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Dental Implant Therapy in Patients With Autoimmune Diseases: A Scoping Review

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ABSTRACT

Objectives: The aim of this scoping review is to determine the effects of autoimmune diseases (ADs) and the agents used for treatment on dental implant survival and biologic outcomes.

Material and Methods: An electronic database search was performed in MEDLINE (PubMed), The Cochrane Library, and Embase on 29-04-2024. Clinical studies in English on implant therapy in patients with ADs were potentially eligible. Recorded variables included study information, patient demographics, ADs, immunosuppressants, antiresorptives, dental implant survival rate, biologic complications, and oral health-related quality of life. Descriptive statistics were performed.

Results: A total of 6319 records were retrieved through database search and hand search, of which 87 studies could be included with an overweight of case reports and retrospective studies. The available evidence was characterized by a high number of studies placed low on the hierarchy of evidence. Several outcome parameters were heterogeneously reported. Glucocorticoids were the most frequently administrated immunosuppressant. The implant survival rate was overall 85.3%–100%; hereof, 46.7%–100% of implant losses occurred early, indicating a certain risk of implant failure. Despite high implant survival in oral lichen planus (OLP) patients, one study lost 42 of 55 implants in patients with untreated flare-up of OLP.

Conclusions: Dental implant treatment is generally predictable with a high implant survival rate, after mid-term follow-up, in patients with ADs, of whom many receive immunosuppressants. Implant losses occurred predominantly before prosthetic loading. Particularly, patients with mucosal manifestations of their ADs seem to benefit from implant-supported restorations provided mucosal lesions are well treated. However, overall low-level scientific evidence was available.

1 | Introduction

With the demographic shift towards an aging population, the number of years lived with disabilities has also increased,

influencing health-care expenditure (Salomon et al. 2012). As a result of numerous studies involving systemically healthy patients reporting high, long-term dental implant survival rates exceeding 95% after 5–10 years of follow-up (Buser et al. 2012;

Abbreviations: ADs, autoimmune diseases; AR, antiresorptive medication; CTDs, connective tissue diseases; DMARDs, disease-modifying antirheumatic drugs; EB, recessive dystrophic epidermolysis bullosa; MRONJ, medication-related osteonecrosis of the jaw; OHIP-14, oral health impact profile-14; OHRQoL, oral health-related quality of life; OLP, oral lichen planus; PCC, population, concept and context; PRISMA-ScR, preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews; RA, rheumatoid arthritis; SS, Sjögren's syndrome; κ , Cohen's kappa.

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Hjalmarsson et al. 2016; Jung et al. 2012; Kern et al. 2016), the range of indications for dental implant therapy has increased over time. This involves patients with systemic diseases and some potentially immunocompromised as a consequence of for example, an autoimmune disease (AD) and/or immunosuppressive therapy (Alsaadi et al. 2008b; Maarse et al. 2022; Mozzati et al. 2021; Petsinis et al. 2017). Several of these systemic diseases have been reported as risk factors or contraindications for the placement of dental implants; however, with varying degrees of evidence (Alsaadi et al. 2008a; Bornstein et al. 2009; Diz et al. 2013; Isidor et al. 1999).

ADs occur as a result of immune dysregulation failing to distinguish pathogens from self-antigens damaging host tissue (Gutierrez-Arcelus et al. 2016). Depending on the tissues and organs involved, ADs are often clinically classified as either systemic/connective tissue diseases (CTDs) (e.g., Sjögren's syndrome [SS]) or organ-specific (e.g., mucous membrane pemphigoid) (Davidson and Diamond 2001). ADs typically arise from a combination of environmental factors and a genetic predisposition. Infection appears as a common trigger for AD, yet the microbiota can also impact their development (Conrad et al. 2023; Gutierrez-Arcelus et al. 2016; Pisetsky 2023). More than 80 diseases have been identified as having an autoimmune origin, with more than half of them classified as rare (Hayter and Cook 2012). The prevalence of ADs is estimated to be 10% of the population and higher among females. In addition, the incidence of numerous ADs is increasing (Conrad et al. 2023).

ADs may exhibit several oral manifestations including erythema, erosions, blisters, ulcerations, caries, periodontal disease, xerostomia, hyposalivation, candidiasis, and limited mouth opening (Baglama et al. 2018; Mustafa et al. 2015). Many of these manifestations potentially interfere with oral rehabilitation, particularly when mucosa-supported removable dental prostheses are involved (Isidor et al. 1999).

ADs typically exhibit interchanging exacerbations and remissions, and the latter may be attained using immunosuppressants. The current focus of AD treatment is either an inhibition of the overall immune response or to target specific defects using immunosuppressive agents (Pisetsky 2023; Rose 2004). The most frequently used immunosuppressive agents include glucocorticoids (e.g., cortisone), conventional disease-modifying antirheumatic drugs (DMARDs) (e.g., hydroxychloroquine) and biologics (e.g., infliximab) (Li et al. 2017). Side effects of long-term and high dosage immunosuppressive therapy may include increased risk of infection and reduction of bone mineral density, ultimately resulting in osteoporosis and increased risk of fractures (Henrickson et al. 2016; Li et al. 2017; Löfdahl and Rådegran 2017; Maricic 2011).

Uncompromised bone and soft tissue healing is essential to accomplish successful dental implant therapy. An adequate immune response is directly related to the processes of achieving and sustaining hard tissue healing, osseointegration, and soft tissue healing, hindering microbial colonization on the implant surface (Aboushelib and Elsafi 2017; Albrektsson et al. 1981; Colnot et al. 2007; Esposito et al. 1998). Patients with ADs may therefore be expected to be at higher risk of early implant failure

due to compromised osseointegration and late implant failure due to an increased risk of peri-implantitis (Esposito et al. 1998).

Antiresorptive medication (AR) is often prescribed for the management of osteoporosis, which may follow long-term and high dosage use of glucocorticoids in patients with ADs. Medication-related osteonecrosis of the jaw (MRONJ) is a well-described complication of the use of AR. However, immunosuppressants have also been described as general risk factors for the development of MRONJ. In addition, the placement of dental implants is a trauma to the hard and soft tissues, which is recognized as a local risk factor for developing MRONJ (Nicolatou-Galitis et al. 2019; Ruggiero et al. 2022).

Previous systematic reviews on dental implant therapy in patients with ADs report, in general, high implant survival rates based on numerous heterogeneous studies with a low-level of evidence. There has only been limited focus on the effects of the immunosuppressive agents and ARs on implant survival in these patients with ADs (Esimekara et al. 2022; Hyldahl et al. 2024; Reichart et al. 2016; Sarafidou et al. 2024; Strietzel et al. 2019).

Thus, the aim of the present scoping review is to elucidate the effect of ADs and the agents used for treatment on dental implant survival and biologic outcomes.

