REVIEW PAPER

SYSTEMIC DISEASES WITH ORAL MANIFESTATIONS AND THEIR IMPACT ON HEALTH-RELATED QUALITY OF LIFE

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ABBREVIATIONS:

COMDQ - Chronic Oral Mucosal Disease Questionnaire
EuroQol-5D - European Quality of Life 5D
HRQoL - Health-Related Quality of Life
IBD - Inflammatory Bowel Disease
OHRQoL - Oral Health-Related Quality of Life
OLP - Oral lichen planus
SF-36 - 36 - Item Short Form Survey Instrument
SLE - Systemic lupus erythematosus
SS - Sjögren syndrome
SSc - Systemic sclerosis
SScQoL - The Systemic Sclerosis Quality of Life Questionnaire
QoL – Quality of Life
MS - Multiple sclerosis
AD - Alzheimer's disease
PD - Parkinson's disease

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ABSTRACT

Health-related quality of life is a multidimensional concept established to evaluate the physical, psychological, and social impacts of health conditions on individuals' well-being. Various tools for measuring health-related quality of life can be categorized into two subsets: generic and disease–specific instruments. The oral cavity can be stricken by a broad range of local and systemic diseases and their systemic treatment modalities. The most common systemic illnesses associated with oral lesions are hematologic disorders, endocrinopathies, neurological disorders, gastrointestinal conditions, mucocutaneous and rheumatic diseases, and neoplastic processes. Their manifestations in the oral cavity are, in most cases, rather nonspecific but should not be overlooked. Oral health is one of the most important parts of overall health, thus it has been proposed that poor oral health may affect health–related quality of life. The presence of oral manifestations of systemic diseases has a negative impact on the daily functioning of patients, decreasing their overall well-being. This article will review the most common systemic diseases with oral manifestations and their impact on the health–related quality of life. Oral health researchers should put a stronger emphasis on the patient-reported quality of life as a primary outcome in future clinical trials. The significance of this area has still not been widely understood in the current dental literature even though it could help improve patients' health-related quality of life.

Keywords: *Oral manifestations, systemic diseases, health-related quality of life.*

INTRODUCTION

Health-related quality of life (HRQoL) is a multidimensional concept established to evaluate the physical, psychological, and social impacts of health conditions on individuals' well-being (1). It cannot be measured using only one domain, so key aspects of HRQoL include physical status and functioning, mental health, and social interactions (2). Oral health is one of the most important parts of overall health, thus it has been proposed that poor oral health may impact health–related quality of life (3). The oral cavity can be stricken by a broad range of both local and systemic diseases and their systemic treatment modalities (4). Oral changes in systemic disorders may help in their diagnosis, as many of them first present in the oral cavity and ensure guidance for their adequate treatment (5, 6). This article will review the most common systemic diseases with oral manifestations and their impact on the health–related quality of life.

HEALTH-RELATED QUALITY OF LIFE

The World Health Organization defines the quality of life as "individuals' position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (7). Quantification of quality of life, used in health studies to assess physical, psychological, and social functioning, refers to the term health-related quality of life (8). Various tools for measuring HRQoL can be categorized into two subsets: generic and disease-specific instruments. Generic tools are used in the general population, their validity has been confirmed in different chronic conditions and disorders, but they are not specific for a certain disease or a group of patients (9, 10). SF – 36 (36-Item Short Form Survey Instrument) and EuroQol-5D (European Quality of Life 5D) questionnaires are generic instruments and, according to published studies, the most broadly used tools for measuring HRQoL (11, 12). Their validity and reliability have been confirmed in a great number of clinical studies, and they are available in multiple world languages. Disease-specific HRQoL questionnaires are focused on a particular illness and are characterized by greater sensitivity and specificity than the generic ones (13). Their main limitation is that they are unable to compare health conditions of different natures, which is not the case with generic instruments (14). In recent years, many questionnaires for HRQoL evaluation have been developed because this concept has been recognized as one of the most important outcomes in clinical and health services research. It is a valuable predictor of treatment success, and it has a prognostic significance (15). Therefore, its routine use in clinical trials is highly recommended (16). Expressing HRQoL as a single value, called health state utility value, scored on a scale from 0 (death) to 1 (perfect health), is significant for health economic evaluations. It allows for comparison between different therapeutic areas since outcomes are given in the standard units (17). They can be derived through direct (standard gamble and time trade-off) and indirect (generic HRQoL questionnaires) methods (18). Health state utility values are used for assessing disease burden and calculating quality-adjusted life years (QALYs) that comprise both quantity and quality of life.

