, 1.10 ± 1.04 and 1.04 ± 0.75 mm, respectively ($p = .87$). Clinical performance was good with no differences between the groups for all outcome measures ($p > .05$). OHRQoL in patients with pSS/sSS had improved significantly after placement of implant supported crowns at all measuring moments compared to baseline ($p < .05$). Nevertheless, patient satisfaction and OHRQoL remained significantly higher for patients without SS at all measuring moments ($p < .05$).

Conclusion: Dental implants can be successfully applied in dentate patients with pSS/sSS and have a positive effect on OHRQoL.

KEYWORDS
dental implants, Sjögren's syndrome, xerostomia, prosthodontics

1 | INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disorder characterized by progressive lymphocytic infiltration of the exocrine glands, notably the lacrimal and salivary glands (Fox, 2004). After rheumatoid arthritis (RA), SS is considered to be the most common rheumatic autoimmune disorder and it affects mainly women (female-to-male ratio, 9:1) (Fox, 2004). SS can be divided in primary (pSS) and secondary SS (sSS). Secondary SS is associated with connective tissue diseases, such as RA or systemic lupus erythematosus (SLE). The pathogenesis of SS is still largely unknown. It has become apparent that disturbances of the immune system play a central role. Whether this is a primary cause or a result of a prior (viral) infection or other extrinsic factors remains uncertain (Mariette & Criswell, 2018). SS is characterized by mononuclear infiltrates and IgG-producing plasma cells in the salivary and lacrimal glands. This infiltration leads to irreversible destruction of glandular tissue with a subsequent decrease in saliva secretion rate (Daniels & Fox, 1992; Mariette & Criswell, 2018).

Saliva possesses many important functions including antimicrobial activity, mechanical cleansing, regulation of pH, removal of food debris from the oral cavity, lubrication of the oral cavity, control of mineralization and demineralization of teeth, and maintaining the integrity of the oral mucosa (Dawes et al., 2015; Hsu & Dickinson, 2006; Mathews et al., 2008). A change in saliva composition or a lack of saliva subsequently increases caries risk, which results in progressive degradation of the dentition of SS patients (Dawes et al., 2015; Maarse et al., 2018; Maarse et al., 2019).

If there is a qualitative or quantitative problem with saliva, loss of retention, pain, and ulceration may occur while wearing full or partial dentures (Okuno et al., 2014; Turner et al., 2008). In addition, dry mouth is associated with the occurrence of the sensation of burning mouth (nonidiopathic burning mouth syndrome), which makes wearing conventional dentures difficult (Ritchie & Kramer, 2018). A recent review of the literature emphasized the important role of saliva in the success of a denture. Speaking and chewing skills, as well as denture stability, were found to be reduced in patients with dry mouth symptoms compared to healthy subjects (Tanaka et al., 2021).

For patients with SS, an implant supported restoration could be a better treatment option. Dental implant treatment is a clinically validated and practice-proven therapy for the replacement of teeth (Derks et al., 2015). To date, no prospective clinical trials have been published in which the success and survival of implants in patients with SS were investigated and compared to healthy subjects. Only retrospective studies and case series reported on the use of dental implants in patients with SS, often with favorable outcomes (Albrecht et al., 2016; Almeida et al., 2017; Barros et al., Barros et al., 2021; Chrcanovic et al., 2019; Korfage et al., 2016), but also with less favorable outcomes such as an above average loss of implants (Isidor et al., 1999; Payne et al., 1997). Therefore, this study aims to prospectively investigate the clinical performance and patient-reported outcomes of dental implants in dentate patients with SS compared to subjects without SS up to 18 months after placement of the suprastructure. We hypothesize that there is no difference in marginal peri-implant bone loss and patient-reported outcomes between dentate patients with SS and dentate control subjects.

2 | MATERIAL AND METHODS

2.1 | Study design

This clinical study was designed as a prospective multicenter clinical trial with a noninferiority design and an 18-month follow-up period and was conducted between May 2015 and September 2020. The study was conducted at the Amsterdam University Medical Center, department of Oral and Maxillofacial Surgery and Oral Pathology, Amsterdam; Center for Special Care Dentistry, Amsterdam; University Medical Center Utrecht, department of Oral and Maxillofacial Surgery, Prosthodontics and Special Dental Care, Utrecht; University Medical Center Groningen, Department of Oral and Maxillofacial Surgery, Groningen; and private dental practice Bocht Oosterdiep, Veendam. All centers are located in the Netherlands. At all centers, two or more investigators were involved in study-related activities. Recruitment took place at all sites. The surgical procedure was performed at the Amsterdam UMC, UMC Utrecht, UMC Groningen, and private practice Bocht Oosterdiep, Veendam. The prosthetic procedures (including placement of the crown) and measuring outcome measures were performed at all sites by co-authors other than who inserted the implants. One trained examiner (FM), unaware of the group allocations, evaluated all radiographs to measure loss of bone. The study protocol is registered at ClinicalTrials.gov (no. NCT02661243). The design and reporting of this study are consistent with STROBE statement recommendations (von Elm et al., 2014).

2.2 | Participants

The study population consisted of dentate patients with and without pSS or sSS referred for single-implant treatment in the posterior region. The patients were considered for inclusion if they fulfilled the following criteria:

- Between 18 and 80 years of age.
- One or more missing (pre)molars in the maxilla and/or mandible.
- Sufficient mesio-distal (at least 7 mm) and interocclusal space for an anatomic restoration.
- Sufficient bone volume to insert a dental implant. In case of implant dehiscences or fenestrations, it was allowed to cover these by autogenous bone chips collected during implant bed preparation.
- Adequate oral hygiene (modified plaque index and modified sulcus bleeding index ≤1) and with an infection of the oral mucosa as determined by visual inspection and periodontal investigation (pocket probing >4 mm) were excluded (Loe & Silness, 1963; Mombelli et al., 1987).
- The patient was capable of understanding and giving an informed consent.