2 | Material and Methods

The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (Tricco et al. 2018). Given the vast heterogeneity and limited quantity of the available literature on the topic, conventional data synthesis methods for systematic reviews and meta-analyses could not be performed. Therefore, it is relevant to determine the scope of the existing literature on the effect of ADs and the agents used for treatment on dental implant survival and biologic outcomes. This will allow determining and mapping the available literature and providing an overview on the topic (Munn et al. 2018).

2.1 | Research Question

The subsequent research question was prepared utilizing the population, concept, and context (PCC) framework.

- Population (P): Patients diagnosed with an AD with an edentulous or partially edentulous jaw.
- Concept (C): Performed dental implant therapy.
- Context (C): Dental implant survival rate and biologic complications (crestal bone loss, peri-implantitis rate, and MRONJ).

2.2 | Search Strategy

An electronic database search was conducted in MEDLINE (PubMed), The Cochrane Library, and Embase on 29-04-2024

by EH in collaboration with a librarian. The search included MeSH Terms/Subject Headings and Text Words. The search was limited to publications in English, and in MEDLINE (PubMed) and Embase, it was further restricted to studies involving only humans. The electronic database search strategy for MEDLINE (PubMed) is displayed in Appendix S1. Furthermore, a hand search was conducted using reference lists of identified studies.

2.3 | Inclusion and Exclusion Criteria

Inclusion criteria involved:

- Clinical studies published in English
- Patients diagnosed with an AD who received dental implant treatment

Exclusion criteria involved:

- Patients <18 years of age
- In vitro studies
- Preclinical studies
- Review articles

2.4 | Study Selection

First, duplicates were removed. Subsequently, one reviewer (E.H.) screened titles of identified articles to assess their eligibility. Then, two calibrated reviewers (E.H. and S.S.J.) independently screened articles on abstract and thereafter on full-text level. In case of absence of abstracts, articles were directly evaluated by full-text. A Cohen's kappa (κ) coefficient was calculated to assess the level of agreement between the two reviewers. Disagreements between reviewers were resolved through discussion, and if disagreements persisted, a third author (H.S.) was consulted. Reasons for exclusion were further recorded at full-text screening. The study selection process was conducted using the online screening tool Rayyan (<https://new.rayyan.ai>). Missing information of included studies were sought by contacting corresponding authors through e-mail.

2.5 | Data Extraction

Utilizing a dedicated data extraction form, one reviewer (E.H.) systematically extracted the following parameters from included full-text articles: authors, publication year, study design, number of patients, gender, number of dental implants, ADs, immunosuppressants (e.g., glucocorticoids, biologics, conventional DMARDs and chemotherapeutics), ARs (e.g., bisphosphonates and denosumab), follow-up period, survival rate of dental implants (patient and implant level), early dental implant loss (loss of implant before loading), late dental implant loss (loss of implant after loading), biologic complications (crestal bone loss, peri-implantitis, and MRONJ), and

validated methods for measuring oral health-related quality of life (OHRQoL).

2.6 | Data Synthesis and Statistics

For each AD group, synthesis of the extracted data was categorized into the following three groups:

1. Pooled results of the AD
2. Pooled results of the AD with concomitant ADs (sub-group of group 1)
3. Pooled results of associated control groups

Descriptive statistics were exclusively utilized. Weighted means were determined where feasible, and when data were presented as medians, weighted medians were also determined.

3 | Results

3.1 | Study Selection

Figure 1 outlines the search and selection process in detail. The initial literature search identified 6281 potentially eligible records. Subsequently, duplicates were removed, leaving 4666 articles for screening. After title and abstract screening, 179 articles were assessed as full-text. Finally, 69 articles could be included. A κ coefficient of 0.83 after abstract screening and 0.84 after full-text screening illustrates a high degree of concordance between reviewers. An additional 38 articles were identified through hand search, of which 18 could be included. Appendix S2 discloses reasons for exclusion after full-text assessment of database search and hand search results. Hence, a total of 87 studies were included in the scoping review (Aboushelib and Elsafi 2017; Agustin-Panadero et al. 2019; Alenazi 2021; Alikhasi et al. 2017; Alsaadi et al. 2008a, 2008b; Altin et al. 2013; Anitua et al. 2018; Aseri 2022; Attard and Zarb 2002; Azpiazua-Flores et al. 2023; Baptist 2016; Bayram and Eskin 2022; Bencharit et al. 2010; Bertl et al. 2019; Binon 2005; Cauble 2011; Chatzistavrianou and Shahdad 2016; Chochlidakis et al. 2016; Chrcanovic et al. 2019; Cillo and Barbosa 2019; Coman et al. 2019; Corigliano et al. 2014; Czerninski et al. 2013; D'Orto et al. 2022; de Araújo Nobre et al. 2016; de Mendonça Invernici et al. 2014; Drew et al. 2018; Eder and Watzek 1999; El-Sherbini 2018; Eldidi et al. 2019; Ella et al. 2011; Ergun et al. 2010; Esposito et al. 2003; Fu et al. 2019; Fuschetto et al. 2022; Garces Villala and Zorrilla Albert 2021; Gaur et al. 2021; Haas 2002; Hasanoglu Erbasar et al. 2019; Hernández et al. 2012; In't Veld et al. 2022; Isidor et al. 1999; Jackowski et al. 2024; Jackowski et al. 2021; James et al. 2020; Jensen and Sindet-Pedersen 1990; Khamis et al. 2019; Korfage et al. 2016; Krennmair et al. 2010; Langer et al. 1992; Larrazabal-Moron et al. 2009; Lee et al. 2007; Letelier et al. 2016; Li et al. 2004; Lillis et al. 2023; Lopez-Jornet et al. 2014; Maarse et al. 2022; Maarse et al. 2023; Maló et al. 2016; Martin-Cabezas 2021; Megarbane et al. 2017; Mori et al. 2018; Mozzati et al. 2021; Muller et al. 2010; Nam et al. 2012; Nayyar 2019;