ORAL HEALTH-RELATED QUALITY OF LIFE

Even though most oral health problems are not considered life-threatening, they still pose a serious public health burden due its high prevalence and major socioeconomic and psychological consequences, and thus effects on the quality of life (19). Oral health-related quality of life (OHRQoL) is a construct that represents the impact of oral conditions on daily functioning, and it is associated with functional factors, psychological factors, social factors, and experience of pain or discomfort (20, 21). An impairment of overall quality of life can also potentially affect OHRQoL because OHRQoL is an essential part of the general health-related quality of life and contributes to it at biological, social, and psychological levels (3, 22). Its important role has been recognized in different domains of dentistry, such as clinical dentistry, dental research, and dental education (23). OHRQoL can be assessed using various tools like socio-dental indicators, global self-ratings of oral health, and multiple item questionnaires. Social indicators measure OHRQoL at a community level, global self-ratings estimate an individual's oral health at one point in time, and multiple item questionnaires, generic or specific, are usually used for OHRQoL evaluation (24). OHRQoL instruments have been developed and tested for adults and children, respectively. Some of the most widely used tools include General Oral Health Assessment Index, Subjective Oral Health Status Indicators, Dental Impact on Daily Living, Oral Impact on Daily Performances, and Oral Health Impact Profile-14. The number of questionnaires is increased daily, but their utilization has to be verified in the clinical trials (25). OHRQol contains three domains - physical, social, and psychological and therefore, used along with the clinical indicators, provide a more comprehensive picture of one's health status than a simple clinical evaluation. Assessment of OHRQoL is crucial for insight into individuals' feelings related to their health, a better understanding of the role that oral health plays in patients' daily lives, and developing new protocols for evidence-based clinical practice (26, 27).

ORAL MANIFESTATIONS OF SYSTEMIC DISEASES

There are a lot of conditions and diseases that primarily affect the mouth, but a wide range of systemic illnesses and the effects of their systemic treatment could also manifest in the oral cavity (6). The most common systemic diseases associated with oral lesions are hematologic disorders, endocrinopathies, neurological disorders, gastrointestinal conditions, mucocutaneous and rheumatic diseases, and neoplastic processes (4). Oral manifestations of systemic diseases are, in most cases, rather nonspecific and may be found in a plethora of different conditions. Both soft and hard tissues can be affected during the clinical course of the disease. Gingival bleeding and enlargement, oral ulcers, bacterial, viral, and fungal infections, dry mouth, and mucosal inflammation are

some of the most common soft tissues' findings. When it comes to hard tissues, dental caries, periodontitis, enamel hypoplasia, and loss of the teeth are often diagnosed among patients with systemic illnesses (28). Oral lesions should not be neglected, especially because they may be the initial clinical manifestation of several grave health conditions, and some of the systemic diseases could also be potentially identified based on the oral cavity findings during dental examination (5). Systemic diseases can have a direct effect on the status of the oral tissues but inversely, oral conditions, such as periodontal disease, may negatively impact the general health of the patients with systemic disorders (4).

RHEUMATIC DISEASES

Sjögren syndrome

Sjögren syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration of exocrine glands, especially lacrimal and salivary glands, resulting in their dysfunction and destruction (29). SS appears in 0.5-3% of the general population, predominantly in women. Some of the patients only experience symptoms related to the eyes and mouth (primary SS) and about 50% of them also have another autoimmune condition, such as systemic lupus erythematosus or rheumatoid arthritis (secondary SS) (30). The main clinical signs of SS are manifested in the oral cavity. Due to the reduction of saliva secretion and consequential hyposalivation, patients are prone to tooth caries, gingival inflammation, and opportunistic infections (31, 32). Chronic xerostomia may impair all of the orofacial functions, including chewing, swallowing, and talking, alter the taste and cause sleeping problems (33). Patients also often complain of dry lips, angular cheilitis, and halitosis (34, 35). Still, some other oral lesions, such as ulcers, are not related to a decrease of salivary flow but are probably directly associated with SS (34).

Patients with Sjögren syndrome have significantly decreased HRQoL, which is correlated not only with the main symptoms of the disease but also with psychological, ocular, oral, and sleep disorders. Pain and fatigue are two factors that mainly affect HRQoL, and saliva flow significantly impacts OHRQoL (36). Researchers of the European League Against Rheumatism (EULAR) have developed a set of outcome measures for clinical trials and practice that include both systemic activity and patients' symptoms. The EULAR SS Disease Activity Index (ESSDAI) is a clinical index that clinicians use for the evaluation of disease activity in patients with systemic complications of primary SS. Today it is recommended as a gold standard and primary outcome measure in randomized clinical studies (37). The EULAR SS Patient Reported Index (ESSPRI) has been designated as an instrument for the assessment of patients' symptoms. It consists of three domains that are recognized as the main symptoms that have an impact on HRQoL – overall dryness, pain, and fatigue (38). These tools should be used together for a better understanding of all of the disease's aspects, especially disease activity after therapeutic intervention (39). The first disease-specific instrument for evaluation of HRQoL in patients with SS has been developed in 2018, and it has shown good psychometric properties (40). There is an evident lack of research regarding health state utility values for SS, with only one study reporting impaired utility values compared to the general population (41). Having that in mind, new endpoints that are focused on HRQoL domains and validated exclusively for SS are needed for future clinical trials.

