Survival and Success of Dental Implants in Patients with Autoimmune Diseases: a Systematic Review

Emil Hyldahl[1], Klaus Gotfredsen[2], Anne Marie Lynge Pedersen[3], Simon Storgård Jensen[1,4]

[1]Oral Surgery, Section for Oral Biology and Immunopathology, Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
[2]Oral Rehabilitation, Section for Oral Health, Society and Technology, Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
[3]Oral Pathology and Medicine, Section for Oral Biology and Immunopathology, Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
[4]Department of Oral and Maxillofacial Surgery, Centre of Head and Orthopaedics, Copenhagen University Hospital, Copenhagen, Denmark.

Corresponding Author:
Emil Hyldahl
Nørre Allé 20, 2200, Copenhagen
Denmark
Phone: +45 28 35 69 64
E-mail: emil.hyldahl@outlook.com

ABSTRACT

Objectives: The purpose of this systematic review is to disclose the impact of autoimmune diseases and their medical treatment on dental implant survival and success.
Material and Methods: A literature search was conducted using MEDLINE (PubMed), The Cochrane Library and Embase up to December 6th, 2021. Any clinical study on patients with an autoimmune disease in whom implant therapy was performed was eligible. The quality of included studies was assessed using the Newcastle-Ottawa Scale. For each autoimmune disease group, data synthesis was divided into three groups: 1) overall results of the autoimmune disease, 2) overall results of corresponding control groups and 3) overall results of the autoimmune disease with a concomitant autoimmune disease (a subgroup of group 1). Descriptive statistics were used.
Results: Of 4,865 identified articles, 67 could be included and mainly comprising case reports and retrospective studies with an overall low quality. Implant survival rate was 50 to 100% on patient and implant level after a weighted mean follow-up of 17.7 to 68.1 months. Implant success was sporadically reported. Data on immunosuppressive medication were too heterogeneously reported to allow detailed analysis.
Conclusions: Overall, a high implant survival rate was reported in patients with autoimmune diseases. However, the identified studies were characterized by a low quality. No conclusions could be made regarding implant success and the effect of immunosuppressants due to heterogeneous reporting.

Keywords: alveolar bone loss; autoimmune diseases; connective tissue diseases; dental implants; immunosuppressive agents; systematic review.

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INTRODUCTION

Since the first preclinical and clinical studies with dental implants carried out by Brånemark et al. [1] in the 1960s, dental implant therapy has become a reliable method for replacement of missing teeth. Several studies have documented high implant survival rates > 95% after 5 to 10 years of follow-up in systemically healthy individuals [2,3]. Based on these successful and predictable long-term outcomes, the indications for using dental implant therapy have gradually extended to include patients with various systemic diseases, including patients who may be immunocompromised due to autoimmune diseases (ADs) and/or treatment with immunosuppressants [4-7].

ADs are characterized by an abnormal immunologic response to self-antigens, leading to an organ-specific or systemic inflammatory tissue destruction. The cardinal characteristics of autoimmunity are the presence of self-reactive T cells, circulating autoantibodies, and inflammation [8]. The exact aetiology of ADs is largely unknown but is believed to be an interplay between genetic, endocrinologic and environmental factors e.g., nutrition, lifestyle, and exposure to infection. ADs are estimated to affect 3 to 5% of the global population, with a predilection for females [8,9]. The reason for this predilection is unknown [8-10]. Some ADs are classified as systemic connective tissue diseases (CTDs) or as organ-specific diseases. Autoimmune CTDs such as rheumatoid arthritis (RA) affect several organs and tissues, whereas e.g. pemphigus vulgaris is an organ-specific mucocutaneous disease characterized by the presence of autoantibodies directed against keratinocyte surface antigens [11].

Patients with ADs may display a variety of oral manifestations including mucosal ulcerations, erosions, erythema, soreness and pain, xerostomia, salivary gland dysfunction, candidiasis, dental caries, periodontal disease, temporomandibular disorder, and limited mouth opening [12,13]. A number of these manifestations may compromise oral rehabilitation, especially when treatment includes mucosa-supported removable dental prostheses [14].

Patients with ADs often require medical treatments including immunosuppressive agents [15,16]. Commonly used immunosuppressants include glucocorticoids (e.g., prednisone), conventional disease-modifying antirheumatic drugs (DMARDs) (e.g., methotrexate) and biologics (e.g., adalimumab). Many of these agents also have antiinflammatory properties [15-20]. However, treatment with immunosuppressants make patients more susceptible to infections, and some agents have adverse effects compromising bone metabolism potentially leading to loss of bone mineral density [16,18,20-22]. It is also well-documented that long-term (and high dose) treatment with glucocorticoids predispose to the development of secondary osteoporosis [16,21,22].

Soft and hard tissue healing is crucial to obtain and preserve successful dental implant therapy. Osseointegration, which is defined as the direct contact between living bone and the implant surface, at a light microscopic level, results from the process of osseous wound healing around an implant [23]. In addition, healing of the oral mucosa surrounding the implant is important as the mucosa forms a barrier that protects the implant surface against microbial colonization [23-25]. The processes of obtaining and preserving osseointegration and soft tissue healing are therefore directly linked to an adequate immune response. The suppressed immune system, increased risk of infection, and the inhibitory effect on bone metabolism can potentially influence osseointegration and, ultimately, impair the survival and success of dental implants in patients with ADs. Hence, patients with ADs may be additionally prone to early implant loss characterized by failure to establish osseointegration and late implant loss caused by failure to maintain the established osseointegration e.g., due to peri-implantitis (PI) [26].

As patients with ADs often suffer from severe oral manifestations, implant-supported rehabilitation appears to offer a better therapeutic option than mucosa-supported prostheses [12-14]. A comprehensive understanding of the potential influence of ADs and their medical treatment on the prognosis of dental implant therapy is therefore needed. The aim of this systematic review is to disclose the impact of autoimmune diseases and their medical treatment on dental implant survival and success.

MATERIAL AND METHODS

Protocol and registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27]. The study protocol was registered in International Prospective Register of Systematic Reviews (PROSPERO). Prospero registration number: CRD42022323010.

The protocol can be accessed at:
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=323010

Focus question

The focus question of this study was conducted following the PICO format (population, intervention, comparison, and outcome) as described in Table 1.

Information sources

The following databases were utilized for the literature search through a combination of Medical Subject Headings (MeSH) and text terms: MEDLINE (PubMed), The Cochrane Library and Embase. A hand search was additionally performed using reference lists of identified articles.

Search

A systematic literature search was performed by E.H. on the 6th of December 2021 in collaboration with a librarian. A detailed description of the search strategy for Embase, MEDLINE (PubMed) and The Cochrane Library is presented in Appendices 1 - 4.

Types of studies

Randomized controlled trials (RCT), prospective cohort studies, retrospective cohort studies, cross-sectional studies, case-control studies, case series and case reports up to December 6th, 2021 were considered eligible.

Types of participants

Patients diagnosed with an AD who have been rehabilitated with dental implants.

Inclusion and exclusion criteria

Clinical studies written in English language regarding patients diagnosed with an AD who have been rehabilitated with dental implants were included in the present study. *In vitro* studies, preclinical studies, reviews, and studies involving patients < 18 years of age were excluded.

Sequential search strategy

Initially, duplicate publications were removed. One author (E.H.) screened titles for eligibility and abstracts and full-text articles were subsequently screened independently by two authors (E.H., S.S.J.). Title and abstract screenings were performed using an online screening tool Rayyan® (Qatar Computing Research Institute; HBKU, Doha, Qatar [www.rayyan.ai]). Studies that did not fulfil the inclusion criteria were excluded. Disagreements were resolved through discussion by the two reviewers. If consensus could not be reached, disagreements were resolved by consulting a third author (K.G.). The level of concordance between the two reviewers after abstract and full-text screening was calculated through Cohen's kappa (κ) coefficient.

Data extraction

Data extraction of included full-text articles was performed by one author (E.H.) using a dedicated data extraction sheet. The corresponding authors were contacted through e-mail for clarification if missing data were identified.

Data items

The following parameters were extracted when available: Authors, year of publication, study design, period when the study was conducted, aim of the study, follow-up period, number of patients, dropouts, age, gender, smoking habits, number of implants, location of implants, timing of implant placement, timing of implant loading, ADs, immunosuppressants (e.g., steroids, conventional DMARDs, chemotherapeutics and biologics), prophylactic antibiotic treatment, survival rate of dental implants (patient and implant level), survival rate of suprastructures (patient and suprastructure level), success rate (patient and implant level), crestal bone loss, biologic complications (PI and peri-implant mucositis), other biologic complications, pain, crestal bone loss at first year, annual crestal

Table 1. PICO guidelines

Population (P)	Edentulous or partially edentulous patients with autoimmune diseases
Intervention (I)	Dental implant therapy
Comparison (C)	None
Outcomes (O)	Primary: implant survival rate Secondary: suprastructure survival rate and success rate including biological complications (e.g., crestal bone loss, peri-implantitis, and peri-implant mucositis), technical complications and patient-reported outcomes
Focused question	What is the impact of autoimmune diseases and their medical treatment on dental implant survival and success?

bone loss thereafter, radiolucency, mobility, infection, probing depth, suppuration, bleeding, swelling, plaque, width of keratinized mucosa, recession, minor complications, major complications/failures, functional outcome, aesthetic outcome, discomfort/paraesthesia, satisfaction with appearance, ability to chew, ability to taste and general satisfaction.
Parameters from crestal bone loss up to and including general satisfaction are implant success criteria described by Papaspyridakos et al. [28].

Risk of bias within studies

The scientific quality and risk of bias of the included cohort studies (case series, prospective studies and retrospective studies) and case-control studies were evaluated using The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis [29]. This was conducted independently by two authors (E.H., S.S.J.). Disagreements were resolved through discussion by the two authors. If consensus could not be reached, disagreements were resolved by consulting a third author (K.G.). The level of quality is represented through the number of stars given for each study within each category. In the selection and outcome/exposure categories, a study can receive at the most one star for each of the four and three numbered items. In the comparability category, a study can receive the highest score of two stars. A study can be given an overall maximum score of 9 stars. The quality of a study is classified as either low quality (0 to 3 stars), medium quality (4 to 6 stars), or high quality (7 to 9 stars).

Data synthesis

The data synthesis for each AD group was divided into three groups: 1) overall results of the AD, 2) overall results of corresponding control groups and 3) overall results of the AD with a concomitant AD (a subgroup of group 1).

Statistical analysis

Only descriptive statistics were applied. Where possible, weighted means were calculated. If data were presented as medians, weighted medians were also calculated.

RESULTS

Study selection

Initially 4,865 articles were identified via literature search through databases and citation search. After removal of duplicates, 3,535 titles were screened. Then 500 abstracts were evaluated and thereafter 176 full-text articles. Articles were directly assessed by full-text screening when no abstracts were available. A total of 67 studies could therefore be included in the present systematic review [4-7,14,24,25,30-89]. The κ value representing the level of concordance between the two reviewers after abstract and full-text screening were 0.85 and 0.86, respectively, disclosing a high level of agreement. The search, screening, and selection process is presented in Figure 1.
Reasons for excluding a total of 109 studies after full-text assessment are presented in Appendix 5.

Risk of bias within studies

The quality assessment and risk of bias of included cohort and case-control studies is displayed in Table 2. The quality of the 37 case reports [30-66] could not be assessed using NOS and therefore these studies were classified as low quality. Of the 24 cohort [4-7,14,24,25,67-83] and six case-control studies [84-89], fourteen articles were classified as low [5-7,24,67,70,73,74,78,79,81-83,86], fifteen as medium [4,14,25,68,69,71,72,75-77,80,84,85,87-89] and one as high quality [85]. Based on the predominance of case reports and studies with low quality, the overall risk of bias of the identified studies was judged to be high.

