

Autoimmune Diseases with Oral Manifestations in Children: A Systematic Review

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Abstract

Autoimmune disease is a general term for a variety of conditions that involve damage to the immune system's complex. In a normal immune response to infection or invasion, the immune system causes temporary inflammation in reaction to kill cells that cause damage. Oral symptoms and signs are often the first manifestations of autoimmune disease in children. Oral manifestations are often seen as the main sign of autoimmune disease. Oral lesions that are a manifestation of autoimmune disease may show clinical signs in the form of ulcers, erosions, vesicobuloses, plaques or papules, etc. Oral lesions must be handled properly to prevent secondary infection, manage pain and improve the quality of life of the patient. Therefore, dentists can play an important role in detecting and during multidisciplinary care related diseases. This review is aimed to describing the presentation of oral manifestations in autoimmune diseases occurring in children, because early and appropriate diagnosis increases the efficiency and efficacy of autoimmune disease treatment strategies in children.

Keywords: *Autoimmune Diseases, Oral Manifestations, Children*

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Introduction

The human body basically has the ability to defend itself when experiencing a disease, which is known as the immune system or immune system. In healthy individuals, the immune system constantly protects us from foreign microorganisms, such as viruses, bacteria, and parasites that can cause a person to develop a disease. However, in some individuals this protection can be mistaken, leading to the tissues and cells themselves, giving rise to autoimmunity. The disease that results from this occurrence is known as an autoimmune disease.¹

Autoimmune disease is an immune response that causes damage to the body's own tissues and disrupts the body's physiological functions. Autoimmune diseases can attack any part of the body with the classic autoimmune sign of inflammation.² Autoimmune disease is a general term for a variety of conditions that involve damage to the complex immune system. In a normal immune response to infection or invasion, the immune system causes temporary inflammation in response to killing cells that cause damage.³ In autoimmune diseases, this inflammation becomes chronic, causing pain and permanent changes or damage to the tissues involved. There is no specific cause for autoimmune disorders; they show patterns of remission and recurrence and they are difficult to diagnose because specific disorders have different symptoms and individual symptoms varies.² The cause of autoimmune disease is not known with certainty, but the course of the disease can be acute or

chronic and there are periods of remission or exacerbation accompanied by changes in autoantibody levels in the body. The pathogenic mechanism of autoimmunity is multifactorial and largely unknown.³ The combination of genetic predisposing factors and environmental factors is known through various references to contribute to the development of autoimmune diseases.³ However, there are many factors that influence autoimmune diseases, such as genetics, age, sex, reproductive status, and hormones.⁴ The immune system is a set of cellular, chemical and protein dissolved mechanisms, which function to protect the body against foreign substances such as infection and tumor cells, without any self-molecules. The distinction between self-molecules and foreign substances occurs through a complex mechanism that depends on the molecules recognizing certain substances that enter on the surface of competent cells and activate the immune system, in particular, T and B lymphocytes. A small proportion of T and B lymphocytes form a normal part of the immune cell pool. Autoimmunity is defined as the development of immune system reactivity in the form of auto-antibodies and T-cell responses to the body's own structures.⁵ The clinical appearance of autoimmune diseases with a similar appearance between autoimmune diseases requires additional methods of diagnosis. Additional testing methods, such as special staining, immunohistochemical (IHC) testing, and immunopathological and serological testing, can help differentiate between seemingly similar lesions. A brief

overview of immunopathological testing is provided: in direct immunofluorescence (DIF) testing, a frozen perillated tissue biopsy specimen is preserved with fluorescein labeled antibodies and evaluated under a fluorescence microscope. Specimens for DIF must be brought to the laboratory in a special medium, most commonly Michel's solution, but other options include Zeus medium, liquid nitrogen, or sometimes saline but rarely, only short term storage. Fibrinogen, C3, IgA, IgM, and IgG represent antibodies that are evaluated during the test. In contrast, indirect immunofluorescence testing (IIF) uses patient serum applied to a secondary substrate that is tested for the presence of fluorescein labeled antibodies.⁶ The salt breakdown technique can be performed either directly on the patient's tissue or indirectly using serum and is used to differentiate between specific entities. with similar histology and DIF results.^{6,7}