Systemic lupus erythematosus

The systemic lupus erythematosus (SLE) is a chronic, autoimmune disease with a variable clinical course (4, 29). SLE predominantly affects the skin, joints, muscles, lungs, kidneys, blood cells, and nervous system (42). Oral lesions appear in 8–45 % of patients, and they represent one of the most significant clinical aspects of SLE (4). They can manifest as white plaque or erosive lesions in the center, with lines in the periphery, most commonly localized on the labial, buccal, and gingival mucosa (43). Mucosal macules, plaque, and lesions that resemble oral lichen planus or leukoplakia can also be noted in patients with SLE (4). Petechial bleeding and erosive mucosal lesions may be a sign of serious thrombocytopenia (29). Recurrent aphthous stomatitis and ulcers not only accompany SLE but are also linked to the disease activity. Sometimes they might be the initial manifestations of SLE. Chronic ulcers in SLE have a higher risk of malignant transformation into squamous cell carcinoma compared to other ulcerative lesions (4). Some of the less frequent oral symptoms include xerostomia, dysphagia, and fungal infections (44, 45).

SLE has a detrimental effect on the patients' HRQoL because of the pain, physical appearance, and neurological impairment. Several specific patient-reported outcome measures have been developed so far for assessment of their HRQoL. Lupus Quality of Life questionnaire consists of 34 items, with a 5-point response format and a score ranging from 0 (worst HRQoL) to 100 (best HRQoL). SLE-specific Quality of Life questionnaire covers six domains with a 7-point response scale, and scores range from 40 to 280, with higher values corresponding to worse HRQoL. SLE Quality of Life Questionnaire includes 25 items and a "true/not true" response format with a score ranging from 0 to 25 (higher scores representing worse HRQoL) (46). Mean health state utility values for patients with SLE may vary, depending on a measure used, from 0,67 to 0,80, as results from a recent study showed (47).

Systemic sclerosis (Scleroderma)

Systemic sclerosis (SSc) is a rare connective tissue disorder characterized by progressive fibrosis of the skin, organs, and systems (48). The orofacial region is among the most affected by SSc (49). Sclerosis of the skin around the mouth area leads to the limited mouth opening called microstomia, resulting in problems with eating and potential malnutrition, speaking, oral hygiene, and dental treatments (50, 51). Submucosal fibrosis causes atrophy of the oral mucosa, which becomes pale, with telangiectasias located at the tongue (52). Patients frequently complain of burning mouth syndrome,

dysesthesia, and xerostomia (50). SSc might be associated with trigeminal neuralgia, temporomandibular joint dysfunction, and idiopathic tooth resorption (53, 54).

Results of previous studies suggest that patients with SSc have poorer HRQoL than patients with other rheumatic diseases, such as rheumatoid arthritis and systemic lupus erythematosus (55). The extent of skin involvement is a significant factor associated with reduced physical and mental domains of HRQoL in SSc patients. Several instruments are validated for use, but only a few of them are specific for SSc, such as The Systemic Sclerosis Quality of Life Questionnaire (SScQoL) (56). SScQoL consists of five domains – physical functioning, emotional functioning, social functioning, sleep, and pain. Higher scores indicate the more prominent effect of the disease on HRQoL. Results of a recent study showed that mean health state utility values for patients with shorter disease duration (less than two years) ranged from 0,63 to 0,80, whereas for longer disease span, they varied from 0,67 to 0,87, depending on the technique used (57).

MUCOCUTANEOUS DISEASES

Lichen planus

Lichen planus is a chronic inflammatory condition of unknown etiology that can affect the skin and mucous membranes, including the oral mucosa (58). The oral lichen planus (OLP) is a relatively common form, with a prevalence of 0,5 to 2% in the general adult population (59). Oral lesions often appear before skin lesions, and most of the time remain the sole manifestation of the disease (60). All parts of the oral cavity can be affected, but the lesions are predominantly located on the buccal mucosa, with bilateral and symmetrical distribution (61, 62). There are six forms of OLP: reticular, papular, plaque-like, atrophic, erosive-ulcerous, and bullous-erosive (60, 63, 64). The reticular OLP is presented as white keratotic lesions, resembling lace, called Wickham striae (65). The papular OLP is characterized by papules on the buccal mucosa predominantly. The plaque-like type is hard to differentiate from leukoplakia because they share the same localization - the dorsal surface of the tongue (64). These forms of OLP are generally asymptomatic (60). Atrophic, erosive, and bullous types are followed by a different range of symptoms, from mild to intense pain. Clinically, atrophic and erosive forms present like atrophic lesions with white radiating lines at the periphery, and the bullous one can resemble erosive type as the fragile bullae easily get ruptured (64, 66). Oral lichen planus is characterized by periods of remissions and exacerbations and can be triggered by different factors (58, 67).