Study characteristics and outcomes

An overview of characteristics and outcomes of included studies is presented in Table 3A-F, 4A-B and 5A-E. The included studies comprised 37 case reports [30-66], fourteen retrospective studies [4,5,7,24,67-76], eight case series [6,77-83], six case-control studies [84-89] and two prospective studies [14,25].
Due to large heterogeneity among included studies a meta-analysis could not be performed. Instead, a qualitative synthesis of data was conducted. In addition, due to heterogeneous reporting, the following parameters were excluded from the final tables: dropouts, age, smoking habits, location of implants, timing of implant placement, timing of implant loading, immunosuppressants, prophylactic antibiotic treatment, peri-implant mucositis, other biologic complications, pain, crestal bone loss at first year, annual crestal bone loss thereafter, radiolucency, mobility, infection, probing depth, suppuration, bleeding, swelling, plaque, width of keratinized

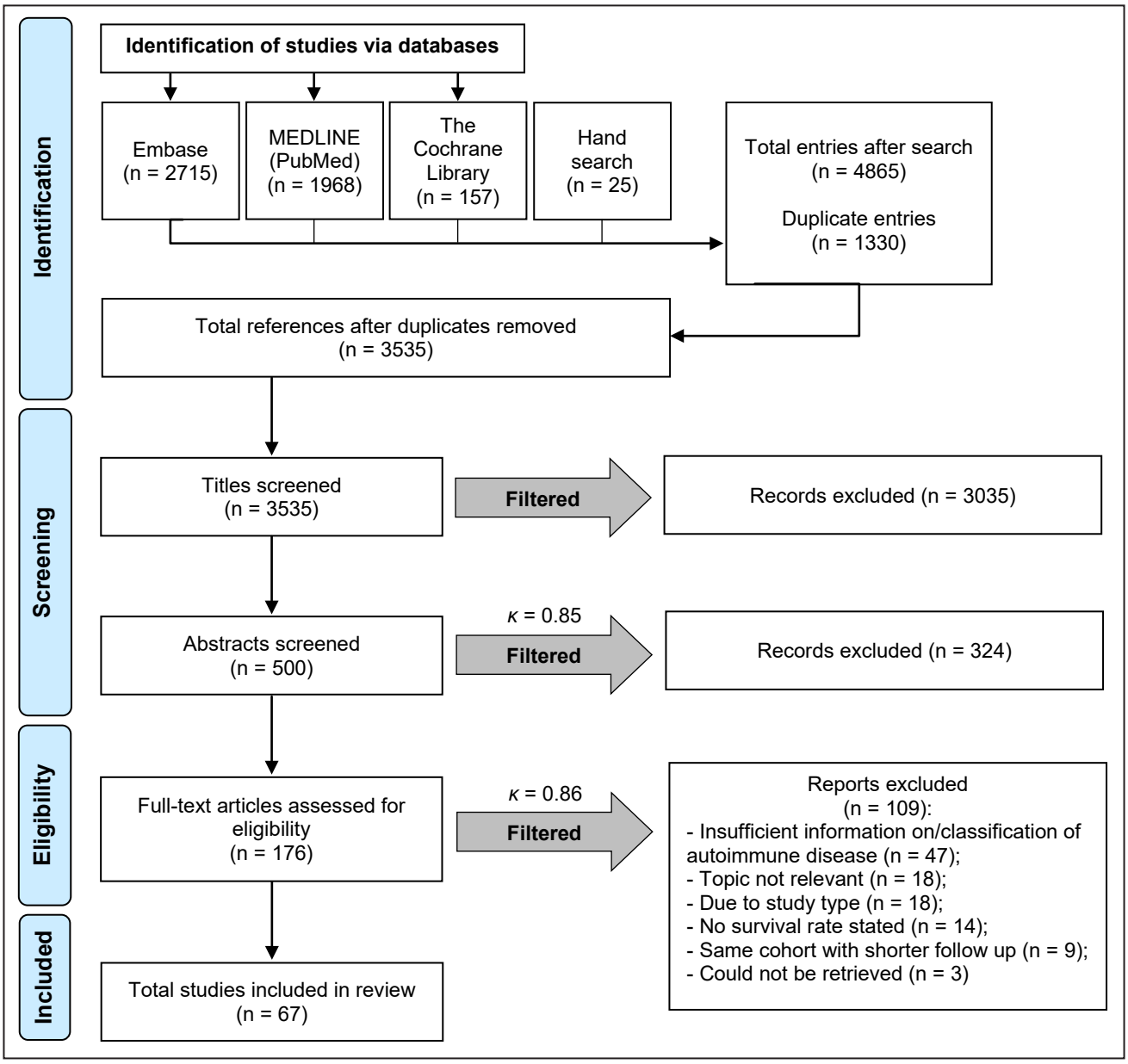

Figure 1. PRISMA flow diagram of the search, screening, and selection process.
The literature search through databases and citation search resulted in 4,865 articles. After removal of duplicates 3,535 titles were screened and thereafter 500 abstracts (κ = 0.85). Then 176 articles were screened (κ = 0.86) and a total of 67 articles were included in the review.

mucosa, recession, minor complications, major complications/failures, functional outcome, aesthetic outcome, discomfort/paraesthesia, satisfaction with appearance, ability to chew, ability to taste and general satisfaction.

The following disease groups are not emphasized in the sections below due to a low quantity of available data and heterogeneous reporting of studies: polyarthritis (Table 3E) [38-40], other autoimmune CTDs (Table 3F) [7,33,51,81], type 1 diabetes (Table 4B) [4,67,70], dermatomyositis (Table 4D) [7,71,84] and other ADs (Table 4E) [7,36,46,57,75].

Overall, a predominance of females was present in the disease groups and the most prevalent immunosuppressive treatment included glucocorticoids. In general, implant success was inconsistently reported using a variety of success criteria. In most disease groups, a predominance of early implant loss was observed. Autoimmune CTDs comprise the largest disease group in terms of quantity of articles, patients, and implants.

Autoimmune connective tissue diseases

Rheumatoid arthritis

Twelve articles (six retrospective studies, four case reports, one case series and one case-control study) were included [4,5,7,24,34,43,58,66,67,71,81,84]. A total of 363 implants were documented in 124 patients (male/female (M/F) ratio: 1/6.5) with RA.

Table 2. Quality assessment of included cohort and case-control studies using Newcastle-Ottawa scale

Study	Year of publication	Study design	Selection	Comparability	Outcome/ exposure	Score
Alsaadi et al. [4]	2008	Cohort	★☆☆★	☆☆	☆★★	4/9
Mozzati et al. [5]	2021	Cohort	☆☆☆★	☆☆	☆★☆	2/9
Oczakir et al. [6]	2005	Cohort	☆☆☆★	☆☆	☆★★	3/9
Petsinis et al. [7]	2017	Cohort	★☆☆★	☆☆	☆★☆	3/9
Isidor et al. [14]	1999	Cohort	★☆★★	☆☆	☆★★	5/9
Bertl et al. [24]	2019	Cohort	☆☆☆★	☆☆	★★☆	3/9
Aboushelib et al. [25]	2017	Cohort	★☆★★	☆☆	☆★★	5/9
Alsaadi et al. [67]	2008	Cohort	★☆☆★	☆☆	☆★☆	3/9
Anitua et al. [68]	2018	Cohort	★☆★★	☆☆	☆★☆	4/9
Czerninski et al. [69]	2013	Cohort	★☆★★	☆☆	☆★☆	4/9
Hasanoglu Erbasar et al. [70]	2019	Cohort	☆☆☆★	☆☆	☆★☆	2/9
Krennmair et al. [71]	2010	Cohort	★☆★★	☆☆	☆★★	5/9
Peñarrocha-Oltra et al. [72]	2020	Cohort	★☆★★	☆☆	★★☆	5/9
Siddiqui et al. [73]	2017	Cohort	☆☆☆★	☆☆	☆★☆	2/9
van Steenberghe et al. [74]	2002	Cohort	★☆☆★	☆☆	☆★☆	3/9
Maló et al. [75]	2016	Cohort	★☆☆★	☆☆	★★★	5/9
Nicoli et al. [76]	2017	Cohort	★☆☆★	☆☆	★★☆	4/9
Agustín-Panadero et al. [77]	2019	Cohort	★☆☆★	☆☆	☆★★	4/9
Chatzistavrianou et al. [78]	2016	Cohort	☆☆☆★	☆☆	☆★★	3/9
Chrcanovic et al. [79]	2019	Cohort	★☆☆★	☆☆	☆★☆	3/9
Esposito et al. [80]	2003	Cohort	★☆★★	☆☆	☆★★	5/9
Payne et al. [81]	1997	Cohort	☆☆☆★	☆☆	☆★★	3/9
Reichart [82]	2006	Cohort	☆☆☆★	☆☆	☆★★	3/9
Corigliano et al. [83]	2014	Cohort	☆☆☆☆	☆☆	☆★☆	1/9
Alenazi [84]	2021	Case-control	★★☆★	★★	★☆☆	6/9
Hernández et al. [85]	2012	Case-control	★★★★	★★	★☆★	8/9
Khamis al. [86]	2019	Case-control	☆★☆☆	☆☆	★☆★	3/9
Korfage et al. [87]	2016	Case-control	★★☆★	★★	★☆☆	6/9
López-Jornet et al. [88]	2014	Case-control	★★☆★	☆★	★☆★	6/9
Attard et al. [89]	2002	Case-control	☆★☆☆	★★	★☆☆	4/9

0 to 3 stars = low-quality; 4 to 6 stars = medium quality; 7 to 9 stars = high quality.

Survival rate of implants was 95.2% (118/124) and 97.2% (353/363) on patient and implant level, respectively, after a weighted mean follow-up period of 50.8 months. Of the lost implants, 70% (7/10) were early losses. Survival rate of suprastructures was 100% on patient (67/67) as well as suprastructure (49/49) level. Weighted mean crestal bone loss for the RA group was 0.36 mm and weighted median crestal bone loss was 2 mm [5,58,66,71,84]. In addition, weighted median crestal bone loss for the RA with concomitant ADs group was 2.2 mm (weighted mean follow-up period of 52.8 months) [58,66,71,84]. PI was diagnosed in 8.3% (1/12) of the patients and 1.8% (1/55) of the implants. Implant success rate was 94.4% (119/126) on implant level. Characteristics and outcomes of studies including RA are presented in Table 3A.

Sjögren's syndrome

Twenty articles (eight case reports, six case series, three retrospective studies, two case-control studies and one prospective study) were included [6,7,14,34,45,53,55,58,61,65,66,71,73,78-81,83,84,87]. A total of 120 Sjögren's syndrome (SS) patients (M/F ratio: 1/16.5) with 484 implants were included making it the disease group with the highest number of studies and implants.

Table 3A. Characteristics and outcomes of studies including autoimmune connective tissue diseases - rheumatoid arthritis (RA)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Alsaadi et al. [4]	2008	RS	6/28	RA	NR	24	100% (6/6) 100% (28/28)[c]	NR	NR	NR	NR
Mozzati et al. [5]	2021	RS	19/40	RA	1/18	Mean: 63.4	84.2% (16/19) 90% (36/40) Early loss: 4 Late loss: 0	NR	Mean: 0.42	NR	NR
Petsinis et al. [7]	2017	RS	11/37	RA[b]	2/9	Mean: 59.8	90.9% (10/11) 97.3% (36/37) Early loss: 0 Late loss: 1	NR	NR	9.1% (1/11) 2.7% (1/37)	NR
Bertl et al. [24]	2019	RS	21/NR	RA	NR	Up to prosthetic loading	100% (21/21) NR[d]	NR	NR	NR	NR
Binon [34]	2005	CR	1/6	RA+sSS	1/0	156	100% (1/1) 100% (6/6)	100% (1/1) 100% (1/1)	NR	NR	NR
Gaur et al. [43]	2021	CR	1/18	RA	0/1	48	0% (0/1) 94.4% (17/18) Early loss: 0 Late loss: 1	100% (2/2) 100% (2/2)	NR	0% (0/1) 0% (0/18)	NR
Peron et al. [58]	2017	CR	1/5	RA+sSS	0/1	36	100% (1/1) 100% (5/5)	NR	0	NR	NR
de Mendonça Invernici et al. [66]	2014	CR	1/2	RA+sSS	0/1	72	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	0	NR	NR
Alsaadi et al. [67]	2008	RS	NR/14	RA	NR	Up to prosthetic loading	NR 92.9% (13/14)[d]	NR	NR	NR	NR
Krennmair et al. [71]	2010	RS	25/85	RA	0/25	Mean: 46.6	100% (25/25) 100% (85/85)	100% (25/25) 100% (33/33)	Median: 2	NR	NR 96.5% (82/85)[e,f]
			9/41	RA+sSS, RA+sSS+SSc, RA+DM	0/9	Mean: 48.9	100% (9/9) 100% (41/41)	100% (9/9) 100% (10/10)	Median: 2.8	NR	NR 90.2% (37/41)[e,f]
Payne et al. [81]	1997	CS	1/12	RA+sSS	0/1	96	0% (0/1) 75% (9/12) Early loss: 2, Late loss: 1	100% (1/1) 100% (2/2)	NR	NR	NR
Alenazi [84]	2021	CCS	14/32	RA	5/9	Mean: 42.3	100% (14/14) 100% (32/32)	100% (14/14) NR	Median: 1.2	NR	NR
			14/43	RA+SSc, RA+sSS RA+DM	4/10	Mean: 44.6	100% (14/14) 100% (43/43)	100% (14/14) NR	Median: 2.2	NR	NR
			14/39	Control group	7/7	Mean: 39.4	100% (14/14) 100% (39/39)	100% (14/14) NR	Median: 0.6	NR	NR
Overall											
RA	-	RS: 6 CR: 4 CS: 1 CCS: 1	124/363	-	Ratio: 1/6.5	Mean: 50.8	95.2% (118/124) 97.2% (353/363) Of these: 70% (7/10) early loss	100% (67/67) 100% (49/49)	Mean: 0.36 Median: 2	8.3% (1/12) 1.8% (1/55)	NR 94.4% (119/126)[e,f]
RA + concomitant ADs	-	CR: 3 CS: 1 CCS: 1 RS: 1	27/109	-	Ratio: 1/4.4	Mean: 52.8	96.3% (26/27) 97.2% (106/109) Of these: 66.7% (2/3) early loss	100% (26/26) 100% (14/14)	Mean: 0 Median: 2.2	NR	NR 90.2% (37/41)[e]
Control group	-	CCS: 1	14/39	-	Ratio: 1/1	Mean: 39.4	100% (14/14) 100% (39/39)	100% (14/14) NR	Median: 0.6	NR	NR

[a] = weighted mean or median; [b] = remission at implant placement; [c] = early loss NR; [d] = late loss NR; [e] = criteria by Buser et al. [116]; [f] = criteria by Karoussis et al. [117].
ADs = autoimmune diseases; CCS = case-control study; CR = case report; CS = case series; DM = dermatomyositis; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; RS = retrospective study; SSc = systemic scleroderma; sSS = secondary Sjögren's syndrome.