This multifactorial cause makes autoimmune disease a disease that has continued to increase globally since the end of World War II. The autoimmune pandemic includes 80 diseases that have increased in both incidence and prevalence. This disease is more common in women and is the 10th leading cause of death in girls and women of all ages in the United States. Autoimmune diseases account for about 8% of the population worldwide, 78% of whom are women.^{7,8} The World Health Organization records the number. People with lupus, one of the autoimmune diseases in the world, currently reach five million people, and each year more than 100 thousand new cases are found. According to 2016 Online Hospital Information System (SIRS) data, there were 2,166 hospitalized patients diagnosed with lupus. This trend has more than doubled compared to 2014, when 1,169 new cases were found. The high mortality rate due to lupus needs special attention because 25% or around 550 people died from lupus in 2016. Some lupus sufferers are women from the productive age group (15-50 years), even so lupus can also affect men, children. children and adolescents.⁶

Autoimmune disorders can also be grouped into two categories based on the organ being attacked, namely single and systemic organs. Single organ means that the immune system attacks a particular organ, whereas systemic means that the immune system attacks several organs or broader body systems. Classification or generally grouped as such because it is useful in defining therapy, which may differ according to the pathogenic mechanism.⁷

This autoimmune disease can occur in any organ, for example the skin or oral mucosa. On the oral mucosa autoimmune disease can be a manifestation or a side effect of medication.⁶ Oral manifestations are often found as the main sign of autoimmune disease. Oral lesions that are a manifestation of autoimmune disease may show clinical signs in the form of ulcers, erosions, vesicobuloses, plaques or papules, etc. Oral lesions should be treated properly to prevent secondary infection, manage pain and improve the patient's quality of life.^{7,8} Therefore, dentists can play an important role in detecting and during multidisciplinary treatment of disease. Early and precise diagnosis increases the efficiency and efficacy of treatment strategies.^{9,10,11,12,13} The aim of this systematic review is to present the most common autoimmune diseases presenting early clinical signs and symptoms that are manifestations of common clinical disease. The review in this paper provides details about autoimmune diseases with clinical manifestations in the oral cavity including Systemic Lupus Erythematosus (SLE), and Diabetes Mellitus Type 1 in children.

Systemic lupus erythematosus (SLE) is a chronic, severe autoimmune inflammatory disease of unknown etiopathogenesis and multiple clinical presentations. SLE primarily affects women 8 times more likely than men. The prevalence of SLE worldwide ranges between 12 and 50 per 100,000, depending on location and ethnicity.^{10,14} SLE is a chronic autoimmune disorder characterized by the production of antinuclear autoantibodies. Immune complexes (hypersensitivity type III) are formed and deposited along the basement membrane resulting in basal damage. In cases of SLE, there is involvement of multisystem organs and can lead to kidney, lung, heart and joint disease.^{15,16}

In addition to SLE, other autoimmune diseases that occur in children are diabetes mellitus (DM) type 1. Chronic hyperglycemia in diabetes causes damage to the cardiovascular system, kidneys, eyes, nerves, and patients who are often immunocompromised.¹⁷ There are several implications of oral diabetes. This review focuses on diabetes mellitus type 1 because of its autoimmune pathophysiology.¹⁸ Diabetes treatment focuses on regulating blood glucose levels through regular testing, insulin use, and diet control. Diabetes mellitus type 1 occurs from the destruction of the pancreatic β cells which secrete autoimmune causes decreased insulin production. Further away from this long term illness often results in a total loss of insulin production. However, 10-30% of patients do not have auto-detectable antibodies, and in these cases, the pathogenesis of diabetes remains unclear.^{19,20} . Diabetes mellitus type 1 is caused by autoimmune breakdown of pancreatic β -cells resulting in absolute insulin deficiency. . Diabetes mellitus type 1 is usually diagnosed before the age of 21 and constitutes 5–10% of all diabetes cases.¹⁷ The description above explains how autoimmune diseases can occur with oral symptoms. In this regard, the aim of writing a systematic review is to identify and present the most common autoimmune diseases in children presenting with early oral clinical signs and symptoms that are manifestations of common clinical disease.

Methods

Search Strategy

The data source in this study comes from an online database that provides articles in PDF format, namely Pubmed. Articles were analyzed through objective analysis, topic suitability, research methods used, sample size, and the results of each article. Data search is limited by the period, namely the data taken is data from 2015-2020 and the data collection is not limited by language. The data search was carried out systematically using the keywords *autoimmune disease, systemic lupus erythematosus, diabetes mellitus type 1, children, oral manifestations*. A manual search was also carried out on references from each journal relevant to this research.

Inclusion Criteria

1. Articles published from 2015-2020
2. Published scientific articles available online.
3. An article that discusses autoimmune diseases, SLE and Type 1 DM with oral manifestations.