Patients were excluded from participation in this study if they met one of the following criteria:

- Medical and general contraindications for the surgical procedures. This was defined as an American Society of Anesthesiologists score ≥3 (Owens et al., 1978).
- Presence of an active and uncontrolled periodontal disease as expressed by probing pockets depths >4 mm with bleeding upon probing;
- History of radiotherapy to the head and neck region or the use of intravenous bisphosphonates/use of oral bisphosphonates for more than 3 years or other medication, to date known for inhibiting bone remodeling (e.g., Denosumab);
- Smoking within 6 weeks before implant placement/bone augmentation.

Patients with SS only:

- Diagnosed with primary or secondary Sjögren's syndrome according to the 2002 American European Consensus Group Criteria (AECG) guidelines (Vitali et al., 2002).

Patients without SS only:

- No xerostomia as measured by the EULAR (European League Against Rheumatism) Sjögren's Syndrome Patient Reported Index (ESSPRI) score Dryness Domain Score (score <3) (Seror et al., 2015).

Participants with SS were recruited from the Drymouth Outpatient Clinic Amsterdam, through rheumatologists from the University Medical Centers in Amsterdam, Utrecht, and Groningen. Before inclusion, all possible participants for the patients with SS group were strictly screened for compliance with the 2002 American European Consensus Group (AECG) criteria (Vitali et al., 2002). Retrospectively, all patients with SS fulfilled the 2016 American Congress of Rheumatology (ACR)/EULAR criteria as well (Shiboski et al., 2017).

Patients without SS were referred to the participating centers by general practitioners. For every patient, a treatment plan was written in which it was examined how to fulfill the patient's care needs. The number of implants placed was thus determined on a case-by-case basis and based on individual care needs. The study was performed in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonization on Good Clinical Practice and the applicable Dutch regulatory requirements. Written informed consent was obtained from each patient. Patients were included between July 2014 and August 2018. The VU Medical Center/Amsterdam University Medical Center Research Ethics Board (#NL2014.541) approved the study.

2.3 | Patient and public involvement

A patient advisory group from the Dutch Federation for Sjögren's syndrome participated in the design of the study and the development of the informational material. Furthermore, they reviewed the burden of the intervention from the patient's perspective. This patient advisory group met on a regular basis for the duration of the study. At the end of the study, the patient advisory group commented on the findings and they contributed to the dissemination plan.

2.4 | Intervention

All patients received Biohorizon Laser-Lok tapered internal implants (Biohorizons, Birmingham, Alabama, USA) to replace missing (pre) molars in the upper and/or lower jaw. All implants were placed with preservation of the remaining (but healthy) dentition.

2.4.1 | Preoperative procedure

Prophylactic antibiotic therapy was applied 1 h before implant placement surgery (amoxicillin 3 g). Patients were instructed to use a 0.2% chlorhexidine mouthwash (two times daily for 7 days) for oral disinfection starting 1 day before surgery.

2.4.2 | Surgical procedure

Under local anesthesia, an incision was made and the implant site was examined and if necessary smoothed to obtain the correct relation between bone-plain and the vertical position of the implant. According to a standard procedure supplied by the manufacturer, the implant site was prepared and the implant inserted in the desired position. After implant placement, a cover screw was placed and hand-tightened on the fixture. The buccal margin of the wound including the soft tissue and papillae were repositioned over the cover screw without tension on the wound (2-stage procedure). Closure was obtained with resorbable sutures (Braun or Vicryl 4–0 SH-1 Ethicon, Johnson & Johnson Medical NV, Belgium). After 3 months of healing and osseointegration, the implant was uncovered and a maxillofacial surgeon placed a healing abutment. At least 1 week after this second procedure, the prosthetic treatment was started.

2.4.3 | Prosthetic procedure

Three months after implant placement, an individual impression was made on implant level for fabrication of the final crown. In the laboratory, a soft tissue cast was prepared. First, a wax-up model of the final restoration was made on a titanium abutment (Biohorizons Inc, Birmingham, AL., USA) to visualize the location of the screw access hole in relation to the crown. The wax-up model was scanned for fabrication of a lithium disilicate crown (Emax, Ivoclar Vivadent, Schaan, Liechtenstein). This crown was fused directly to the titanium abutment with Panavia composite resin (Kuraray, Tokyo, Japan) in order to create a screw-retained one-piece final restoration. The restoration was seated on the implant and the abutment screw was torqued with 30 Ncm, according to the manufacturer's instructions.

2.5 | Outcome measures

Before implant placement (T0) and 1 (T1), 6 (T6), 12 (T12) and 18 (T18) month(s) after definitive crown placement, patients were seen for clinical data collection. Outcome variables were survival rate, complication rate, plaque index (PI), bleeding index (BI), gingival index (GI), probing pocket depth, marginal bone level changes, chewing ability, and oral health-related quality of life.

2.5.1 | Survival rate

Survival rate was determined at all timepoints and is defined as whether the implant is still present in the mouth or not.

2.5.2 | Complication rate

Complications are defined as fracture of the implant, superstructure (including chipping of the crown) or abutment screw, or the detachment of the superstructure from the abutment or detachment of the abutment from the implant. Complications were recorded continuously.

2.5.3 | Plaque index

At T0, T1, T6, T12, and T18, the PI for each implant was measured on a scale of 0/1/2/3 (0 = no plaque; 1 = a film of plaque adhering to the free gingival margin and adjacent area of the crown/implant. The plaque may be seen in situ only after application of disclosing solution or by using the probe on the tooth surface; 2 = moderate accumulation of soft deposits within the gingival pocket, or the tooth/implant and gingival margin which can be seen with the naked eye; 3 = abundance of soft matter within the gingival pocket and/or on the tooth/implant and gingival margin) (Loe & Silness, 1963; Mombelli et al., 1987).

2.5.4 | Bleeding index

At T0, T1, T6, T12, and T18, the BI for each implant was measured on a scale of 0/1/2/3 (0 = no bleeding when probe is passed along the gingival margin; 1 = isolated bleeding, gingiva looks normal; 2 = blood forms a confluent red line on margins; 3 = heavy or profuse bleeding) (Loe & Silness, 1963; Mombelli et al., 1987).