Table 3B. Characteristics and outcomes of studies including autoimmune connective tissue diseases - Sjögren's syndrome (SS)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Oczakir et al. [6]	2005	CS	1/4	pSS	0/1	24	100% (1/1) 100% (4/4)	100% (1/1) 100% (2/2)	NR	0% (0/1) 0% (0/4)	NR
			1/8	sSS+SSc	0/1	60	100% (1/1) 100% (8/8)	100% (1/1) 100% (2/2)	NR	0% (0/1) 0% (0/8)	NR
Petsinis et al. [7]	2017	RS	2/7	SS (type NR)[b]	0/2	Mean: 110	100% (2/2) 100% (7/7)	100% (2/2) NR	NR	0% (0/2) 0% (0/7)	NR
Isidor et al. [14]	1999	PS	8/54	sSS+RA, sSS+SSc	0/8	48	50% (4/8) 87% (45/54) Early loss: 7 Late loss: 2	100% (8/8) 100% (11/11)	Mean: 0.74	NR	NR
Binon [34]	2005	CR	1/6	sSS+RA	1/0	156	100% (1/1) 100% (6/6)	100% (1/1) 100% (1/1)	NR	NR	NR
In 't Veld et al. [45]	2022	CR	1/4	SS (type NR)	0/1	2	100% (1/1) 100% (4/4)	100% (1/1) 100% (1/1)	NR	NR	NR
Mori et al. [53]	2018	CR	1/8	pSS	0/1	36	100% (1/1) 100% (8/8)	100% (1/1) 100% (4/4)	0	0% (0/1) 0% (0/8)	NR
Nam et al. [55]	2012	CR	1/14	sSS+SSc	0/1	4	100% (1/1) 100% (14/14)[d]	Irr.	NR	NR	NR
Peron et al. [58]	2017	CR	1/5	sSS+RA	0/1	36	100% (1/1) 100% (5/5)	NR	0	NR	NR
Spinato et al. [61]	2010	CR	1/6	pSS	0/1	12	100% (1/1) 100% (6/6)	100% (1/1) 100% (1/1)	0	NR	NR
Chochlidakis et al. [65]	2016	CR	1/6	sSS+SLE+HT	0/1	14	100% (1/1) 100% (6/6)	100% (1/1) 100% (2/2)	NR	NR	NR
de Mendonça Invernici et al. [66]	2014	CR	1/2	sSS+RA	0/1	72	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	0	NR	NR
Krennmair et al. [71]	2010	RS	8/39	sSS+RA, sSS+RA+SSc	0/8	Mean: 51.9	100% (8/8) 100% (39/39)	100% (8/8) 100% (9/9)	NR	NR	NR
Siddiqui et al. [73]	2017	RS	11/23	SS (type NR)	NR	40	81.8% (9/11) 87% (20/23) Early loss: 3 Late loss: 0	NR	NR	NR	NR
Chatzistavrianou et al. [78]	2016	CS	1/2	pSS	0/1	24	100% (1/1) 100% (2/2)	NR	NR	NR	NR
			1/8	sSS (concomitant CTD NR)	0/1	18	100% (1/1) 100% (8/8)	NR	NR	NR	NR
Chrcanovic et al. [79]	2019	CS	19/107	SS (type NR)	1/18	Mean: 125.5	89.5% (17/19) 97.2% (104/107) Early loss: 2 Late loss: 1	NR	Mean: 2.19	NR	NR
Esposito et al. [80]	2003	CS	1/2	pSS+OLP	0/1	18	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	0	0% (0/1) 0% (0/2)	100% (1/1) 100% (2/2)[e]
Payne et al. [81]	1997	CS	1/6	pSS	0/1	12	100% (1/1) 100% (6/6)	100% (1/1) 100% (1/1)	NR	NR	NR
			2/20	sSS+RA, sSS+ST	0/2	Mean: 54	50% (1/2) 85% (17/20) Early loss: 2 Late loss: 1	100% (2/2) 100% (4/4)	NR	NR	NR
Corigliano et al. [83]	2014	CS	2/13	pSS, SS (type NR)	0/2	Mean: 27	100% (2/2) 100% (13/13)	100% (2/2) 100% (3/3)	NR	0% (0/1). NR: 1 0% (0/2). NR: 11	NR
Alenazi [84]	2021	CCS	4/NR	sSS+RA	NR	Mean: 44.6[c]	100% (4/4) NR	100% (4/4) NR	NR	NR	NR
			14/39	Control group	7/7	Mean: 39.4	100% (14/14) 100% (39/39)	100% (14/14) NR	Median: 0.6	NR	NR
Korfage et al. [87]	2016	CCS	50/140	pSS, sSS (concomitant CTD NR)	4/46	Median: 46	96% (48/50) 97.1% (136/140) Early loss: 4 Late loss: 0	NR	Median: 0.89	14% (7/50) 11.4% (16/140)	NR
			50/125	Control group	4/46	Median: 45.6	100% (50/50) 100% (125/125)	NR	Median: 0.66	12% (6/50) 8.8% (11/125)	NR
Overall											
SS	-	CR: 8 CS: 6 RS: 3 CCS: 2 PS: 1	120/484	-	Ratio: 1/16.5	Mean: 68.1 Median: 46	90.8% (109/120) 95.5% (462/484) Of these: 81.8% (18/22) early loss	100% (36/36) 100% (43/43)	Mean: 1.49 Median: 0.89	12.3% (7/57) 9.4% (16/171)	100% (1/1) 100% (2/2)[e]
SS+ concomitant ADs	-	CR: 5 CS: 4 CCS: 1 PS: 1 RS: 1	30/164	-	Ratio: 1/25	Mean: 49.4	83.3% (25/30) 92.7% (152/164) Of these: 75% (9/12) early loss	100% (27/27) 100% (31/31)	Mean: 0.63	0% (0/2) 0% (0/10)	100% (1/1) 100% (2/2)[e]
Control group	-	CCS: 2	64/164	-	Ratio: 1/4.8	Mean: 39.4 Median: 45.6	100% (64/64) 100% (164/164)	100% (14/14) NR	Median: 0.66	12% (6/50) 8.8% (11/125)	NR

[a] = weighted mean or median; [b] = remission at implant placement; [c] = reported for RA+CTDs but NR specific for sSS; [d] = late loss NR; [e] = criteria by Esposito et al. [26].
ADs = autoimmune diseases; CCS = case-control study; CR = case report; CS = case series; CTDs = connective tissue diseases; HT = hypothyroidism; Irr. = irrelevant; M/F = male/female; N = number; NR = not reported; OLP = oral lichen planus; PI = peri-implantitis; PS = prospective study; pSS = primary Sjögren's syndrome; RA = rheumatoid arthritis; RS = retrospective study; SLE = systemic lupus erythematosus; SSc = systemic scleroderma; sSS = secondary Sjögren's syndrome; ST = Still's disease.

Table 3C. Characteristics and outcomes of studies including autoimmune connective tissue diseases - systemic scleroderma (SSc)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Oczakir et al. [6]	2005	CS	1/8	SSc+sSS	0/1	60	100% (1/1) 100% (8/8)	100% (1/1) 100% (2/2)	NR	0% (0/1) 0% (0/8)	NR
Baptist [31]	2016	CR	1/6	SSc	0/1	24	100% (1/1) 100% (6/6)	100% (1/1) 100% (2/2)	Mean: 0.58	100% (1/1) 16.7% (1/6)	NR
Bayram et al. [32]	2021	CR	1/7	SSc	0/1	57.6	100% (1/1) 100% (7/7)	NR	0	0% (0/1) 0% (0/7)	NR
Garces Villala et al. [42]	2021	CR	1/12	SSc	0/1	120	100% (1/1) 100% (12/12)	100% (1/1) 100% (2/2)	Mean: 1.22	0% (0/1) 0% (0/12)	NR
Haas [44]	2002	CR	1/7	SSc	0/1	6	100% (1/1) 100% (7/7)[c]	Irr.	NR	NR	NR
Jensen et al. [47]	1990	CR	1/9	SSc	1/0	19	0% (0/1) 88.9% (8/9) Early loss: 1 Late loss: 0	100% (1/1) 100% (1/1)	0	0% (0/1) 0% (0/8)	NR
Langer et al. [48]	1992	CR	1/2	SSc	0/1	6	100% (1/1) 100% (2/2)	NR	NR	NR	NR
Nam et al. [55]	2012	CR	1/14	SSc+sSS	0/1	4	100% (1/1) 100% (14/14)[c]	Irr.	NR	NR	NR
Patel et al. [57]	1998	CR	1/4	SSc+FA	0/1	Up to prosthetic loading	100% (1/1) 100% (4/4)[c]	NR	NR	NR	NR
Raviv et al. [59]	1996	CR	1/3	SSc	0/1	24	100% (1/1) 100% (3/3)	100% (1/1) 100% (1/1)	NR	NR	NR
Smojver et al. [60]	2021	CR	1/4	SSc	0/1	12	100% (1/1) 100% (4/4)	100% (1/1) 100% (2/2)	NR	NR	NR
Zigdon et al. [62]	2011	CR	1/12	SSc	0/1	36	100% (1/1) 100% (12/12)	NR	0	NR	NR
Krennmair et al. [71]	2010	RS	1/4	SSc+RA+sSS	0/1	34	100% (1/1) 100% (4/4)	100% (1/1) 100% (1/1)	NR	NR	NR
Alenazi [84]	2021	CCS	7/NR	SSc+RA	NR	Mean: 44.6[b]	100% (7/7) NR	100% (7/7) NR	NR	NR	NR
			14/39	Control group	7/7	Mean: 39.4	100% (14/14) 100% (39/39)	100% (14/14) NR	Median: 0.6	NR	NR
Overall											
SSc	-	CR: 11 CS: 1 CCS: 1 RS: 1	20/92	-	Ratio: 1/12	Mean: 33.6	95% (19/20) 98.9% (91/92) Of these: 100% (1/1) early loss	100% (14/14) 100% (11/11)	Mean: 0.37	20% (1/5) 2.4% (1/41)	NR
SSc+concomitant ADs	-	CR: 2 CS: 1 CCS: 1 RS: 1	11/30	-	Ratio: 0/4	Mean: 32.7	100% (11/11) 100% (30/30)	100% (9/9) 100% (3/3)	NR	0% (0/1) 0% (0/8)	NR
Control group	-	CCS: 1	14/39	-	Ratio: 1/1	Mean: 39.4	100% (14/14) 100% (39/39)	100% (14/14) NR	Median: 0.6	NR	NR

[a] = weighted mean or median; [b] = reported for RA+CTDs but NR specific for SSc; [c] = late loss NR.
ADs = autoimmune diseases; CCS = case-control study; CR = case report; CS = case series; CTDs = connective tissue diseases; FA = fibrosing alveolitis; Irr. = irrelevant; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; RA = rheumatoid arthritis; RS = retrospective study; sSS = secondary Sjögren's syndrome.

Table 3D. Characteristics and outcomes of studies including autoimmune connective tissue diseases - systemic lupus erythematosus (SLE)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Mozzati et al. [5]	2021	RS	5/12	SLE	3/2	Mean: 58.5	100% (5/5) 100% (12/12)	100% (5/5) NR	Mean: 0.49	0% (0/5) 0% (0/12)	NR
Petsinis et al. [7]	2017	RS	3/14	SLE	1/2	Mean: 50.3	100% (3/3) 100% (14/14)	100% (3/3) NR	NR	0% (0/3) 0% (0/14)	NR
Drew et al. [37]	2018	CR	1/15	SLE	0/1	> 18	0% (0/1) 93.3% (14/15) Early loss: 1 Late loss: 0	100% (1/1) 100% (2/2)	NR	0% (0/1) 0% (0/15)	NR
Ergun et al. [40]	2010	CR	1/6	SLE+PA	0/1	24	100% (1/1) 100% (6/6)	100% (1/1) 100% (5/5)	NR	NR	NR
Li et al. [51]	2004	CR	1/5	SLE+MCTD	0/1	36	100% (1/1) 100% (5/5)	100% (1/1) NR	NR	NR	NR
Chochlidakis et al. [65]	2016	CR	1/6	SLE+HT+sSS	0/1	14	100% (1/1) 100% (6/6)	100% (1/1) 100% (2/2)	NR	NR	NR
Overall											
SLE	-	CR: 4 RS: 2	12/58	-	Ratio: 1/2	Mean: 47	91.7% (11/12) 98.3% (57/58) Of these: 100% (1/1) early loss	100% (12/12) 100% (9/9)	Mean: 0.49	0% (0/9) 0% (0/41)	NR
SLE + concomitant ADs	-	CR: 3	3/17	-	Ratio: 0/3	Mean: 24.7	100% (3/3) 100% (17/17)	100% (3/3) 100% (7/7)	NR	NR	NR

[a] = weighted mean or median.
ADs = autoimmune diseases; CR = case report; HT = hypothyroidism; M/F = male/female; MCTD = mixed connective tissue disease; N = number; NR = not reported; PA = polyarthritis; PI = peri-implantitis; RS = retrospective study; sSS = secondary Sjögren's syndrome.