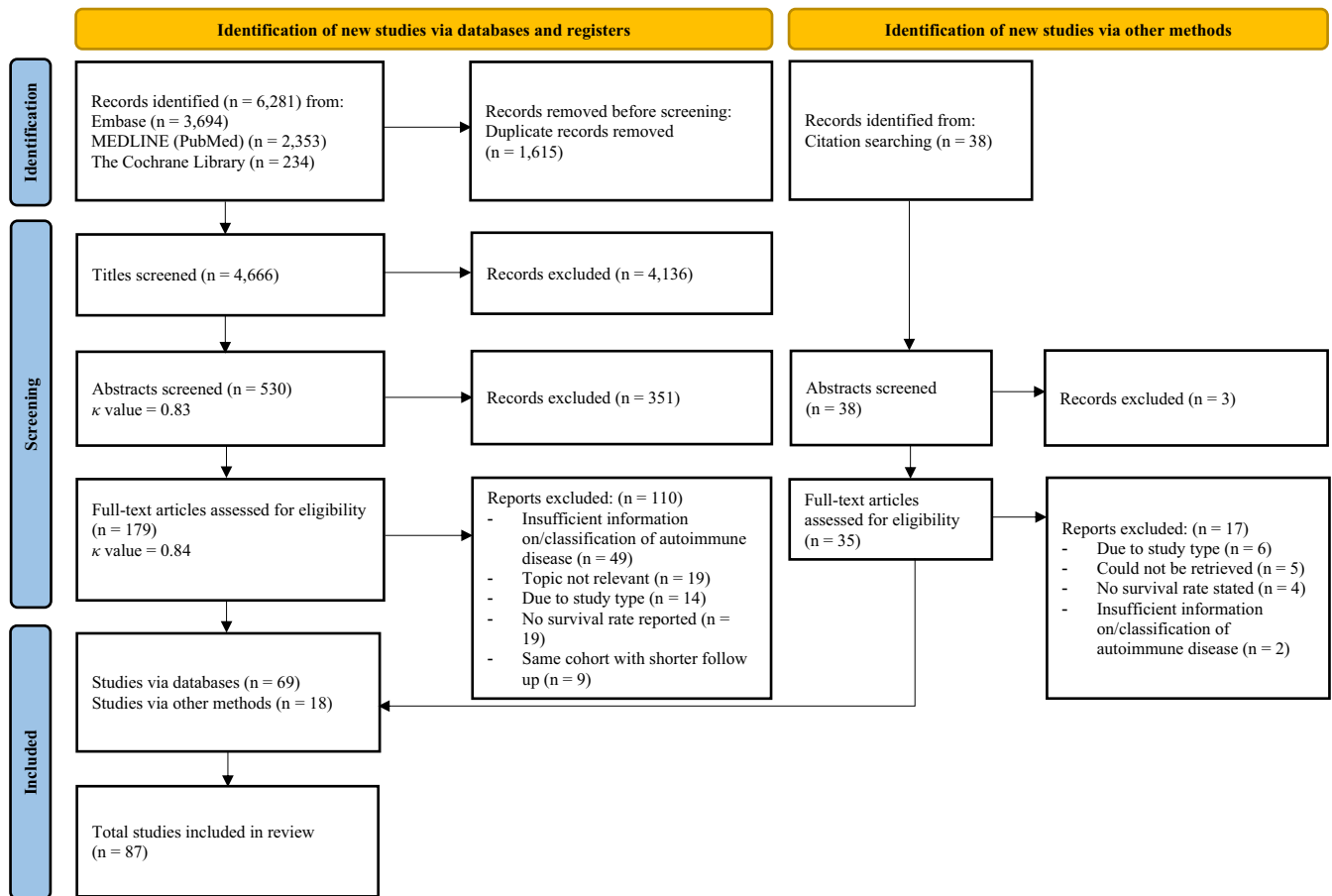


FIGURE 1 | PRISMA flow diagram of the search and selection process. κ , Cohen's kappa; n , number.

Nicoli et al. 2017; Oczakir et al. 2005; Oliveira et al. 2010; Patel et al. 1998; Payne et al. 1997; Penarrocha-Oltra et al. 2020; Peron et al. 2017; Petsinis et al. 2017; Raviv et al. 1996; Reichart 2006; Sannino et al. 2020; Shokri et al. 2019; Siddiqui et al. 2017; Smojver et al. 2021; Spinato et al. 2010; Todorovic et al. 2018; Turkyilmaz and Unsal 2019; van Steenberghe et al. 2002; Yokokoji et al. 2009; Zigdon et al. 2011).

3.2 | Study Characteristics and Outcomes

The included 87 articles comprise:

- 11 case-control studies (Alenazi 2021; Attard and Zarb 2002; D'Orto et al. 2022; El-Sherbini 2018; Hernández et al. 2012; Khamis et al. 2019; Korfage et al. 2016; Lopez-Jornet et al. 2014; Maarse et al. 2022; Maarse et al. 2023; Sannino et al. 2020)
- 3 prospective studies (Aboushelib and Elsafi 2017; Eldidi et al. 2019; Isidor et al. 1999)
- 17 retrospective studies (Alsaadi et al. 2008a, 2008b; Anitua et al. 2018; Bertl et al. 2019; Czerninski et al. 2013; de Araújo Nobre et al. 2016; Hasanoglu Erbasar et al. 2019; Jackowski et al. 2024; Jackowski et al. 2021; Krennmair et al. 2010; Maló et al. 2016; Mozzati et al. 2021; Nicoli et al. 2017; Penarrocha-Oltra et al. 2020; Petsinis et al. 2017; Siddiqui et al. 2017; van Steenberghe et al. 2002)

- 9 case series (Agustin-Panadero et al. 2019; Chatzistavrianou and Shahdad 2016; Chrcanovic et al. 2019; Corigliano et al. 2014; Esposito et al. 2003; Oczakir et al. 2005; Payne et al. 1997; Reichart 2006; Shokri et al. 2019)
- 47 case reports (Alikhasi et al. 2017; Altin et al. 2013; Aseri 2022; Azpiaz-Flores et al. 2023; Baptist 2016; Bayram and Eskan 2022; Bencharit et al. 2010; Binon 2005; Cauble 2011; Chochlidakis et al. 2016; Cillo and Barbosa 2019; Coman et al. 2019; de Mendonça Invernici et al. 2014; Drew et al. 2018; Eder and Watzek 1999; Ella et al. 2011; Ergun et al. 2010; Fu et al. 2019; Fuschetto et al. 2022; Garces Villala and Zorrilla Albert 2021; Gaur et al. 2021; Haas 2002; In't Veld et al. 2022; James et al. 2020; Jensen and Sindet-Pedersen 1990; Langer et al. 1992; Larrazabal-Moron et al. 2009; Lee et al. 2007; Letelier et al. 2016; Li et al. 2004; Lillis et al. 2023; Martin-Cabezas 2021; Megarbane et al. 2017; Mori et al. 2018; Muller et al. 2010; Nam et al. 2012; Nayyar 2019; Oliveira et al. 2010; Patel et al. 1998; Peron et al. 2017; Raviv et al. 1996; Smojver et al. 2021; Spinato et al. 2010; Todorovic et al. 2018; Turkyilmaz and Unsal 2019; Yokokoji et al. 2009; Zigdon et al. 2011)

The available evidence was thus characterized by a high number of studies placed low on the hierarchy of evidence ("Levels of Evidence," March 2009). The extracted parameters, ARs, MRONJ, and OHRQoL, were excluded from tables as a result

of infrequent reporting. Three studies reported administration of ARs in three patients and hereof two patients also received immunosuppressants. None of these studies reported development of MRONJ (Chochlidakis et al. 2016; Chrcanovic et al. 2019; Ella et al. 2011). However, one study reported MRONJ, in a patient with hypothyroidism and ulcerative colitis receiving a biologic agent, adalimumab. The patient also developed a submental abscess with bilateral spread into the submandibular space. The patient experienced mobility of the implants resulting in an early loss of all five implants (Cillo and Barbosa 2019). Furthermore, a qualitative synthesis of data was performed because of a substantial heterogeneity among studies.

