Review

New Approach to Addison Disease: Oral Manifestations Due to Endocrine Dysfunction and Comorbidity Burden

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Abstract: This review highlights oral anomalies with major clinical impact in Addison disease (AD), including dental health and dermatologic features, through a dual perspective: pigmentation issues and AD comorbidities with oral manifestations. Affecting 92% of AD patients, cutaneomucosal hyperpigmentation is synchronous with or precedes general manifestations by up to a decade, underlying melanocytic infiltration of the basal epidermal layer; melanophages in the superficial dermis; and, rarely, acanthosis, perivascular lymphocytic infiltrate, and hyperkeratosis. Intraoral pigmentation might be the only sign of AD; thus, early recognition is mandatory, and biopsy is helpful in selected cases. The buccal area is the most affected location; other sites are palate arches, lips, gums, and tongue. Pigmented oral lesions are patchy or diffuse; mostly asymptomatic; and occasionally accompanied by pain, itchiness, and burn-like lesions. Pigmented lingual patches are isolated or multiple, located on dorsal and lateral areas; fungiform pigmented papillae are also reported in AD individuals. Dermoscopy examination is particularly indicated for fungal etiology; yet, it is not routinely performed. AD’s comorbidity burden includes the cluster of autoimmune polyglandular syndrome (APS) type 1 underlying AIRE gene malfunction. Chronic cutaneomucosal candidiasis (CMC), including oral CMC, represents the first sign of APS1 in 70–80% of cases, displaying autoantibodies against interleukin (IL)-17A, IL-17F ± IL-22, and probably a high mucosal concentration of interferon (IFN)-γ. CMC is prone to systemic candidiasis, representing a procarcinogenic status due to Th17 cell anomalies. In APS1, the first cause of mortality is infections (24%), followed by oral and esophageal cancers (15%). Autoimmune hypoparathyroidism (HyP) is the earliest endocrine element in APS1; a combination of CMC by the age of 5 years and dental enamel hypoplasia (the most frequent dental complication of pediatric HyP) by the age of 15 is an indication for HyP assessment. Children with HyP might experience short dental roots, enamel opacities, hypodontia, and eruption dysfunctions. Copresence of APS-related type 1 diabetes mellitus (DM) enhances the risk of CMC, as well as periodontal disease (PD). Anemia-related mucosal pallor is related to DM, hypothyroidism, hypogonadism, corresponding gastroenterological diseases (Crohn’s disease also presents oral ulceration (OU), mucogingivitis, and a 2–3 times higher risk of PD; Biermer anemia might cause hyperpigmentation by itself), and rheumatologic diseases (lupus induces OU, honeycomb plaques, keratotic plaques, angular cheilitis, buccal petechial lesions, and PD). In more than half of the patients, associated vitiligo involves depigmentation of oral mucosa at different levels (palatal, gingival, alveolar, buccal mucosa, and lips). Celiac disease may manifest xerostomia, dry lips, OU,

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sialadenitis, recurrent aphthous stomatitis and dental enamel defects in children, a higher prevalence of caries and dentin sensitivity, and gingival bleeding. Oral pigmented lesions might provide a useful index of suspicion for AD in apparently healthy individuals, and thus an adrenocorticotropic hormone (ACTH) stimulation is useful. The spectrum of autoimmune AD comorbidities massively complicates the overall picture of oral manifestations.

**Keywords:** Addison disease; cortisol; adrenal insufficiency; oral; tongue; periodontal disease; pigmentation; candidiasis; ACTH; autoimmune

1. Introduction

Adrenal insufficiency, either primary, known as Addison disease (AD), or secondary, represents a life-threatening condition, affecting 20–50 persons per 100,000 in Europe [1]. Depending on the acute or chronic presentation of AD, the clinical picture can include low blood pressure and collapse; unintentional weight loss; loss of appetite; chronic asthenia; nausea; vomiting; and abdominal, muscle, or joint pain [2].

A high adrenocorticotropic hormone (ACTH) level causes lingual and buccal anomalies of melanocytes in AD, which are responsible for hyperpigmentation [2,3]. An intraoral pigmentation might be the only sign of AD, and an acute event requiring a higher cortisol amount such as an illness or an accident might cause an acute form of adrenal insufficiency, while the patient is still associated with this single hallmark of the underlying condition [4]. Anomalies of oral pigmentation might not always reflect the level of disease control, but they represent a particular clue for clinicians of different specialties, and it should be noted that AD is a severe disease with a fatal outcome without adequate hormonal replacement. Additional oral manifestations are found in AD patients through the association of nonadrenal diseases such as autoimmune conditions or genetic syndromes such as autoimmune polyglandular syndrome 1 (APS) [5].

AD requires lifelong substitution with glucocorticoids (two or three times daily) and mineralocorticoids (once per day) [6–8]. Despite advances in therapy and adequate patient education, subjects with AD are associated with a higher cardiovascular risk than the general population and a more affected quality of life (QL) [9,10]. Prompt recognition is mandatory, while treatment of associated complications and comorbidities, including oral manifestations, improves the prognosis and overall QL [9,10]. Modern management of AD seeks to identify new regimes of glucocorticoid administration in order to improve associated morbidity and mortality [6,11].

This review highlights multidisciplinary aspects of AD, focusing on oral anomalies that might have a major clinical impact. The perspective includes dental health aspects and dermatologic features. We followed two main aspects of oral manifestations: pigmentation issues which are related to specific hormonal anomalies in AD, and potential oral lesions in AD patients, especially in autoimmune AD, that are induced by AD-related diseases with a common genetic background or similar autoimmune mechanisms (Figure 1).
Figure 1. Overview of the main oral manifestations in Addison disease, either related to endocrine and immune dysfunction accompanying the disease itself (left side) or associated with a heterogeneous panel of comorbidities based on a common genetic or autoimmune background as seen in APS1, anemia, DM, vitiligo, and celiac disease (right side) (abbreviations: APS = autoimmune polyglandular syndrome; DM = diabetes mellitus) (see references in text).

2. Methods

The research was based on full-length, English literature, mostly PubMed papers, published between 2022 and 2012. The keywords of research were “Addison disease”, “adrenal insufficiency”, and “polyglandular autoimmune syndrome”, each in different combinations with “oral”, “dental”, “tongue”, “periodontal disease”, “candidiasis”, “diabetes”, “hypoparathyroidism”, “celiac disease”, “vitiligo”, “anemia”, etc. We introduce two figures showing oral manifestations in AD; the patients agreed to the use of these images.

2.1. AD and Mucosal Pigmentations

Proopiomelanocortin (POMC) is synthetized in corticotroph and melanotroph cells of the hypophyseal gland (anterior and intermediate lobes); POMC represents the subject of a tissue-specific post-translational cleavage that leads to active peptides such as ACTH which controls the adrenal cortex in addition to alpha-melanocyte stimulating hormone (MSH) or alpha-melanotropin that controls skin pigmentation through enhancing the dermal translocation of melanin granules and stimulation of melanogenesis [12,13]. Melanocortin receptors (MCRs) are responsible for these actions: MC1R is found in the skin, ACTH stimulates adrenal glucocorticoid production through MC2R activation, and MC3R and MC4R play different roles in several metabolic pathways (the role of MC5R is still incompletely described) [14]. On the other hand, hypothalamic corticotropin-releasing hormone (CRH) stimulates POMC gene expression in the pituitary gland, most of its actions being mediated by CRF1R and CRF2R receptors; CRH expression and its receptors in addition to POMC expression have also been identified in skin and mucosa, confirming a complex interaction between glucocorticoid axes and the cutaneomucosal system [15]. Conditions with POMC- and ACTH-associated pigmentation lesions include AD and Nelson’s syn-
drome (which develops in Cushing’s disease after bilateral adrenalectomy—typically a last option of therapy when all the other well-known methods have been unsuccessful), both of them underlying pituitary ACTH anomalies, while nonpituitary ACTH disorders include paraneoplastic (ectopic) Cushing’s syndrome, which particularly accompanies some types of neuroendocrine neoplasia and lung cancers that may produce abnormal ACTH with skin actions [16–20].

2.1.1. Oral Mucosa Pigmentation in AD

AD of different etiologies is associated with hyperpigmentation of the skin (mostly at the level of sun-exposed and friction areas, and tissues surrounding scars) as well as mucosa, including oral mucosa [21–23] (Figure 2).

![Figure 2. Young adult with Addison disease: clinical aspect of the pigmentary mucosa in the palatine arch in association with dental impressions (red arrow = pigmentary mucosa palatine, yellow arrow = dental impressions). The female patient was already diagnosed with AD with partial compliance with hormonal replacement therapy; oral manifestations were registered while she was under endocrine surveillance.](image)

Hyperpigmentation is identified in 92% of AD patients; it might be synchronous or precede general clinical manifestations by up to a decade [24]. Biopsy of pigmented lesions in AD shows not only melanocytic infiltration of the basal epidermal layer and melanophages in the superficial dermis, but also acanthosis, perivascular lymphocytic infiltrate, and hyperkeratosis [25]. While the buccal area is the most affected by oral mucosal lesions, the pigmentation may also be located on the palatine arches, lips, gums, and tongue [26–35].

