The nature and impact of oral disease of systemic sclerosis

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DECLARATION

Except for the help listed in the acknowledgements, the contents of this thesis are entirely my own work. This has not previously been submitted, in part or in full, for a degree or diploma of this or any other university or examination board.

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ABSTRACT

Systemic Sclerosis (SSc) is a multisystem immune-mediated disorder that by virtue of its many possible orofacial features has the potential to adversely affect oral function, impact on oral health care and lessen the quality of life.

This thesis has sought to determine the oral and dental consequences of SSc upon a substantial group of affected individuals in the UK. A retrospective analysis of 138 patients with SSc found that the most frequent extra-oral feature was facial skin fibrosis followed by perioral skin tightening, 37% and 35% respectively. Intra-oral features were common, as 73% of patients had microstomia and 47% had xerostomia and generalised chronic periodontitis.

An assessment of the online information regarding the treatment of the oral manifestations of SSc found that there are general scarcity of websites providing relevant content with most sites being of poor quality and difficult to read.

A cross-sectional observational questionnaire study of the implications of SSc upon the access to dental care services and oral health-related quality of life (OHRQoL) indicated that SSc has a negative impact on general and OHRQoL with a high level of psychological disability that included pain, anxiety and depression.

A detailed study of the psychometric properties of the only specific patient-reported outcome measure Mouth Handicap in Systemic Sclerosis (MHISS) in a large group of patients with SSc found that this instrument had good levels of validity and reliability with respect to patients resident in the UK.

The results of this thesis indicate that many patients with SSc may have oral manifestations that can potentially impact adversely upon their oral function, ability to maintain good oral health and lessen OHRQoL. They will not be able to obtain reliable,

understandable information from the world wide web concerning oral aspects of SSc – although their OHRQoL can be assessed well using the MHISS.

IMPACT STATEMENT

Systemic sclerosis is a multisystem immune-mediated disease that negatively impacts upon the oral health and delivery of oral health care of affected individuals. While only a few studies of the nature and impact of oral features of SSc have been detailed, one objective of this research is to determine the orofacial complications in the largest cohort of individuals with SSc in the UK.

The present study comprised 138 patients with different types of SSc and thus represents the largest group of patients of SSc resident in the UK to have ever been examined for aspects of their oral health. The orofacial manifestations and related complications the data described have enabled better understanding and prediction of the oral health care needs of such patients. As suggested by the present pattern of referral, and subsequent oral health care, the oral health needs of patients with SSc may sometimes require the skills and experience of clinicians from a variety of dental specialities.

The present study also sought to explore the effect of the disease on access to dental care in the UK. Although the majority of patients readily accessed dental health care services, 32.1% expressed worries about their future dental needs and where to seek treatment in emergency situations and reported their concern about the lack of the appropriate level of knowledge of dentists regarding their conditions. Indeed, present results highlighted the need to develop appropriate patient-centred protocols for oral self-care and to ensure patients with SSc have appropriate, ready, access to dental care to lessen the risk of related oral disease.

As it has been reported that about 85% of SSc patients are using the internet websites seeking for information on their condition, and 58-63% of those patients were looking for information about treatment options and management of their lifestyle. Further

assessment of the available online information regarding the treatment of the mouth in SSc has been examined, and results show the reliability and quality of the online content remain questionable to be used as a source of knowledge due to the lack of accurate contents and difficult level of readability. Therefore, patients should be aware of the substantial unmet needs regarding the available online information about the treatment of the mouth and further work is required to ensure accurate, comprehensible and relevant online content is accessible to patients with SSc.

Other objectives were to measure the impact of SSc upon the oral health-related quality of life (OHRQoL) and explore the psychometric properties of the Mouth Handicap in Systemic Sclerosis (MHISS) in a UK population. Given the impact of poor OHRQoL and psychological distress on the lives of patients with SSc, health care providers should make efforts to collaborate and develop early multidisciplinary targeted interventions to improve the disease comorbidity in patients with SSc. Current results demonstrate good preliminary psychometric properties of MHISS in a UK population with further exploration of psychometric properties with an emphasis on interpretability required.

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ABBREVIATIONS

ACA – Anti-centromere Antibody
ACE - Angiotensin-converting enzyme
ACR - American College of Rheumatology
ADHS – Adult dental health survey
ADSC - Adipose-derived stromal cell
AFGT - Autologous fat grafting
ANA – Anti-nuclear Antibodies
ATA – Anti-topoisomerase Antibody
BMS – Burning mouth syndrome
CBCT – Cone-beam computerised tomography
CNS – Central nervous system
CREST- Calcinosis, Raynaud's phenomenon, Oesophageal dysmotility, Sclerodactyly and Telangiectasia
CRISS - Composite Response Index in SSc
CTD – Connective Tissue Disease
DcSSc – Diffuse cutaneous systemic sclerosis
EDH – Eastman Dental Hospital
EDS - Ehlers-Danlos Syndrome
ENT – Ear, Nose and Throat
ESR- Erythrocyte sedimentation rate
EULAR - European League Against Rheumatism
FDA - Food and Drug Administration
FRES - Flesch Reading Ease Scores
GDP – General Dental Practitioner
GIT – Gastro-intestinal tract
GORD – Gastroesophageal reflux disease
HADS - Hospital Anxiety and Depression scale
HAMIS - Hand Mobility in SSc
HAQ – Health assessment questionnaire
HON – Health on the Net
HRQoL – Health-Related Quality of life
ILD – Interstitial lung disease
JAMA - Journal of the American Medical Association
jLSSc - Juvenile localised systemic sclerosis
jSSc - Juvenile systemic sclerosis
lcSSc – Limited cutaneous systemic sclerosis
lSSc – Localised systemic sclerosis
MCTD – Mixed connective tissue disease
MDAS – Modified depression and anxiety scale
MHC - Major histocompatibility complex
MHISS – Mouth handicap in systemic sclerosis
MRONJ - Medication-related osteonecrosis of the jaw