In general, the data set was characterized by a predominance of autoimmune CTDs. This disease group also comprises the disease group with the greatest number of ADs with a concomitant AD. In addition, overall, an overweight of females and early dental implant losses (46.7%–100%) occurred in the data set. Further, glucocorticoids were the most frequently administered immunosuppressive agent. In the disease groups, 108 patients with oral lichen planus (OLP), 61 patients with rheumatoid arthritis (RA), and 24 patients with SS received glucocorticoids.

Included studies were categorized into disease groups comprising:

- Autoimmune CTDs
 - SS
 - RA
 - Systemic scleroderma
 - Systemic lupus erythematosus
 - Polyarthritis
 - Other autoimmune CTDs
- ADs with mucosal manifestations
 - OLP
 - Bullous diseases
 - Mucous membrane pemphigoid
 - Pemphigus Vulgaris
 - Recessive dystrophic epidermolysis bullosa (EB)
- Other ADs
 - Type 1 diabetes
 - Hypothyroidism
 - Crohn's disease
 - Dermatomyositis
 - Other ADs

3.2.1 | Autoimmune Connective Tissue Diseases

Table 1 provides an overview of the characteristics and outcomes of implant therapy in patients with autoimmune CTDs. Table 2 provides an overview of the characteristics and outcomes of implant therapy in patients with autoimmune CTDs with concomitant ADs. The latter group included a smaller patient cohort compared to the autoimmune CTDs group. In general, characteristics and outcomes did not otherwise differ significantly from those of autoimmune CTDs. Tables representing concomitant ADs of disease groups, ADs with mucosal manifestations,

and other ADs were not displayed in this manuscript due to an inadequate quantity of data to sufficiently present this in a meaningful way.

SS was the disease group including most studies, patients, and implants. Hereof, 25 studies comprising a total of 152 patients with SS and 607 dental implants. In the disease group SS with concomitant ADs, the dental implant survival rate was 93.6% (175/187) on implant level, of which 75% (9/12) of the implant losses occurred early. These results were primarily influenced by one prospective study including eight patients with secondary SS who previously reported problems using conventional removable dentures. In this patient cohort, 54 implants were placed. After a follow-up of 48 months, the survival rate was 87% (45/54) on implant level, of which seven out of 10 implant losses occurred early. Half of the patients experienced an implant loss. All patients received implant-supported complete dental prostheses, and at 2 years follow-up, improved OHRQoL was reported (Isidor et al. 1999).

In addition, two case-control studies reported OHRQoL in SS patients receiving dental implants using Oral Health Impact Profile-14 (OHIP-14). The rehabilitation protocol comprised exclusively implant-supported crowns in one of the studies, and in the other study, it involved implant-supported overdentures. Both studies reported significantly improved OHIP-14 scores for the SS groups at all time points compared to baseline. The study including overdentures also reported significantly improved OHIP-14 scores for the control group at all time points (Maarse et al. 2022; Maarse et al. 2023).

For the RA group, the median crestal bone loss was 2 mm after a mean follow-up period of 45.5 months. In RA patients with concomitant ADs, the median crestal bone loss was 2.2 mm after a mean follow-up period of 42.7 months. These outcomes were primarily influenced by results from two studies (Alenazi 2021; Krennmair et al. 2010). One study including 25 patients with isolated RA, of whom 19 patients on glucocorticoids, received 85 implants and were followed up for a mean period of 46.6 months. Additionally, the study also included nine patients with RA and concomitant CTDs, of whom seven patients received glucocorticoids. This study group received 41 implants and were followed up for a mean period of 48.9 months. The median crestal bone loss was 2 mm for the isolated RA group and 2.8 mm for the group with RA and concomitant CTDs (Krennmair et al. 2010). In the other study, 14 patients with isolated RA, receiving 32 implants, were followed up for a mean period of 42.3 months. The study also included 14 patients with RA and concomitant CTDs, receiving 43 implants, and were followed up for a mean period of 44.6 months. Five patients in both groups received glucocorticoids. The median crestal bone loss was 1.2 and 2.2 mm for the isolated RA group and the group with RA and concomitant CTDs, respectively (Alenazi 2021).

3.2.2 | Autoimmune Diseases With Mucosal Manifestations

Table 3 provides an overview of the characteristics and outcomes of implant therapy in patients with ADs with mucosal manifestations.

TABLE 1 | Characteristics and outcomes of implant therapy in patients with autoimmune connective tissue diseases.

Autoimmune diseases	Study design	Patients/ Implants	Gender	Immunosuppressants	Follow-up period	Survival rate of implants and		Crestal bone loss	Peri-implantitis
						% (n/n patients)	% (n/n implants)		
Sjögren's syndrome	n studies	n patients/ n implants	M/F ratio	Agent: n patients	Months				% (n/n patients) and % (n/n implants)
	CCS: 4	152/607	1/12.7	Glucocorticoids: 24	Mean: 51.4	92.8% (141/152)		Mean: 1.37	12.1% (7/58)
	PS: 1			Hydroxychloroquine: 15	Median: 46	96.4% (585/607)		Median: 0.89	8.5% (16/189)
	RS: 3			Methotrexate: 1		Of these: 81.8%			
	CS: 6			Cyclosporine: 1		(18/22) early loss			
Rheumatoid arthritis	CR: 11			Other					
				immunosuppressives: 5					
	CCS: 4	145/419	1/7.5	Glucocorticoids: 61	Mean: 45.5	95.9% (139/145)		Mean: 0.36	8.3% (1/12)
	RS: 6			Methotrexate: 2		97.6% (409/419)		Median: 2	1.8% (1/55)
	CS: 2			Sulfasalazine: 1		Of these: 70%			
Systemic sclerosis	CR: 5			Infliximab: 1		(7/10) early loss			
	CCS: 1	40/157	1/15.5	Glucocorticoids: 3	Mean: 56.8	95% (19/20)		Mean: 0.78	20% (1/5)
	RS: 3			Methotrexate: 2		94.9% (149/157)			2.4% (1/41)
	CS: 1			Penicillamine: 1		Of these: 62.5%			
	CR: 11					(5/8) early loss			
Systemic lupus erythematosus	RS: 2	13/68	1/2.3	Glucocorticoids: 6	Mean: 46.1	92.3% (12/13)		Mean: 0.49	0% (0/10)
	CR: 5			Hydroxychloroquine: 3		98.5% (67/68)			0% (0/51)
				Methotrexate: 2		Of these: 100%			
				Chloroquine: 1		(1/1) early loss			
				Cyclosporine: 1					
Polyarthrititis				Immunoglobulin: 1					
	CR: 3	3/14	0/3	Glucocorticoids: 2	Mean: 40	100% (3/3)		Mean: 1.38	100% (1/1)
				Methotrexate: 1		100% (14/14)			NR
				Hydroxychloroquine: 1					
				Mycophenolatmofetil: 1					
Other autoimmune connective tissue diseases				Glucocorticoids: 5	Mean: 35	100% (6/6)		NR	0% (0/3)
	RS: 1	6 ^a /32	1/5	Chloroquine: 1		100% (32/32)			0% (0/7)
	CS: 1			Methotrexate: 1					
	CR: 2								

Note: Follow-up period and crestal bone loss: weighted mean and/or median.