Pigmented oral lesions vary from a patchy lesion (for instance, macular-like or nodular-like) to a diffuse colored area, underlying various histological types [26–35]. Different colors are described; the most frequent is dark brown or black [26–35]. The dark-blue tendency might be misinterpreted as cyanosis [34]. Many cases of oral hyperpigmentation are asymptomatic, but some are accompanied by local pain, itchiness, and burn-like lesions [26–35]. The combination of color, localization, and surface arrangement represents a useful index of suspicion for AD, especially in previously unrecognized AD cases [26–35]. It is essential to adequately investigate oral lesions since they are frequently registered before extraoral manifestations of AD, as opposed to skin hyperpigmentation which accompanies general signs and symptoms such as hypotension, nausea, vomiting, anorexia, and weight loss [26–35].

A tissue biopsy performed by an experienced dermatologist might prove useful in differentiating AD-related lesions from other conditions; yet, biopsy is not routinely indicated [29,30]. Further on, specific endocrine exploration is mandatory for confirmation and adequate therapy of AD in addition to multidisciplinary surveillance.
Other endocrine conditions displaying mucosal hyperpigmentation that should be differentiated from AD include Cushing’s disease, Graves’ disease, Nelson’s syndrome, and McCune–Albright syndrome, as well as other syndromes with potential endocrine involvement such as Peutz–Jeghers syndrome [33,36,37]. Among nonendocrine conditions, we mention smoker’s melanosis, drug- or tattoo-pigment-associated pigmentation, and Laugier–Hunziker syndrome [33,36–40]. Laugier–Hunziker syndrome represents a rare, noncongenital, benign pigmentation of the oral mucosa, lips, and nails, a condition that is typically a diagnostic of exclusion [38–40]. Genetic and inflammatory causes represent endogenous factors of pigmentation, while iatrogenic and environmental exposure is considered an exogenous factor [37]. Some authors reported a parallelism of oral pigmentation with similar lesions on nails [37,39,41].

From a histological perspective, melanocytic lesions, either solitary or multiple, involve a high concentration of reactive melanocytes due to hormonal stimulation, regardless of whether AD is caused by an autoimmune background or not [26–35]. The oral hyperpigmentation might not regress under glucocorticoid replacements for AD, despite clinical improvement and the control of serum ACTH levels being achieved [26–35]. Generally, the color of mucosal lesions is also related to nonmelanocyte elements such as vascularization of the adjacent conjunctive tissue and epithelial keratinization [33,42]. Gingival tissues commonly have a pale pink color, although the color may be related to the person’s skin color, tissue thickness, degree of keratinization, and various comorbidities [33,42]. Additionally, the level of circulating hemoglobin may influence the coloration, and it should be noted that AD-related anemia is not uncommon due to a heterogeneous panel of digestive complications; some anemia-related oral anomalies are also detectable before the actual diagnosis of the underlying condition [43,44]. Dantas et al. described the first case of oral multifocal melanoacanthoma (a rare, benign, pigmented lesion, usually involving both melanocytes and keratinocytes) in a 50-year-old patient who was newly diagnosed with synchronous AD and Basedow–Graves disease [31]. The patient was admitted for two pigmented spots at the level of her upper lip mucosa, and further investigations were necessary. Biopsy provided pathological confirmation as well as immunohistochemistry analysis for HMB-45, a promelanosome marker [31]. The lesion was not regressive at the moment the subject was treated for endocrine conditions of both the thyroid and adrenal glands [31]. Melanoacanthoma has a reactive pathogenesis in more than two-thirds of cases underlying different factors [32]. A rapidly growing lesion or the presence of an irregular shape indicates a biopsy [32].

2.1.2. AD-Related Tongue Anomalies of Color

Recently, tongue analysis has been the subject of interesting clinical and preclinical studies concerning general autoimmune conditions [45,46]. This muscle represents a frequently neglected subject of examination, yet it has a major role in daily life due to its involvement in eating, speech, and thus in overall QL [45,46]. Tongue evaluation is part of the orofacial assessment in patients with AD on first admission or during follow-up for adrenal disease [45–48] (Figure 3).

In AD, tongue discoloration is reported sometimes as the first sign of adrenal involvement; thus it is important to adequately investigate a patient who otherwise may be asymptomatic [47]. Seeker and Osswald recently reported a 33-year-old female admitted for tongue hyperpigmentation [47]. After an ACTH stimulation test was performed, AD was confirmed [47]. Even in apparently healthy subjects with an irrelevant general clinical exam and negative medical family history who are admitted for patchy changes in tongue color, the index of suspicion regarding AD should not be dismissed [45–48]. The pigmented lingual patches may be single or multiple; they are situated at the level of dorsal and lateral areas, either isolated or synchronous with similar lesions at other anatomical parts such as lips and palatine arches [45–48]. In addition to hormonal imbalance-related pigmentation, fungiform pigmented papillae are reported in AD individuals [49–51]. The dermoscopy examination is particularly useful for fungal etiology; yet, it does not represent a popular
method of investigation in dental and oral daily practice [50]. In addition, AD represents one of the rarest noncongenital causes of blue tongue, a temporary dyschromia that has been described in relationship with cyanosis or thrombocytosis [52].

Figure 3. Addison disease with poor control of disease in an adult male: tongue anomalies revealing depapillation with fissured and brown pigmented lingual features (red arrow shows brown pigmented lingual features; yellow arrow shows depapillation of the tongue in addition to fissured lesions). The patient was partially compliant with glucocorticoid substitution and showed poor nutritional status.

2.2. Spectrum of AD-Related Comorbidities: Oral Health Perspective
2.2.1. Oral Candidiasis in Patients with APS1

Candidiasis is part of APS1, also called autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), a rare monogenic condition underlying autoimmune regulator (AIRE) gene mutation on chromosome 21q22.3 [53–55]. The AIRE protein is responsible for immune self-tolerance which causes immune dysregulation and autoimmune conditions in APS1, typically involving the classical triad: AD, hypoparathyroidism, and chronic cutaneomucosal candidiasis [53–55]. Hypoparathyroidism is usually the first endocrine manifestation and the most common condition; moreover, APS1 includes type 1 diabetes mellitus (DM), autoimmune hypothyroidism, premature ovarian failure, and other nonendocrine disorders [56,57].

Chronic mucosal and skin candidiasis represents an early sign of APS1 which is caused by autoantibodies against interleukin (IL)-17A, IL-17F ± IL-22, and probably a high mucosal concentration of IFN-γ; excessive amounts of different autoantibodies represent an effect of defective thymic deletion induced by AIRE-mediated autoreactive T cells [58,59]. The assessment of autoantibodies against IL-17A/F and IL-6 might help in early clinical diagnosis [60].

Oral candidiasis must be recognized in relationship with APS-related adrenal insufficiency, especially in the pediatric population, since the syndrome onset typically occurs during childhood with a progressive risk of multiple organ involvement [54,61]. One particular clue before the actual endocrine diagnosis might be recurrent oral thrush [62]. Atypical presentations with adult onset of APS-related mucocutaneous candidiasis are reported; this rare syndrome represents a challenge in the adult population as well [63–65]. Tenório et al. recently reported a 42-year-old female diagnosed with chronic hyperplastic candidiasis, including angular cheilitis, in association with AD and hypoparathyroidism as part of APS1 [53]. She also presented microstomia, xerostomia, and dental anomalies such as hypoplastic teeth [53]. Local and/or systemic therapy with antifungal medication is useful in addition to careful hormonal substitution for AD [53].

A study published in 2021 on 938 cases of APECED showed the following: 57% of cases had classical triad; candidiasis was the earliest sign in 82% of subjects; hypoparathyroidism was the most frequent disorder (84%) while AD was the latest manifestation (72%); and 58% of patients had different infections, with 5% of them being adults at first APS1 diagnosis [66].
Another survey published in 2021 on 158 patients with APS1 who were followed for 23.7 ± 15.1 years showed that APS1 prevalence was 2.6 cases per 1 million, and the prevalence of AD, hypoparathyroidism, and chronic candidiasis was 77%, 86%, and 74%, respectively [67]. We also mention a prevalence of 29% for autoimmune intestinal disorders, 25% for pernicious anemia with atrophic gastritis, 17% for vitiligo, and 2.5% for celiac disease, all of these comorbidities with other potential oral manifestations [67].

The long-term evolution of untreated or suboptimally treated mucocutaneous candidiasis can lead to systemic candidiasis or even oral squamous cell carcinoma, chronic candidiasis being considered a procarcinogenic status in APS1 as suggested by some authors, based on Th17 cell anomalies [68,69].

Overall mortality is increased in APS1, and prompt treatment of each endocrine component, especially AD, and infections is mandatory [70,71]. A Finnish study on 91 patients with APS1 (between 1971 and 2018) confirmed the overall increased mortality, as expressed by a standardized mortality ratio of 11 (95% confidence interval between 7.2 and 16, p < 0.001) [71]. A cohort study on deceased patients with APS1 (between 1970 and 2019) showed that the most common cause of death was infections in 24% of the cases, followed by oral and esophageal cancers in 15% of them, followed by disturbances of the circulatory system with potential contribution of an adrenal crisis [70].

We also mention that diabetic patients (including APS-related DM) are prone to opportunistic infections such as oral candidiasis; the production of different exoenzymes such as phospholipases, hemolysinases, and esterase explains various virulence profiles among Candida species [72,73]. A study from 2021 on diabetic subjects with oral candidiasis identified 108 Candida species (75 of Candida albicans with the most powerful exoenzyme activity and 33 not of Candida albicans type) [72]. Generally, oral candidiasis may remain a superficial condition, or it might become invasive with multiorgan dissemination, especially in immunocompromised patients as seen in AD, APS1, and uncontrolled DM ± AD/APS [72,73]. The spectrum of effective antimycotic drugs includes nystatin, amphotericin, and miconazole; some of them might impair steroidogenesis through cytochrome 450 activity and precipitate an acute adrenal crisis in a previously unrecognized AD patient [72,73].