In the last decade, several disease-specific HRQoL instruments for OLP have been designed to assess all the aspects of disease important to patients, including the Chronic Oral Mucosal Disease Questionnaire (COMDQ) (68). COMDQ is a Likert – type scale that covers four areas - physical discomfort, medication and treatment, social and emotional, and patient support, with 60 points being the highest score. It is considered the most appropriate instrument for measuring HRQoL in OLP patients, and it is the only one designed with input from them (68). General tools have also been used for assessing HRQoL, but their psychometric properties or interpretability have not been tested in the OLP population (69). Therefore, it is necessary to develop a core set of outcome measures, especially patient-related, to improve the quality of the future clinical studies and clinical meaningfulness of their results. Pain, disease activity, and depression are factors associated with impairment of the patients' HRQoL (70).

Pemphigus

Pemphigus is a group of chronic, antibody-mediated autoimmune vesiculobullous diseases that manifest on the skin and mucous membranes (71). Pemphigus vulgaris and pemphigus foliaceus are the most widespread subtypes (72). The majority of the patients (up to 70%) with pemphigus vulgaris have mucosal lesions that initially appear in the oral cavity, while the skin is not always affected. On the opposite, patients with pemphigus foliaceus do not experience mucosal changes (73). Oral lesions in pemphigus vulgaris are often the first and only sign of the disease. They appear as vesicles and bullae, filled with fluid, that burst very easily and leave irregular erosions and ulcers (74). Most lesions do not tend to leave a scar but can be very painful for the patients. The commonest parts of the mouth that are affected include gingival, buccal, and palatal tissues (75). In severe cases, desquamative gingivitis can also be found (4).

Even though treatment options for pemphigus have improved in recent years, there is still a great need for new therapy modalities. To enhance the quality of clinical trials that are testing innovative pharmacological agents, disease severity and HRQoL should be appropriately evaluated. HRQoL is usually measured with generic tools, but a disease-specific instrument has also been developed - the Autoimmune Bullous Disease Quality of Life (76). It represents a valid and reliable patient-based measure that correlates with disease severity indices and can accurately quantify how the disease impacts a patient's HRQoL. This instrument could also be used as an endpoint in clinical trials as it may successfully measure disease burden, activity, and therapy response (76). A recent study reported a mean utility value of 0,76 for pemphigus patients, which is relatively low compared with other chronic dermatological conditions, such as psoriasis and atopic dermatitis (77).

Pemphigoid

Pemphigoid diseases are autoimmune diseases represented by autoantibodies directed against various structural components of the dermal-epidermal junction, resulting in the formation of subepithelial blisters (4). Of all the entities in this group, bullous pemphigoid and mucous membrane pemphigoid are the most commonly presented in the oral cavity. Their clinical manifestations are fairly similar – vesicles and bullae, sometimes blood-filled, located predominantly on epithelialized mucosa (especially gingiva), bleeding, and pain. Irregular erosions and ulcers can be noted after

blisters burst, and the Nikolsky sign might be positive (78). Oral lesions are prone to scarring, forming multiple mucosal contractures (4).

Bullous pemphigoid has a significant effect on the psychological status of the patients due to the appearance of the lesions on the skin and oral mucosa, functional problems, and disease chronicity (79). Their HRQoL can be measured using both generic and disease-specific instruments, such as the Autoimmune Bullous Disease Quality of Life (77). It is a 17-item scale that includes questions about pain, pruritus, healing, anxiety, and depression. The maximum score is 51, and the higher results indicate more severe impairment of HRQoL (80). Bullous pemphigoid affects all aspects of patients' daily lives, so it is of importance to incorporate HRQoL as the primary outcome in future clinical trials to accurately measure treatment efficacy.

GASTROINTESTINAL DISEASES

Ulcerative colitis and Crohn's disease

Ulcerative colitis and Crohn's disease are systemic diseases classified as chronic inflammatory bowel disease (IBD) (81). Periodontitis, aphthous stomatitis, and in severe cases, pyostomatitis vegetans are particularly pronounced in patients with Crohn's disease (81, 82). Patients in the acute phase of the disease show a significantly higher degree of oral lesions (83). The most commonly affected regions are the lips, gingiva, and less often the vestibule and tongue, with predominant clinical symptoms in the form of ulcers, papules, and edema. Mucogingivitis, labial swelling, and linear ulcerations located in the buccal sulci often occur (83). A specific indicator of ulcerative colitis is pyostomatitis vegetans, while other manifestations often appear but are not specific, such as aphthae, halitosis, dry mouth, and various forms of gingivitis (84).