2.5.5 | Gingival index

At T0, T1, T6, T12, and T18, the GI by Loe and Silness was measured for each implant. GI scores the marginal and interproximal tissues separately on a 0–3 scale. The criteria are: 0 = normal gingiva; 1 = mild inflammation – slight change in color and slight edema, but no bleeding on probing; 2 = moderate inflammation – redness, edema and glazing, bleeding on probing; 3 = severe inflammation – marked redness and edema, ulceration with tendency to spontaneous bleeding. The bleeding is assessed by probing gently along the wall of soft tissue of the gingival sulcus. The GI of an individual implant was be obtained by adding the values of each side of the implant (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual) and dividing by the number of sides examined (Loe & Silness, 1963; Mombelli et al., 1987).

2.5.6 | Probing pocket depth

Probing depth was measured at six sites for each implant (mesiobuccal, labial, distobuccal, mesiolingual, lingual, and distolingual) using a manual periodontal probe (Williams Colour Coded Probe; HuFriedy, Chicago, Il, USA) at T1, T6, T12, and T18. The distance between the marginal border of the mucosa and the tip of the periodontal probe was scored as the probing depth. The six scores were averaged, resulting in a single score per implant expressed in millimeters (mm).

2.5.7 | Radiographic evaluation

Changes in marginal bone level were calculated from standardized digital intra-oral radiographs taken with an individualized aiming device as previously described (Meijndert et al., 2004). Full-screen analysis of the radiographs was performed using the known implant diameter as a reference value for calibration of the radiograph. One trained examiner (FM), unaware of group allocations, evaluated all radiographs. A single observer was chosen to prevent interobserver variability. The vertical distance from the shoulder of the implant to the first bone-to-implant contact was measured at both the distal and mesial site of the implant using VisiQuick software (Citodent Imaging B.V, Amsterdam, the Netherlands). Mesial and distal bone changes in this region were averaged and considered as radiographic bone height change. Bone height changes are expressed in mm.

2.5.8 | Chewing ability

All patients were requested to fill out a “Chewing ability” questionnaire. In this questionnaire, patients gave their opinion about the ability to chew nine different kinds of food on a three-point rating scale (0 = good, 1 = moderate, 2 = bad). The nine items were grouped into three subgroups of three items each, representing the ability to chew soft food, tough food, and hard food (Stellingsma et al., 2005).

2.5.9 | Evaluation of oral health-related quality of life

Oral health-related quality of life (OHRQoL) was defined as “the absence of negative impacts of oral conditions on social life

FIGURE 1 Flow diagram of the allocation of participants

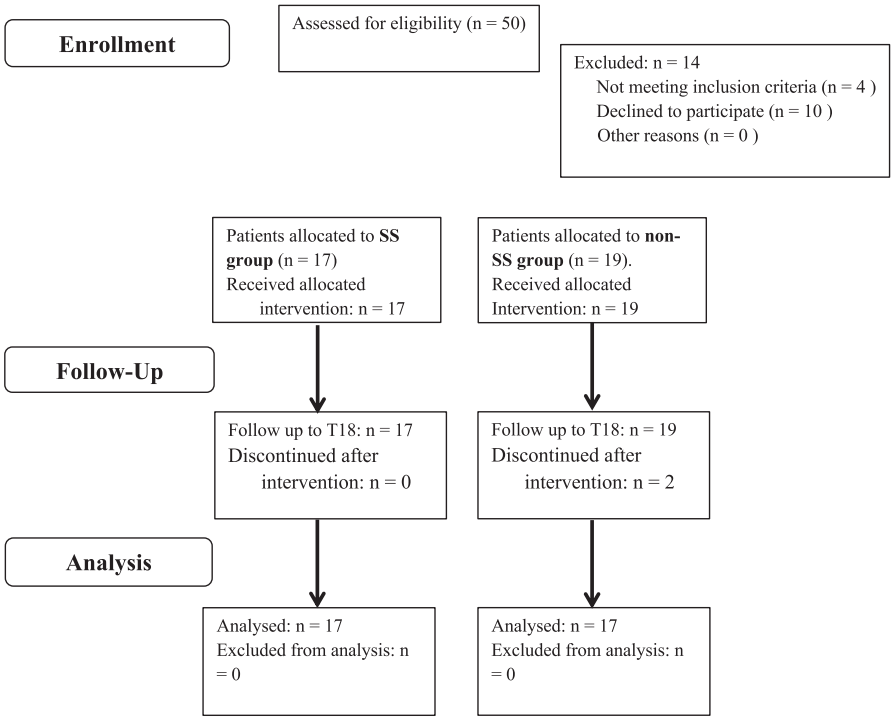

TABLE 1 Characteristics of the study population

Patient variables	Sjögren's syndrome	Non-Sjögren syndrome
N (patients)	17	19 (1 lost to follow-up before and 1 after T1); 17 patients in a per-protocol analysis
Age (median; IQR)	65 (59–69)	58 (48–61.5)
Female gender, *n*(%)	17 (100%)	12 (70.6%)
No. smokers (6 weeks prior to treatment)	0	3
Mean no. of medications used	4.8	0.9
Mean disease duration (years)[a]	13.4	n/a
Primary SS, *n*(%)[2]	11 (64.7%)	n/a
Secondary SS, *n*(%)[2]	6 (35.3%)	n/a
Autoantibodies to anti-SSA or anti-SSB(%)	69%	n/a
Positive salivary gland biopsy (%)	75%	n/a
Objective ocular involvement (Schirmer test) (%)	100%	n/a
Mean ESSPRI (SD) (dryness domain)	6.9 (2.51)	1.3 (0.47)
Remaining teeth/patient (Mean/SD)	21.3 (5.6)	24.0 (2.5)
Remaining molars/patient (Mean/SD)	4.4 (2.1)	6.1 (1.9)
Remaining premolars/patient (Mean/SD)	5.5 (1.8)	5.8 (1.4)
Inserted implants (*N*)	37	26 placed, but 1 lost to follow-up after T1
Mean no. implants/patient	1.9	1.3
Locations of inserted implants		
1st premolar region (*N*)	9	6
2nd premolar region (*N*)	9	8
1st molar region (*N*)	19	11
2nd molar region (*N*)	0	1
N implants upper: lower jaw	21:16	9:17

[a]Disease duration is years since diagnosis. [2]Classified according the 2002 American European Consensus Group Criteria (AECG); All patients classified as secondary SS had rheumatoid arthritis. [3]Defined as the total EULAR (European League Against Rheumatism) Sjögren's Syndrome Patient Reported Index (ESSPRI) score divided by 3.