Table 3E. Characteristics and outcomes of studies including autoimmune connective tissue diseases - polyarthritis (PA)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Eder et al. [38]	1999	CR	1/6	PA	0/1	48	100% (1/1) 100% (6/6)	100% (1/1) 100% (1/1)	Mean: 1.38	100% (1/1) NR	NR
Ella et al. [39]	2011	CR	1/2	PA	0/1	48	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	NR	NR	NR
Ergun et al. [40]	2010	CR	1/6	PA+SLE	0/1	24	100% (1/1) 100% (6/6)	100% (1/1) 100% (5/5)	NR	NR	NR
Overall											
PA	-	CR: 3	3/14	-	Ratio: 0/3	Mean: 40	100% (3/3) 100% (14/14)	100% (3/3) 100% (7/7)	Mean: 1.38	100% (1/1) NR	NR

[a] = weighted mean or median.
ADs = autoimmune diseases; CR = case report; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; SLE = systemic lupus erythematosus.

Table 3F. Characteristics and outcomes of studies including autoimmune connective tissue diseases - other autoimmune connective tissue diseases (CTDs)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Petsinis et al. [7]	2017	RS	2/5	GCA	0/2	Mean: 47.5	100% (2/2) 100% (5/5)	100% (2/2) NR	NR	0% (0/2) 0% (0/5)	NR
			1/2	PN	1/0	48	100% (1/1) 100% (2/2)	100% (1/1) NR	NR	0% (0/1) 0% (0/2)	NR
Bencharit et al. [33]	2010	CR	1/12	PR (without GCA)	0/1	19	100% (1/1) 100% (12/12)	NR	NR	NR	NR
Li et al. [51]	2004	CR	1/5	MCTD+SLE	0/1	36	100% (1/1) 100% (5/5)	100% (1/1) NR	NR	NR	NR
Payne et al. [81]	1997	CS	1/8	ST+sSS	0/1	12	100% (1/1) 100% (8/8)	100% (1/1) 100% (2/2)	NR	NR	NR
Overall											
Other autoimmune CTDs	-	CR: 2 CS: 1 RS: 1	6/32	-	Ratio: 1/5	Mean: 35	100% (6/6) 100% (32/32)	100% (5/5) 100% (2/2)	NR	0% (0/3) 0% (0/7)	NR
Other autoimmune CTDs +concomitant ADs	-	CR: 1 CS: 1	2/13	-	Ratio: 0/2	Mean: 24	100% (2/2) 100% (13/13)	100% (2/2) 100% (2/2)	NR	NR	NR

[a] = weighted mean or median.
ADs = autoimmune diseases; CR = case report; CS = case series; GCA = giant cell arteritis; M/F = male/female; MCTD = mixed connective tissue disease; N = number; NR = not reported; PI = peri-implantitis; PN = polyarteritis nodosa; PR = polymyalgia rheumatica; RS = retrospective study; SLE = systemic lupus erythematosus; sSS = secondary Sjögren's syndrome; ST = Still's disease.

Table 4A. Characteristics and outcomes of studies including other autoimmune diseases - hypothyroidism (HT)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Alsaadi et al. [4]	2008	RS	25/111	HT	NR	24	NR 93.7% (104/111)[c]	NR	NR	NR	NR
Cillo et al. [36]	2019	CR	1/5	HT+UC	0/1	0.5	0% (0/1) 0% (0/5) Early loss: 5 Late loss: 0	Irr.	NR	100% (1/1)[b] 100% (5/5)	NR
Chochlidakis et al. [65]	2016	CR	1/6	HT+sSS+SLE	0/1	14	100% (1/1) 100% (6/6)	100% (1/1) 100% (2/2)	NR	NR	NR
Alsaadi et al. [67]	2008	RS	NR/21	HT	NR	Up to prosthetic loading	NR 100% (21/21)[d]	NR	NR	NR	NR
Nicoli et al. [76]	2017	RS	4/NR	HT	NR	Range: 96 - 120	100% (4/4) NR	NR	NR	25% (1/4) NR	NR
Attard et al. [89]	2002	CCS	21/82	HT	0/21	Mean: 90	NR 96.3% (79/82) Early loss: 2 Late loss: 1	NR	Mean: 0.05	NR	NR 96.3% (79/82)[e]
			29/81	Control group	0/29	Mean: 7.7	NR 97.5% (79/81) Early loss: 2 Late loss: 0	NR	Mean: 0.04	NR	NR 97.5% (79/81)[e]
Overall											
HT	-	RS: 3 CR: 2 CCS: 1	52/225	-	Ratio: 0/23	Mean: 52.2	83.3% (5/6) 93.3% (210/225) Of these: 46.7% (7/15) early loss	100% (1/1) 100% (2/2)	Mean: 0.05	40% (2/5) 100% (5/5)	NR 96.3% (79/82)[e]
HT +concomitant ADs	-	CR: 2	2/11	-	Ratio: 0/2	Mean: 7.3	50% (1/2) 54.5% (6/11) Of these: 100% (5/5) early loss	100% (1/1) 100% (2/2)	NR	100% (1/1) 100% (5/5)	NR
Control group	-	CCS: 1	29/81	-	Ratio: 0/29	Mean: 7.7	NR 97.5% (79/81) Of these: 100% (2/2) early loss	NR	Mean: 0.04	NR	NR 97.5% (79/81)[e]

[a] = weighted mean or median; [b] = submental abscess with extension to submandibular spaces; [c] = early loss NR; [d] = late loss NR; [e] = criteria by Zarb et al. [118].
ADs = autoimmune diseases; CCS = case-control study; CR = case report; Irr. = irrelevant; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; RS = retrospective study; SLE = systemic lupus erythematosus; sSS = secondary Sjögren's syndrome; UC = ulcerative colitis.

Table 4B. Characteristics and outcomes of studies including other autoimmune diseases - type 1 diabetes (T1D)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Alsaadi et al. [4]	2008	RS	1/1	T1D	NR	24	100% (1/1) 100% (1/1)[b]	NR	NR	NR	NR
Alsaadi et al. [67]	2008	RS	NR/1	T1D	NR	Up to prosthetic loading	NR 0% (0/1)[c]	NR	NR	NR	NR
Hasanoglu Erbasar et al. [70]	2019	RS	7/NR	T1D	NR	≥ 6	85.7% (6/7) NR	NR	NR	28.6% (2/7) NR	71.4% (5/7) NR[d]
Overall											
T1D	-	RS: 3	8/2	-	NR	Mean: 24	87.5% (7/8) 50% (1/2) Of these: 100% (1/1) early loss	NR	NR	28.6% (2/7) NR	71.4% (5/7) NR[d]
T1D +concomitant ADs	-	Irr.	None	-	Irr.	Irr.	Irr.	Irr.	Irr.	Irr.	Irr.

[a] = weighted mean or median; [b] = early loss NR; [c] = late loss NR; [d] = criteria by Albrektsson et al. [119].
ADs = autoimmune diseases; Irr. = irrelevant; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; RS = retrospective study.

Table 4C. Characteristics and outcomes of studies including other autoimmune diseases - Crohn's disease (CD)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Alsaadi et al. [4]	2008	RS	2/9	CD	NR	24	NR 66.7% (6/9)[b]	NR	NR	NR	NR
Cauble [35]	2011	CR	1/10	CD	1/0	5	100% (1/1) 100% (10/10)[c]	NR	NR	NR	NR
Alsaadi et al. [67]	2008	RS	NR/12	CD	NR	Up to prosthetic loading	NR 91.7% (11/12)[c]	NR	NR	NR	NR
van Steenberghe et al. [74]	2002	RS	3/13	CD	NR	Up to prosthetic loading	33.3% (1/3) 76.9% (10/13)[c]	NR	NR	NR	NR
Overall											
CD	-	RS: 3 CR: 1	6/44	-	Ratio: 1/0	Mean: 17.7	50% (2/4) 84.1% (37/44) Of these: 57.1% (4/7) early loss	NR	NR	NR	NR
CD +concomitant ADs	-	Irr.	None	-	Irr.	Irr.	Irr.	Irr.	Irr.	Irr.	Irr.

[a] = weighted mean or median; [b] = early loss NR; [c] = late loss NR.
ADs = autoimmune diseases; CR = case report; Irr. = irrelevant; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; RS = retrospective study.

Table 4D. Characteristics and outcomes of studies including other autoimmune diseases - dermatomyositis (DM)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Petsinis et al. [7]	2017	RS	1/3	DM[b]	0/1	52	100% (1/1) 100% (3/3)	100% (1/1) NR	NR	0% (0/1) 0% (0/3)	NR
Krennmair et al. [71]	2010	RS	1/2	DM+RA	0/1	25	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	NR	NR	NR
Alenazi [84]	2021	CCS	3/NR	DM+RA	NR	Mean: 44.6[c]	100% (3/3) NR	100% (3/3) NR	NR	NR	NR
			14/39	Control group	7/7	Mean: 39.4	100% (14/14) 100% (39/39)	100% (14/14) NR	Median: 0.6	NR	NR
Overall											
DM	-	RS: 2 CCS: 1	5/5	-	Ratio: 0/2	Mean: 38.5	100% (5/5) 100% (5/5)	100% (5/5) 100% (1/1)	NR	0% (0/1) 0% (0/3)	NR
DM +concomitant ADs	-	RS: 1 CCS: 1	4/2	-	Ratio: 0/1	Mean: 25	100% (4/4) 100% (2/2)	100% (4/4) 100% (1/1)	NR	NR	NR
Control group	-	CCS: 1	14/39	-	Ratio: 1/1	Mean: 39.4	100% (14/14) 100% (39/39)	100% (14/14) NR	Median: 0.6	NR	NR

[a] = weighted mean or median; [b] = remission at implant placement; [c] = reported for RA+CTDs but NR specific for DM.
ADs = autoimmune diseases; CCS = case-control study; CTDs = connective tissue diseases; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; RA = rheumatoid arthritis; RS = retrospective study.

Table 4E. Characteristics and outcomes of studies including other autoimmune diseases - other autoimmune diseases

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Petsinis et al. [7]	2017	RS	2/4	MG[b]	1/1	Mean: 51.5	100% (2/2) 100% (4/4)	100% (2/2) NR	NR	0% (0/2) 0% (0/4)	NR
			1/7	PSO[b]	1/0	48	0% (0/1) 85.7% (6/7) Early loss: 1 Late loss: 0	100% (1/1) NR	NR	0% (0/1) 0% (0/7)	NR
Cillo et al. [36]	2019	CR	1/5	UC+HT	0/1	0.5	0% (0/1) 0% (0/5) Early loss: 5 Late loss: 0	Irr.	NR	100% (1/1) 100% (5/5)[c]	NR
James et al. [46]	2020	CR	1/2	SA	0/1	48	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	NR	NR	NR
Patel et al. [57]	1998	CR	1/4	FA+SSc	0/1	Up to prosthetic loading	100% (1/1) 100% (4/4)[d]	NR	NR	NR	NR
Maló et al. [75]	2016	RS	3/16	MS	NR	60	100% (3/3) 100% (16/16)	NR	Mean: 1.63	0% (0/3) 0% (0/16)	NR
Overall											
Other ADs	-	CR: 3 RS: 2	9/38	-	Ratio: 1/2	Mean: 47.4	77.8% (7/9) 84.2% (32/38) Of these: 100% (6/6) early loss	100% (4/4) 100% (1/1)	Mean: 1.63	14.3% (1/7) 15.6% (5/32)	NR
Other ADs +concomitant ADs	-	CR: 2	2/9	-	Ratio: 0/2	Mean: 0.5	50% (1/2) 44.4% (4/9) Of these: 100% (5/5) early loss	NR/Irr.	NR	100% (1/1) 100% (5/5)	NR

[a] = weighted mean or median; [b] = remission at implant placement; [c] = submental abscess with extension to submandibular spaces; [d] = late loss NR.
ADs = autoimmune diseases; CR = case report; FA = fibrosing alveolitis; HT = hypothyroidism; Irr. = irrelevant; M/F = male/female; MG = myasthenia gravis; MS = multiple sclerosis; N = number; NR = not reported; PI = peri-implantitis; PSO = psoriasis; RS = retrospective study; SA = sarcoidosis; SSc = systemic scleroderma; UC = ulcerative colitis.