Abbreviations: CCS, case-control study; CR, case report; CS, case series; M/F, male/female; n, number; NR, not reported; PS, prospective study; RS, retrospective study.

^aComprises two patients with giant cell arteritis and four patients with either of the following diseases: Still's disease and secondary Sjögren's syndrome, mixed connective tissue disease and systemic lupus erythematosus, polymyalgia rheumatica (without giant cell arteritis) and polyarteritis nodosa.

TABLE 2 | Characteristics and outcomes of implant therapy in patients with autoimmune connective tissue diseases with concomitant autoimmune diseases.

Autoimmune diseases	Study design	Patients/ Implants	Gender	Immunosuppressants	Follow-up period	Survival rate of implants	Crestal bone loss	Peri-implantitis
	<i>n</i> studies	<i>n</i> patients/ <i>n</i> implants	M/F ratio	Agent: <i>n</i> patients	Months	% (<i>n</i> / <i>n</i> patients) and % (<i>n</i> / <i>n</i> implants)	mm	% (<i>n</i> / <i>n</i> patients) and % (<i>n</i> / <i>n</i> implants)
Sjögren's syndrome	CCS: 3	41/187	1/36	Glucocorticoids: 13	Mean: 40.1	87.8% (36/41)	Mean: 0.63	0% (0/2)
	PS: 1			Cyclosporine: 1		93.6% (175/187)		0% (0/10)
	RS: 1			Hydroxychloroquine: 1		Of these: 75%		
	CS: 4			Methotrexate: 1		(9/12) early loss		
	CR: 5							
Rheumatoid arthritis	CCS: 3	38/132	1/6.6	Glucocorticoids: 16	Mean: 42.7	97.4% (37/38)	Mean: 0	NR
	RS: 1					97.7% (129/132)	Median: 2.2	
	CS: 1					Of these: 66.7%		
	CR: 3					(2/3) early loss		
Systemic scleroderma	CCS: 1	11/30	0/4	Glucocorticoids: 1	Mean: 32.7	100% (11/11)	NR	0% (0/1)
	RS: 1					100% (30/30)		0% (0/8)
	CS: 1							
	CR: 2							
Systemic lupus erythematosus	CR: 4	4/27	0/4	Glucocorticoids: 3	Mean: 27.5	100% (4/4)	NR	0% (0/1)
				Hydroxychloroquine: 3		100% (27/27)		0% (0/10)
				Methotrexate: 2				
Polyarthritis				Chloroquine: 1				
				Cyclosporine: 1				
	CR: 1	1/6	0/1	Glucocorticoids: 1	24	100% (1/1)	NR	NR
Other autoimmune connective tissue diseases				Hydroxychloroquine: 1		100% (6/6)		
	CS: 1	2 ^a /13	0/2	Glucocorticoids: 1	Mean: 24	100% (2/2)	NR	NR
	CR: 1			Methotrexate: 1		100% (13/13)		
				Chloroquine: 1				

Note: Follow-up period and crestal bone loss: weighted mean and/or median.

Abbreviations: CCS, case-control study; CR, case report; CS, case series; M/F, male/female; n, number; NR, not reported; PS, prospective study; RS, retrospective study.

^aComprises one patient with Still's disease and secondary Sjögren's syndrome and one patient with mixed connective tissue disease and systemic lupus erythematosus.

TABLE 3 | Characteristics and outcomes of implant therapy in patients with autoimmune diseases with mucosal manifestations.

	Study design	Patients/Implants	Gender	Immunosuppressants	Follow-up period	Survival rate of implants	Crestal bone loss	Peri-implantitis
	<i>n</i> studies	<i>n</i> patients/ <i>n</i> implants	M/F ratio	Agent: <i>n</i> patients	Months	% (<i>n</i> / <i>n</i> patients) and % (<i>n</i> / <i>n</i> implants)	mm	% (<i>n</i> / <i>n</i> patients) and % (<i>n</i> / <i>n</i> implants)
Autoimmune diseases	CCS: 3	143/306	1/2.7	Glucocorticoids: 108	Mean: 43.3	83.5% (106/127)	Mean: 1.04	20% (1/5)
	PS: 1				85.3% (261/306)	24.3% (17/70)		
	RS: 2				Of these: 97.7% (42/43) early loss			
	CS: 3							
	CR: 3							
Bullous diseases	RS: 1	26 ^a /167	1/2.3	Glucocorticoids: 2	Mean: 67.1	100% (13/13)	Mean: 1.42	0% (0/5)
	CS: 1				98.8% (165/167)	0% (0/28)		
	CR: 9				Of these: 50% (1/2) early loss			

Note: Follow-up period and crestal bone loss: weighted mean and/or median.

Abbreviations: CCS, case-control study; CR, case report; CS, case series; M/F, male/female; n, number; NR, not reported; PS, prospective study; RS, retrospective study.

^aComprises 23 patients with recessive dystrophic epidermolysis bullosa, two patients with mucous membrane pemphigoid, and one patient with pemphigus vulgaris.

The disease groups consist of patients with OLP and bullous diseases. The bullous disease group comprises patients with EB, mucous membrane pemphigoid, and pemphigus vulgaris.

In the OLP group, the implant survival rate was 83.5% (106/127) on patient level and 85.3% (261/306) on implant level after a mean follow-up period of 43.3 months (median follow-up period: 48 months). In one study involving 23 untreated patients with OLP experiencing flare-up of their disease, 55 implants were placed. A total of 42 early implant losses occurred, yielding a survival rate of 23.6% (13/55) on implant level and 13% (3/23) on patient level. Implant therapy was repeated after complete remission of the disease after systemic treatment with glucocorticoids. At 48 months follow-up, none of the 42 newly placed implants were lost (Aboushelib and Elsafi 2017; Khamis et al. 2019).

The peri-implantitis rate in the OLP group was 24.3% (17/70) on implant level. This result was primarily influenced by one study with a peri-implantitis rate of 25% (14/56 implants) in 16 patients, of whom seven patients received glucocorticoids. However, the peri-implantitis rate of the healthy control group was 16% (8/50 implants), and the difference between the two groups was non-significant. This article also included a study group of patients suffering from OLP without implants. In this article, OHRQoL was reported using OHIP-14. Patients with OLP and implants had a significantly better OHIP-14 score than patients with OLP without implants. However, the healthy control group with implants had a significantly better OHIP-14 score than the OLP group with and without implants (Lopez-Jornet et al. 2014).