TABLE 2 Medication use in the SS and non-SS groups stratified according to the anatomical therapeutic chemical (ATC) codes

ATC	Description of ATC group	Medication use SS group ($n = 17$)	Medication use non-SS group ($n = 17$)
A	Alimentary tract and metabolism (incl Colecalciferol (vit-D), Ascorbic acid (vit-C) and Calcium carbonate (Calci-chew))	22	2
B	Blood and blood forming organs	4	1
C	Cardiovascular system	11	2
D	Dermatologicals	2	0
G	Genito-urinary system and sex hormones	0	1
H	Systemic hormonal preparations, excluding sex hormones and insulins	1	0
J	Anti-infectives for systemic use	2	0
L	Anti-neoplastic and immunomodulating agents	2	0
M	Musculo-skeletal system (incl. anti-inflammatory and anti-rheumatic products)	7	2
N	Nervous system	13	3
P	Antiparasitic products (incl. hydroxychloroquine)	2	0
R	Respiratory system	5	5
S	Sensory organs	11	0
V	Varia (i.e., over the counter drymouth relieving products)	15	0

and a positive sense of dentofacial self-confidence" (Tashbayev et al., 2020). To quantify the OHRQoL, all patients completed the Dutch version of the Oral Health Impact Profile-14 at all time-points. The OHIP-14 comprises 14 items that measure seven domains of impact, each based on two questions: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and social handicap. Respondents were instructed to indicate their experience for each item on a five-point Likert scale ranging from 0 to 4 (0 = never; 1 = hardly ever; 2 = occasionally; 3 = fairly often; 4 = very often)(van der Meulen et al., 2012). This results in a score for each question ranging from 0 to 4, and a summated score ranging from 0 to 56, where low scores indicate high OHRQoL. The benchmark to assess whether a change in OHRQoL is clinically relevant, known as the Minimally Important Difference (MID), was set at 2 OHIP-14 units (Bassetti et al., 2016). Accordingly, a change of 2 units of the summated OHIP-14 score was assumed to be clinically relevant.

2.5.10 | Feeling of oral dryness

All patients were asked to complete the EULAR (European League Against Rheumatism) Sjögren's Syndrome Patient Reported Index (ESSPRI) questionnaire (37) at T0. Disease symptoms (pain, fatigue, dryness) were assessed using a 10-point scale patient-administered questionnaire (Seror et al., 2015). Only the dryness domain was used to compare groups.

2.6 | Sample size and statistical analysis

A sample size was calculated using G*power (Faul et al., 2007). The effect size was calculated based on available data published in literature (den Hartog, Raghoebar, et al., 2011 den Hartog, Meijer, et al., 2011; Pecora et al., 2009). As outcome measure was chosen, the marginal bone loss measured in mm after 1 year. In the literature, a bone loss of 1 mm (SD: 0.6) after 1 year is considered acceptable, but 1.5 mm of bone loss after 1 year unacceptable (den Hartog, Raghoebar, et al., 2011; den Hartog, Meijer, et al., 2011; Pecora et al., 2009). For the sample size analysis, we hypothesized that 1 year after insertion of the implants there is no difference between patients without SS and patients with SS with regard to peri-implant bone loss. No difference is defined as 0.5 mm or less of additional marginal bone loss. With an alpha of 0.05 (two-sided) and a power of 80%, this resulted in an estimated sample size of 23 implants in 23 unique patients per group.

The data were presented as mean and their standard deviations to clarify relatively small differences and to make comparison with

TABLE 3 Results (Mean/SD) of the outcome variables bone loss, probing depth, gingival index, and chewing ability at 1, 6, 12, and 18 months after crown placement

	Sjögren's syndrome group: 37 implants in 17 patients					Non-Sjögren's syndrome group: 25 implants in 17 patients				
	T0	T1	T6	T12	T18	T0	T1	T6	T12	T18
Radiographic bone loss (mm)	n/a	0.97(0.70)	1.00(0.86)	0.93(0.82)	1.10(1.04)	n/a	1.02(0.71)	1.00(0.65)	0.96(0.67)	1.04(0.75)
Probing depth (mm)	n/a	2.13(0.85)	2.06(0.85)	2.15(0.92)	2.29(0.88)	n/a	1.82(0.50)	1.62(0.54)	1.56(0.64)	1.70(0.71)
Gingival Index	n/a	0.07(0.19)	0.07(0.23)	0.09(0.25)	0.04(0.11)	n/a	0.06(0.14)	0.00(0.00)	0.007(0.03)	0.00(0.00)
Chewing ability:										
Soft food	1.31(0.48)	1.34(0.46)	1.36(0.52)	1.33(0.54)	1.33(0.47)	1.14(0.49)	1.10(0.34)	1.00(0.00)	1.02(0.09)	1.00(0.00)
Tough food	1.84(0.65)	1.71(0.71)	1.69(0.65)	1.80(0.69)	1.75(0.74)	1.35(0.64)	1.06(0.25)	1.02(0.06)	1.00(0.00)	1.00(0.00)
Hard food	1.92(0.63)	1.71(0.66)	1.86(0.83)	1.90(0.69)	1.82(0.69)	1.55(0.75)	1.08(0.26)	1.00(0.00)*	1.04(0.12)*	1.04(0.12)*

Note: Radiographic bone loss is the average of 2 measurements on the distal and mesial side of the implant expressed in mm. Probing depth is the average of 6 measurements on the distobuccal, buccal, mesiobuccal, distolingual/palatal, lingual/palatal, and mesiolingual/palatal sides expressed in mm. Chewing ability is the patients' opinion about the ability to chew nine different kinds of food on a three-point rating scale (0 = good, 1 = moderate, 2 = bad). The items were grouped into three scales: soft food, tough food, and hard food. Within group, significant differences ($p < .05$) compared to baseline (T0) are marked with an asterix; Corresponding *p*-values are reported in the results section.