Exclusion Criteria

1. Articles included in the systematic review or literature review
2. Incomplete or inaccessible articles for free

Data Collection

The data that will be used in this research are secondary

data. The data is obtained from the articles that are searched in the article database which will then be reviewed according to the research criteria set by the researcher. A literature search was carried out on the PubMed online database, and several other online sites. In addition, a search for the list of references to articles that fall into the inclusion criteria was also carried out to find out whether there were other related studies that were relevant to this research. The data search was carried out systematically using the keywords *autoimmune disease, systemic lupus erythematosus, diabetes mellitus type 1, children, oral manifestations*. Elimination of duplicated literature Articles were screened for title, abstract, and keyword, year of publication. Read complete or partial articles that have not been eliminated to determine whether the articles meet the eligibility criteria. Data collection was done manually by making data extraction formulas.

Based on the articles that have been included in this study, it can be seen that autoimmune diseases can impact oral health, both directly and indirectly.¹ It is important for dental and medical practitioners to understand the relationship of autoimmune diseases to oral health, and the two-way impact between autoimmune diseases and oral health.³ Oral lesions are common in people with autoimmune diseases as a manifestation of disease or a side effect of medication. Oral lesions that are manifestations of autoimmune disease can include ulcers, erosions, vesicobuloses, plaques or papules, and others. Oral lesions must be handled properly to prevent secondary infection, manage pain and improve the quality of life of people with autoimmune diseases.¹⁰ The overall articles found that oral lesions are common in people with SLE, type 1 DM, and several other autoimmune diseases. happens to children.

Discussion

The infectious rate that can occur in pediatric patients with SLE was observed to account for 61% of cases of invasive fungal infections that can occur in SLE patients.¹⁵ The oral mucosa is involved in 30 to 45% of cases. Clinically, there are extensive painful erosions, or ulcers surrounded by a red or whitish zone. Common findings include petechiae, edema, bleeding, and xerostomia. White hyperkeratotic lesions are rarely observed. The palate, lips, and buccal mucosa are the sites most commonly involved. The oral manifestations of SLE are not pathognomonic.⁹

Research by Rita Fonseca et al explained Demographic analysis, clinical and immunological variables were compared between two groups according to age at diagnosis JSLE in children (≤ 16 years) and adult with SLE (> 16 years).³⁰ Apart from the general factors that can cause manifestations due to autoimmune diseases such as in the case we got from the article that a patient had a history of mosquito bites on his cheek which became red and swollen without any symptoms of infection such as pain, tenderness, and warmth. This can occur. Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease.

The patient's previous condition was fine until he was bitten by a mosquito. Researchers suspect that mosquito bites in genetically susceptible patients can trigger several of the mechanisms mentioned above, resulting in ongoing inflammation and triggering a recurrence of lupus.^{23,34,35,36,37}

There is an increasing incidence of diabetes mellitus in children and adolescents around the world. These increases include type-1 diabetes mellitus and early-onset type-2.^{38,39} Previous studies have been conducted aimed at examining the impact of type-1 diabetes mellitus on oral health-related

quality of life (OHRQoL) of children aged 12–15 years in Saudi Arabia. is based on the fact that this age group exhibits significant physiological and psychological changes.⁴⁰ The onset of adolescence has been shown to increase significant challenges for glycemic control in pediatric patients with diabetes mellitus.⁴¹

Diabetes Mellitus type 1 sufferers often show clinical signs and symptoms, namely polydipsia, polyuria, polyphagia, pruritus, a weak body and fatigue more easily than type 2 diabetes. In type 1 or type 2 diabetes there are macrovascular complications which are the development of atherosclerosis and microvascular complications, retinopathy, nephropathy and neuropathy.¹⁶ Various complications of diabetes can manifest in the oral cavity. Neuropathy causes hyposalivation so that the mucosal surface becomes dry, a burning sensation in the mouth, an increase in the incidence of caries and an increase in the frequency and severity of bacterial or fungal infections.¹⁷ Periodontal disease is included in the six complications of diabetes so diabetes does not directly cause periodontal disease but is a risk factor. Periodontal disease is more caused by plaque accumulation which is exacerbated by predisposing factors, one of which is diabetes. In addition, periodontal disease can also worsen glycemic control in diabetics.^{17,18} The management of each manifestation of the oral cavity due to systemic diseases must still be considered because not all autoimmune diseases have the same manifestations, here is a further explanation regarding the handling of each case of oral manifestations due to autoimmune diseases.

Systemic lupus erythematosus (SLE)

Regular oral examinations are recommended to provide treatment and diagnosis of SLE because of the specific symptoms of the disease. Regular follow-up is also highly recommended and invasive dental procedures require expert advice. However, it is very important to consider the treatment used by the patient to improve the treatment strategy while minimizing the risk of complications.⁴¹ Regarding the treatment of oral mucosal SLE lesions, no randomized clinical trials have been conducted. Oral lesions can respond to systematic treatment used to alleviate the disease and should be evaluated first. When symptomatic intraoral lesions are present, topical steroids should be considered. The following are types of topical steroids that can be used.