2.2.2. Early-Onset APS-Related Hypoparathyroidism and Dental Anomalies

As mentioned, autoimmune hypoparathyroidism is the earliest endocrine dysfunction in APS1, and thus children might experience the dental complications of persistent low parathormone (PTH) and low calcium levels [74–76]. Short dental roots, a challenge for orthodontists, with or without enamel hypoplasia/dysplasia are mostly reported [74,75,77]. These may be identified before the actual diagnosis of autoimmune AD [74,75]. While oral candidiasis is reported before the age of 5 in APS1 cases, enamel hypoplasia is typically registered before the age of 15, and thus the presence of chronic candidiasis in a child with dental enamel hypoplasia represents a warning sign for autoimmune hypoparathyroidism [74]. A systematic review on nonsurgical hypoparathyroidism and pseudohypoparathyroidism included 88 studies (9 transversal studies, 1 prospective study, 26 case series, and 55 case reports); the research revealed the most frequent dental anomalies in patients with low PTH are enamel hypoplasia, enamel opacities, hypodontia, and eruption anomalies [78]. Other dental anomalies that have been reported in hypoparathyroidism include delayed tooth eruption, poorly calcified dentin, and anomalies of dental development [79–81]. All mentioned dental manifestations are part of the more complex picture of oral manifestations in APS1 patients which includes not only chronic oral candidiasis and ACTH-related mucosal pigmentation, but also general symptoms/signs of chronic hypocalcemia such as paresthesia of the tongue and lips and facial muscle cramps (as seen in other body parts) [79–81].
2.2.3. From AD-Related type 1 DM to Periodontal Disease

AD is associated with type 1 DM in APS2 and rarely in APS1; the most common autoimmune associations of type 1 DM are AD and autoimmune diseases of the thyroid, and it has been noted that 8% of the general population suffers from an autoimmune disease [82–85]. A registry-based study on type 1 DM showed that patients with associated AD and/or antibody-induced thyroid diseases require higher insulin doses than patients with isolated type 1 DM [85]. Concerning DM and AD, both conditions involve abnormal T-cell behavior [82–84]. While no particular studies address the issue of periodontal disease (PD) in AD subjects, PD is essentially important in diabetic patients, and thus PD should be particularly taken into consideration in the diabetic subgroup of individuals with AD [86,87]. Currently, there is a very large number of studies targeting the topic of PD in the diabetic population as it represents a major health concern; for instance, a meta-analysis from 2022 identified 2151 scientific papers regarding DM–PD [88]. DM and PD are linked to chronic inflammation; adequate control of glycemia improves PD [89,90].

Generally, severe periodontal inflammation or bleeding requires prompt investigation of conditions such as DM, human immunodeficiency virus infection, thrombocytopenia (which also has been reported in autoimmune AD individuals due to similar antibodies), and leukemia [91,92]. As mentioned, DM causes anomalies of the oral microbiome at subgingival and salivary levels [93–95]. However, PD represents a multifactorial entity that is typically triggered by an infection with Gram-negative bacteria (for instance, Bacteroides forsythus, Porphyromonas gingivalis, and Prevotella intermedia), thus contributing to the onset of a local, progressive immune response based on the main features of bacteria: invasiveness and toxigenicity [96–100]. The bacterial cells interfere with periodontal cells through exotoxins, enzymes, and metabolites; then, exotoxins and leukotoxins interfere with polymorphonuclear leukocytes (PMNs), destroying the leukocytes in the gingival ditch and causing the colonization and invasion of the periodontal tissue [96–100]. Inflammatory mediators act on gingival conjunctive tissue, the periodontal ligament, and the alveolar bone [96–100]. Marginal periodontitis is triggered and supported by the activity of microorganisms within the bacterial plaque; still, the single presence of microorganisms is not the exclusive factor responsible for PD [97,101]. Porphyromonas gingivalis, for instance, was frequently associated with various endocrine conditions such as DM, obesity, and acromegaly [97–100]. This bacteria is able to disseminate within the peripheral blood flow, causing general inflammation [96–102]. Chronic periodontal inflammation induces the destruction of periodontal ligaments and alveolar bone, with consecutive tooth loss [103–105]. The covering periodontium (gingival fibromucosa) is affected, as is the support or apical periodontium, which is made of cementum, alveolar bone, and periodontal ligament [106–108]. An important role in the onset of endocrine periodontopathy is played by not only local factors within the oral cavity, but also an abnormal immune response at the level of periodontium [109,110]. Bacteria in the subgingival biofilm cause the migration of PMNs from the gingival ditch into the tissues, with the consecutive release of chemotactic factors for the circulating neutrophils [111–117]. Macrophages play an important role due to their main function, namely phagocytosis of pathogenic germs and cellular debris, and subsequently present the antigen information to B and T lymphocytes, triggering the adaptive specific immune response; macrophages also release cytokines such as IL-1, IL-17, tumor necrosis factor α (TNF), leukotrienes, and prostaglandins with a role in tissue destruction, finally causing alveolar bone resorption [111–117]. In the presence of a bacterial infection, PMNs release a high amount of metalloproteinase (MMP) in an attempt to neutralize the pathogens invading the periodontium [111–117]. Overproduction of MMPs leads to collagen (the main component of the periodontium) being damaged; thus, PMNs, which normally play a part in the organism’s defense, are the factor deteriorating the periodontium [111–117]. MMPs are endopeptidase enzymes, proteases with a role in the extracellular matrix, and are released by the epithelial keratinocytes, fibroblasts, macrophages, and leukocytes [111–117]. In chronic marginal periodontitis, levels of MMPs (for example, MMP-2, MMP-8, and MMP-9) are higher than those in the healthy periodon-
tium, and these high levels are associated with irreversible tissue damage and periodontitis progression; MMP-2 and MMP-9 may damage collagen type IV of the basal lamina and other matrix proteins, such as collagen types V and VII, fibronectin, laminin, and elastin, while MMP-8 destroys collagen types I, II, III, and VII [111–117]. Alterations of immune status are found in AD and DM patients, while generally both pathologies are associated with a higher risk of infections, especially in patients with suboptimal glucocorticoid replacement and patients with high levels of advanced glycation end-products (AGEs) [118]. Half of the acute presentations concerning AD are related to an infection that requires increasing glucocorticoid doses or switching to intravenous regimes, indicating that these individuals are more exposed to chronic complications as well, including infections and/or oral manifestations [119].

2.2.4. Anemia in AD Individuals

Anemia in AD has multifactorial mechanisms, clinically being manifested with oral mucosal pallor, among other manifestations; the panel of AD comorbidity-related anemia varies from endocrine disorders (autoimmune hypogonadism, DM, autoimmune hypothyroidism/myxoedema) to a heterogeneous group of nonendocrine autoimmune conditions [120,121]. Rheumatologic diseases such as lupus erythematosus and systemic sclerosis involve particular oral features; for instance, lupus induces ulcerations, honeycomb plaques, keratotic plaques, angular cheilitis, buccal petechial lesions, and a higher risk of periodontitis [120–126]. Gastroenterological conditions such as Crohn’s disease, ulcerative colitis, and gastritis have various oral anomalies; Crohn’s disease presents oral ulcerations, mucogingivitis, and a 2–3 times higher risk of PD than the general population [127–130]. One systematic review of six studies showed that patients with inflammatory bowel disease, either Crohn’s disease or ulcerative colitis, had a decayed, missing, and filled teeth (DMFT) index 3 times higher than that of the healthy population, which is suggestive of a more frequent past and present diagnosis of dental caries [129]. Autoimmune atrophic gastritis, more frequent in adults than in the pediatric population, requires a complex gastroenterological evaluation, even a gastric biopsy, as well as adequate replacements with vitamin B12; it is caused by antibodies against parietal cells and intrinsic factor [131,132]. The underlying vitamin B12 deficiency of Biermer’s disease might cause hyperpigmentation by itself, mimicking AD-associated hyperpigmentation [133]. Regardless of the presence of clear criteria for APS, individuals with gastric antibodies may present similar antibody-related conditions such as Hashimoto thyroiditis and myasthenia gravis and dermatologic disorders such as chronic urticaria, vitiligo, and lichen planus, all of these comorbidities with a heterogeneous potential for oral mucosa anomalies [132].

2.2.5. Oral Features of Other Non-DM, Autoimmune Comorbidities in AD Patients

Hashimoto thyroiditis accompanies autoimmune AD in APS2 (Schmidt syndrome), and rarely in APS1; generally, it is considered that autoimmune thyroid disease is the most frequent autoimmune condition associated with AD [134–136]. APS2 is a polygenic condition traditionally related to the human leukocyte antigen (HLA) complex on chromosome 6; APS2 includes AD and autoimmune hypothyroidism, as well as other endocrine disorders such as DM and premature ovarian failure [134–136]. A nationwide registry-based study published in 2022 including 912 subjects with autoimmune AD confirmed that 48% of them had an autoimmune thyroid disease (20% with hypothyroidism, 73% with subclinical hypothyroidism) as the most frequent endocrine comorbidity [137]. Congenital hypothyroidism and severe forms of hypothyroidism with early onset during childhood are associated with oral manifestations such as macroglossia, micrognathia, thick lips, enamel hypoplasia, and delayed tooth eruption, a picture which is less likely to be manifested in AD-associated autoimmune thyroid dysfunction [138]. A study from 2021 on 635 patients with hypothyroidism, mostly of autoimmune cause, who received 1480 implants between 2000 and 2017 showed that peri-implant bone loss was statistically significantly lower than
in patients with normal thyroid function, suggesting that the condition is not associated with a higher risk of dental implant failure, probably via lower metabolic rate [139].