TABLE 4 Frequency distribution of plaque and bleeding index scores at 1, 6, 12, and 18 months after crown placement

	T1				T6				T12				T18			
Plaque index	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
SS group	100%	0%	0%	0%	89.2%	8.1%	2.7%	0%	89.2%	8.1%	2.7%	0%	94.6%	5.4	0%	0%
Non-SS group	100%	0%	0%	0%	87.5%	12.5%	0%	0%	87.5%	12.5%	0%	0%	100%	0%	0%	0%
Bleeding index	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
SS group	64.9%	29.7%	5.4%	0%	64.9%	35.1%	0%	0%	70.3%	24.3%	5.4%	0%	75.7%	18.9%	5.4%	0%
Non-SS group	87.5%	12.5%	0%	0%	58.3%	41.7%	0%	0%	58.3%	41.7%	0%	0%	83.3%	16.7%	0%	0%

Note: Plaque Index was measured on a scale of 0/1/2/3 (0 = no plaque; 1 = a film of plaque adhering to the free gingival margin and adjacent area of the crown/implant; 2 = moderate accumulation of soft deposits within the gingival pocket, or the tooth/implant and gingival margin which can be seen with the naked eye; 3 = abundance of soft matter within the gingival pocket and/or on the tooth/implant and gingival margin). Bleeding Index for each implant was measured on a scale of 0/1/2/3 (0 = no bleeding when probe is passed along the gingival margin; 1 = isolated bleeding, gingiva looks normal; 2 = blood forms a confluent red line on margins; 3 = heavy or profuse bleeding).

TABLE 5 Analysis of the differences between the Sjögren's syndrome group (37 implants in 17 patients) and the non-Sjögren's syndrome group (25 implants in 17 patients) for all outcome measures after correction for gender and age

			95% CI	
	Coefficient	*p*	Lower	Upper
Radiographic bone loss				
T1	0.32	.25	−0.22	0.85
T6	0.25	.36	−0.28	0.78
T12	0.28	.31	−0.26	0.81
T18	0.18	.50	−0.35	0.72
Gingival index				
T1	−0.04	.46	−0.16	0.07
T6	−0.09	.14	−0.21	0.03
T12	−0.11	.08	−0.22	0.01
T18	−0.06	.33	−0.18	0.06
Plaque index				
T1	−0.04	.96	−1.89	1.80
T6	n/a[$]	n/a[$]	n/a[$]	n/a[$]
T12	n/a[$]	n/a[$]	n/a[$]	n/a[$]
T18	n/a[$]	n/a[$]	n/a[$]	n/a[$]
Bleeding Index				
T1	−0.74	.40	−2.44	0.96
T6	0.86	.35	−0.94	2.66
T12	1.11	.13	−0.34	2.56
T18	−0.08	.93	−1.77	1.61
Probing pocket depth				
T1	−0.15	.58	−0.65	0.36
T6	−0.26	.32	−0.76	0.25
T12	−0.42	.10	−0.93	0.09
T18	−0.14	.21	−0.35	0.08
Chewing ability: Soft food				
T0	−0.11	.48	−0.40	0.19
T1	−0.16	.282	−0.46	0.13
T6	−0.29	.055	−0.59	0.01
T12	−0.25	.100	−0.55	0.05
T18	−0.27	.073	−0.57	0.03
Chewing ability: Tough food				
T0	−0.38	.06	−0.77	0.01
T1	−0.55	.007	−0.95	−0.15
T6	−0.59	.004	−0.99	−0.18
T12	−0.72	<.001	−1.12	−0.32
T18	−0.66	.001	−1.06	−0.26
Chewing ability: Hard food				
T0	−0.29	.17	−0.71	0.13
T1	−0.57	.009	−0.99	−0.14
T6	−0.80	<.001	−1.23	−0.38
T12	−0.80	<.001	−1.23	−0.38
T18	−0.72	.001	−1.15	−0.30

TABLE 5 (Continued)

	Coefficient	*p*	95% CI	
			Lower	Upper
OHIP-14				
T0	−13.46	<.001	−19.50	−7.42
T1	−11.93	<.001	−18.00	−5.87
T6	−10.30	.001	−16.39	−4.20
T12	−12.07	<.001	−18.17	−5.98
T18	−13.46	<.001*	−19.56	−7.37

Note: The coefficient is the estimated difference of the means between the non-Sjögren's Syndrome group and the Sjögren's Syndrome group. A negative value means that the outcome score in the Sjögren's Syndrome group is higher compared to the non-Sjögren Syndrome group. *p*-values marked with bold indicate statistically significant differences between the groups. [$]No results due to low numbers.

other studies more convenient. Difference between the groups in the outcome variables over time was analyzed with linear mixed model analysis (for the normally distributed continuous outcome variables) or with logistic generalized estimating equations (GEE) analysis. Mixed model analysis and GEE analysis are used to take into account the dependency of the observations within the patient over time. The models included time (a categorical variable represented by dummy variables), group, and the interaction between time and group. The analysis was adjusted for age and gender and was performed by a statistician (JWRT) unaware of group allocation. Data were analyzed with STATA (StataCorp, College Station, TX, USA). A *p*-value of 0.05 or lower was considered statistically significant.

3 | RESULTS

At the start of the study, we included 34 patients in which 63 implants were placed. Thirty-two patients completed the study between May 2015 and September 2020 (Figure 1). One patient in the non-SS group was lost due to loss of the implant before T1 and another was lost to follow up due to personal reasons after T1. These patients were not replaced. Only data from implants with a complete follow-up period were used in a per-protocol analysis (37 implants in the SS group and 25 implants in the non-SS group). Characteristics of the study population are presented in Table 1. The median age of the patients with SS (65 years; IQR: 59–69) was significantly higher compared to the age of the patients without SS (58 years; SD: 48–61.5; $p = .006$). In the SS group, only females were included. All patients needed implant treatment because of tooth loss directly or indirectly related to caries. Patients with SS used on average 4.8 medications and patients without SS used on average 0.9 medications. Medication use of the included patients is presented in Table 2, stratified according to the Anatomical Therapeutic Chemical (ATC) codes.