Topical anti-inflammatory drugs are the treatment of choice for oral ulcers in SLE in children. Topical corticosteroids (eg, triamcinolone oral paste 0.1%) are one of the most commonly used drugs in JSLE patients, and shorten the course and severity of ulcers. The duration of corticosteroid use depends on the severity of the symptoms. If the oral lesion is refractory to treatment, then stronger drugs (eg betamethasone or clobetasol in oral preparations) or systemic drugs may be required.^{34,35} However, some oral ulcers are very difficult to treat even when high potency topical corticosteroids are applied, especially palatal erythematous ulcers and oral DLE. Steroid-sparing agents, such as calcineurin inhibitors (eg, 0.03 or 0.1% tacrolimus) may also be applied when corticosteroid side effects are a concern.³⁶ Another route of administration of corticosteroids, intra-lesional injection, is rarely used, especially in children, because of pain. It appears that systemic corticosteroids are usually prescribed as first-line drugs for the treatment of SLE because most patients develop multiorgan involvement and these drugs

dramatically improve clinical signs and symptoms, including mouth ulcers.³⁷

However, some types of immunosuppressive drugs used to treat SLE can trigger opportunistic fungal and viral infections. Opportunistic oral infections can also result from immunological defects, which are part of the pathogenesis. Another complication of the drugs used in the treatment of SLE is mucosal ulceration caused by the frequent exploitation of NSAIDs. Oral mucosal lesions often reflect disease activity. They may subside spontaneously but can also last for months or even years.⁴

The prognosis of children with SLE has improved due to advances in medical care. According to one study, adolescent-onset SLE has a 5-year survival rate of 92% and a 10-year survival rate of 85%. Causes of death in affected children are kidney disease, infection, and CNS disease. A multidisciplinary team approach to the care of children and their families is ideal.^{42,43,44}

Antimalarial drugs, such as hydroxychloroquine, are usually used as first-line drugs in combination with systemic corticosteroids if the patient requires systemic therapy. However, it can be used as monotherapy in mild cases of SLE with mucocutaneous manifestations (eg, malar rash, discoid rash, photosensitivity, including oral ulcers). Complete blood counts, eye examinations and liver function tests should be monitored, as drug toxicity can occur in children.^{45,46}

Diabetes mellitus type 1

Health is a state of health both physically, mentally, spiritually, and socially, which enables everyone to live productively socially and economically. A person is said to be healthy not only determined by general health but also the health of their teeth and mouth.¹⁵ Dental and oral health have an important role and are related to general health. One of the most common dental and oral health problems is periodontal disease and can be associated with various systemic diseases such as diabetes mellitus.¹⁶

Oral hygiene is an important factor that determines the health of the oral cavity. How to maintain oral hygiene can be achieved by brushing your teeth 2 times a day, flossing, using mouthwash, and visiting the dentist regularly every 6 months. Periodontal disease is one of the six complications of diabetes. The management of periodontal tissue infections can be done by maintaining oral hygiene and by improving glycemic control, although this does not appear to be significant in type 1 diabetes. Thus, good oral hygiene still needs to be established from the start, especially to prevent the severity of the oral manifestations of type 1 diabetes, whose onset begins at an early age.¹⁵

The important thing that must be given priority to diabetics is because diabetes is a chronic disease whose treatment requires a patient's cooperative attitude, among others, regularly controlling his blood sugar levels. People with uncontrolled diabetes plus the long duration of the disease can exacerbate oral complications and worsen the level of oral hygiene. Several studies suggest that uncontrolled type 1 diabetics tend to have a higher index of oral hygiene than people with controlled diabetes. So the importance of maintaining oral health and always followed by controlling the condition of diabetes sufferers.^{15,16}

Another important thing related to the management of type 1 diabetes mellitus in children is the role of parents. Parents' knowledge regarding the problem of diabetes mellitus is not only limited to what this disease is like in general, but also related to the handling of manifestations in the oral cavity,

namely by regularly visiting the dentist. In a study conducted by Diaz et al. demonstrated that parents of children with type 1 diabetes have poor knowledge of their children's oral health and its effects on general health as well as on diabetes metabolic control. like the data in table 4 below. Therefore, the education of the parents and their active involvement in the self-management of their child's diabetes are important tools to achieve the desired goals.²¹ Lifestyle management is also important for pediatric patients with diabetes mellitus type 1 and allows health maintenance, prevention of cardiovascular disease (CVD), and glycemic control. Lifestyle management includes a healthy approach to nutrition and exercise. Training young patients and their families in medical nutritional therapy and approaches to reducing the hypo- and hyperglycemic effects of exercise is part of diabetes self-management education and support, which registered dietitians, diabetes educators, exercise specialists / physiologists, and endocrinologists should provide. pediatric. Extensive training should be carried out at diagnosis, with annual updates by a registered dietitian. Quarterly visits with diabetes educators and endocrinologists ensure ongoing training throughout childhood and adolescence.^{47,48,49,50,51,52}