Two studies including patients suffering from EB treated with implant-supported rehabilitation reported on OHRQoL utilizing a satisfaction score. The satisfaction score was based on a VAS scale of 0–10 and on the following parameters: hygiene, aesthetics, mastication, phonation, self-esteem, and comfort. In one study, 80 implants supported 20 full-arch prostheses in 13 patients suffering from EB (Penarrocha-Oltra et al. 2020). In another study, 31 implants were placed to support 8 full-arch prostheses in four patients with EB (Agustin-Panadero et al. 2019). Apart from the parameter hygiene with a score of 6–8, both studies yielded a mean satisfaction score of >9 for all evaluated parameters (Agustin-Panadero et al. 2019; Penarrocha-Oltra et al. 2020).

3.2.3 | Other Autoimmune Diseases

Table 4 provides an overview of the characteristics and outcomes of implant therapy in patients with other ADs.

The implant survival rate in the hypothyroidism group was 93.4% (213/228) on implant level after a mean follow-up period of 51.4 months and was primarily influenced by two studies (Alsaadi et al. 2008a; Cillo and Barbosa 2019). After a follow-up period of 24 months in 25 hypothyroidism patients, one study reported a late implant survival rate of 93.7% (104/111 implants) (Alsaadi et al. 2008b). The other study, mentioned previously, reported an early implant survival rate of 0% (0/5 implants) in a patient with hypothyroidism and ulcerative

TABLE 4 | Characteristics and outcomes of implant therapy in patients with other autoimmune diseases.

Autoimmune diseases	Study design	Patients/ implants	Gender	Immunosuppressants	Follow-up period	Survival rate of implants	Crestal bone loss	Peri-implantitis
	<i>n</i> studies <i>n</i> patients/ <i>n</i> implants	<i>n</i> patients/ <i>n</i> implants	M/F ratio	Agent: <i>n</i> patients	Months	% (<i>n</i> / <i>n</i> patients) and % (<i>n</i> / <i>n</i> implants)	mm	% (<i>n</i> / <i>n</i> patients) and % (<i>n</i> / <i>n</i> implants)
Type 1 diabetes	CCS: 2	97/247	9/0	NR	Mean: 48.3	86.4% (19/22) 94.5% (208/220) Of these: 58.3% (7/12) early loss	Mean: 1.2	28.6% (2/7) 2.9% (3/104)
	PS: 1 RS: 4							
Hypothyroidism	CCS: 1	53/228	0/24	Glucocorticoids: 2 Adalimumab: 1 Cyclosporine: 1 Hydroxychloroquine: 1 Methotrexate: 1	Mean: 51.4	85.7% (6/7) 93.4% (213/228) Of these: 46.7% (7/15) early loss	Mean: 0.05	16.7% (1/6) 0% (0/8)
	RS: 3 CR: 3							
Crohn's disease	RS: 3	7/54	1/0	Glucocorticoids: 1 Infliximab: 1	Mean: 16.3	60% (3/5) 87% (47/54) Of these: 57.1% (4/7) early loss	NR	NR
	CR: 2							
Dermatomyositis	CCS: 1	5/5	0/2	Glucocorticoids: 1	Mean: 38.5	100% (5/5) 100% (5/5)	NR	0% (0/1) 0% (0/3)
	RS: 2							
Other autoimmune diseases	RS: 2	11 ^a /50	1/1.7	Glucocorticoids: 6 Adalimumab: 1 Hydroxychloroquine: 1	Mean: 42.2	81.8% (9/11) 88% (44/50) Of these: 100% (6/6) early loss	Mean: 1.63	0% (0/9) 0% (0/44)
	CR: 5							

Note: Follow-up period and crestal bone loss: weighted mean and/or median.

Abbreviations: CCS, case-control study; CR, case report; M/F, male/female; *n*, number; NR, not reported; PS, prospective study; RS, retrospective study.

^aComprises three patients with multiple sclerosis, two patients with myasthenia gravis, and six patients with either of the following diseases: fibrosing alveolitis and SSC, psoriasis, antiphospholipid syndrome and SLE, ulcerative colitis and HT, sarcoidosis, and Guillain-Barré syndrome.

colitis receiving a biologic agent, adalimumab. This patient also suffered from severe biological complications (Cillo and Barbosa 2019).

For the Crohn's disease group, the implant survival rate was 87% (47/54 implants) after a mean follow-up period of 16.3 months. Three studies lost each one to three implants with an implant survival rate of 66.7%–91.7% on implant level (Alsaadi et al. 2008a, 2008b; van Steenberghe et al. 2002) and the remaining two studies, comprising case reports, presented an implant survival rate of 100% (Cable 2011; Nayyar 2019).

For the disease group, other ADs, the implant survival rate was 88% (44/50 implants) after a mean follow-up period of 42.2 months. This reduced implant survival rate was primarily influenced by one study (Cillo and Barbosa 2019).

A detailed documentation of characteristics and outcomes of all disease groups is presented in Appendix S3–S15.

4 | Discussion

Despite the nature of ADs and the fact that most patients receive immunosuppressants, dental implant therapy in patients with ADs seems predictable with an overall high survival rate after mid-term follow-up. A predominance of early implant losses was present. However, overall low-level scientific evidence was available.

All levels of clinical evidence were assessed for eligibility because of an absence of numerous high-quality studies. Due to the available low-level scientific evidence, results should therefore be interpreted with caution. The absence of many high-quality studies was consistent with the relatively low prevalence of ADs covering more than 80 disease entities (Conrad et al. 2023).

In general, most patients with ADs were female and CTDs was the disease group with the highest number of concomitant ADs. These findings are in accordance with a large population-based cohort study (Conrad et al. 2023). However, the occurrence of concomitant ADs complicates the interpretation of the influence of the individual ADs on implant therapy.

In the current review, overall dental implant survival was high in patients with ADs and comparable to that reported in the general population (Jung et al. 2012). This tendency occurred despite many patients being immunosuppressed because of their AD and/or the administration of immunosuppressive agents, especially glucocorticoids. This is in accordance with the results of a systematic review regarding dental implant therapy in patients immunosuppressed following organ transplant treatment. This study included 249 implants in 93 organ-transplanted patients receiving immunosuppressants. After a mean follow-up period of 60 months, the implant survival rate was 100% with no critical biologic complications (Burtscher and Dalla Torre 2022).

Animal studies have additionally been conducted regarding implant therapy in immunosuppressed rabbits. The studies identify a significantly lower removal torque and bone-to-implant

contact of implants placed in the tibia of rabbits receiving either cyclosporine A or prednisolone (Fujimoto et al. 1998; Sakakura et al. 2003). One of these studies further evaluated implant placement in the mandibles and reported a non-significant difference in removal torque between the immunosuppressed rabbits, receiving prednisolone, and the healthy control group. The authors concluded that the inhibitory effect of glucocorticoid treatment on implant osseointegration in the mandible may be reduced compared to long bones (Fujimoto et al. 1998). However, a high survival rate of cementless total knee arthroplasties, also requiring osseointegration, has been reported in patients with RA in a review (Dalury 2016; Salem et al. 2020). The review shows comparable results of cementless total knee arthroplasties in patients with RA and dental implants in patients with RA, disclosed by the present review.