Implant survival was 100% in the SS group and 96.2% in the non-SS group. One implant was lost in the non-SS group due to lack of osseointegration before T1. In one patient in the SS group, the crown had to be replaced at T12 because the patient felt it was too big. No other complications were reported with relation to the implants or crowns.

Analysis of the data for normality revealed that the outcome measures were not normally distributed (Shapiro–Wilk; $p < .001$). Means and standard deviations of the outcome measures are presented in Tables 3 and 4. The results of the Mixed Models and GEE analyses are presented in Table 5. At T18, mean bone loss was 1.10 mm (SD: 1.04) in the SS group and 1.04 mm (SD: 0.75) in the non-SS group. At all timepoints, bone loss was higher in the non-SS group compared to the SS group, but the Mixed Models analysis revealed no significant differences in mean marginal bone loss, measured on the standardized x-rays, between both groups at all timepoints. The radiographic bone height changes of implants inserted in the upper jaw or the lower jaw were analyzed separately.

At T18, no significant differences between the groups were found for probing depth (SS group: M = 2.29 mm; non-SS group: M = 1.70 mm; $p = .06$) and GI (SS group: M = 0.04; non-SS group: M = 0.00; $p = .42$). Also, at previous time-points, no significant differences were found although probing depths were numerically higher in the SS group.

Chewing ability increased significantly after placement of the crowns in the non-SS group compared to baseline (M = 1.55) only for hard food at T6 (M = 1.00; $p = .006$), T 12 (M = 1.04; $p = .007$) and T18 (M = 1.04; $p = .02$). In the SS group, no significant improvement in chewing ability compared to baseline was found.

Before placement of the crowns, the ability to chew soft food (SS group: M = 1.31.; non-SS group: M = 1.14; $p = .48$), tough food (SS group: M = 1.84; non-SS group: M = 1.35; $p = .06$), and hard food (SS group: M = 1.92.; non-SS group: M = 1.55; $p = .17$) were comparable between patients with SS patients and patients without SS. After placement of the crowns, patients without SS were able the chew soft, hard, and though food significantly better at all timepoints compared to patients with SS (Tables 3 and 5[for exact *p*-values at all time-points]).

The BI and PI are presented in a frequency table (Table 4). Both outcome measures were numerically higher in the SS group, but the GEE-analysis revealed no significant differences for bleeding index at all timepoints between patients with SS and patients without SS.

Oral health-related QoL, as determined with the summated OHIP-14 questionnaire, was significantly improved in the SS group

TABLE 6 Mean OHIP-14 scores and standard deviations for each question and the summated scores at each timepoint (T0, T1, T6, T12, and T18). For the within and between group analysis, a correction for age and gender was applied. In both groups, 17 patients were analyzed

	T0 SS	T0 non-SS	*p*	T1 SS	T1 non-SS	*p*	T6 SS	T6 non-SS	*p*	T12 SS	T12 non-SS	*p*	T18 SS	T18 non-SS	*p*
Functional limitations															
1. Trouble pronouncing words	2.24 (1.25)	1.20 (0.41)	.002	2.18 (1.24)	1.13 (0.35)	.002	2.00 (1.12)	1.00 (0.00)	.004	2.24 (1.03)	1.07 (0.26)	.007	2.24 (1.03)	1.00 (0.00)	<.001
2. Sense of taste worsened	2.29 (1.16)	1.60 (1.06)	.04	2.41 (1.50)	1.20 (0.56)	.001	2.29 (1.31)	1.07 (0.28)	.001	2.41 (1.37)	1.07 (0.26)*,	<.001	2.41 (1.37)	1.20 (0.56)	.001
Physical pain															
3. Pain in mouth	2.81 (1.11)	1.87 (1.41)	.013	2.47 (1.18)	1.60 (1.12)	.02	2.18 (1.07)*	1.47 (0.99)	.06	2.18 (1.01)	1.47 (1.06)	.03	2.18 (1.01)*	1.33 (0.62)	.03
4. Discomfort eating food	3.41 (1.28)	2.07 (1.39)	.004	2.65 (1.46)*,	1.33 (0.82)	.006	2.53 (1.55)*,	1.07 (0.26)	.002	3.00 (1.41)*	1.20 (0.56)	.001	3.00 (1.41)	1.07 (0.26)	<.001
Psychological discomfort															
5. Feeling self-conscious	2.65 (1.46)	1.80 (1.21)	.08	2.00 (1.22)*	1.00 (0.00)	.03	2.35 (1.17)	1.00 (0.00)	.002	2.53 (1.37)	1.13 (0.35)	.003	2.53 (1.37)	1.07 (0.26)	.001
6. Felt tense	2.65 (1.17)	1.53 (0.92)	.002	2.06 (1.39)*	1.07 (0.26)	.006	1.71 (0.77)*	1.07 (0.26)	.08	2.00 (1.00)*	1.07 (0.26)	.01	2.00 (1.00)*	1.07 (0.26)	.01
Physical disability															
7. Unsatisfactory diet	2.59 (1.50)	1.53 (0.99)	.003	1.94 (1.14)*	1.13 (0.35),	.02	1.82 (1.01)*	1.07 (0.26)	.04	1.94 (1.03)*	1.00 (0.00)	.01	1.94 (1.03)*	1.00 (0.00)	.008
8. Interrupted meals	2.29 (1.36)	1.20 (0.56)	.004	2.24 (1.39)	1.60 (0.51)	.12	1.88 (1.17)*	1.07 (0.26)	.04	2.06 (0.97)	1.20 (0.56)	.007	2.06 (0.97)	1.00 (0.00)	.006
Psychological disability															
9. Difficulty relaxing	2.53 (1.37)	1.27 (0.59)	<.001	1.82 (1.13)*,	1.13 (0.35)*,	.03	1.71 (0.92)*	1.07 (0.26)*	.04	2.00 (0.94)*	1.13 (0.35)*	.10	2.00 (0.94)*	1.07 (0.26)*	.003
10. Embarrassment	2.76 (1.52)	1.40 (0.74)	<.001	1.88 (0.99)*	1.13 (0.35)*	.05	2.00 (0.79)*	1.00 (0.00)	.007	2.18 (1.13)*	1.07 (0.26)	.001	2.18 (1.13)*	1.00 (0.00)	.001
Social disability															
11. Irritability with other people	1.88 (1.05)	1.20 (0.41)	.003	1.47 (0.80)*,	1.00 (0.00)	.04	1.18 (0.39)*	1.00 (0.00)*	.42	1.71 (0.92)*	1.07 (0.26)	.07	1.71 (0.92)	1.00 (0.00)	.002
12. Difficulties doing usual jobs	2.12 (1.05)	1.20 (0.41)	<.001	1.41 (0.71)*	1.00 (0.00)*	.08	1.24 (0.56)*	1.00 (0.00)*	.35	1.59 (0.80)*	1.00 (0.00)*	.08	1.59 (0.80)*	1.07 (0.26)	.01
Handicap															
13. Life less satisfying	2.35 (1.27)	1.20 (0.77)	<.001	1.71 (0.99).	1.13 (0.52)*	.06	1.53 (0.80)*	1.00 (0.00)*	.08	1.94 (1.14)*,	1.00 (0.00)	.004	1.94 (1.14)*	1.00 (0.00)	.004
14. Ability to function	1.53 (0.72)	1.00 (0.00)	.001	1.35 (0.70)	1.00 (0.00)	.02	1.18 (0.39)*	1.00 (0.00)*	.27	1.29 (0.47).	1.00 (0.00)*	.27	1.29 (0.47)*	1.00 (0.00)	.07
Summated OHIP-14	33.70 (12.12)	19.59 (8.03)	<.001	28.17 (10.99)*	15.87 (3.28)	<.001	25.46 (9.47)*	14.86 (1.30)	.001	27.83 (9.34)*	15.45(3.06)	<.001	28.83(9.61)*	15.06(1.58)	<.001