Conclusion

Autoimmune diseases in children can directly and indirectly affect the oral cavity and have various clinical presentations. While doctors or dentists still need to understand the signs and symptoms as well as the mechanisms that cause autoimmune disease manifestations of the mouth or the mechanisms by which systemic autoimmune diseases affect the oral cavity, there is clearly a two-way relationship. It is important to always educate the patient that not only curing the disease but maintaining good oral health is an important component to support the management of pediatric patients with autoimmune diseases.

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Figure 1. A flow chart describing the search methodology and numbers of articles included/excluded at each stage

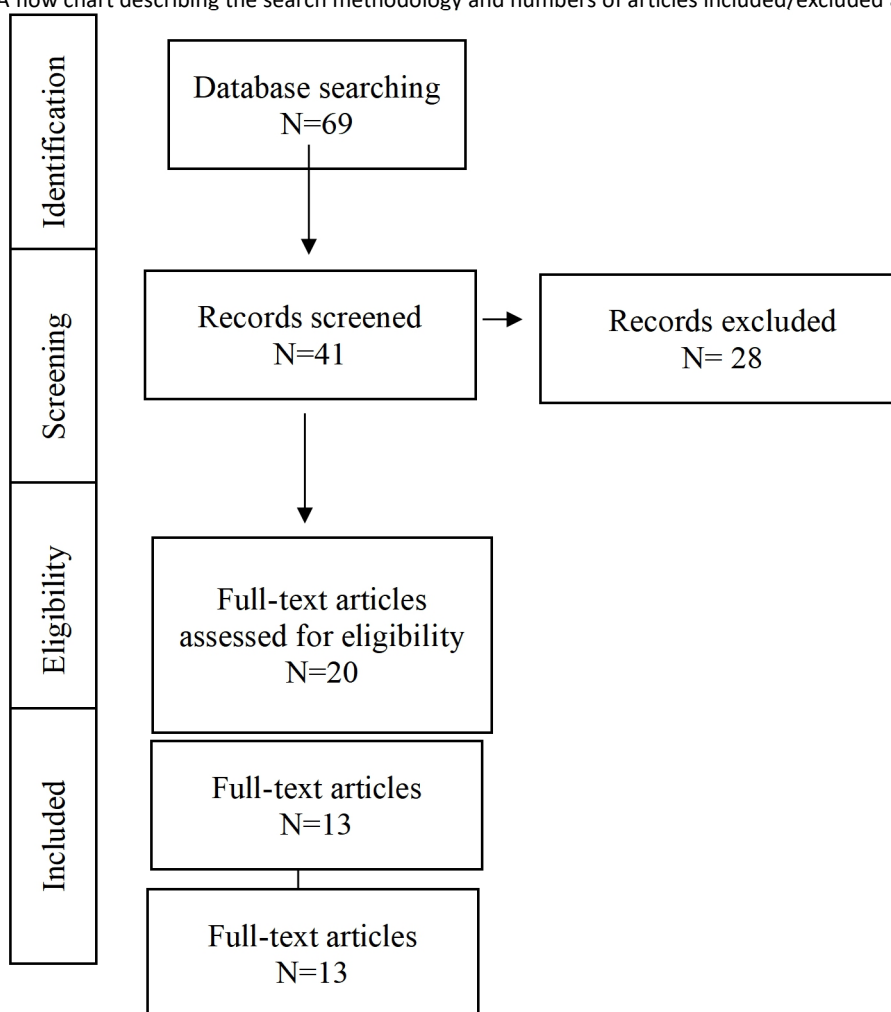


Table 1. Oral manifestations in autoimmune disease, SLE, and Type 1 DM in children

Author, country (year)	Journal	Title	Sampel	Result	Conclusion
Díaz Rosas, et al., Mexico (2018) ²¹	Europe an Journal of Paediat ric Dentistr y	Dental, periodontal and salivary conditions in diabetic children associated with metabolic control variables and nutritional plan adherence	60 paediatric patients	This study identified several correlated variables, which show a strong relationship between patient nutrition and the occurrence of physiopathological changes in the oral cavity.	The results of this study concluded that there was a significant relationship between diabetes mellitus and an increase in the prevalence of oral cavity-related diseases in the pediatric population. This is also related to non-compliance with the nutrition plan.