Ulcerative colitis and Crohn's disease are associated with the significant psychological and social burden. The use of HRQoL as an endpoint in clinical trials involving IBD has increased dramatically over the past decades and has become an essential outcome measure. Inflammatory Bowel Disease Questionnaire is a 32-item-instrument, divided into four domains: bowel symptoms, systemic symptoms, social and emotional functioning (85). The total score ranges from 32 (poor HRQoL) to 224 (good HRQoL). A score higher than 170 is usually found in patients in clinical remission (86). Health state utility values, reported from a recent analysis, for patients with the active form of the disease were 0.69 (for ulcerative colitis) and 0.75 (for Crohn's disease). Patients in remission recorded significantly higher values of 0.87 and 0.84 (87).

Celiac disease

Celiac disease is an autoimmune disease that implies a permanent sensitivity to gluten, and it develops in people with a genetic predisposition under the influence of environmental factors. Gluten sensitivity leads to various intestinal symptoms with accompanying extraintestinal manifestations, and it often happens that extraintestinal symptoms are pronounced more significantly than intestinal ones (88). Oral lesions appear in the form of hypoplasia of the dental enamel, which has a higher prevalence in children than in adults. Aphthous lesions that regress after a gluten-free diet can be noticed (89). Glossodynia and atrophic glossitis, more frequent incidence of caries and bleeding tendency are also clinical indicators of Celiac disease (88).

Intestinal and extraintestinal symptoms, medical comorbidities, and major dietary restrictions are associated with impairment of HRQoL in patients with celiac disease (90). Celiac Disease Quality of Life is a specific tool that consists of 20 questions, distributed into four domains: dysphoria, limitations, health concerns, and inadequate treatment (91). The overall Celiac Disease Quality of Life score is expressed in a 100-point scale (0 – worst HRQoL, 100 – best HRQoL). HRQoL should become a key outcome in the evaluation of novel treatments for celiac disease, so new valid and well-designed patient-related measures are necessary.

HEMATOLOGIC DISEASES

Anemia

Anemia is a condition characterized by the decline in the content of hemoglobin and oxygen due to the reduced number or function of red blood cells (92). Anemia can present as an iron deficiency or pernicious anemia. Both mentioned could manifest in the oral cavity. Iron deficiency anemia is associated with atrophic glossitis and pale mucosa. The condition known as the magenta tongue is characteristic of pernicious anemia, which manifests as tongue erythema with atrophy (5). An extremely reddened tongue with atrophic borders is usually the preliminary sign of anemia (92). Angular cheilitis, burning sensations of the tongue, lips, and buccal mucosa are very common findings for anemia (5).

Thrombocytopenia

Thrombocytopenia has been identified as a disorder associated with a substantial decrease in platelets. A reduction in the number of platelets leads to various oral manifestations, most commonly petechiae and purpura. Such oral signs include the occurrence of bleeding from minor cuts, inefficiency in the formation of clots, and gingival hyperplasia, and depending on the platelet counts, bleeding on trauma or spontaneous bleeding (5, 74).

The intensity and recurrence of the oral manifestations of hematological diseases can cause significant discomfort and have a great impact on a patient's HRQoL. Swollen lips, dry mouth, cuts, pain, and bleeding in the mouth often compromise mastication. Patients also complain about feeling embarrassed during mealtimes because of the judgment from others. All that can cause a patient to feel different and excluded from the environment. Regarding speech problems,

patients mainly complain of the lack of saliva. They often state that their social interaction, being with others, and recreational activities are impaired and jeopardized by oral alterations as a result of their primary disease (93). HRQoL of patients with hematologic diseases has mostly been measured using generic instruments so far, but an effort should be made to include more patient-reported outcome measures as endpoints in future clinical trials.