Implant failures in patients with ADs predominantly occurred before prosthetic loading (early implant loss) (46.7%–100%). The process of osseointegration is similar to the healing process of bone fractures, both requiring an adequate immune response. Hence, failure to establish osseointegration can be a consequence of impaired osseous healing, characterizing early implant loss (Colnot et al. 2007; Esposito et al. 1998). In a large retrospective study including >10,000 implants, 642 implants were lost and compared to the current review, fewer implants were lost early (27.4%). Additionally, the study revealed a non-significant correlation between early implant loss and immunosuppressive therapy (Chrcanovic et al. 2016). The reason for the predominance of early implant losses identified in this scoping review is currently unknown but may be due to immunosuppression as a result of ADs themselves and/or administration of immunosuppressants.

Overall, the success criteria of implant therapy in terms of crestal bone loss were met in the majority of AD groups (Papaspnyridakos et al. 2012). Furthermore, most disease groups reported peri-implantitis rates comparable to the ones reported for the general population, after 5–10 years of follow-up, comprising 20% on patient level and 10% on implant level (Mombelli et al. 2012).

Patients with ADs receiving implants may be at increased risk of developing MRONJ as some patients receive AR for osteoporosis management and immunosuppressants for the management of the AD, both increasing the susceptibility for MRONJ. These immunosuppressants include glucocorticoids, methotrexate, and biologics including monoclonal antibodies. Infection of and trauma to the oral mucosa and alveolar bone further increase the risk of developing MRONJ (Nicolatou-Galitis et al. 2019; Ruggiero et al. 2022) in patients with ADs undergoing dental implant therapy. In this review, three studies reported administration of ARs in three patients, of whom two patients also received immunosuppressants. None of these studies reported cases of MRONJ (Chochlidakis et al. 2016; Chrcanovic et al. 2019; Ella et al. 2011). However, one case report including a patient with hypothyroidism and ulcerative colitis administering the biologic agent and monoclonal antibody, adalimumab, developed MRONJ in the mandible and lost all dental implants early (Cillo and Barbosa 2019). However, the risk of MRONJ should be expected to be substantially lower for patients receiving low-dose ARs due to osteoporosis compared to high-dose in patients with

malignancies (Ruggiero et al. 2022). The data regarding this topic was too heterogeneously reported to draw any firm conclusions.

4.1 | Autoimmune Connective Tissue Diseases

In patients with autoimmune CTDs and patients with autoimmune CTDs with concomitant ADs, the implant survival rate on implant level was 93.6%–100%, which overall is similar to the survival rate after 5 years of follow-up in the general population (97.2%) (Jung et al. 2012). Despite the high implant survival rate reported in most studies, one prospective study including only patients with secondary SS reported a low implant survival rate of 87%, and the majority of implant losses occurred early (Isidor et al. 1999). Results from this prospective study may imply that the presence of concomitant ADs may have a higher impact on osseointegration and ultimately dental implant survival than SS itself.

Based on the present review, patients with RA may suffer an increased crestal bone loss. In the group RA with concomitant ADs, a median crestal bone loss of 2.2 mm after 42.7 months follow-up was observed, which is beyond the criteria for success. These criteria are defined as crestal bone loss <1.5 mm in the first year and <0.2 mm annually thereafter (Papaspnyridakos et al. 2012). The crestal bone loss observed in patients with RA may be attributed to an overall accentuated administration of glucocorticoids. Nearly half of the patients with RA received glucocorticoids. This tendency also occurs in the two studies primarily influencing the increased crestal bone loss in the RA group (Alenazi 2021; Krennmair et al. 2010). Sustained and high-dose glucocorticoid therapy may result in an altered bone metabolism. While osteoclast numbers are preserved, an increased osteocyte apoptosis and a decrease in the number of osteoblasts potentially compromise osteogenesis. In addition, the osteocyte apoptosis causes a decrease in skeletal angiogenesis, hence also reducing local circulation, volume of bone interstitial fluids, and bone strength. Ultimately, these alterations reduce bone mineral density and predispose for secondary osteoporosis (Weinstein 2012). Low local blood flow may be further compromised due to reduced vasodilation due to endothelial dysfunction in patients with RA (Bordy et al. 2018).

4.2 | Autoimmune Diseases With Mucosal Manifestations

Most OLP patients receive glucocorticoids to preserve local disease control. Despite several studies reporting implant placement during complete remission (Anitua et al. 2018; Aseri 2022; Fu et al. 2019; Hernández et al. 2012; Khamis et al. 2019), an implant survival rate of 85.3% should be considered low (Jung et al. 2012). Out of 45 implants lost, 97.7% occurred early. However, most implant losses in OLP patients occurred in one prospective study, whereas the remaining studies reported a high implant survival rate (96.4%–100%). This prospective study involved 55 implants placed in 23 patients with OLP flare-up without glucocorticoid treatment. In the 20 patients experiencing 42 early implant losses, systemic glucocorticoid treatment was prescribed, and implant therapy was repeated after complete remission of disease symptoms. This resulted in a 100% survival rate of the newly placed implants after 48 months

follow-up (Aboushelib and Elsafi 2017; Khamis et al. 2019). This study demonstrates a high susceptibility of a severely compromised soft tissue healing and osseointegration in medically uncontrolled OLP patients with flare-ups. The increased implant loss in this group may be due to inflammatory changes in the epithelium and connective tissue of patients with OLP, altering the bacteria barrier function, and hereof the capacity of the epithelium to adhere to the implant titanium surface. An increased secretion of pro-inflammatory cytokines in these patients may also influence osseointegration (Czerninski et al. 2013). Hence, placement of dental implants in patients with flare-up of OLP cannot be recommended, and complete remission through glucocorticoid treatment prior to implant therapy seems more critical than the potential risk associated with glucocorticoids themselves. It may be speculated that a similar recommendation could be given for other ADs with mucosal manifestations.

In contrast to other ADs, for example, RA often treated with systemic glucocorticoids and exhibiting high crestal bone loss, the glucocorticoid treatment of OLP, often consisting of topical administration, may have less impact on bone metabolism. This corresponds to a crestal bone loss in the OLP group meeting the success criteria for this parameter, as opposed to the RA group with concomitant ADs (Papaspnyridakos et al. 2012).

In the OLP group, the peri-implantitis rate was high, comprising 24.3% (17/70 implants), compared to the general population (10%) (Mombelli et al. 2012). This high occurrence of peri-implantitis in patients with OLP was primarily based on one study, in which a high peri-implantitis rate was also observed in the healthy control group (Lopez-Jornet et al. 2014).