<p>Elise et al., North and South America (2014)²²</p>	<p>JCI Insight</p>	<p>Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy</p>	<p>35 consecutive patients</p>	<p>This study identified several manifestations that occur in the oral cavity due to American autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in children, namely chronic mucocutaneous candidiasis and enamel hypoplasia.</p>	<p>Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare primary immunodeficiency disorder typically caused by homozygous AIRE mutations. It classically presents with chronic mucocutaneous candidiasis and autoimmunity that primarily targets endocrine tissues; hypoparathyroidism and adrenal insufficiency are most common. Developing any two of these classic triad manifestations establishes the diagnosis. Although widely recognized in Europe, where nonendocrine autoimmune manifestations are uncommon, APECED is less defined in patients from the Western Hemisphere</p>
<p>Monisha et al., USA (2016)²³</p>	<p>Oral Disease</p>	<p>Elucidating the Role of Hyposalivation and Autoimmunity in Oral Candidiasis</p>	<p>1526 patients</p>	<p>Salivary gland dysfunction (hyposalivation with WUS being a stronger predictor than TSS) and autoimmunity (SS, other autoimmune disorders, medications i.e., DMARDS) are both independent predictors of Oral Candidiasis (OC). Diabetes mellitus is an independent predictor of OC among those with salivary gland dysfunction. Our findings suggest that these independent predictors should be considered in the prevention and management of OC in this population.</p>	<p>In conclusion, this study not only resolves the inconsistencies reported in the literature regarding the type of salivary flow associated with oral candidiasis, the role of autoimmunity in oral candidiasis, but also reports additional independent predictors of oral candidiasis such as diabetes mellitus and medications for extraglandular manifestations.</p>
<p>Øyvind et al., Norway (2016)²⁴</p>	<p>JClin Endocrinol Metab</p>	<p>A longitudinal follow-up of Autoimmune polyendocrine syndrome type 1</p>	<p>52 patients</p>	<p>The majority presented with one of the major disease components during childhood. Enamel hypoplasia, hypoparathyroidism, and CMC were the most frequent components. With age, most patients presented three to five disease manifestations, although some had milder phenotypes diagnosed in adulthood.</p>	<p>Multiple presumable autoimmune manifestations, in particular hypoparathyroidism, CMC, and enamel hypoplasia, should prompt further diagnostic workup using autoantibody analyses (e.g. IFN) and AIRE sequencing to reveal APS1, even in adults. Treatment is complicated and mortality high. Structured follow-up should be performed in a specialized centre.</p>

<p>Yi-Chen et al., Taiwan (2016)²⁵</p>	<p>Journal of the Formosan Medical Association</p>	<p>Clinical characteristics of type 1 diabetes mellitus in Taiwanese children aged younger than 6 years: A single-center experience</p>	<p>52 children aged younger than 6 years, and 94 children aged 6e18 years</p>	<p>The most common initial clinical manifestations in children aged < 6 years were polyuria (96%), polydipsia (92%), dry lips (81%), body weight loss (79%), nocturia (77%), previous history of respiratory tract infection (48%), dyspnea (46%), sunken eyeballs (24%), and polyphagia (21%).</p>	<p>Most Taiwanese children younger than 6 years old have T1DM due to autoimmune destruction of pancreatic b-cells. Most of them have severe ketoacidosis as the initial manifestation. Primary care physicians should have a high index of suspicion when managing young children with classic symptoms and signs of diabetes mellitus in the presence of a respiratory tract infection for proper timely intervention.</p>
<p>Lul'ejeta et al., Kosovo (2018)²⁶</p>	<p>Hindawi International Journal of Dentistry</p>	<p>The Influence of Type 1 Diabetes Mellitus on Dental Caries and Salivary Composition</p>	<p>80 children with type 1 diabetes mellitus aged 10–15 years,</p>	<p>The significant level was set at $p < 0.05$. Results. DMFT in children with type 1 diabetes was significantly higher than that in the control group ($p < 0.001$). Diabetic children have a low level of stimulated salivary flow rate compared to control children (0.86 ± 0.16 and 1.10 ± 0.14). The buffer capacity showed statistically significant differences between children with type 1 diabetes and control group ($p < 0.001$). Also, children with type 1 diabetes had a higher count and a higher risk of Lactobacillus compared to the control group ($p < 0.05$ and $p < 0.001$).</p>	<p>The findings we obtained showed that type 1 diabetes mellitus has an important part in children's oral health. It appears that children with type 1 diabetes are exposed to a higher risk for caries and oral health than nondiabetic children.</p>
<p>Wu et al., USA (2016)²⁷</p>	<p>SAGE Journal</p>	<p>Lenalidomide for refractory cutaneous manifestations of pediatric systemic lupus erythematosus</p>	<p>34 patients</p>	<p>Nine subjects were girls and six were African-American. Indications for lenalidomide treatment included alopecia, nasal and oral ulcers, extensive malar rash, discoid lesions, bullous lesions, panniculitis, cutaneous vasculitis, and Raynaud's phenomenon with digital ulcerations.</p>	<p>Lenalidomide is an effective and safe treatment for a spectrum of dermatological conditions in pediatric systemic lupus erythematosus. Its use may allow a reduction in prednisone dose and decreased disfigurement. Prospective study is needed to clarify lenalidomide's role in treating cutaneous manifestations of systemic lupus erythematosus.</p>