A high rate of vitamin D deficiency (VDD) is reported among AD individuals; for instance, a study from 2022 on five European cohorts, a total of 1028 patients with autoimmune AD, found that 34–57% of them had VDV, defined as a level of 25-hydroxyvitamin D (25OHD) between 10 and 20 ng/mL, while 5–22% had severe VDV (a value of 25OHD below 10 ng/mL) [140]. VDV impacts general oral health, especially in children, pregnant women, and seniors (where reports showed correlations with bone density); it is suggested to be an additional contributor to PD, and probably to dental implant failure [141–143]. VD replacement might help the process of osseous integration after dental implants, as its role in bone healing has been noted [144,145].

Malabsorption in addition to celiac disease (CD) has been reported in AD patients; CD is an immune-mediated small intestinal disease affecting both children and adults, with a general prevalence in the general population of 0.5–1%; the diagnosis is based on clinical, serological assessments and small intestinal biopsies [146–148]. CD is associated with other autoimmune diseases: most often type 1 DM in children and teenagers and autoimmune thyroid disorders (mostly hypothyroidism) in adults, but also autoimmune types of AD, hepatitis, hypoparathyroidism, hypopituitarism, premature ovarian failure, etc. [147,149]. The enteropathy triggered by the ingestion of gluten is correlated with various oral manifestations such as xerostomia, dry lips, mucosal ulcerations, and sialadenitis [150]. A recent pediatric study confirmed that children with CD have a higher rate of recurrent aphthous stomatitis and dental enamel defects than the healthy population [151]. Moreover, CD is significantly associated with a higher prevalence of caries and dentin sensitivity, while an adequate gluten-free diet controls gingival bleeding [152].

Vitiligo has been reported in association with autoimmune AD, as well as other endocrine conditions, especially conditions of the thyroid, type 1 DM, etc. [153–155]. Vitiligo-associated depigmentation affects both teguments and mucosa, including the oral cavity [155,156]. One study on 100 patients diagnosed with vitiligo showed that 5% of them had buccal mucosa involvement, 8% had palatal lesions, 2% had gingival depigmentation, and 1% had alveolar mucosa anomalies, while lips (one or both) were affected in 42% of cases, with most of these subjects having associated facial extension [156]. Overall, more than half of the patients diagnosed with vitiligo had oral involvement of a different form [156].

2.2.6. Exceptional Entities of AD with Potential Oral Manifestations

Triple-A syndrome (also named Allgrove syndrome), another autosomal recessive disorder involving primary adrenal insufficiency (due to an ACTH resistant status), is a very rare condition with underlying mutations of the AAA (or AAAS) gene on chromosome 12q13 in 90% of cases; it also includes alacrimia (defects of tear formation) and (esophageal) achalasia, which induces difficulties of swallowing, dry mouth, and vomiting due to esophagitis with potential dental damage [157–160]. Tadini et al. reported a case of triple-A syndrome associated with peculiar dental anomalies [161].

Histoplasmosis, a common fungal infection caused by the fungus Histoplasma capsulatum, may cause both oral lesions and, rarely, dissemination to adrenals inducing AD [162–164]. The oral mucosa may be affected at any level, mostly being affected by tongue, buccal, and palatal ulcers with local pain, lesions that frequently cannot be distinguished from a malignant lesion unless a biopsy is performed [162]. A particular presentation is acquired perforating dermatosis with underlying damage to dermal proteins with pruritic nodules and hyperpigmentation [163]. Antifungal therapy is mandatory and cortisol replacement is lifesaving in adrenal histoplasmosis [163].

2.3. Oral Surgery Procedures in Patients with AD

Oral surgery procedures such as surgical third-molar removal, implant surgery, maxillary bone augmentation, and mucogingival surgery require higher doses of hydrocortisone
replacement or intravenous supplementation with close control of blood pressure in AD subjects [165–167]. On the other hand, there is the general issue of dental implants in patients with different autoimmune disorders. While no particular guidelines address this issue, most studies agree that the implant survival rates seem similar to those of the healthy population; however, the management of implant prosthetic treatment and follow-up needs to be adjusted depending on the disease [168–170].

Although limited data are specifically provided for AD individuals, the new implant techniques seem safe for a patient under adequate glucocorticoid replacement in addition to strict oral hygiene and serial check-up [171]. Another concern is related to a potential adrenal crisis in a dental patient. One review of the literature identified 148 articles concerning this particular matter and selected 34 papers for final analysis [172]. The results showed that an acute adrenal insufficiency under these circumstances is mostly triggered by pain, local infection, insufficient hormonal replacement, poor general health status, an invasive dental procedure, and the use of a barbiturate as a general anesthetic, and the risk of crisis was estimated by authors to be 1 in 650,000 AD patients [172]. Dental health practitioners must take into consideration the special needs of an AD patient, and they should be aware of particular orodental aspects in these subjects [173,174].

Generally, a patient with AD is more prone to develop any type of infection, including in the oral area, which requires prompt recognition and specific anti-infectious therapy and adjustment of hydrocortisone substitution [175,176]. Patient education is essential for good long-term management, including dose adjustment to daily stress; the indication for switching the oral regime; and the recognition of infections and other general health issues, including dental health, that might interfere with glucocorticoid replacement [175,177].

3. Conclusions

It is essential to adequately investigate oral pigmented lesions since they are frequently registered before extraoral manifestations of AD, as opposed to skin hyperpigmentation which accompanies general signs and symptoms. An oral lesion might provide a useful index of suspicion in apparently healthy individuals. The spectrum of autoimmune/non-autoimmune comorbidities massively complicates the overall picture of oral manifestations in AD, and thus awareness is important. The key operative strategy under these circumstances is a multidisciplinary team, from the first diagnosis of an AD-associated oral lesion to the entire period of endocrine surveillance.

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Abbreviations

- ACTH: adrenocorticotropic hormone
- AGEs: advanced glycation end-products
- AD: Addison disease
- APS: autoimmune polyglandular syndrome
- APECED: autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy
- CD: celiac disease
- DM: diabetes mellitus
- DMFT index: decayed, missing, and filled teeth index
- HLA: human leukocyte antigen
- 25OHD: 25-hydroxyvitamin D
- IL: interleukin
- MMP: metalloproteinase
- MSH: melanocyte stimulating hormone
- MCR: melanocortin receptor
- PD: periodontal disease
- PMC: proopiomelanocortin
- PMN: polymorphonuclear leukocyte
- PTH: parathormone
- TNF: tumor necrosis factor
- QL: quality of life
- VDD: vitamin D deficiency

References

1. Nowotny, H.; Ahmed, S.F.; Bensing, S.; Beun, J.G.; Brösamle, M.; Chifu, I.; Claahsen van der Grinten, H.; Clemente, M.; Falhammar, H.; Hahner, S.; et al. Therapy options for adrenal insufficiency and recommendations for the management of adrenal crisis. Endocrine 2021, 71, 586–594. [CrossRef]
2. Husebye, E.S.; Pearce, S.H.; Krone, N.P.; Kämpe, O. Adrenal insufficiency. Lancet 2021, 397, 613–629. [CrossRef]
3. Rehman, H.U.; Lohrenz, S. Hyperpigmentation of the Tongue and Buccal Mucosa. Am. Fam. Physician 2020, 102, 181–182. [PubMed]
4. Sarkar, S.B.; Sarkar, S.; Ghosh, S.; Bandyopadhyay, S. Addison’s disease. Contemp. Clin. Dent. 2012, 3, 484–486. [CrossRef] [PubMed]
5. Napier, C.; Pearce, S.H. Current and emerging therapies for Addison’s disease. Curr. Opin. Endocrinol. Diabetes Obes. 2014, 21, 147–153. [CrossRef]
6. Michelet, R.; Melin, J.; Parra-Guillen, Z.P.; Neumann, U.; Whitaker, J.M.; Stachanow, V.; Huisinga, W.; Porter, J.; Blankenstein, O.; Ross, R.J.; et al. Paediatric population pharmacokinetic modelling to assess hydrocortisone replacement dosing regimens in young children. Eur. J. Endocrinol. 2020, 183, 357–368. [CrossRef]
7. Oprea, A.; Bonnet, N.C.G.; Pollé, O.; Lysy, P.A. Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. Ther. Adv. Endocrinol. Metab. 2019, 10, 2042018818821294. [CrossRef]
8. Giordano, R.; Guaraldi, F.; Berardelli, R.; Karamouzis, I.; D’Angelo, V.; Zichi, C.; Grottioli, S.; Ghigo, E.; Arvat, E. Dual-release Hydrocortisone in Addison’s Disease—A Review of the Literature. Eur. Endocrinol. 2014, 10, 75–78. [CrossRef]
9. Mundell, L.; Lindemann, R.; Douglas, J. Monitoring long-term oral corticosteroids. BMJ Open Qual. 2017, 6, e000209. [CrossRef]
10. Arshad, M.F.; Debono, M. Current and future treatment options for adrenal insufficiency. Curr. Opin. Endocrinol. Diabetes Obes. 2021, 28, 303–311. [CrossRef]
11. Sandru, F.; Petrova, E.; Petrov, B.; Draghici, A.; Ghemigian, A.; Carsote, M.; Dumitrascu, A.; Dumitrascu, M.C. Not just weight loss. Ro J. Med. Pract. 2021, 16, 529–532. [CrossRef]
12. Hasenmajer, V.; Bonaventura, I.; Minnetti, M.; Sada, V.; Sbardella, E.; Isidori, A.M. Non-Canonical Effects of ACTH: Insights Into Adrenal Insufficiency. Front. Endocrinol. 2021, 12, 701263. [CrossRef] [PubMed]
13. Pondeljak, N.; Lugović-Mihilić, L. Stress-induced Interaction of Skin Immune Cells, Hormones, and Neurotransmitters. Clin. Ther. 2020, 42, 757–770. [CrossRef] [PubMed]
14. Novoselova, T.V.; Chan, L.F.; Clark, A.J.L. Pathophysiology of melanocortin receptors and their accessory proteins. Best Pract. Res. Clin. Endocrinol. Metab. 2018, 32, 93–106. [CrossRef] [PubMed]
15. Rassouli, O.; Liapakis, G.; Venihaki, M. Role of Central and Peripheral CRH in Skin. Curr. Mol. Pharmacol. 2018, 11, 72–80. [CrossRef]
16. Tutal, E.; Yılmazer, D.; Demirci, T.; Cakir, E.; Gültakin, S.S.; Celep, B.; Topaloğlu, O.; Çakal, E. A rare case of ectopic ACTH syndrome originating from malignant renal paraganglioma. Arch. Endocrinol. Metab. 2017, 61, 291–295. [CrossRef]
17. Mehta, R.; Lam-Chung, C.E.; Hinojosa-Amaya, J.M.; Roldán-Sarmiento, P.; Guillen-Placencia, M.F.; Villanueva-Rodriguez, G.; Juarez-Leon, O.A.; Leon-Dominguez, J.; Grajales-Gomez, M.; Ventura-Gallegos, J.L.; et al. High Molecular Weight ACTH-
Precursor Presence in a Metastatic Pancreatic Neuroendocrine Tumor Causing Severe Ectopic Cushing’s Syndrome: A Case Report. Front. Endocrinol. 2020, 11, 557. [CrossRef]