ENDOCRINOPATHIES

Diabetes mellitus

Diabetes mellitus is a disease that changes the resistance of tissues to local irritations due to the deposition of acidic mucopolysaccharides and glycoproteins on the walls of blood vessels. Because of the mentioned disorders, proliferative changes, microthrombosis, and microhemorrhage on the endothelium are likely to occur (94). Microcirculatory pathways, nutritional imbalance, and oxygenation disorders affect periodontal tissues (95). Oral changes appear in the form of inflammation of the gingiva, which is swollen, hyperemic, the periodontium is hypersensitive, and its destruction is accelerated, while the periodontal pockets are very deep with abundant suppuration present. Alveolar bone resorption is extremely pronounced and rapid (96). In addition to the above, the main oral manifestation of diabetes mellitus is the appearance of multiple periodontal abscesses (95). Xerostomia, candidiasis, and burning in the mouth are present, as well as slowed healing of wounds and oral ulcers. Diabetes does not cause periodontitis, but it can lead to its deterioration, while oral manifestations of diabetes may help in its diagnosis (97). Severe periodontal disease is associated with worsening glycemic control (74). The relationship is explained by the fact that chronic infection with Gram-negative bacteria in dental plaque in diabetics leads to increased insulin resistance in tissues and increased hyperglycemia (74, 98, 99). Periodontal therapy affects the metabolic control of diabetes, so if this disease is suspected, appropriate diagnostic tests should be performed immediately (99).

Many disease-specific instruments for diabetes mellitus exist in the literature, and they cover all the relevant aspects of HRQoL concept. The use of appropriate, up-to-date measures is very important for the evaluation of patient's experiences with their disease and treatment (100). Diabetes mellitus affects various parts of the organism and therefore has physical, psychological, and social implications. The impaired HRQoL in patients with diabetes mellitus is mostly a result of the local and systemic complications of the disease, including oral alterations (101). Diabetes-related complications are associated with lower health utility scores, and the impact of various complications on the HRqOL differs significantly (102). Painful neuropathy and amputations have the greatest decline in the health utility scores (up to 0,1), while heart disease and peripheral vascular disease show a relatively small decrease (less than 0,03) (102). Utility scores, generated from the HRQoL instruments, could be used for multiple purposes: measuring quality-adjusted life-years and evaluating improvement of diabetes management (103).

Addison's disease

Addison's disease develops as the result of the destruction of the adrenal cortex. Characteristic clinical signs of adrenal disease begin with general patient weakness, malaise, and fatigue accompanied by weight loss due to loss of appetite (104). Oral manifestations of this disease are characterized by the pigmentation of the mucous membranes, lips, and skin. Hyperpigmentation of the oral mucosa occurs due to elevated adrenocorticotrophic hormone and is one of the first signs of Addison's disease (105). Bluish-black spots are seen in the mouth in up to 82% of patients (6). During treatment, skin pigments most often disappear while oral pigments stay longer (106).

AddiQoL is Addison's disease-specific instrument that consists of 30 items, with a total score ranging from 30 to 120. Higher scores indicate better HRQoL. Patients with Addison disease have reduced HRQoL mainly due to fear of potentially life-threatening adrenal crisis (107).

NEUROLOGICAL DISORDERS

Multiple sclerosis

Multiple sclerosis (MS) is a chronic, demyelinating, neurodegenerative disease of the central nervous system (108). It is the most common neurologic disorder of the young population, with more than 2,8 million people affected worldwide, predominantly women (109). MS is characterized by fatigue, pain, muscle weakness, vision and speech impairment, and cognitive dysfunction (110). Various oral health problems may also be associated with MS. They are mostly caused by patients' inability to maintain adequate oral hygiene due to severe fatigue and motoric disability. Studies suggest a higher prevalence of dry mouth, dental caries, periodontal disease, temporomandibular joint dysfunction, and other neurological disorders such as trigeminal neuralgia and dysgeusia in MS patients (111, 112). Side effects of the medications used in MS treatment might affect oral mucosa, resulting in deterioration of the overall oral health (110).

Both generic and disease-specific tools are widely used in the HRQoL evaluation of MS patients. Several disease-specific instruments are available, including the Multiple Sclerosis Quality of Life-54 questionnaire, the Multiple Sclerosis Quality of Life Inventory, Functional Assessment of Multiple Sclerosis, Multiple Sclerosis Impact Scale-29, and Multiple Sclerosis International Quality of Life questionnaire (113). Cognitive and physical impairment are the most important predictors of HRQoL in MS patients (114). Future clinical studies are needed for a more profound understanding of oral manifestations' impact on HRQoL aspects of patients suffering from MS.

Alzheimer's disease

Alzheimer's disease (AD) represents a progressive neurodegenerative disorder associated with a decline in cognitive functions. The number of cases is constantly growing, and it is estimated that 5-7% of all people over the age of 60 are affected worldwide (115). AD is characterized by the deposition of amyloid plaques in the brain, leading to a decrease in cognitive and physical abilities (116). With the progression of the disease, patients' oral health status is worsening, mainly due to their reduced capacity to maintain adequate oral hygiene. That can result in a higher prevalence of dental caries, periodontal disease, and mucosal lesions, which might affect certain HRQoL domains (117). Patients also report problems with wearing dentures and subsequent insufficient mastication.