Table 5A. Characteristics and outcomes of studies including autoimmune diseases with mucosal manifestations - oral lichen planus (OLP)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Oczakir et al. [6]	2005	CS	1/4	OLP	0/1	72	100% (1/1) 100% (4/4)	100% (1/1) 100% (1/1)	NR	0% (0/1) 0% (0/4)	NR
Aboushelib et al. [25]	2017	PS	23/55	OLP (active)	11/12	4	13% (3/23) 23.6% (13/55) Early loss: 42 Late loss: 0	NR	Mean: 0.26	NR	NR
Fu et al. [41]	2019	CR	1/4	OLP[c]	0/1	36	100% (1/1) 100% (4/4)	100% (1/1) 100% (1/1)	Range: 3 - 4	NR	NR
Martin-Cabezas [52]	2021	CR	1/3	OLP	0/1	360	100% (1/1) 100% (3/3)	NR	NR	100% (1/1) 100% (3/3)	NR
Anitua et al. [68]	2018	RS	23/66	OLP	3/20	Mean: 63	95.7% (22/23) 98.5% (65/66) Early loss: 0 Late loss: 1	NR	Mesial: mean: 0.96 Distal: mean: 0.99	NR	NR
Czerninski et al. [69]	2013	RS	14/54	OLP	3/11	Range: 12 - 24	100% (14/14) 100% (54/54)[d]	NR	NR	NR	100% (14/14) 100% (54/54)[h]
Esposito et al. [80]	2003	CS	1/2	OLP	0/1	18	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	0	0% (0/1) 0% (0/2)	100% (1/1) 100% (2/2)
			1/2	OLP+pSS	0/1	18	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	0	0% (0/1) 0% (0/2)	100% (1/1) 100% (2/2)[g]
Reichart [82]	2006	CS	1[b]/1	OLP	0/1	36	100% (1/1) 100% (1/1)	NR	NR	NR	NR
Hernández et al. [85]	2012	CCS	18/56	OLP	4/14	Median: 56.5	100% (18/18) 100% (56/56)	NR	Mean: 1.95	NR	NR
			18/62	Control group	6/12	Median: 52.5	NR 96.8% (60/62) Early loss: 0 Late loss: 2	NR	Mean: 1.87	NR	NR
Khamis et al. [86]	2019	CCS	20/NR	OLP[c,e]	NR	48	100% (20/20) NR	NR	Mean: 0.76	NR	NR
			22/NR	OLP[c,f]	NR	48	100% (22/22) NR	NR	Mean: 2.53	NR	NR
			17/NR	Control group	NR	48	100% (17/17) NR	NR	Mean: 0.8	NR	NR
López-Jornet et al. [88]	2014	CCS	16/56	OLP	6/10	Median: 42	NR	NR	NR	NR 25% (14/56)	NR
			16/50	Control group	8/8	Median: 48	NR	NR	NR	NR 16% (8/50)	NR
Overall											
OLP	-	CCS: 3 CS: 3 CR: 2 RS: 2 PS: 1	142/303	-	Ratio: 1/2.7	Mean: 43.6 Median: 48	83.3% (105/126) 82.6% (204/247) Of these: 97.7% (42/43) early loss	100% (4/4) 100% (4/4)	Mean: 1.05	25% (1/4) 25.4% (17/67)	100% (16/16) 100% (58/58)[g,h]
OLP +concomitant ADs	-	CS: 1	1/2	-	Ratio: 0/1	Mean: 18	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	Mean: 0	0% (0/1) 0% (0/2)	100% (1/1) 100% (2/2)[g]
Control group	-	CCS: 3	51/112	-	Ratio: 1/1.4	Mean: 48 Median: 48	100% (17/17) 96.8% (60/62) Of these: 0% (0/2) early loss	NR	Mean: 1.85	NR 16% (8/50)	NR

[a] = weighted mean or median; [b] = the remaining 2 patients in this CS were excluded from data extraction due to insufficient information; [c] = remission at implant placement; [d] = early loss NR; [e] = continued systemic glucocorticoids administration post implant placement; [f] = discontinued systemic glucocorticoids administration 12 weeks post implant placement; [g] = criteria by Esposito et al. [26]; [h] = criteria by Buser et al. [116].
ADs = autoimmune diseases; CCS = case-control study; CR = case report; CS = case series; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; PS = prospective study; pSS = primary Sjögren's syndrome; RS = retrospective study.

Table 5B. Characteristics and outcomes of studies including autoimmune diseases with mucosal manifestations - bullous diseases (BDs)

Study	Year of publication	Study design	Patients/ implants	ADs	Gender	Follow-up period[a]	Survival rate of implants	Survival rate of suprastructures	Crestal bone loss[a]	PI	Success rate
			n/n		M/F	Months	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n suprastructures)	mm	% (n/n patients) % (n/n implants)	% (n/n patients) % (n/n implants)
Altin et al. [30]	2013	CR	1/2	PV	0/1	32	100% (1/1) 100% (2/2)	NR	Mean: 0.9	NR	NR
Larrazabal-Moron et al. [49]	2009	CR	1/2	RDEB	0/1	12	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	NR	0% (0/1) 0% (0/2)	100% (1/1) 100% (2/2)[b]
Lee et al. [50]	2007	CR	1/8	RDEB	1/0	17	100% (1/1) 100% (8/8)	0% (0/1) 50% (1/2)	NR	0% (0/1) 0% (0/8)	NR
Muller et al. [54]	2010	CR	1/10	RDEB	1/0	36	100% (1/1) 100% (10/10)	0% (0/1) 66.7% (2/3)	0	0% (0/1) 0% (0/10)	NR
Oliveira et al. [56]	2010	CR	1/2	RDEB	0/1	24	100% (1/1) 100% (2/2)	100% (1/1) 100% (1/1)	0	0% (0/1) 0% (0/2)	NR
Alikhasi et al. [63]	2017	CR	1/8	RDEB	1/0	18	100% (1/1) 100% (8/8)	NR	NR	NR	NR
Letelier et al. [64]	2016	CR	1/6	RDEB	0/1	30	100% (1/1) 100% (6/6)	100% (1/1) 100% (1/1)	NR	0% (0/1) 0% (0/6)	NR
Peñarrocha-Oltra et al. [72]	2020	RS	13/80	RDEB	4/9	Mean: 92	NR 97.5% (78/80) Early loss: 1 Late loss: 1	100% (13/13) 100% (20/20)	Mean: 1.65	NR	NR
Agustín-Panadero et al. [77]	2019	CS	4/31	RDEB	1/3	48	100% (4/4) 100% (31/31)	100% (4/4) 100% (8/8)	NR	NR	NR
Overall											
BDs	-	CR: 7 CS: 1 RS: 1	24/149	-	Ratio: 1/2	Mean: 64.9	100% (11/11) 98.7% (147/149) Of these: 50% (1/2) early loss	90.9% (20/22) 94.4% (34/36)	Mean: 1.42	0% (0/5) 0% (0/28)	100% (1/1) 100% (2/2)[b]
BDs +concomitant ADs	-	Irr.	None	-	Irr.	Irr.	Irr.	Irr.	Irr.	Irr.	Irr.

[a] = weighted mean or median; [b] = criteria by Albrektsson et al. [119].
ADs = autoimmune diseases; CR = case report; CS = case series; Irr. = irrelevant; M/F = male/female; N = number; NR = not reported; PI = peri-implantitis; PV = pemphigus vulgaris; RDEB = recessive dystrophic epidermolysis bullosa; RS = retrospective study.

After a weighted mean follow-up period of 68.1 months (weighted median: 46 months) an implant survival rate of 95.5% (462/484) at implant level and 90.8% (109/120) at patient level could be calculated. Of the lost implants, 81.8% (18/22) were early losses. The suprastructure survival rate was 100% on patient (36/36) and suprastructure (43/43) level. Weighted mean crestal bone loss was 1.49 mm (weighted median: 0.89 mm). PI was diagnosed in 12.3% (7/57) of the patients and around 9.4% (16/171) of the implants. However, PI was only reported to occur in one study [87]. In a study on eight patients with secondary SS, 9/54 implants were lost in 4/8 patients. In addition, all patients had problems wearing conventional dentures prior to rehabilitation with implant-supported dental prosthesis. Improved patient-reported outcome measures were recorded at two years follow-up after loading of the implant-supported dental prostheses [14]. Characteristics and outcomes of studies including SS are presented in Table 3B.

Systemic scleroderma

Fourteen articles (eleven case reports, one case series, one case-control study and one retrospective study) were included [6,31,32,42,44,47,48,55,57,59,60,62,71,84]. A total of 20 patients with systemic scleroderma (M/F ratio: 1/12), were documented with 92 implants. The implant survival rate was 98.9% (91/92) and 95% (19/20) on implant and patient level, respectively, after a weighted mean follow-up period of 33.6 months. Suprastructure survival rate was 100% on patient (14/14) as well as on suprastructure (11/11) level. The weighted mean crestal bone loss was 0.37 mm and PI was diagnosed in 20% (1/5) of the patients and 2.4% (1/41) of the implants. No valid patient-reported outcome was available for this disease group. Characteristics and outcomes of studies including SSc are presented in Table 3C.

Systemic lupus erythematosus

Six articles (four case reports and two retrospective studies) were included [5,7,37,40,51,65]. A total of 58 implants were documented in twelve patients (M/F ratio: 1/2) with systemic lupus erythematosus. After a weighted mean follow-up period of 47 months the implant survival rate was 98.3% (57/58) and 91.7% (11/12) on implant and patient level respectively. The suprastructure survival rate was 100% on patient (12/12) and suprastructure (9/9) level. PI was diagnosed in 0% of the patients (0/9) and implants (0/41). Characteristics and outcomes of studies including SLE are presented in Table 3D.

Autoimmune diseases with mucosal manifestations

Oral lichen planus

Eleven studies (three case-control studies, three case series, two case reports, two retrospective studies and one prospective study) characterized by a low to medium quality were included [6,25,41,52,68,69,80,82,85,86,88]. Of the included cohort and case-control studies three were low [6,82,86], five were medium [25,68,69,80,88] and one was high quality [85]. This was the only disease group where the prognosis of dental implant therapy could be based on studies with a low to medium quality.

A total of 303 implants were documented in 142 oral lichen planus (OLP) patients (M/F ratio: 1/2.7) making it the disease group with the highest number of included patients. The implant survival rate was 83.3% (105/126) on patient level and 82.6% (204/247) on implant level after a weighted mean follow-up period of 43.6 months (weighted median: 48 months). Of the lost implants 97.7% (42/43) occurred early. The weighted mean crestal bone loss was 1.05 mm. PI was diagnosed in 25.4% (17/67) implants and in 25% (1/4) of the patients.

In one study, 55 implants were placed in 23 patients with OLP and flare-up of their disease. Of those, 42 implants were lost (survival rate: 23.6%). Subsequently, the OLP lesions were treated with systemic glucocorticoids leading to complete remission. Hereafter implant therapy was repeated. None of the 42 newly placed implants were lost after a follow-up of 36 [25] and 48 months [86]. In another study, sixteen patients with OLP received 56 implants. Of these seven patients used topical glucocorticoids daily. PI developed around 25% (14/56) implants and in contrast, PI developed around 16% (8/50) implants in the control group without OLP. This difference was not statistically significant (P = 0.254) [88].

One study reported a median Oral Health Impact Profile (OHIP)-14 score (a measure of oral quality of life performed in relation to dental treatment) [90]. Lower scores indicate improved oral quality of life [90]. For sixteen patients with OLP and 56 implants (three overdentures and thirteen partial fixed prosthesis) the score was 7 (0 - 22), for sixteen patients with OLP without implants it was 13 (1 - 23), and for sixteen controls with 50 implants (three overdentures and thirteen partial fixed prosthesis) the score was 0.5 (0 - 14). The differences in OHIP-14 scores were statistically significant (P < 0.001) between all groups [88]. Characteristics and outcomes

of studies including OLP are presented in Table 5A.

Bullous diseases

Nine articles (seven case reports, one case series and one retrospective study) were included [30,49,50,54,56,63,64,72,77]. A total of 24 patients (M/F ratio: 1/2) with bullous diseases and 149 implants were reported. One patient suffered from pemphigus vulgaris, and the remaining patients were affected by recessive dystrophic epidermolysis bullosa (RDEB). After a weighted mean follow-up of 64.9 months the implant survival rate was 98.7% (147/149) and 100% (11/11) on implant and patient level respectively. The suprastructure survival rate was 90.9% (20/22) on patient level and 94.4% (34/36) on suprastructure level. The weighted mean crestal bone loss was 1.42 mm and PI was diagnosed in 0% patients (0/5) and implants (0/28).
A study on thirteen patients with RDEB treated with 80 implants and 20 full-arch prosthesis reported a mean satisfaction score (VAS ranging from 0 to 10) with the received treatment of > 9 for all assessed parameters (comfort, self-esteem, aesthetics, phonation and mastication) except for hygiene with a score of 6 to 8 [72]. Characteristics and outcomes of studies including BDs are presented in Table 5B.

Other autoimmune diseases
Hypothyroidism

Six studies (three retrospective studies, two case reports and one case-control study) were included [4,36,65,67,76,89]. The studies comprised 52 hypothyroidism patients (M/F ratio: 0/23) with 225 implants. The implant survival rate was 83.3% (5/6) on patient and 93.3% (210/225) on implant level after a weighted mean follow-up of 52.2 months. Of the lost implants, 46.7% (7/15) were early losses. One study reported a late survival rate of 93.7% (104/111) implants in 25 hypothyroidism patients [4]. In another study, a patient with hypothyroidism and ulcerative colitis, treated with adalimumab, lost all five placed implants early. Pain, mobility, PI, and osteonecrosis were present at all implants. In addition, a submental abscess developed with extension into the submandibular space bilaterally [36]. Survival rate of suprastructures was 100% on patient (1/1) and suprastructure (2/2) level. PI was diagnosed in 40% (2/5) on patient level and 100% (5/5) on implant level. Success rate was 96.3% (79/82) on implant level. Characteristics and outcomes of studies including HT are presented in Table 4A.