Tan, H.; Chen, D.; Yu, Y.; Yu, K.; He, W.; Cai, B.; Jiang, S.; Tang, Y.; Tong, N.; An, Z. Unusual ectopic ACTH syndrome in a patient with orbital neuroendocrine tumor, resulted false-positive outcome of BIOPSSa case report. BMC Endocr. Disord. 2020, 20, 116. [CrossRef] [PubMed]

Sandra, F.; Dumitrescu, M.C.; Albu, S.E.; Carsote, M.; Valea, A. Hyperpigmentation and ACTH—An overview of literature. Rom. Med. J. 2019, 66, 309–312. [CrossRef]

Morar, A.; Chemigian, A.; Tupea, C.; Petrova, E.; Popescu, M.; Carsote, M.; Dumitru, N.; Valea, A. Twist of endocrine scenario: Approach of ectopic Cushing syndrome (review). Rom. J. Med. Pract. 2020, 15, 405–409. [CrossRef]

Ramawaka, N.; Welikumbura, N.H. Addison’s disease as a primary manifestation of extrapulmonary tuberculosis; A case report. Indian J. Tuberc. 2021, 68, 405–407. [CrossRef] [PubMed]

Soedarso, M.A.; Nugroho, K.H.; Meira Dewi, K.A. A case report: Addison disease caused by adrenal tuberculosis. Urol Case Rep. 2018, 20, 12–14. [CrossRef] [PubMed]

Freitas, P.F.S.; Oliveira, J.M.; Kater, C.E. Crisis? What crisis? Abdominal pain and darkening skin in Addison’s disease. Lancet 2020, 396, 498. [CrossRef]

Freedt, M.E.; Topor, L.S. Case 3: Emesis and Oral Hyperpigmentation in a 17-year-old Girl. Pediatr. Rev. 2018, 39, 421–423. [CrossRef] [PubMed]

Fernandez-Flores, A.; Cassarino, D.S. Histopathologic Findings of Cutaneous Hyperpigmentation in Addison Disease and Immunostain of the Melanocytic Population. Am. J. Dermatopathol. 2017, 39, 924–927. [CrossRef] [PubMed]

Gondak, R.O.; da Silva-Jorge, R.; Jorge, J.; Lopes, M.A.; Vargas, P.A. Oral pigmented lesions: Clinicopathologic features and review of the literature. Med. Oral Patol. Oral Cir. Bucal 2012, 17, e919–e924. [CrossRef] [PubMed]

das Chagas e Silva de Carvalho, L.F.; Farina, V.H.; Cabral, L.A.G.; Brandão, A.A.H.; Coletta RDella Almeida, J.D. Immunohistochemi cal features of multifocal melanoacanthoma in the hard palate: A case report. BMC Res. Notes 2013, 6, 30. [CrossRef] [PubMed]

Rohilla, K.; Ramesh, V.; Balamurali, P.D.; Singh, N. Oral melanoacanthoma of a rare intraoral site: Case report and review of literature. Int. J. Clin. Pediatr. Dent. 2013, 6, 40–43. [CrossRef]

Maymone, M.B.C.; Greer, R.O.; Burdine, L.K.; Dao-Cheng, A.; Venkatesh, S.; Sahitya, P.C.; Maymone, A.C.; Kesecker, J.; Vashi, N.A. Benign oral mucosal lesions: Clinical and pathological findings. J. Am. Acad. Dermatol. 2019, 81, 43–56. [CrossRef]

Maymone, M.B.C.; Greer, R.O.; Kesecker, J.; Sahitya, P.C.; Burdine, L.K.; Cheng, A.D.; Maymone, A.C.; Vashi, N.A. Premalignant and malignant oral mucosal lesions: Clinical and pathological findings. J. Am. Acad. Dermatol. 2019, 81, 59–71. [CrossRef]

Dantas, T.S.; Nascimento, I.V.D.; Verde, M.E.Q.L.; Alves, A.P.N.N.; Sousa, F.B.; Mota, M.R.L. Multifocal oral melanoacanthoma associated with Addison’s disease and hyperthyroidism: A case report. Arch. Endocrinol. Metab. 2017, 61, 403–407. [CrossRef] [PubMed]

Cantundo-Sanagustín, E.; Gutiérrez-Corralles, A.; Vigo-Martínez, M.; Serrera-Figallo, M.Á.; Torres-Lagares, D.; Gutiérrez-Pérez, J.L. Pathogenesis and clinicopathohistopathometrics of melanoacanthoma: A systematic review. J. Clin. Exp. Dent. 2016, 8, e327–e336. [CrossRef]

Lee, K.; Lian, C.; Vaidya, A.; Tsibris, H.C. Oral mucosal hyperpigmentation. JAAD Case Rep. 2020, 6, 993–995. [CrossRef] [PubMed]

Takagi, D.; Ben-Ari, J.; Nemet, D.; Eliakim, A. The interpretation of color—An endocrine cause of skin discoloration mimicking cyanosis. J. Pediatr. 2018, 26, 579–581. [CrossRef] [PubMed]

Manna, R.; Bianchi, A.; Gerardino, L.; Cipolla, C.; Rigante, D.; Landolfi, R. Neuropsychiatric symptoms, oral pigmentation and fever as revealing hints of autoimmune Addison’s disease. Minerva Endocrinol. 2021, 36, 421–423. [CrossRef] [PubMed]

Alawi, F. Pigmented lesions of the oral cavity: An update. Dent. Clin. N. Am. 2013, 57, 699–710. [CrossRef] [PubMed]

Rosebush, M.S.; Briody, A.N.; Cordell, K.G. Black and Brown: Non-neoplastic Pigmentation of the Oral Mucosa. Head Neck Pathol. 2019, 13, 47–55. [CrossRef]

Sputa-Grzegrzolka, P.; Wozniak, Z.; Akutko, K.; Pytrus, T.; Baran, W.; Calik, J.; Glatzel-Plucinska, N.; Domagala, Z.; Podhorska- Okolow, M.; Stawarski, A.; et al. Laugier-Hunziker syndrome: A case report of the pediatric patient and review of the literature. Int. J. Dermatol. 2020, 59, 1513–1519. [CrossRef]

Milićević, T.; Žaja, I.; Tešanović, D.; Radman, M. Laugier-Hunziker syndrome—a case report of the pediatric patient and review of the literature. J. Dtsch. Dermatol. Ges. 2013, 12, 59–65. [CrossRef] [PubMed]

Lalosevic, J.; Zivanovic, D.; Skiljevic, D.; Medenica, L. Laugier-Hunziker syndrome—Case report. Bras Dermatol. 2015, 90 (Suppl. S1), 223–225. [CrossRef] [PubMed]

Díka, E.; Starace, M.; Lamberti, M.; Patrizi, A.; Veronesi, G.; Alessandrin, A.; Piraccini, B.M. Oral and nail pigments: A useful parallelism for the clinician. J. Dtsch. Dermatol. Ges. 2020, 18, 7–14. [CrossRef]

Malpartida-Carrillo, V.; Tinedo-Lopez, P.L.; Guerrero, M.E.; Amaya-Pajas, S.P.; Özcan, M.; Rösing, C.K. Periodontal phenotype: A review of historical and current classifications evaluating different methods and characteristics. J. Esthet. Restor. Dent. 2021, 33, 432–445. [CrossRef]