Siti Khadijah et al., Malaysia (2018) ²⁸	Saudi Med Journal	Pediatric systemic lupus erythematosus. Retrospective analysis of clinico-laboratory parameters and their association with Systemic Lupus Erythematosus Disease Activity Index score	32 patients SLE	The most common symptom was renal disorder (n=21; 65.6%) followed by malar rash (n=9; 28.1%), oral ulcers (n=7; 21.9%), prolonged fever (n=5; 15.6%) and arthritis (n=4; 12.5%).	Pediatric systemic lupus erythematosus patients with higher SLEDAI score were most significantly associated with pyuria, high ANA titers, and elevated ESR.
Vadood et al., Iran (2019) ²⁹	Dovepress Journal	Systemic lupus erythematosus flare triggered by a mosquito bite: the first case report	A 13 years old girl with the first presentation of systemic lupus erythematosus triggered by a mosquito bite.	The study presented a 13-year-old girl with the first presentation of systemic lupus erythematosus triggered by a mosquito bite. She presented with a malar rash started after a mosquito bite on her left cheek. She had oral ulcers, photosensitivity, lymphopenia, proteinuria, and positive serologic tests for SLE. Renal biopsy revealed class II lupus nephritis.	Environmental factors can trigger the onset of SLE in genetically susceptible cases. Besides microbial agents, UV radiation, hormones, drugs, emotional stresses, immunization, and chemicals are some of the published examples. We presented a case with a mosquito bite as the possible environmental trigger.
Rita et al., Portugal (2016) ³⁰	Reumatol Clinica Journal	Clinical phenotype and outcome in lupus according to age: a comparison between juvenile and adult onset	204 patients diagnosed with SLE were included, com-prising 38 (18.6%) Juvenile SLE and 166 (81.4%) adult-onset SLE patients.	Juvenile-SLE patients had malar rash more often (78.9% vs 53%; p = 0.001), oral ulcers (45.5% vs 17.5%; p = 0.001), neurological involvement (13.1% vs 3.6%; p = 0.02) nephritis (50% vs 33.9%), p = 0.04) and haematological manifestations such as hemolytic anaemia (23.6% vs 5.4%; p = 0.002) and leukopenia (46.1% vs 4.2%; p < 0.001)	In summary, our study confirms the existence of differences in clinical manifestations, according to age at diagnosis of SLE. Juvenile-SLE patients showed a more aggressive clinical presentation.
Vadood et al., Iran (2019) ³¹	Dovepress Journal	Guillain–Barre syndrome as the first manifestation of juvenile systemic lupus erythematosus: a case report	A 12-year-old boy with progressively worsening neurological symptoms as first manifestation	We describe a 12-year-old boy with progressively worsening neurological symptoms as first manifestation. Legs pain, loss of balance, and lower extremity weakness were the reason for his admission in neurologic ward. The patient was started on intravenous immunoglobulin therapy due to the possibility of Guillain– Barre syndrome and acute inflammatory demyelinating polyneuropathy (AIDP).	SLE and AIDP/CIDP are different entities, but ADP/CIDP can be part of the neurologic manifestations of the SLE. Although the association between AIDP/CIDP and SLE is very rare especially as a first manifestation of SLE, it should be early recognized for rapid appropriate treatment.
Wei Wang et al., China (2019) ³²	Pediatric Rheumatology	RAS-associated Autoimmune Leukoproliferative disease (RALD) manifested with	3 patients with clinical characteristic SLE	Gene analysis: NRAS mutations (c.38G > A, p.G13D or c.37G > T, p.G13C) were found in the blood of the patients.	For those early-onset SLE-like patients with predominant hematologic disorders, monocytosis, recurrent infectious history, accompanied with