Crohn's disease

Four studies (three retrospective studies and one case report) were included comprising a total of six Crohn's disease patients (M/F ratio: 1/0) with 44 implants [4,35,67,74]. After a weighted mean follow-up period of 17.7 months, the implant survival rate was 50% (2/4) on patient and 84.1% (37/44) on implant level. One case report reported survival of all implants [35], but the remaining studies reported loss of one to three implants [4,67,74]. Suprastructure survival was not reported. Characteristics and outcomes of studies including CD are presented in Table 4C.

DISCUSSION

The aim of this review was to disclose the effect of ADs and their medical treatment on the prognosis of dental implants. Overall, dental implant survival was documented to be high in patients with ADs. However, higher proportions of early implant loss were observed for certain ADs, which may indicate a compromised capacity of establishing osseointegration. All levels of clinical evidence were considered, and a total of 67 articles could be included characterized by a high risk of bias and a low quality. Therefore, the results should be interpreted with caution.
Several of the included studies report on cohorts with different ADs and/or co-existing ADs. Co-existing ADs obviously complicate the interpretation of results on how a specific AD affects dental implant survival. However, simultaneous presence of ADs is relatively common, and about 25% of patients with an AD are prone to develop an additional AD [91,92].
ADs predominantly affect females [93]. Therefore, as anticipated, most of the implant patients included in the studies were females.
In the various disease groups, most implant losses occurred early, ranging between 46.7 to 100% of the lost implants. Early implant loss is characterized by failure to establish osseointegration due to impaired bone healing [26]. In contrast to the findings of the present review, a large retrospective study on a broad unselected population, including more than 10,000 implants, reported an implant failure rate of 6.4% of which 27.4% were lost early [94]. It is presently unknown whether the relatively high rate of early implant loss among patients with ADs disclosed by the present review is related to the ADs and/or the immunosuppressive agents often taken by these groups of patients. One case report included

in this review reported early loss of all five placed implants and a severe infection in a patient with hypothyroidism and ulcerative colitis receiving adalimumab [36]. However, Chrcanovic et al. [94] did not find a significant correlation between early implant loss and immunosuppressive treatment and hypothyroidism.

The overall suprastructure survival rate for all disease groups (94.4 to 100%) was comparable to the one reported for the general population (96.4%) after five years follow-up [95]. Most disease groups fulfilled the success criteria regarding crestal bone loss [28]. In general, most disease groups reported PI rates similar to the one reported for the general population (20% and 10% on patient and implant level, respectively) after 5 to 10 years follow-up [96].

Autoimmune connective tissue diseases

The overall implant survival rate in patients with autoimmune CTDs (95.5 to 100%) was comparable to the one reported for the general population (97.2%) after five years follow-up [97]. However, a lower implant survival rate (87%) was reported in patients with SS in a prospective study [14]. In contrast to other studies with higher survival rates in patients with SS [12,13,98], the study included exclusively patients with secondary SS (seven patients with SS and RA and one patient with SS and systemic scleroderma) [14]. These findings indicate that the impaired implant survival rate may not entirely be related to SS itself, but potentially rather to the compromised oral health and healing processes caused by the additional CTDs [12,13,98].

In the present review, patients with RA had the highest crestal bone loss, and RA with concomitant ADs was the only group of patients that did not fulfil the implant success criteria regarding crestal bone loss [28]. Crestal bone loss is mainly caused by dental plaque-induced inflammation, which may be accentuated by an impaired blood flow due to endothelial dysfunction in patients with RA [99,100]. The increased crestal bone loss [71,84] may also be ascribed to the frequent treatment of RA patients with glucocorticoids. Thus, in the study by Krennmair et al. [71], 76.5% of the 34 patients were treated with glucocorticoids. Prolonged administration of glucocorticoids has an adverse effect on bone metabolism and may lead to reduction of bone mineral density and development of osteoporosis. Glucocorticoids reduce the number of osteoblasts because of apoptosis of mature osteoblasts and a depressed formation of osteoblast precursors. Glucocorticoids also affect osteoclasts reducing osteoclastogenesis and increasing the osteoclast lifespan. Ultimately, this leads to a sustained osteoclast quantity but a pronounced reduction in the number of osteoblasts and bone formation. Furthermore, an increased osteocyte apoptosis appears reducing vascular endothelial growth factor, skeletal angiogenesis, bone interstitial fluid and bone strength [101].

Autoimmune diseases with mucosal manifestations

In the present review, ADs with mucosal manifestations include OLP and bullous diseases. Studies on OLP generally had the highest quality of all included studies, with the lowest risk of bias. Nevertheless, they were still categorized as low to medium quality studies [6,25,41,52,68,69,80,82,85,86,88].

The implant survival rate on implant level was 82.6% for patients with OLP, and thus lower than that reported after five years follow-up in the general population (97.2%) [97]. Findings indicate that the reduced implant survival rate is related to impaired control of OLP and flare-up of the disease in relation to implant therapy. Accordingly, one study reported a low implant survival rate (13% and 23.6% on patient and implant level, respectively) in patients with acute flare-up of OLP [25]. Systemic treatment with glucocorticoids resulted in complete remission of OLP, and implant therapy was repeated and none of the newly placed implants were lost [25,86]. Most studies on OLP reported treatment with glucocorticoids [41,68,69,80,85,86,88] and some also reported implant placement during OLP remission [41,68,85,86]. These studies report a high implant survival rate between 98.5 to 100%, emphasizing the importance of implant placement in successfully treated OLP patients and in remission of the disease. The level of disease control appears to be of greater importance for implant survival than OLP itself [102], and may be of even more importance than the potential risk of using glucocorticoids. On the other hand, most often, OLP is treated with topical glucocorticoids as opposed to RA patients on systemic glucocorticoids and may thus be expected to have a less compromised bone metabolism. Based on clinical appearance, OLP can be classified into six types, i.e., the: ulcerative, erosive, bullous, reticular, papular, and plaque-like type. The first three types are usually symptomatic causing e.g., burning, itching sensation and pain [103]. Serval studies describe clinical challenges for OLP patients to tolerate conventional removable prostheses due to the fragile oral mucosa and associated pain [41,54,68,77,80,104].

The prevalence of PI in patients with OLP (25.4%) is relatively high within a shorter follow-up period compared to the general implant population (10%) [96]. However, the high prevalence of PI was mainly based on one study that also reported high prevalence in the control group [88]. Therefore, patients with OLP may be strong candidates for dental implant therapy, provided the OLP is well treated and that patients are enrolled in a strict maintenance program.

The implant survival rate in patients with bullous diseases (98.7%) is comparable to the general population (97.2%) after five years follow-up [97]. Epidermolysis bullosa (EB) is characterized by mechanical fragility of the skin and mucosa with formation of painful erosions, blisters, and ulcerations often caused by minor trauma. Additional oral manifestations of EB include microstomia, ankyloglossia, and caries compromising food intake and swallowing [105,106]. Use of removable dental prostheses in patients with EB is challenging, especially because of microstomia and the formation of mucosal blisters due to friction between mucosa and the prostheses [54,77,104]. Implant-supported oral rehabilitation may therefore be highly beneficial for patients with EB as a sufficient masticatory function decreases the risk of oral and esophageal soft tissue injury and therefore scar formation. This reduces progression of esophageal strictures, dysphagia, and the risk of malnutrition [105,107,108]. Patient satisfaction scores after implant treatment in patients with RDEB were high for almost all parameters, except for oral hygiene [72]. This is consistent with the literature reporting limitations regarding oral hygiene procedures in EB patients due to pseudosyndactyly, microstomia, ankyloglossia, and blistering of oral mucosa and on hands [77,109,110].

Other autoimmune diseases

In the group with other ADs, the implant survival rate (50 to 100%) was markedly reduced for all diseases, except for hypothyroidism (93.3%) and dermatomyositis (100%) compared to the general population (97.2%) after five years follow-up [97]. The studies comprised a limited number of patients and implants, and even small variations had a marked impact on the overall results.

Prosthetic treatment

Problems regarding conventional removable dentures have also been described for CTDs and particularly for patients with SS and systemic scleroderma. SS patients have sensitive and dry mucosa causing pain and functional complications [14,87]. Systemic scleroderma patients have microstomia and sclerodactyly [12,13,111] compromising oral hygiene and the former making patients unable to use removable dentures [42,47,55,59,62,104]. Due to oral manifestations implant-supported fixed rehabilitation can be highly beneficial for OLP, RDEB, SS and systemic scleroderma patients relative to conventional removable dentures reducing mucosal load and for the first three mentioned diseases positively influencing patients' quality of life [14,72,88,104]. For systemic scleroderma patients it is conceivable that implant-supported fixed rehabilitation will positively effect patients' quality of life. The quality of life and functional benefits attained from implant-supported rehabilitation may outweigh the risks related to implant therapy [102] and a slightly reduced implant survival rate may therefore be acceptable in selected groups of patients.

When treating patients of ADs, it is important as a clinician to consider the chronic nature of the diseases. ADs progress [112] and for that reason when making a treatment plan it is equally important to treat the present dental problems as well as considering long-term consequences of the disease, such as dental decay and microstomia. In some cases, it may therefore be relevant with a more radical treatment strategy.

Successful cementless total knee arthroplasties rely today also on osseointegration similar to dental implants [113]. Retrospective studies on cementless total knee arthroplasties in RA patients report similar survival rates of 97 to 99% as for dental implants documented by the present systematic review [114,115].

Limitations

The current review comprises several limitations: Only articles published in English were included and gray literature was not sought. However, taken this into consideration the authors estimate that the risk of missing important data is low and without major impact on the overall results.

The literature search, screening and selection process revealed that studies in the field of dental implant therapy in patients with ADs, mainly comprise case reports and retrospective studies. Additionally, it revealed a lack of high-quality prospective studies with large patient cohorts and long-term follow-up. Accordingly, the results in the various groups of patients with ADs should be interpreted with caution.

Furthermore, systematic long-term documentation of implant therapy in patients with ADs is highly encouraged.

In addition, one author extracted data from included articles. Most of the examined parameters were heterogeneous reported and some barely reported (e.g., suppuration, width of keratinized mucosa, recession, and aesthetic outcome). Success criteria were inconsistently reported using different criteria. Also, it was not possible to determine the implant survival relative to administration of immunosuppressants, due to heterogeneous reporting of included studies. Meta-analysis of included studies could not be performed due to heterogeneous study designs, treatments, and reporting.

In general, due to low quantity of available data, for each individual disease group, small variations in the data set often resulted in a big impact on the overall results. This is in most disease groups represented through differences in implant survival rate on patient and implant level. The implant survival rate is frequently lower on patient level due to the occurrence of a small cohort of patients, treated with a high number of implants.

CONCLUSIONS

Within the limitations of the present systematic review, dental implant therapy can be considered feasible in patients with autoimmune diseases. Overall, the review discloses a high implant survival rate in patients with autoimmune diseases, many of which receiving immunosuppressive therapy, after mid-term follow-up. Implant success rates were inconsistently reported using a variety of criteria. Outcomes after implant placement in patients on immunosuppressive therapy could rarely be related to the individual types of medication. In general, the level of evidence was low with a high risk of bias. Therefore, systematic long-term documentation of implant therapy in patients with autoimmune diseases is encouraged.

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All authors declare no conflicts of interest related to this study.