Wémeau, J.L.; Proust-Lemoine, E.; Ryndak, A.; Vanhove, L. Thyroid autoimmunity and polyglandular endocrine syndromes. Hormones 2013, 12, 39–45. [CrossRef]
44. Al-Zahrani, M.S.; Alhassani, A.A.; Zawawi, K.H. Clinical manifestations of gastrointestinal diseases in the oral cavity. *Saudi Dent. J.* 2021, 33, 835–841. [CrossRef]
45. Gameiro, R.S.; Reis, A.I.A.; Grilo, A.C.; Noronha, C. Following leads: Connecting dysphagia to mixed connective tissue disease. *BMJ Case Rep.* 2018, 2018, bcr2017223699. [CrossRef]
46. Goto, A.; Kokabu, S.; Dusadeemeelap, C.; Kawae, H.; Matsubara, T.; Tominaga, K.; Addison, W.N. Tongue Muscle for the Analysis of Head Muscle Regeneration Dynamics. *J. Dent. Res.* 2022, 22, 220345221075966. [CrossRef]
47. Seeker, P.; Osswald, S. Tongue Discoloration. *N. Engl. J. Med.* 2021, 384, e102. [CrossRef]
48. Rodríguez-Jiménez, P.; Muñoz-Aceituno, E.; Vargas, E. Hyperpigmentation of the tongue. *Cutis* 2020, 106, E21–E22. [CrossRef] [PubMed]
49. Ross, C.L.; Ring, C.; Yang, S. Pigmented Fungiform Papillae of the Tongue. *JAMA Dermatol.* 2022, 156, 1249. [CrossRef]
50. Ko, E.; Panchal, N. Pigmented Lesions. *Dermatol. Clin.* 2022, 38, 485–494. [CrossRef] [PubMed]
51. Cohen, F.R. Acquired Asymptomatic Blue Tongue: A Report of Exogenous Agent-associated Tongue Dyschromia and Review of Blue Tongue Etiologies. *Cureus* 2019, 11, e6243. [CrossRef] [PubMed]
52. Tenório, J.R.; Tuma, M.M.; Andrade, N.S.; Santana, T.; Galliotini, M. Oral manifestations of autoimmune polyglandular syndrome type 1. *Spec. Care Dentist.* 2022. [CrossRef] [PubMed]
53. Nisticò, D.; Bossini, B.; Benvenuto, S.; Pellegrin, M.C.; Tornese, G. Pediatric Adrenal Insufficiency: Challenges and Solutions. *Ther. Clin. Risk Manag.* 2018, 14, 47–60. [CrossRef] [PubMed]
54. Halabi, I.; Barohom, M.N.; Peleg, S.; Trougouboff, P.; Elias-Assad, G.; Agbaria, R.; Tenenbaum-Rakover, Y. Case Report: Severe Hypocalcemic Episodes due to Autoimmune Enteropathy. *Front. Endocrinol.* 2021, 12, 645279. [CrossRef]
55. Cranston, T.; Boon, H.; Olesen, M.K.; Ryan, F.J.; Shears, D.; London, R.; Rostom, H.; Elajnaf, T.; Thakker, R.V.; Hannan, F.M. Spectrum of germline AIRE mutations causing APS-1 and familial hypoparathyroidism. *Eur. J. Endocrinol.* 2022, 187, 111–122. [CrossRef] [PubMed]
56. Peterson, P.; Kisand, K.; Kluger, N.; Ranki, A. Loss of AIRE-Mediated Immune Tolerance and the Skin. *J. Investig. Dermatol.* 2022, 142 Pt B, 760–767. [CrossRef]
57. Philippot, Q.; Casanova, J.L.; Puel, A. Candidiasis in patients with APS-1: Low IL-17, high IFN-γ, or both? *Curr. Opin. Immunol.* 2021, 72, 318–323. [CrossRef]
58. Oikonomou, V.; Break, T.J.; Gaffen, S.L.; Moutsopoulos, N.M.; Lionakis, M.S. Infections in the monogenic autoimmune syndrome APECED. *Curr. Opin. Immunol.* 2022, 72, 286–297. [CrossRef]
59. Puel, A.; Bastard, P.; Bustamante, J.; Casanova, J.L. Human autoantibodies underlying infectious diseases. *J. Exp. Med.* 2022, 219, e20211387. [CrossRef]
60. Besnard, M.; Padonou, F.; Provín, N.; Giraud, M.; Guillonneau, C. AIRE deficiency, from preclinical models to human APECED disease. *Dis. Model Mech.* 2021, 14, dmm046359. [CrossRef] [PubMed]
61. Sivabalan, S.; Mahadevan, S.; Srinath, M.V. Recurrent oral thrush. *Indian J. Pediatr.* 2014, 81, 394–396. [CrossRef] [PubMed]
62. Pontannini, V.C.; Jayachandran, S.; Mahadevan, S.; Kayal, L.; Bakyalakshmi, K. Autoimmune polyglandular syndrome type 1. *J. Clin. Imaging Sci.* 2012, 2, 62. [CrossRef] [PubMed]
63. Sanjeevi, A.; Asirvatham, A.R.; Balachandran, K.; Mahadevan, S. Atypical presentation of autoimmune polyglandular syndrome type 1 in the fifth decade. *BMJ Case Rep.* 2014, 2014, bcr20142381. [CrossRef]
64. Ferré, E.M.N.; Schmitt, M.M.; Lionakis, M.S. Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy. *Front Pediatr.* 2021, 9, 723532. [CrossRef]
65. Sharifinejad, N.; Zaki-Dizaji, M.; Tebyanian, S.; Zainaldin, H.; Jamee, M.; Rizvi, F.S.; Hosseinzadeh, S.; Fayyaz, F.; Hamedifar, H.; Sabzevari, A.; et al. Clinical, immunological, and genetic features in 938 patients with autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED): A systematic review. *Expert Rev. Clin. Immunol.* 2021, 17, 807–817. [CrossRef]
66. Garelli, S.; Dalla Costa, M.; Sabbadin, C.; Barollo, S.; Rubin, B.; Scarpa, R.; Masiero, S.; Fierabracci, A.; Bizzarri, C.; Criniò, A.; et al. Autoimmune polyglandular syndrome type 1: An Italian survey on 158 patients. *J. Endocrinol. Invest.* 2021, 44, 2493–2510. [CrossRef]
67. Gambardella, L.; Cornu, M.; Proust-Lemoine, E.; Bayry, J.; Wemeau, J.L.; Vantyghem, M.C.; Sendid, B. Chronic Mucocutaneous Candidiasis in Autoimmune Polyendocrine Syndrome Type 1. *Front. Immunol.* 2018, 9, 2570. [CrossRef]
68. Shephard, M.K.; Schifter, M.; Palme, C.E. Multiple oral squamous cell carcinomas associated with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* 2012, 114, e46–e42. [CrossRef]
69. Borchers, J.; Måktie, O.; Laakso, S. Infections and demanding endocrine care contribute to increased mortality in patients with APECED. *Eur. J. Endocrinol.* 2021, 185, K13–K17. [CrossRef]
70. Borchers, J.; Pukkala, E.; Måktie, O.; Laakso, S. Patients With APECED Have Increased Early Mortality Due to Endocrine Causes, Malignancies and infections. *J. Clin. Endocrinol. Metab.* 2020, 105, e2207–13. [CrossRef] [PubMed]
71. Nouraei, H.; Jahromi, M.G.; Jahromi, L.R.; Zomorodian, K.; Pakshir, K. Potential Pathogenicity of Candida Species Isolated from Oral Cavity of Patients with Diabetes Mellitus. *Biomed Res. Int.* 2021, 9982744. [CrossRef]
73. Pallavan, B.; Ramesh, V.; Dhanasekaran, B.P.; Oza, N.; Indu, S.; Govindarajan, V. Comparison and correlation of candidal colonization in diabetic patients and normal individuals. J. Diabetes Metab. Disord. 2014, 13, 66. [CrossRef] [PubMed]

74. Perniola, R.; Fierabracci, A.; Falorni, A. Autoimmune Addison’s Disease as Part of the Autoimmune Polyglandular Syndrome Type I: Historical Overview and Current Evidence. Front. Immunol. 2021, 12, 606860. [CrossRef]

75. Fierabracci, A.; Lanzillotta, M.; Vorguín, I.; Palma, A.; Kataníč, D.; Betterle, C. Report of two siblings with APECED in Serbia: Is there a founder effect of c.769C>T AIRE genotype? Ital. J. Pediatr. 2021, 47, 126. [CrossRef] [PubMed]

76. Gallacher, A.A.; Pemberton, M.N.; Waring, D.T. The dental manifestations and orthodontic implications of hypoparathyroidism in childhood. J. Orthod. 2018, 45, 46–50. [CrossRef] [PubMed]

77. Kamarthi, N.; Venkatraman, S.; Patil, P.B. Dental findings in the diagnosis of idiopathic hypoparathyroidism. Ann. Saudi Med. 2013, 33, 411–413. [CrossRef] [PubMed]

78. Hejlesen, J.; Underbjerg, L.; Gjørup, H.; Bloch-Zupan, A.; Sikjaer, T.; Rejnmark, L.; Haubek, D. Dental Findings in Patients With Non-surgical Hypoparathyroidism and Pseudohypoparathyroidism: A Systematic Review. Front. Physiol. 2018, 9, 701. [CrossRef] [PubMed]

79. Mittal, S.; Gupta, D.; Sekhn, S.G. Oral manifestations of parathyroid disorders and its dental management. J. Dent. Allied Sci. 2014, 3, 34–38. [CrossRef]