The presence of less than five natural teeth, carious teeth, and poor periodontal status are predictive factors of OHRQoL impairment in AD patients (117). Various measures have been developed for measuring their HRQoL, such as Alzheimer Disease Related Quality of Life and Quality of Life in Alzheimer's Disease (118). Recent research showed that non-cognitive symptoms, like depression and loss of functional ability, influenced HRQoL in AD more than cognitive ones (119). Prevention and timely treatment of oral disease are necessary for proper nutrition and oral health of patients with AD, which will positively impact their overall HRQoL.

Parkinson's disease

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by tremor, rigidity, and hypokinesia. It affects 2-3% of all people over the age of 65, mostly men (120). Motor inability often leads to improper oral hygiene, which results in a higher prevalence of caries, periodontal disease, and loss of teeth (121). Drooling, xerostomia, and dysphagia are also common symptoms in the later stages of PD. They have a significant detrimental influence on OHRQoL in PD patients (121). Decreased saliva production due to medication or autonomic dysfunction results in the onset of caries and periodontal disease. Adequate oral hygiene is therefore essential for PD patients and improvement of their OHRQoL.

Evaluation of HRQoL in PD patients poses a great challenge. Research suggests that fatigue, walking problems, and non-motor symptoms, like nocturia and forgetfulness, remarkably contribute to their worse HRQoL (120). HRQoL in PD might be assessed using different generic and disease-specific instruments, such as 39-item Parkinson's Disease Questionnaire. Frequent evaluation of HRQoL of PD patients is fundamental for the identification of factors associated with its decline and their proper management.

ONCOLOGICAL DISEASES

Leukemia

Leukemia is considered one of the most life-threatening cancers and represents a major therapeutic challenge. Early diagnosis of the disease is of great importance, where the doctor of dental medicine can also play an essential role because the illness causes oral changes (106). Clinical manifestations of leukemia include anemia, pallor, bleeding, splenomegaly, hepatomegaly, and lymphadenopathy (74). Oral manifestations exist both in the case of chronic and acute leukemia. They can be primary (a direct consequence of leukemic cell infiltration) or secondary (a result of neutropenia, thrombocytopenia, reduced granulocyte function) (122). Common oral manifestations of leukemia are mucosal pallor and significant gingival bleeding, which may be the disease's first symptom (5, 74, 106, 122). Hemorrhages on the hard and soft palate may occur when the platelet count falls below 20,000 / μL (20×10^9 / L) (5). An enlargement of the gingiva can also be noticed, which is explained by the cellular infiltrate and inadequate oral hygiene (5, 74, 106, 122). Ulcerations that can be found are usually very deep, with a necrotic base (5). Opportunistic infections often accompany leukemia, and usually, Candida albicans or Herpesviruses cause them (5, 122).

The Functional Assessment of Cancer Therapy-Leukemia and Medical Research Council/EORTC Quality of Life Questionnaire Leukemia Module are used for evaluation of HRQoL in patients with leukemia. Health utility values cannot be derived from these tools since they are not preference-based, so generic instruments are implemented for that purpose (e.g. EuroQoL-5D) (123). The mean utility score of patients with leukemia is lower when compared to the general population, which highlights the negative effect of leukemia on HRQoL. Infections, anemia, and bleeding are factors mainly associated with worse HRQoL, while social support seems to be the predictor of better HRQoL (124).

Multiple myeloma

Oral manifestations may also develop in the later stages of multiple myeloma. The most common changes occur in the mandible, and asymmetry can even be very noticeable. Patients frequently complain of pain, swelling, paresthesias, and tooth mobility (5, 125). Imaging exams often show osteolytic lesions, which can also lead to pathological fractures (125). Macroglossia can sometimes be seen as a consequence of amyloid deposition (5).

Patients with multiple myeloma have reduced HRQoL due to pain, fatigue, psychological and social factors (126). Multiple Myeloma-Specific Core Questionnaire 20 is a validated instrument that consists of 20 questions and includes four myeloma-specific aspects of HRQoL: body image, disease symptoms, treatment side effects, and future perspective (127). Domain scores are transformed to a linear score ranging from 0 to 100. Higher scores for disease symptoms and treatment side effects indicate more severe symptomatology,

whereas high scores for body image and future perspective are associated with better outcomes (128). Health utility values derived from EuroQol-5D may range from -0,025 to 0,9 (for asymptomatic patients), according to a systematic review that analyzed 26 publications and included 11 112 patients (129).

Oral squamous cell carcinoma

The most common cancer in the oral cavity is squamous cell carcinoma. The symptoms that accompany its appearance are discomfort, dysphagia, odynophagia, limited movement, neck mass, and weight loss. It is clinically manifested as long-term ulceration, which does not go away with the removal of potential irritating factors. It may have an irregular, granular, rough, or crusty structure and may be present as a red or white lesion (92, 130).