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Appendix 1. Search history

Databases	Interfaces	Results	Dates
Embase	ovidsp.ovid.com	2,715	6th December 2021
MEDLINE (PubMed)	pubmed.ncbi.nlm.nih.gov	1,968	6th December 2021
The Cochrane Library	cochranelibrary.com	157	6th December 2021
Total	-	4,865	-
After duplicate-removal	-	3,535	-

Appendix 2A. Search strategy for Embase until 6th December 2021

Search	Query	Items found
#1	exp tooth implant/	16,680
#2	exp tooth implantation/	27,627
#3	exp osseointegration/	3,862
#4	exp periimplantitis/	2,052
#5	(dental implant* or implant dentistry or dental implant therapy or dental implantation or implantology or periimplantitis or peri-implantitis or peri-implant infection or periimplant infection or peri-implant disease or osseointegration).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	31,394
#6	1 or 2 or 3 or 4 or 5	50,242
#7	exp autoimmune disease/	688,956
#8	exp autoimmunity/	72,878
#9	exp systemic sclerosis/	33,294
#10	exp vasculitis/	123,335
#11	exp mixed connective tissue disease/	4,035
#12	exp polymyositis/	9,068
#13	exp dermatomyositis/	17,141
#14	exp ulcerative colitis/	82,110
#15	exp multiple sclerosis/	142,712
#16	exp rheumatic fever/	7,864
#17	exp reactive arthritis/	3,736
#18	exp Hashimoto disease/	14,160
#19	exp vitiligo/	13,727
#20	exp alopecia areata/	7,038
#21	exp Crohn disease/	100,788
#22	exp celiac disease/	33,591
#23	exp pernicious anemia/	4,290
#24	exp lichen planus/	12,629
#25	exp epidermolysis bullosa/	8,703
#26	exp mucous membrane pemphigoid/	2,248
#27	exp erythema multiforme/	15,523
#28	exp Behcet disease/	16,559
#29	(autoimmune disease* or autoimmunity or systemic disease* or systemic condition* or neonatal systemic lupus erythematosus or neonatal lupus syndrome or neonatal lupus or systemic lupus erythematosus or rheumatoid arthritis or systemic scleroderma or systemic sclerosis or vasculitis or granulomatosis with polyangiitis or wegener s granulomatosis or wegener granulomatosis or mixed connective tissue disease or antiphospholipid syndrome or polymyositis or dermatomyositis or sjogren s syndrome or sjogren syndrome or addison disease or myasthenia gravis or graves* disease or ulcerative colitis or colitis ulcerosa or multiple sclerosis or hemolytic anemia or rheumatic fever or reactive arthritis or dermatomyositis or hashimoto disease or hashimoto thyroiditis or vitiligo or alopecia areata or crohn* disease or diabetes mellitus type 1 or type 1 diabetes or diabetes mellitus type I or type I diabetes or celiac disease or coeliac disease or pernicious anemia or lichen planus or oral lichen planus or epidermolysis bullosa* or pemphigus or pemphigus vulgaris or pemphigus vegetans or pemphigoid or mucous membrane pemphigoid or benign mucous membrane pemphigoid or linear IgA disease or linear IgA bullous disease or linear IgA bullous dermatosis or bullous pemphigoid or dermatitis herpetiformis or erythema multiforme or behcet s disease or behcet disease or behcet s syndrom or behcet syndrom).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,194,114
#30	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29	1,362,155
#31	exp antirheumatic agent/	948,480
#32	exp immunosuppressive agent/	1,159,741
#33	exp biosimilar agent/	5,768
#34	exp biological control agent/	3,117
#35	exp biological factor/	3,112,963

Appendix 2B. Search strategy for Embase until 6th December 2021

Search	Query	Items found
#36	exp biological product/	769,484
#37	exp antimetabolite/	646,897
#38	exp immunocompromised patient/	22,322
#39	exp glucocorticoid/	782,787
#40	exp prednisolone/	136,731
#41	exp prednisone/	185,595
#42	exp betamethasone/	18,234
#43	exp hydrocortisone/	133,836
#44	exp dexamethasone/	168,961
#45	exp methylprednisolone/	108,608
#46	exp triamcinolone/	15,553
#47	exp triamcinolone acetonide/	15,801
#48	exp cytostatic agent/	9,376
#49	exp methotrexate/	193,714
#50	exp cyclophosphamide/	233,203
#51	exp azathioprine/	100,742
#52	exp cyclosporin derivative/	1,985
#53	exp cyclosporine/	21,992
#54	exp mycophenolic acid/	21,344
#55	exp rituximab/	94,656
#56	exp Janus kinase inhibitor/	22,087
#57	exp salazosulfapyridine/	27,606
#58	exp antimalarial agent/	158,478
#59	exp hydroxychloroquine/	38,378
#60	exp chloroquine/	41,330
#61	exp leflunomide/	13,592
#62	exp tumor necrosis factor inhibitor/	107,173
#63	exp adalimumab/	39,695
#64	exp ustekinumab/	9,673
#65	exp omalizumab/	9,749
#66	exp infliximab/	57,075
#67	exp etanercept/	34,838
#68	exp certolizumab pegol/	8,058
#69	exp interleukin 1 receptor blocking agent/	14,930
#70	exp abatacept/	10,920
#71	(antirheumatic agent* or immunosuppressive agent* or biosimilar pharmaceutical* or biological control agent* or biological factor* or biological product* or antimetabolite* or medically compromised patient* or immunocompromised host* or immunocompromised patient* or glucocorticoid* or cytostatic agent* or triamcinolone hexacetonide or baricitinib or upadacitinib or tofacitinib or golimumab or anakinra or tocilizumab or secukinumab or belimumab or guselkumab or ixekizumab or brodalumab or tildrakizumab or secukinumab or costimulation modulator or co-stimulation modulator or interleukin 1 antagonist* or interleukin 1 inhibitor* or interleukin 6 antagonist* or interleukin 6 inhibitor* or interleukin 17 antagonist* or interleukin 17 inhibitor* or interleukin 12 antagonist* or interleukin 12 inhibitor* or interleukin 23 antagonist* or interleukin 23 inhibitor*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	413,368
#72	((CD20 or CD-20) and (immunoglobulin or antibody)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	24,342
#73	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	5,454,806
#74	6 and 30	589
#75	6 and 73	3,364
#76	74 or 75	3,820
#77	limit 76 to english	3,654
#78	exp animal/	28,033,905
#79	exp human/	23,179,392
#80	78 not 79	4,854,513
#81	77 not 80	2,715

Appendix 3. Search strategy for MEDLINE (PubMed) until 6th December 2021

Search	Query	Items found
#1	((((((((((((((dental implant*[MeSH Terms]) OR (dental implantation, endosseous[MeSH Terms])) OR (osseointegration[MeSH Terms])) OR (peri-implantitis[MeSH Terms])) OR (dental implant*[Text Word])) OR (implant dentistry[Text Word])) OR (dental implant therapy[Text Word])) OR (dental implantation[Text Word])) OR (implantology[Text Word])) OR (periimplantitis[Text Word])) OR (peri-implantitis[Text Word])) OR (peri-implant infection[Text Word])) OR (periimplant infection[Text Word])) OR (peri-implant disease[Text Word])) OR (osseointegration [Text Word])	52,570
#2	((autoimmune diseases*[MeSH Terms]) OR (autoimmunity[MeSH Terms])) OR (scleroderma, systemic[MeSH Terms])) OR (vasculitis[MeSH Terms])) OR (mixed connective tissue disease[MeSH Terms])) OR (polymyositis[MeSH Terms])) OR (dermatomyositis[MeSH Terms])) OR (colitis, ulcerative[MeSH Terms])) OR (multiple sclerosis[MeSH Terms])) OR (rheumatic fever[MeSH Terms])) OR (arthritis, reactive[MeSH Terms])) OR (hashimoto disease[MeSH Terms])) OR (vitiligo[MeSH Terms])) OR (alopecia areata[MeSH Terms])) OR (crohn disease[MeSH Terms])) OR (celiac disease[MeSH Terms])) OR (anemia, pernicious[MeSH Terms])) OR (lichen planus[MeSH Terms])) OR (lichen planus, oral[MeSH Terms])) OR (epidermolysis bullosa[MeSH Terms])) OR (pemphigoid, benign mucous membrane[MeSH Terms])) OR (erythema multiforme[MeSH Terms])) OR (behcet syndrome[MeSH Terms])) OR (autoimmune disease*[Text Word])) OR (autoimmunity[Text Word])) OR (systemic disease*[Text Word])) OR (systemic condition*[Text Word])) OR (neonatal systemic lupus erythematosus[Text Word])) OR (neonatal lupus syndrome[Text Word])) OR (neonatal lupus[Text Word])) OR (systemic lupus erythematosus[Text Word])) OR (rheumatoid arthritis[Text Word])) OR (systemic scleroderma[Text Word])) OR (systemic sclerosis[Text Word])) OR (vasculitis[Text Word])) OR (granulomatosis with polyangiitis[Text Word])) OR (wegener's granulomatosis[Text Word])) OR (wegener granulomatosis[Text Word])) OR (mixed connective tissue disease[Text Word])) OR (antiphospholipid syndrome[Text Word])) OR (polymyositis[Text Word])) OR (dermatomyositis[Text Word])) OR (sjögren's syndrome[Text Word])) OR (sjögren syndrome[Text Word])) OR (sjogren's syndrome[Text Word])) OR (sjogren syndrome[Text Word])) OR (addison disease[Text Word])) OR (myasthenia gravis[Text Word])) OR (graves* disease[Text Word])) OR (ulcerative colitis[Text Word])) OR (colitis ulcerosa[Text Word])) OR (multiple sclerosis[Text Word])) OR (hemolytic anemia[Text Word])) OR (rheumatic fever[Text Word])) OR (reactive arthritis[Text Word])) OR (dermatomyositis[Text Word])) OR (hashimoto disease[Text Word])) OR (hashimoto thyroiditis[Text Word])) OR (vitiligo[Text Word])) OR (alopecia areata[Text Word])) OR (crohn* disease[Text Word])) OR (diabetes mellitus type 1[Text Word])) OR (type 1 diabetes[Text Word])) OR diabetes mellitus type I[Text Word])) OR (type I diabetes[Text Word])) OR (celiac disease[Text Word])) OR (coeliac disease[Text Word])) OR (pernicious anemia[Text Word])) OR (lichen planus[Text Word])) OR (oral lichen planus[Text Word])) OR (epidermolysis bullosa*[Text Word])) OR (pemphigus[Text Word])) OR (pemphigus vulgaris[Text Word])) OR (pemphigus vegetans[Text Word])) OR (pemphigoid[Text Word])) OR (mucous membrane pemphigoid[Text Word])) OR (benign mucous membrane pemphigoid[Text Word])) OR (linear IgA disease[Text Word])) OR (linear IgA bullous disease[Text Word])) OR (linear IgA bullous dermatosis[Text Word])) OR (bullous pemphigoid[Text Word])) OR (dermatitis herpetiformis[Text Word])) OR (erythema multiforme[Text Word])) OR (behcet's disease [Text Word]) OR (behcet disease [Text Word])) OR (behcet's syndrom[Text Word])) OR (behcet syndrom[Text Word])	958,367
#3	((antirheumatic agents[MeSH Terms]) OR (immunosuppressive agents[MeSH Terms])) OR (biosimilar pharmaceuticals[MeSH Terms])) OR (biological control agents[MeSH Terms])) OR (biological factors[MeSH Terms])) OR (biological products[MeSH Terms])) OR (antimetabolites[MeSH Terms])) OR (immunocompromised host*[MeSH Terms])) OR (glucocorticoids[MeSH Terms])) OR (prednisolone[MeSH Terms])) OR (prednisone[MeSH Terms])) OR (betamethasone[MeSH Terms])) OR (hydrocortisone[MeSH Terms])) OR (dexamethasone[MeSH Terms])) OR (methylprednisolone[MeSH Terms])) OR (triamcinolone[MeSH Terms])) OR (triamcinolone acetonide[MeSH Terms])) OR (cytostatic agents[MeSH Terms])) OR (methotrexate[MeSH Terms])) OR (cyclophosphamide[MeSH Terms])) OR (azathioprine[MeSH Terms])) OR (cyclosporins[MeSH Terms])) OR (cyclosporine[MeSH Terms])) OR (mycophenolic acid[MeSH Terms])) OR (rituximab[MeSH Terms])) OR (janus kinase inhibitors[MeSH Terms])) OR (sulfasalazine[MeSH Terms])) OR (antimalarials[MeSH Terms])) OR (hydroxychloroquine[MeSH Terms])) OR (chloroquine[MeSH Terms])) OR (leflunomide[MeSH Terms])) OR (tumor necrosis factor inhibitors[MeSH Terms])) OR (adalimumab[MeSH Terms])) OR (ustekinumab[MeSH Terms])) OR (omalizumab[MeSH Terms])) OR (infliximab[MeSH Terms])) OR (etanercept[MeSH Terms])) OR (certolizumab pegol[MeSH Terms])) OR (interleukin 1 receptor antagonist protein[MeSH Terms])) OR (interleukin 1/antagonists and inhibitors[MeSH Terms])) OR (interleukin 6/antagonists and inhibitors[MeSH Terms])) OR (receptors, interleukin 17/antagonists and inhibitors[MeSH Terms])) OR (interleukin 12/antagonists and inhibitors[MeSH Terms])) OR (interleukin 23/antagonists and inhibitors[MeSH Terms])) OR (abatacept[MeSH Terms])) OR (antirheumatic agent*[Text Word])) OR (immunosuppressive agent*[Text Word])) OR (biosimilar pharmaceutical*[Text Word])) OR (biological control agent*[Text Word])) OR (biological factor*[Text Word])) OR (biological product*[Text Word])) OR (antimetabolite*[Text Word])) OR (medically compromised patient*[Text Word])) OR (immunocompromised host*[Text Word])) OR (immunocompromised patient*[Text Word])) OR (glucocorticoid*[Text Word])) OR (cytostatic agent*[Text Word])) OR (triamcinolone hexacetonide[Text Word])) OR (baricitinib[Text Word])) OR (upadacitinib[Text Word])) OR (tofacitinib[Text Word])) OR (golimumab[Text Word])) OR (anakinra[Text Word])) OR (tocilizumab[Text Word])) OR (secukinumab[Text Word])) OR (belimumab[Text Word])) OR (guselkumab[Text Word])) OR (ixekizumab[Text Word])) OR (brodalumab[Text Word])) OR (tildrakizumab[Text Word])) OR (secukinumab[Text Word])) OR (costimulation modulator[Text Word])) OR (co-stimulation modulator[Text Word]) OR ((CD20[Text Word] OR CD-20[Text Word]) AND (immunoglobulin[Text Word] OR antibody[Text Word]))	4,535,782
#4	#1 AND #2	438
#5	#1 AND #3	2,568
#6	#4 OR #5	2,955
#7	#4 OR #5 Filters: English	2,809
#8	#7 NOT ("animals"[MeSH] NOT "humans"[MeSH]) Filters: English	1,968