In patients with bullous diseases, the implant survival rate on implant level was 98.8% and comparable to the survival rate of 97.2% after 5 years of follow-up for the general population (Jung et al. 2012).

4.3 | Other Autoimmune Diseases

Patients with type 1 diabetes, hypothyroidism, and dermatomyositis yielded a high implant survival rate of 93.4%–100%. On the other hand, a low implant survival rate was indicated in patients with Crohn's disease and other ADs (87%–88%). However, these two disease groups included only a few patients and implants, thus overall outcomes were sensitive to small fluctuations in the dataset.

4.4 | Influences of Oral Manifestations on Dental Rehabilitation

Patients with SS exhibit xerostomia and hyposalivation; the latter may lead to erosions, ulcers, mucositis, candidiasis, and dental caries (Baglama et al. 2018). Due to these manifestations, some causing discomfort and/or pain, patients with SS may have severe challenges using conventional removable dental prostheses (Azpiazu-Flores et al. 2023; Isidor et al. 1999; Reichart et al. 2016). This is in accordance with findings in a systematic review regarding patient satisfaction with removable dentures in patients with xerostomia (Tanaka et al. 2021).

Patients with systemic scleroderma often suffer from microstomia, rigid tongue, xerostomia, dental caries, and periodontitis. Further, the performance of oral hygiene procedures is complicated for these patients due to the microstomia (Baglama et al. 2018; Parel 1972) and sclerodactyly, compromising manual dexterity. Therefore, patients with systemic scleroderma may as well have challenges using removable dental prostheses (Garces Villala and Zorrilla Albert 2021; Jensen and Sindet-Pedersen 1990; Parel 1972; Raviv et al. 1996; Reichart et al. 2016).

OLP is clinically divided into six subtypes: reticular, plaque, papular, atrophic (erythematous), erosive (ulcerative), and bullous. OLP lesions may manifest anywhere on the oral mucosa; however, they most often occur bilaterally on the cheek mucosa, gingiva, and tongue. Especially the atrophic, erosive, and bullous lesions are associated with discomfort and/or pain (Chiang et al. 2018; Louisy et al. 2024) that may render OLP patients unable to utilize removable dental prostheses (Esposito et al. 2003; Fu et al. 2019; Reichart et al. 2016).

EB is characterized by blisters, erosions, and ulcerations arising spontaneously or following minor trauma. Secondary scarring and contractures may occur, resulting in for example, pseudosyndactyly, dysphagia, and microstomia. Pseudosyndactyly, microstomia, and pain related to mucosal blisters may hinder daily oral hygiene procedures (Bardhan et al. 2020; Krämer et al. 2020). These manifestations often compromise the use of removable dental prostheses in patients with EB (Agustin-Panadero et al. 2019; Krämer et al. 2020; Muller et al. 2010; Reichart et al. 2016). Finally, the use of removable dental prostheses has been reported to be problematic in patients with other bullous diseases, including pemphigus vulgaris and mucous membrane pemphigoid (Altin et al. 2013; Fuschetto et al. 2022).

To avoid stress and mechanical irritation by removable dental prostheses on soft tissue, implant-supported dental prostheses may be particularly favourable in patients with SS, systemic scleroderma, OLP, and bullous diseases. This is supported by the few available studies including patient-reported outcomes. Hence, improved OHRQoL has been reported after oral rehabilitation with implant-supported fixed and removable dental prostheses in patients with SS, OLP, and EB (Agustin-Panadero et al. 2019; Isidor et al. 1999; Lopez-Jornet et al. 2014; Maarse et al. 2022; Maarse et al. 2023; Penarrocha-Oltra et al. 2020). It may even be argued that a slightly reduced implant survival rate may be acceptable for some patients with ADs, as the potential improvement in masticatory function and OHRQoL provided by implant-supported rehabilitation may outweigh the risk and consequences of implant-related biological complications.

4.5 | Limitations

Several limitations were encountered in this scoping review. Overall, few studies of high quality and with long-term follow-up could be included. When reviewing a bulk of literature with the present characteristics, the most common types of bias identified were reporting, publication, confounding, selection, and information bias. Given the predominance of studies placed low on the hierarchy of evidence, in particular case reports and retrospective studies, reporting and publication bias are potentially

prominent in the present research area. Reporting bias appears as researchers are more prone to report news- and noteworthy results (Higgins et al. 2024). Publication bias arises when the decision to publish or withhold research is dependent on the direction or strength of the evidence (Ayorinde et al. 2020). Confounding bias appears primarily as the confounding domain in several studies has not been adjusted for in statistical analysis (Aboushelib and Elsafi 2017; Penarrocha-Oltra et al. 2020). Selection bias exists through partial registration of follow-up in some studies, for example, exclusively reporting late implant survival rate (Alsaadi et al. 2008a; Czerninski et al. 2013). Further, selection bias is found through missing data in some studies, for example, due to patients lost to follow-up (Attard and Zarb 2002; Isidor et al. 1999). Information bias appears mainly due to studies not using or using different classifications, for example, for diagnosis of ADs and peri-implantitis (Mozzati et al. 2021; Oczakir et al. 2005). Additionally, information bias appears as most studies do not include a blinded examiner (Higgins et al. 2024; Mozzati et al. 2021; Petsinis et al. 2017).

Heterogeneous reporting of extraction parameters was present in studies, especially the administration of ARs, the occurrence of MRONJ, and validated methods for measuring OHRQoL. Due to the sparse availability of high-quality studies and heterogeneous reporting in included studies, the results should be interpreted with caution. It is therefore strongly encouraged, in the field of implant dentistry, to carry out high-quality studies with long-term follow-up in patients with ADs. Hereby, the different types of bias encountered in the present review will be reduced in future studies and should allow for the preparation of clear clinical guidelines on this topic in the future.

5 | Conclusions

Within the limitations of the available low-level scientific evidence, upon which the present review is based, it can be concluded that dental implant treatment in general is predictable in patients with ADs. Despite the nature of ADs and the fact that many patients with ADs receive immunosuppressants, an overall high implant survival rate was reported after mid-term follow-up. When implant failures were reported in patients with ADs, they predominantly occurred before prosthetic loading. Particularly, patients with mucosal manifestations of their ADs seems to benefit significantly from implant-supported restorations provided that the mucosal lesions are well treated.

It is highly recommended to prospectively and systematically document implant therapy in patients with ADs to further increase the level of evidence in a group of patients that will truly benefit from this treatment approach. This should allow for the preparation of clear clinical guidelines on this topic in the future.

Author Contributions

Emil Hyldahl: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, writing – original draft. **Henning Schliephake:** conceptualization, methodology, supervision, writing – review and editing. **Simon**

Storgård Jensen: conceptualization, methodology, project administration, supervision, validation, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study, Appendix S1–S15, are openly available in “figshare” at https://figshare.com/articles/dataset/Appendix_S1-15/28790849?file=53658614.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.