Patients with oral squamous cell carcinoma report a great number of symptoms that reduce their HRQoL, including pain and problems with chewing, swallowing, and talking (131). Psychological and social domains are also affected. The Basal and Squamous Cell Carcinoma Quality of Life is a recently developed questionnaire that encompasses five subscales, scored from 0 to 3, with higher scores representing worse HRQoL (132). It can be used in future clinical trials for comparison of different cancer treatment modalities.

Head and neck cancer therapy

Cancer therapy of the head and neck region can have various side effects and impact significantly OHRQoL. Anesthesia, paraesthesia, hyperesthesia, dysgeusia, tongue mobility changes, and trismus may occur as surgical therapy complications (92). The most common accompanying complications of radiotherapy are oral mucositis, opportunistic infections, and osteoradionecrosis. Periodontal tissue damage can also happen (92, 133).

Impairment of HRQoL of cancer patients that received therapy might persist over a long time after treatment in the form of various physical and psychological problems. Different health utility values for head and neck cancer survivors are reported in the literature, depending on the technique used, and range from 0,45 (distant metastasis at initial treatment) to 0,79 (patients initially treated at a locally advanced stage) (134).

The main oral manifestations and disease-specific instruments for measuring HRQoL of the aforementioned systemic diseases are summarized in Table 1.

Table 1. Various systemic diseases – main oral manifestations and HRQoL disease-specific tools

Disease	Main oral manifestations	Disease-specific tools	Published	Authors	References
Sjögren syndrome	Xerostomia	pSS - QoL	2018.	Lackner A. et al.	(33, 40)
Systemic lupus erythematosus	Aphthous stomatitis, ulcers	The SLE QoL Questionnaire	2009.	Galen Research	(43, 135)
Systemic sclerosis	Microstomia, dysphagia	The Systemic Sclerosis QoL Questionnaire	2008.	Reay N.	(50, 56)
Lichen planus	Symmetrical white lesions	COMDQ	2011.	Riordain N. et al.	(65, 136)
Pemphigus	Vesicles and bullae, ulcers	Autoimmune Bullous Disease QoL	2012.	Murrell D. et al.	(67, 77)
Pemphigoid	Vesicles and bullae, ulcers	Autoimmune Bullous Disease QoL	2012.	Murrell D. et al.	(77, 78)
Ulcerative colitis	Pyostomatitis vegetans	Inflammatory Bowel Disease Questionnaire	1989.	Guyatt G. et al.	(84, 137)
Crohn's disease	Aphthous stomatitis	Crohn's Life Impact Questionnaire	2015.	Galen Research	(81, 138)
Celiac disease	Aphthous lesions, atrophic glossitis	Celiac Disease QoL	2009.	Drossman D, Dorn S	(88, 139)
Diabetes mellitus	Periodontitis, candidiasis, ulcers	Diabetes QoL Questionnaire	2010.	Speight J. et al.	(97, 140)
Addison's disease	Mucosal hyperpigmentation	AD-specific QoL Questionnaire	2010.	Euradrenal	(105, 141)

Disease	Main oral manifestations	Disease-specific tools	Published	Authors	References
Multiple sclerosis	Xerostomia, periodontal disease, trigeminal neuralgia	Multiple Sclerosis QoL-54	1995.	Ellison GW. et al.	(111, 113)
Alzheimer's disease	Dental caries, mucosal lesions	Alzheimer Disease Related QoL	1999.	Black Bs. et al.	(117, 118)
Parkinson's disease	Drooling, xerostomia, dysphagia	Parkinson's Disease QoL Questionnaire	1996.	De Boer A.	(120, 121)
Leukemia	Mucosal pallor, gingival infiltration	The FACT-Leukemia	2012.	Cella D. et al.	(74, 123)
Multiple myeloma	Swelling, paresthesias	QoL - Multiple Myeloma	1999.	EORTC	(125, 127)
Squamous cell carcinoma	Persistent ulceration	The Basal and Squamous Cell Carcinoma QoL	2018.	Waalboer-Spuij R. et al.	(92, 132)

CONCLUSION

Various systemic diseases, such as rheumatic and mucocutaneous diseases, gastrointestinal conditions, hematologic disorders, endocrinopathies, neurological disorders, and neoplastic processes manifest in the oral cavity and cause a wide range of oral symptoms and signs. Their presence affects both oral and general health-related quality of life and negatively impacts the daily functioning of patients, decreasing their overall well–being. Oral health researchers should put a stronger emphasis on the patient-reported quality of life as a primary outcome in future clinical trials. The significance of this area has still not been widely understood in the current dental literature, even though it could help improve patients' health-related quality of life.

CONFLICT OF INTEREST

All authors of the manuscript declare there is no conflict of interest regarding this paper.

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