80. Giusti, F.; Brandi, M.L. Clinical Presentation of Hypoparathyroidism. Front. Horm. Res. 2019, 51, 139–146. [CrossRef]

81. Al-Azem, H.; Khan, A.A. Hypoparathyroidism. Best Pract. Res. Clin. Endocrinol. Metab. 2012, 26, 517–522. [CrossRef] [PubMed]

82. Bouça, B.; Nogueira, A.; Caetano, J.; Cardoso, R.; Dinis, I.; Mirante, A. Clinical characteristics of polyglandular autoimmune syndromes in pediatric age: An observational study. J. Pediatr. Endocrinol. Metab. 2022, 35, 477–480. [CrossRef] [PubMed]

83. Nelson, H.A.; Joshi, H.R.; Straseski, J.A. Mistaken Identity: The Role of Autoantibodies in Endocrine Disease. J. Appl. Lab. Med. 2022, 7, 206–220. [CrossRef] [PubMed]

84. Røyrvik, E.C.; Husebye, E.S. The genetics of autoimmune Addison disease: Past, present and future. Nat. Rev. Endocrinol. 2022, 18, 399–412. [CrossRef]

85. Prinz, N.; Tittel, S.R.; Bachran, R.; Birnbacher, R.; Brückel, J.; Dunstheimer, D.; Haberland, H.; Hess, M.; Karges, W.; Oeverink, R.; et al. Characteristics of Patients with Type 1 Diabetes and Additional Autoimmune Disease in the DPV Registry. J. Clin. Endocrinol. Metab. 2021, 106, e3381–e3389. [CrossRef]

86. Silva, N.; Abusleme, L.; Bravo, D.; Dutzan, N.; García-Sesních, J.; Vernal, R.; Hernández, M.; Gamonal, J. Host response mechanisms in periodontal diseases. J. Appl. Oral Sci. 2015, 23, 329–355. [CrossRef] [PubMed]

87. John, V.; Alqallaf, H.; De Bedout, T. Periodontal Disease and Systemic Diseases: An Update for the Clinician. J. Indiana Dent. Assoc. 2016, 95, 16–23. [PubMed]

88. Sun, S.; Mao, Z.; Wang, H. Relationship between periodontitis and diabetes: A bibliometrics analysis. Ann. Transl. Med. 2022, 10, 401. [CrossRef] [PubMed]

89. Mathew, A.; Mn, P.; Menon, P.K.; Radeideh, A.; Varma, S.; Thomas, S.; Varughese, N.; Hamed, G.M. A Clinical Study on Obesity, bariatric surgery and periodontal disease: A literature update. J. Contemp. Dent. Pract. 2021, 22, 329–355. [CrossRef] [PubMed]

90. Marchio, V.; Derchi, G.; Cinquini, C.; Miceli, M.; Gabriele, M.; Alfonsi, F.; Barone, A. Tissue level implants in healthy versus between Periodontal and Systemic Diseases. J. Evid. Based Dent. Pract. 2022, 20, 16–23. [PubMed]

91. Kudiyirickal, M.G.; Pappachan, J.M. Diabetes mellitus and oral health. Endocrine 2015, 49, 23–34. [CrossRef] [PubMed]

92. Elebrashy, I.; Yousief, E.; Saif, A. Primary anti-phospholipid antibody syndrome causing recurrent venous thrombosis and thrombocytopenia in a patient with Addison’s disease. JRM Open 2014, 5, 2054270414562985. [CrossRef] [PubMed]

93. Silva, D.N.A.; Casarin, M.; Monajemzadeh, S.; Bezerra, B.B.; Lux, R.; Pirihi, E.Q. The Microbiome in Periodontitis and Diabetes. Front. Metab. Physiol. Drug Targets 2021, 21, 777–784. [CrossRef] [PubMed]

94. Ozdemir, Y.; Keceli, H.G.; Helvaci, N.; Erbas, T.; Nohutcu, R.M. The tendency of reduced periodontal destruction in acromegalic patients showing similar inflammatory status with periodontitis patients. Endocrine 2019, 66, 622–633. [CrossRef]

95. Jain, A.; Gupta, S.; Bhansali, A.; Gupta, M.; Jain, A.; Bhaskar, N.; Kaur, R.K. Impact of concurrent diabetes on periodontal health in patients with acromegaly. Sci. Rep. 2020, 10, 19170. [CrossRef] [PubMed]

96. Sun, X.; Li, M.; Xia, L.; Fang, Z.; Yu, S.; Gao, J.; Feng, Q.; Yang, P. Alteration of salivary microbiome in periodontitis with or without type-2 diabetes mellitus and metformin treatment. Sci. Rep. 2020, 10, 15363. [CrossRef] [PubMed]

97. Isacco, C.G.; Ballini, A.; De Vito, D.; Nguyen, K.C.D.; Cantore, S.; Bottalico, L.; Quagliuolo, L.; Boccellino, M.; Di Domenico, M.; Santacroce, L.; et al. Rebalancing the Oral Microbiota as an Efficient Tool in Endocrine, Metabolic and Immune Disorders. Endocr. Metab. Immune Disord. Drug Targets 2021, 21, 777–784. [CrossRef] [PubMed]

98. Yang, Y.; Liu, S.; Wang, Y.; Wang, Z.; Ding, W.; Sun, X.; He, K.; Feng, Q.; Zhang, X. Changes of salivary microbiota in the onset and after the treatment of diabetes in patients with periodontitis. Aging 2020, 12, 13090–13114. [CrossRef] [PubMed]
Diagnostics 2022, 12, 2080

102. Ding, W.; Xiao, Z.; Wen, C.; Ge, C.; Liu, L.; Xu, K.; Cao, S. Correlation between salivary developmental endothelial locus-1, interleukin 1 expression level and severity of periodontal disease in patients with type 2 diabetes mellitus. *Am. J. Transl. Res.* 2021, 13, 11704–11710. [PubMed]

103. Holmstrup, P.; Piemons, J.; Meyle, J. Non-plaque-induced gingival diseases. *J. Periodontol.* 2018, 89 (Suppl. S1), S28–S45. [CrossRef] [PubMed]

104. Özşaka, O.; Ceyhan-Öztürk, B.; Gümüş, P.; Akcali, A.; Nalbantsoy, A.; Buduneli, N. Clinical periodontal status and inflammatory cytokines in gestational diabetes mellitus. *Arch. Oral. Biol.* 2016, 72, 87–91. [CrossRef] [PubMed]

105. Islam, S.K.; Seo, M.; Lee, Y.S.; Moon, S.S. Association of periodontitis with insulin resistance, β-cell function, and impaired fasting glucose before onset of diabetes. *Endocr. J.* 2015, 62, 981–989. [CrossRef]

106. Buysschaert, M.; Medina, J.L.; Bergman, M.; Shah, A.; Lonier, J. Prediabetes and associated disorders. *Endocrine* 2015, 48, 371–393. [CrossRef] [PubMed]

107. Akcalı, A.; Bostanci, N.; Ö兹Çaka, O.; Özttürk-Ceyhan, B.; Gümüþ, P.; Buduneli, N.; Belibasakis, G.N. Association between polycystic ovary syndrome, oral microbiota and systemic antibody responses. *PLoS ONE* 2014, 9, e108074. [CrossRef] [PubMed]

108. Khocht, A.; Albandar, J.M. Aggressive forms of periodontitis secondary to systemic disorders. *Periodontol 2000* 2014, 65, 134–148. [CrossRef] [PubMed]

109. Timonen, P.; Saxlin, T.; Knuuttila, M.; Suominen, A.L.; Tervonen, T.; Ylöstalo, P. Role of insulin sensitivity and beta cell function in the development of periodontal disease in adults without diabetes. *J. Clin. Periodontol.* 2013, 40, 1078–1086. [CrossRef]

110. Akcalı, A.; Bostanci, N.; Özçaka, O.; Öztürk-Ceyhan, B.; Gümüþ, P.; Buduneli, N.; Belibasakis, G.N. Association of periodontitis with insulin resistance, β-cell function, and impaired fasting glucose before onset of diabetes. *Endocr. J.* 2015, 62, 981–989. [CrossRef] [PubMed]

111. Umeizudike, K.; Räisänen, L.; Gupta, S.; Nwhator, S.; Grigoriadis, A.; Sakellari, D.; Sorsa, T. Active matrix metalloproteinase-8: A potential biomarker of oral systemic link. *Clin. Exp. Dent. Res.* 2022, 8, 359–365. [CrossRef]

112. Zhang, F.; Liu, E.; Radaic, A.; Yu, X.; Yang, S.; Yu, C.; Xiao, S.; Ye, C. Diagnostic potential and future directions of matrix metalloproteinases as biomarkers in gingival crevicular fluid of oral and systemic diseases. *Int. J. Biol. Macromol.* 2021, 188, 180–196. [CrossRef]

113. Szczepanik, F.S.C.; Grossi, M.L.; Casati, M.; Goldberg, M.; Glogauer, M.; Fine, N.; Tenenbaum, H.C. Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way. *Periodontol 2000* 2020, 84, 45–68. [CrossRef]

114. Checchi, V.; Maravic, T.; Generali, L.; Consolo, U.; Breschi, L.; Mazzoni, A. The Role of Matrix Metalloproteinases in Periodontal Disease. *Int. J. Environ. Res. Public Health* 2020, 17, 4923. [CrossRef]