		early-onset SLE-like syndrome: a case series of RALD in Chinese children		Besides, the same set of mutations was detected in buccal mucosa of patient 1 and nails of patient 3 while the frequency was much lower. However, no mutation was found in other tissues or in their parents' blood. Consequently, they were NRAS somatic mutated RALD.	hepatosplenomegaly and lymphadenopathy, a genetic screening of PIDs might be required.
Faisal et al., Saudi Arabia (2019) ³³	Journal of Family Medicine and Primary Care	Relationship between type- I diabetes mellitus and oral health status and oral health- related quality of life among children of Saudi Arabia	40 patients	Individuals with type- 1 diabetes mellitus (IDDM) had higher Gingival Index and DMFT scores; however, the differences were not statistically significant. The IDDM group showed higher COHIP scores across all domains. However, the differences were only statistically significant for the oral health domain (P = 0.003).	Children with IDDM had better oral health both in terms of dental caries and gingival status when compared to their age- matched controls. However, they had significantly higher oral health domains that suggest a poorer overall OHRQoL in children with IDDM.

Table 2. Demographic, clinical and immunological characteristics of the 204 SLE patients included.³⁰

Characteristic	
Juvenile Lupus, n (%)	38 (18.6)
Adult-onset lupus, n (%)	166 (81.4)
Female gender, n (%)	187 (91.7)
White race, n (%)	203 (99.5)
Age at diagnosis, mean ± SD	30.3 ± 13.7
Disease duration, mean ± SD	17.1 ± 10
Clinical Manifestations, n (%)	
Malar rash	118 (57.8)
Photosensitivity	149 (73)
Discoid rash	13 (6.4)
Oral ulcers	46 (22.5)
Arthritis	180 (88.2)
Serositis	29 (14.1)
Nephritis	82 (40.2)
CNS involvement	11 (5.4)
Haematological involvement	84 (41.2)
Immunological manifestations, n (%)	
ANA positive	204 (100)
Anti-dsDNA positive	189 (92.6)
Anti-Sm positive	33 (16.2)
Lupus anticoagulant positive	33 (16.2)
IgG/IgM anticardiolipin positive	28 (13.7)
IgM/IgG anti-B2GPpositive	26 (12.7)

Source: Fonseca R, Aguiar F, Rodrigues M, Brito I. Clinical phenotype and outcome in lupus according to age: a comparison between juvenile and adult onset. *Reumatol Clin.* 2018 May-Jun;14(3):160-163.³⁰

Table 3. Topical steroids for systemic lupus erythematosus lesions.²⁰

Topical steroid therapy	How to use
0,05 % fluocinonide gel	Apply it on the affected area (2 × /d for 2 wk)
0.05% clobetasol gel	Apply it on the affected area (2 × /d for 2 wk)
Dexamethasone elixir (0.5 mg/mL)	Gargle (10 mL 4 × /d for 2 wk)
Triamcinolone acetonide 5 mg/mL	Intralesional injection
Topical antifungal therapy, 10 mg clotrimazole troches	Dissolve in mouth, put on tongue (5 × /d for 10 d)

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Nystatin suspension (100,000 U/mL)	Gargle (5 mL 4 × /d for 10 d)
Chlorhexidine rinse (0.12%)	Gargle (10 mL 2 × /d) until the lesions heal

Source: Glick M. *Burket's Oral Medicine*. 12th ed. USA: People's Medical Publishing. 2015;251.²⁰

Table 4. Dental visits and parents' education between groups.²¹

Dental Visit	Type 1 DM		Control Grup		Total		Test
	N	%	N	%	N	%	
Once in 6 months	12	15.0	17	21.3	29	18.1	Chi= 20.73 <i>p</i> <0.001
Once a year	19	23.8	42	52.5	61	38.1	
Only when necessary	49	61.3	21	26.3	70	43.8	
<i>Father's education</i>							Chi= 27.22 <i>p</i> <0.001
Low level	19	23.8	5	6.3	24	15.0	
Medium level	56	70.0	45	56.3	101	63.1	
High level	5	6.3	30	37.5	35	21.9	
<i>Father's education</i>							Chi= 27.22 <i>p</i> <0.001
Low level	46	57.5	22	27.5	68	42.5	
Medium level	31	58.8	34	42.5	65	40.6	
High level	3	3.8	24	30.0	27	16.9	

Source: Ferizi L, Dragidella F, Spahiu L, Begzati A, Kotori V. The Influence of Type 1 Diabetes Mellitus on Dental Caries and Salivary Composition. *Int J Dent*. 2018 Oct 2; 2018:5780916.