Note: Within group significant differences ($p < .05$) compared to baseline (T0) are marked with an asterix. The corresponding *p*-values for the summated OHIP-14 are presented in the main text. *p*-values for the differences between the groups at each timepoint are provided in this table.

Abbreviation: OHIP-14: Oral Health Impact Profile-14.

compared to baseline (M = 33.7) at T1 (M = 28.2; $p < .001$), T6 (M = 25.5; $p < .001$), T12 (M = 27.8; $p < .001$) and T18 (M = 28.8; $p = .002$) (Table 6). In the non-SS group, OHRQoL improved also after placement of the crowns, but this difference failed to reach statistical significance compared to baseline at all timepoints. The changes in the summated OHIP-14 score after placement of the implants and crowns changed in both groups more than 2 OHIP units compared to baseline, indicating a clinically relevant improvement up to 18 months. At baseline, the summated OHIP-14 score was already significantly lower in the non-SS group (19.6) compared to the SS group (33.7; $p < .001$), indicating a better OHRQoL for patients without SS. After placement of the crowns, the OHIP-14 score remained significantly lower in the non-SS group compared to the SS group at all timepoints up to T18($p < .05$; see Table 6 for exact p-values at all time-points).

We also analyzed the OHIP-14 for every item separately (Table 6). It was found that in the SS group, the items "Discomfort eating food," "Feeling tense," "Poor diet," "Difficult to relax," "Embarrassment," "Difficulties doing usual jobs," and "life less satisfying" improved significantly compared to baseline. In the non-SS group, the same items (except 'life less satisfying') as in the SS group improved significantly compared to baseline. In the non-SS group items, 'Trouble pronouncing words' and 'Ability to function' were at baseline already at a very low level (at or slightly above 1; indicating no influence on QoL) so improvement on these items was almost not possible.

4 | DISCUSSION

In this study, we evaluated the clinical performance of dental implants in patients with Sjögren's syndrome compared to patients without Sjögren's syndrome. No implants were lost in the SS group and only one implant in the non-SS group. This implant was lost before the superstructure was placed. This result is comparable to the findings of a study in non-SS patients with a different implant system (Derks et al., 2015). They reported that 1.4% of implants are lost before placing the superstructure. Our results are also in line with the results from a retrospective study investigating the implant survival and performance in patients with SS. This previous study reported an implant survival in patients with SS of 97% after 46 months (Korfage et al., 2016).

We found numerically higher pocket probing depth and GI scores in the SS group. It could be speculated that this could have a long-term effect which was not yet measurable in our study. Long standing inflammation of the gingiva could result in an increase of loss of bone. A comparable situation was also found in a study by Korfage et al. (Korfage et al., 2016). In that study, it was found that SS patients seemed to have more signs of peri-implant soft tissue inflammation despite comparable pocket-probing depths compared to non-SS patients. These signs of inflammation could be related to the reduced salivary secretion in patients with SS as well as the subsequent diminished self-clearance of the oral cavity (Pijpe et al., 2007). As a result, debris will more easily accumulate and remain on the tooth surfaces in SS subjects than in patients without SS. Therefore, in patients with SS, the marginal tissue could be more prone to continuous exposure to inflammatory insults. This will probably have resulted in slightly more gingival swelling and bleeding in the SS group, although none of the measured parameters was significantly higher. Although periodontitis is not an increased risk in patients with SS (Maarse et al., 2019), the long-term survival and performance of these implants will be subject of future studies.

Patients with and without SS were equally satisfied about their ability to chew soft, tough, and hard food at baseline. After placement of implant supported crowns, the patients without SS patients experienced significant improvements at all timepoints compared to patients with SS for their ability to chew soft, though, and hard food. This corresponds with previous studies investigating tooth loss and chewing ability (Brennan et al., 2008; Hildebrandt et al., 1997; Leake et al., 1994). Patients with SS did experience some improvement; however, this improvement was not statistically significant. Therefore, it could be concluded that replacing missing molars and/or premolars in patients with SS did not result in an improvement to chew food. This might be explained by the effect of the severe oral dryness these patients are experiencing. Their problems with eating are not only related to the ability to chew but also to the ability to lubricate the mouth and swallow the food. Moreover, this difference could also be explained by the larger number of remaining teeth in patients without SS (SS-group: 21.3 vs. non-SS: 24.0).