Appendix 4A. Search strategy for The Cochrane Library until 6th December 2021

Search	Query	Items found
#1	MeSH descriptor: [Dental Implants] 4 tree(s) exploded	1,830
#2	MeSH descriptor: [Dental Implantation, Endosseous] explode all trees	1,445
#3	MeSH descriptor: [Osseointegration] explode all trees	420
#4	MeSH descriptor: [Peri-Implantitis] explode all trees	238
#5	“dental implant*” OR “implant dentistry” OR “dental implant therapy” OR “dental implantation” OR “implantology” OR “periimplantitis” OR “peri-implantitis” OR “peri- implant infection” OR “periimplant infection” OR “peri-implant disease” OR “osseointegration”	3,399
#6	#1 OR #2 OR #3 OR #4 OR #5	3,763
#7	MeSH descriptor: [Autoimmune Diseases] explode all trees	23,336
#8	MeSH descriptor: [Autoimmunity] explode all trees	166
#9	MeSH descriptor: [Scleroderma, Systemic] explode all trees	676
#10	MeSH descriptor: [Vasculitis] explode all trees	2,411
#11	MeSH descriptor: [Mixed Connective Tissue Disease] explode all trees	13
#12	MeSH descriptor: [Polymyositis] explode all trees	133
#13	MeSH descriptor: [Dermatomyositis] explode all trees	125
#14	MeSH descriptor: [Colitis, Ulcerative] explode all trees	1,866
#15	MeSH descriptor: [Multiple Sclerosis] explode all trees	5,499
#16	MeSH descriptor: [Rheumatic Fever] explode all trees	248
#17	MeSH descriptor: [Arthritis, Reactive] explode all trees	45
#18	MeSH descriptor: [Hashimoto Disease] explode all trees	86
#19	MeSH descriptor: [Vitiligo] explode all trees	434
#20	MeSH descriptor: [Alopecia Areata] explode all trees	334
#21	MeSH descriptor: [Crohn Disease] explode all trees	2,387
#22	MeSH descriptor: [Celiac Disease] explode all trees	472
#23	MeSH descriptor: [Anemia, Pernicious] explode all trees	19
#24	MeSH descriptor: [Lichen Planus] explode all trees	296
#25	MeSH descriptor: [Lichen Planus, Oral] explode all trees	202
#26	MeSH descriptor: [Epidermolysis Bullosa] explode all trees	67
#27	MeSH descriptor: [Pemphigoid, Benign Mucous Membrane] explode all trees	10
#28	MeSH descriptor: [Erythema Multiforme] explode all trees	52
#29	MeSH descriptor: [Behcet Syndrome] explode all trees	141
#30	“autoimmune disease*” OR “autoimmunity” OR “systemic disease*” OR “systemic condition*” OR “neonatal systemic lupus erythematosus” OR “neonatal lupus syndrome” OR “neonatal lupus” OR “systemic lupus erythematosus” OR “rheumatoid arthritis” OR “systemic scleroderma” OR “systemic sclerosis” OR “vasculitis” OR “granulomatosis with polyangiitis” OR “wegener s granulomatosis” OR “wegener granulomatosis” OR “mixed connective tissue disease” OR “antiphospholipid syndrome” OR “polymyositis” OR “dermatomyositis” OR “sjögren s syndrome” OR “sjögren syndrome” OR “sjogren s syndrome” OR “sjogren syndrome” OR “addison disease” OR “myasthenia gravis” OR ”graves* disease” OR ”ulcerative colitis” OR ”colitis ulcerosa” OR ”multiple sclerosis” OR ”hemolytic anemia” OR “rheumatic fever” OR ”reactive arthritis” OR ”dermatomyositis” OR ”hashimoto disease” OR ”hashimoto thyroiditis” OR ”vitiligo” OR ”alopecia areata” OR ”crohn* disease” OR ”diabetes mellitus type 1” OR ”type 1 diabetes” OR ”diabetes mellitus type I” OR ”type I diabetes” OR ”celiac disease” OR ”coeliac disease” OR ”pernicious anemia” OR ”lichen planus” OR ”oral lichen planus” OR ”epidermolysis bullosa*” OR ”pemphigus” OR ”pemphigus vulgaris” OR ”pemphigus vegetans” OR ”pemphigoid” OR ”mucous membrane pemphigoid” OR ”benign mucous membrane pemphigoid” OR ”linear IgA disease” OR ”linear IgA bullous disease” OR ”linear IgA bullous dermatosis” OR ”bullous pemphigoid” OR ”dermatitis herpetiformis” OR ”erythema multiforme” OR ”behcet s disease” OR ”behcet disease” OR “behcet s syndrom” OR ”behcet syndrom”	61,758
#31	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	66,207
#32	MeSH descriptor: [Antirheumatic Agents] explode all trees	11,498
#33	MeSH descriptor: [Immunosuppressive Agents] explode all trees	6,007
#34	MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees	287
#35	MeSH descriptor: [Biological Control Agents] explode all trees	3
#36	MeSH descriptor: [Biological Factors] explode all trees	96,760
#37	MeSH descriptor: [Biological Products] explode all trees	32,036
#38	MeSH descriptor: [Antimetabolites] explode all trees	9,480
#39	MeSH descriptor: [Immunocompromised Host] explode all trees	310
#40	MeSH descriptor: [Glucocorticoids] explode all trees	5,169

Appendix 4B. Search strategy for The Cochrane Library until 6th December 2021

Search	Query	Items found
#41	MeSH descriptor: [Prednisolone] explode all trees	5,334
#42	MeSH descriptor: [Prednisone] explode all trees	4,358
#43	MeSH descriptor: [Betamethasone] explode all trees	1,578
#44	MeSH descriptor: [Hydrocortisone] explode all trees	6,546
#45	MeSH descriptor: [Dexamethasone] explode all trees	5,200
#46	MeSH descriptor: [Methylprednisolone] explode all trees	2,967
#47	MeSH descriptor: [Triamcinolone] explode all trees	1,530
#48	MeSH descriptor: [Triamcinolone Acetonide] explode all trees	1,203
#49	MeSH descriptor: [Cytostatic Agents] explode all trees	5
#50	MeSH descriptor: [Methotrexate] explode all trees	4,623
#51	MeSH descriptor: [Cyclophosphamide] explode all trees	5,998
#52	MeSH descriptor: [Azathioprine] explode all trees	1,315
#53	MeSH descriptor: [Cyclosporins] explode all trees	3,413
#54	MeSH descriptor: [Mycophenolic Acid] explode all trees	1,525
#55	MeSH descriptor: [Rituximab] explode all trees	1,587
#56	MeSH descriptor: [Janus Kinase Inhibitors] explode all trees	102
#57	MeSH descriptor: [Sulfasalazine] explode all trees	522
#58	MeSH descriptor: [Antimalarials] explode all trees	1,953
#59	MeSH descriptor: [Hydroxychloroquine] explode all trees	674
#60	MeSH descriptor: [Chloroquine] explode all trees	1,411
#61	MeSH descriptor: [Leflunomide] explode all trees	187
#62	MeSH descriptor: [Tumor Necrosis Factor Inhibitors] explode all trees	92
#63	MeSH descriptor: [Adalimumab] explode all trees	911
#64	MeSH descriptor: [Ustekinumab] explode all trees	265
#65	MeSH descriptor: [Omalizumab] explode all trees	322
#66	MeSH descriptor: [Infliximab] explode all trees	905
#67	MeSH descriptor: [Etanercept] explode all trees	896
#68	MeSH descriptor: [Certolizumab Pegol] explode all trees	194
#69	MeSH descriptor: [Interleukin 1 Receptor Antagonist Protein] explode all trees	371
#70	MeSH descriptor: [Interleukin-1] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]	86
#71	MeSH descriptor: [Interleukin-6] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]	61
#72	MeSH descriptor: [Interleukin-17] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]	66
#73	MeSH descriptor: [Interleukin-12] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]	22
#74	MeSH descriptor: [Interleukin-23] explode all trees and with qualifier(s): [antagonists & inhibitors - AI]	54
#75	MeSH descriptor: [Abatacept] explode all trees	334
#76	“antirheumatic agent*“ OR “immunosuppressive agent*“ OR “biosimilar pharmaceutical*“ OR “biological control agent*“ OR “biological factor*“ OR “biological product*“ OR “antimetabolite*“ OR “medically compromised patient*“ OR “immunocompromised host*“ OR “immunocompromised patient*“ OR “glucocorticoid*“ OR “cytostatic agent*“ OR “triamcinolone hexacetonide“ OR “baricitinib“ OR “upadacitinib“ OR “tofacitinib“ OR “golimumab“ OR “anakinra“ OR “tocilizumab” OR “secukinumab“ OR “belimumab“ OR “guselkumab“ OR “ixekizumab“ OR “brodalumab“ OR “tildrakizumab“ OR “secukinumab“ OR “costimulation modulator“ OR “co stimulation modulator“	12,929
#77	(”CD20” OR ”CD-20”) AND (”immunoglobulin” OR ”antibody”)	901
#78	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77	181,015
#79	#6 AND #31	34
#80	#6 AND #78	127
#81	#80 OR #81	157

Appendix 5. List of excluded studies subsequent to full text screening

Insufficient information on classification of autoimmune disease	Topic not relevant	Due to study type	No survival rate stated	Same cohort with shorter follow-up	Could not be retrieved
Fiorellini et al. 2000	Gornitsky et al. 2005	Brignardello-Petersen 1939	Cranin 1991	Binon et al. 1993	Portela Tejedor 2012
Sullivan et al. 2001	Balshi et al. 2007	Steiner et al. 1990	Smith et al. 1992	Peñarrocha-Diago et al. 2000	Kato et al. 2016
Ko et al. 2006	Vallecillo Capilla et al. 2007	Garg 1992	Esposito et al. 2000	Peñarrocha et al. 2007	Sannino et al. 2020
Alsaadi et al. 2007	Tischler 2008	Attard 2001	Chimenos Küstner et al. 2003	Peñarrocha et al. 2007	-
Maximo et al. 2008	Hall et al. 2011	Weber et al. 2008	Renvert et al. 2012	Weinlander et al. 2010	-
Lee et al. 2010	Eriksson et al. 2016	Carr 2010	Renvert et al. 2014	Penocha-Oltra et al. 2011	-
Dirschnabel et al. 2011	Kumari et al. 2016	Garg 2010	Yoon et al. 2015	Pearrocha-Oltra et al. 2012	-
Lee et al. 2011	Albrecht et al. 2016	Westhoff et al. 2012	Ardila et al. 2016	Agustín-Panadero et al. 2015	-
Urdaneta et al. 2011	Schlund et al. 2017	Medina 2016	Carr et al. 2017	Agustín-Panadero et al. 2017	-
Morales-Vadillo et al. 2013	Markose et al. 2018	Chatzinikolaou et al. 2017	Dutt et al. 2018	-	-
de Araujo Nobre et al. 2014	Di Murro et al. 2019	Cuifen et al. 2017	Shimoda et al. 2018	-	-
Brugger et al. 2015	Papi et al. 2019	Kaabi et al. 2017	Carr et al. 2019	-	-
Ferreira et al. 2015	Granato et al. 2020	Chatzinikolaou et al. 2018	Takahama et al. 2019	-	
French et al. 2015	Kagan et al. 2020	Bombeccari et al. 2019	Ursomanno et al. 2021	-	-
Olmedo-Gaya et al. 2016	Van Doorne et al. 2020	Brignardello-Petersen 2019	-	-	-
Borba et al. 2017	Wychowanski et al. 2020	Ursomanno et al. 2019	-	-	-
Choi et al. 2017	De Angelis et al. 2021	Richards et al. 2020	-	-	-
Dalago et al. 2017	Goel et al. 2021	Kramer 2020	-	-	-
de Araujo Nobre et al. 2017	-	-	-	-	-
Gurgel et al. 2017	-	-	-	-	-
Lee et al. 2017	-	-	-	-	-
Manor et al. 2017	-	-	-	-	-
Pedro et al. 2017	-	-	-	-	-
Manor et al. 2017	-	-	-	-	-
Pedro et al. 2017	-	-	-	-	-
Chatzopoulos et al. 2018	-	-	-	-	-
Jafar 2018	-	-	-	-	-
Kim et al. 2018	-	-	-	-	-
Neves et al. 2018	-	-	-	-	-
Okamoto et al. 2018	-	-	-	-	-
French et al. 2019	-	-	-	-	-
Malo et al. 2019	-	-	-	-	-
Nguyen et al. 2019	-	-	-	-	-
Rom et al. 2019	-	-	-	-	-
Clauser et al. 2020	-	-	-	-	-
Daneshparvar et al. 2020	-	-	-	-	-
Jagadeesh et al. 2020	-	-	-	-	-
Mameno et al. 2020	-	-	-	-	-
Marchio et al. 2020	-	-	-	-	-
Parihar et al. 2020	-	-	-	-	-
Silva et al. 2020	-	-	-	-	-
Soh et al. 2020	-	-	-	-	-
Staedt et al. 2020	-	-	-	-	-
Al-Hindi et al. 2021	-	-	-	-	-
Ewers et al. 2021	-	-	-	-	-
Malm et al. 2021	-	-	-	-	-
Molinero-Mourelle et al. 2021	-	-	-	-	-
Sultana et al. 2021	-	-	-	-	-
Velasco-Ortega et al. 2021	-	-	-	-	-