115. Ghassib, I.; Chen, Z.; Zhu, J.; Wang, H.L. Use of IL-1 β, IL-6, TNF-α, and MMP-8 biomarkers to distinguish peri-implant diseases: A systematic review and meta-analysis. *Clin Implant Dent. Relat. Res.* 2019, 21, 190–207. [CrossRef]

116. Al-Majid, A.; Alassiri, S.; Rathnayake, N.; Tervahartiala, T.; Gieselmann, D.R.; Sorsa, T. Matrix Metalloproteinase-8 as an Inflammatory and Prevention Biomarker in Periodontal and Peri-Implant Diseases. *Int. J. Dent.* 2019, 2018, 7891323. [CrossRef]

117. de Morais, E.F.; Dantas, A.N.; Pinheiro, J.C.; Leite, R.B.; Galvao Barboza, C.A.; de Vasconcelos Gurgel, B.C.; de Almeida Freitas, R. Matrix metalloproteinase-8 analysis in patients with periodontal disease with prediabetes or type 2 diabetes mellitus: A systematic review. *Arch Oral Biol.* 2018, 87, 43–51. [CrossRef]

118. Chopra, A.; Jayasinghe, T.N.; Eberhard, J. Are Inflamed Periodontal Tissues Endogenous Source of Advanced Glycation End Products (AGEs) in Individuals with and without Diabetes Mellitus? A Systematic Review. *Biomolecules* 2022, 12, 642. [CrossRef]

119. Goubar, T.; Torpy, D.J.; McGrath, S.; Rushworth, R.L. Prehospital Management of Acute Addison Disease: Audit of Patients Attending a Referral Hospital in a Regional Area. *J. Endocr. Soc.* 2019, 3, 2194–2203. [CrossRef]

120. Angelousi, A.; Larger, E. Anaemia, a common but often unrecognized risk in diabetic patients: A review. *Diabetes Metab.* 2015, 41, 18–27. [CrossRef]

121. Valea, A.; Carsote, M. Diagnosis of Addison’s disease in a patient with newly diagnosed renal insufficiency having a context of autoimmune poly-endocrine syndrome. *Acta Med. Transilv.* 2016, 21, 45–47.

122. Hussain, S.B.; Leira, Y.; Zehra, S.A.; Botelho, J.; Machado, V.; Ciurtin, C.; D’Aiuto, F.; Orlandi, M. Periodontitis and Systemic Lupus Erythematosus: A systematic review and meta-analysis. *J. Periodontal. Res.* 2022, 57, 1–10. [CrossRef] [PubMed]

123. Manfredini, M.; Pedroni, G.; Bigi, L.; Apponi, R.; Murri Dello Diago, A.; Dattola, A.; Farnetani, F.; Pellacani, G. Acquired White Oral Lesions with Specific Patterns: Oral Lichen Planus and Lupus Erythematosus. *Dermatol. Pract. Concept.* 2021, 12, 981–989. [CrossRef]

124. Schmalz, G.; Patschan, S.; Szczepanik, F.S.C.; Grossi, M.L.; Casati, M.; Goldberg, M.; Glogauer, M.; Fine, N.; Tenenbaum, H.C. Periodontitis is an inflammatory disease of oxidative stress: We should treat it that way. *Periodontol 2000* 2020, 84, 45–68. [CrossRef]

125. Baumrin, E.; Webster, G.; Werth, V.P. Addison Disease and Discoid Lupus Erythematosus: A Rare Association of Polyclagular Autoimmune Syndrome Type II. *J. Rheumatol. 2016*, 42, 382–383. [CrossRef]

126. Buysschaert, M.; Medina, J.L.; Bergman, M.; Shah, A.; Lonier, J. Prediabetes and associated disorders. *Endocrine* 2015, 48, 371–393. [CrossRef] [PubMed]
Diagnostics 2022, 12, 2080

157. Gaiani, F.; Gismondi, P.; Minelli, R.; Casadio, G.; de’Angelis, N.; Fornaroli, F.; de’Angelis, G.L.; Manfredi, M. Case report of a familial triple: A syndrome and review of the literature. Medicine 2020, 99, e20474. [CrossRef]

158. Nakamura, J.; Hikichi, T.; Inoue, H.; Watanabe, K.; Kikuchi, H.; Takagi, T.; Suzuki, R.; Sugimoto, M.; Konno, N.; Waragai, Y.; et al. Per-oral endoscopic myotomy for esophageal achalasia in a case of Allgrove syndrome. Clin. J. Gastroenterol. 2018, 11, 273–277. [CrossRef]

159. Dhar, M.; Verma, N.; Singh, R.B.; Pai, V.K. Triple A to triple S: From diagnosis, to anesthetic management of Allgrove syndrome. J. Clin. Anesth. 2016, 33, 141–143. [CrossRef]

160. Pogliaghi, G.; Cangiano, B.; Duminuco, F.; Vezzoli, V.; Bonomi, M. Triple-A Syndrome (TAS): An In-Depth Overview on Genetic and Phenotype Heterogeneity. Protein Pept. Lett. 2020, 27, 1192–1203. [CrossRef]

161. Tadini, G.; Besagni, F.; Callea, M.; Brena, M.; Rossi, L.C.; Angiero, F.; Crippa, R. Allgrove syndrome: A report of a unique case characterised by peculiar dental findings resembling those of ectodermal dysplasia. Eur. J. Paediatr. Dent. 2015, 16, 324–326. [PubMed]

162. Folk, G.A.; Nelson, B.L. Oral Histoplasmosis. Head Neck Pathol. 2017, 11, 513–516. [CrossRef] [PubMed]

163. Singh, M.; Chandy, D.D.; Bharani, T.; Marak, R.S.K.; Yadav, S.; Dabadghao, P.; Gupta, S.; Sahoo, S.K.; Pandey, R.; Bhatia, E. Clinical outcomes and cortical reserve in adrenal histoplasmosis-A retrospective follow-up study of 40 patients. Clin. Endocrinol. 2019, 90, 534–541. [CrossRef] [PubMed]

164. Strietzel, F.P.; Schmidt-Westhausen, A.M.; Neumann, K.; Reichart, P.A.; Jackowski, J. Implants in patients with oral manifestations of autoimmune or muco-cutaneous diseases—A systematic review. J. Oral Rehabil. 2016, 43, 388–399. [CrossRef]

165. Facco, E.; Bacci, C.; Zanette, G. Hypnosis as sole anesthesia for oral surgery: The egg of Columbus. Clin. Anesth. 2014, 41, 342–344. [CrossRef] [PubMed]

166. Woodcock, T.; Barker, P.; Daniel, S.; Fletcher, S.; Wass, J.A.H.; Tomlinson, J.W.; Misra, U.; Dattani, M.; Arlt, W.; Vercueil, A. Guideline for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency: Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK. Anaesthesia 2020, 75, 654–663. [CrossRef]

167. Esimekara, J.O.; Perez, A.; Courvoisier, D.S.; Scozzoli, P. Dental implants in patients suffering from autoimmune diseases: A systematic critical review. J. Stomatol. Oral Maxillofac. Surg. 2022. [CrossRef] [PubMed]

168. Khalaf, M.W.; Khader, R.; Cobetto, G.; Yepes, J.F.; Karounos, D.G.; Miller, C.S. Risk of adrenal crisis in dental patients: Results of a systematic search of the literature. J. Am. Dent. Assoc. 2013, 144, 152–160. [CrossRef] [PubMed]

169. Carmona, D.; Ouanounou, A. Adrenal Insufficiency and Its Implications on Dental Treatment. Compend. Contin. Educ. Dent. 2021, 42, 422–428. [PubMed]

170. Reichart, P.A.; Schmidt-Westhausen, A.M.; Khongkhunthian, P.; Strietzel, F.P. Dental implants in patients with oral mucosal diseases—A systematic review. J. Oral Rehabil. 2016, 43, 388–399. [CrossRef]

171. Esimekara, J.O.; Perez, A.; Courvoisier, D.S.; Scozzoli, P. Dental implants in patients suffering from autoimmune diseases: A systematic critical review. J. Stomatol. Oral Maxillofac. Surg. 2022. [CrossRef] [PubMed]

172. Khalaf, M.W.; Khader, R.; Cobetto, G.; Yepes, J.F.; Karounos, D.G.; Miller, C.S. Risk of adrenal crisis in dental patients: Results of a systematic search of the literature. J. Am. Dent. Assoc. 2013, 144, 152–160. [CrossRef] [PubMed]

173. Carmona, D.; Ouanounou, A. Adrenal Insufficiency and Its Implications on Dental Treatment. Compend. Contin. Educ. Dent. 2021, 42, 422–428. [PubMed]

174. Henderson, S. What steroid supplementation is required for a patient with primary adrenal insufficiency undergoing a dental procedure? Dent. Update 2014, 41, 342–344. [CrossRef] [PubMed]

175. Strietzel, F.P.; Schmidt-Westhausen, A.M.; Neumann, K.; Reichart, P.A.; Jackowski, J. Implants in patients with oral manifestations of autoimmune or muco-cutaneous diseases—A systematic review. J. Oral Rehabil. 2016, 43, 388–399. [CrossRef]

176. Guignat, L.; Proust-Lemoine, E.; Reznik, Y.; Zenaty, D. Group 6. Modalities and frequency of monitoring of patients with adrenal insufficiency. Patient education. Ann. Endocrinol. 2017, 78, 544–558. [CrossRef] [PubMed]

177. Falorni, A.; Minarelli, V; Morelli, S. Therapy of adrenal insufficiency: An update. Endocrine 2013, 43, 514–528. [CrossRef] [PubMed]