We found that the oral health-related quality of life (OHR-QoL) was significantly higher in the SS-group at baseline and all subsequent timepoints compared to the non-SS group. This corresponds with the results from other studies investigating oral health-related quality of life of SS patients using the OHIP-14 (Enger et al., 2011; Tashbayev et al., 2020). The same is found for general health-related quality of life (HR-QoL). In a study by Meijer et al., it was found that SS has a large impact on HR-QoL, employment, and disability and that the need to use artificial saliva is a predictor for a reduced HR-QoL in SS indicating the important role of saliva in QoL (Meijer et al., 2009).

Interestingly, the summated OHIP-14 score improved significantly and more than the meaningful important difference (MID) after replacing missing teeth by implant supported crowns in the SS group indicating that replacing missing teeth improves the quality of life in these patients. This difference between the groups could be related to the larger number of remaining teeth in the patients without SS compared to the patients with SS at baseline (SS-group: 21.3 vs. non-SS: 24.0). Despite this improvement, patients with SS still reported a significant lower QoL than patients without SS at all timepoints. As discussed above, this is probably related to the persistent oral dryness and its related problems. In the non-SS group, the summated OHIP-14 score was lower after placement of the implant supported crowns compared to baseline at all timepoints, suggesting an improvement in QoL, but this difference was not significant. An explanation for this could be that the scores on some questions in the non-SS group were already at a very low level at baseline (at or

slightly above 1; indicating no influence on QoL) so improvement on these questions was almost not possible.

Another explanation could be that in the non-SS group, both males and females (4 and 13, respectively) were included and in the SS group only females. In previous research, it was found that OHIP-14 scores of males were lower compared to females (Kang & Kang, 2014). Therefore, we adjusted our analysis for gender. This resulted in slightly higher OHIP-14 scores in the non-SS group, and some of the responses to the items were not significantly different anymore compared to the non-SS group. But overall, the differences in OHIP-14 scores in the SS group remained significantly higher compared to the non-SS group.

A limitation of this study is that we were not able to find a gender- and age-matched non-SS group. In the SS group, no males could be included. We decided to include female and male patients in the non-SS group because it was difficult to find patients without SS that were willing to participate in our study. The same applies to age as patients in the SS group were significantly older than patients in the non-SS group. From previous studies, it is known that a high age is related to more oral health problems and that females have better oral hygiene compared to males (Kim et al., 2012; Razak et al., 2014). This could have influenced the outcomes of our study by increasing the differences between the groups. Therefore, we adjusted our analysis for age and gender.

Another drawback of the limited number of eligible patients was that in some of the patients, more than 1 implant was included in the study. This is reflected in the number of implants which is not corresponding with the number of patients. Therefore, it should be mentioned that our study is slightly underpowered. The minimal number of implants as calculated in our sample size analysis (23) was reached but not in 23 unique patients (SS-group: 37 implants in 17 patients; non-SS group: 25 implants in 17 patients).

In our study, we included patients with primary SS (pSS) and secondary SS (sSS) (respectively 64.7% and 35.3%) and all patients classified as secondary SS had Rheumatoid Arthritis (RA). RA is a known risk factor for periodontal disease (de Pablo et al., 2008). Studies report that periodontal disease is approximately twice as common and more severe in patients with RA. A recent study reported significantly higher pocket probing depths and plaque index in patients with RA compared to patients without RA. These results suggest that RA patients have a higher risk of developing periodontal disease compared to non-RA (Potempa et al., 2017). On the other hand, is it described that there are no differences in periodontal status between patients with pSS, RA, or healthy subjects (Özçaka et al., 2018). Additionally, there could be an effect of the anti-inflammatory medication used by some of the patients with sSS in the present study. To eliminate a potential overestimating effect of RA on periodontal parameters in our study, either all patients with RA should be excluded or only patients with pSS should have been included. Unfortunately, that was not possible because of the limited number of patients with SS eligible for single teeth replacement. In Table 2, we presented all the medication used by the participants.

A strength of our study was the use of standardized intraoral dental radiographs together with the used periodontal parameters. In previous studies, it is suggested that this is the most optimal setting to evaluate peri-implant health (Brown et al., 1989; Lindhe et al., 2015). We could have further optimized our study design by making a standardized intraoral radiograph immediately after placement of the implant. This could have been possible if we fabricated an individualized x-ray holder before placement of the implant. In this way, we could have determined the change in bone height over time more accurately.

In this study, we report results up to 18 months. It would very interesting to study the longer term results (e.g., 5 and 10 years results) especially as less favorable outcomes such as an above average loss of implants is reported in literature (Isidor et al., 1999).

From this study, we conclude that dental implants in patients with SS show a clinical performance comparable to implants in patients without SS up to 18 months. Furthermore, replacing missing molars and premolars by implant supported crowns improves the Oral health-related quality of life of SS-patients. Therefore, it can be concluded that dental implants are a safe and effective treatment option for SS patients up to 18 months. To study the long-term success of dental implants in patients with SS, a follow-up study will be implemented.

AUTHOR CONTRIBUTIONS

Floor Maarse: Conceptualization (supporting); data curation (equal); formal analysis (supporting); investigation (equal); project administration (lead); resources (equal); writing – original draft (lead). **Willem Fennis:** Conceptualization (supporting); data curation (supporting); investigation (equal); methodology (supporting); project administration (equal); resources (equal); writing – original draft (supporting); writing – review and editing (equal). **Jos Twisk:** Formal analysis (lead); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Arjan Vissink:** Conceptualization (supporting); formal analysis (supporting); investigation (supporting); methodology (equal); validation (equal); writing – review and editing (lead). **Henk S Brand:** Formal analysis (equal); methodology (supporting); supervision (equal); validation (supporting); writing – original draft (equal); writing – review and editing (equal). **Derk Jan Jager:** Conceptualization (lead); data curation (lead); formal analysis (supporting); funding acquisition (lead); investigation (equal); methodology (equal); project administration (supporting); resources (supporting); supervision (lead); validation (equal); visualization (supporting); writing – original draft (supporting); writing – review and editing (equal).

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DATA AVAILABILITY STATEMENT

After acceptance of this manuscript, data that support the findings of this study will be openly available in the Dryad repository.

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