NHS - National Health Service
NSAID – Non-steroidal anti-inflammatory drugs
OA – Osteoarthritis
OHIP – Oral health impact profile
OHRQoL – Oral health-related quality of life
OIDP - Oral Impact on Daily Performance
OMFS – Oral maxillofacial surgery
ONS - Office for National Statistics
PAH – Pulmonary arterial hypertension
PDL – Periodontal ligament
PROMS - Patient-reported outcome measures
QoL – Quality of life
RA - Rheumatoid arthritis
RP- Raynaud's phenomenon
SCTC - Scleroderma Clinical Trials Consortium
SF-36 – Short form health questionnaire
SLE - Systemic lupus erythematosus
SS - Sjogren's syndrome
SSA - Skin Symptom Assessment
SSc – Systemic Sclerosis
SWAP - satisfaction with appearance scale
TMD – Temporomandibular disorder
TMJ - Temporomandibular joint
TN - Trigeminal neuralgia
UCLA SCTC GIT - Scleroderma Gastrointestinal Tract Scale
UCLHT – University College London Hospital NHS Trust
VAS – Visual analogue scale
VEDOSS - Very Early Diagnoses clinic for Systemic Sclerosis
WHO – World Health Organisation

CHAPTER 1: Introduction and literature review

Immunologically mediated connective tissue disorders (CTDs) comprise a group of disorders that give rise to a wide variety of systemic and/or oral manifestations that compromise healthy living. Scleroderma or “Systemic Sclerosis” is one of the rare CTDs that can adversely impact upon multiple organs and in some instances can be life-threatening. SSc can adversely impact upon a patient’s quality of life and daily activity.

There remains no definitive cure for SSc although a wide range of different treatment modalities is helpful in lessening or stopping disease progression. Nevertheless, many affected individuals will have lifelong complications that may adversely impact physically and/or psychologically upon their lives and perhaps their families and/or carers.

1.1 History of systemic sclerosis

The term scleroderma is derived from classical Greek terminology: *Skleros* meaning hard and *derma* meaning skin. Historically, in 450-370 BC Hippocrates described a disorder of widespread hardening of the skin (David, 1981). In 1754, Robert Westson translated into English the first convincing description of SSc (which was written by Carlo Curzio in 1753) concerning a female patient complaining of excessive generalised tension and hardness of skin that limited her movement. Curzio had described hardening and tightness of the skin without any involvement of the underlying muscles with constriction and tightness of the skin of the head and neck that limited mouth opening and neck movements (Rocco and Hurd, 1986).

The term “scleroderma” was used for the first time by Giovambattista Fantonetti when describing a patient who had thickened and dark skin lesions with loss of normal joint mobility (Benedek and Rodnan, 1982). In 1837 eight patients with skin disease were

diagnosed as having SSc and in 1865 a comprehensive review by Horteloup described several patients (Benedek and Rodnan, 1982).

The association between SSc and calcinosis was first reported by Webar in 1878. In 1865, the association of SSc and peripheral vasoconstriction was first described by Maurice Raynaud. The changes of peripheral vasoconstriction were further described by Ball in 1871 who detailed marked sclerosis, atrophy of the fingers and painful ulcers which was later termed as “Sclerodactylie” (Benedek and Rodnan, 1982).

Between 1892 and 1898, Wolters and Osler concluded that SSc was a multisystem condition that could affect different organs leading to a wide variety of complications with high mortality and morbidity (Benedek and Rodnan, 1982). Multi-organ involvement in systemic sclerosis was described by Matsui in 1924 while in 1942 Klemperer, Pollack and Baehr emphasised that SSc should be categorised as a systemic connective tissue disorder. Three years later, Goetz considered that SSc is a cutaneous phase of an underlying systemic disorder and introduce the term “Progressive systemic sclerosis” (Klemperer et al., 1984).

CREST syndrome, which was defined by Winterbaure in 1964 as Calcinosis as calcium deposition, Raynaud’s phenomenon, Oesophageal dysfunction, Sclerodactyly as thickening and hardening skin and Telangiectasia (Winterbauer, 1964). Since this time, as medical advances have been made, so the description of SSc has extended and is considered in detail in the classification section.

1.2 Epidemiology

1.2.1 Incidence and prevalence

Systemic sclerosis is rare. It has an estimated incidence of 0.3 – 2.8 per 100.000/year. Some estimates have reported the incidence to be 10 – 20 cases/million per year. However, the incidence of SSc is expected to increase in view of improved awareness of clinical disease, improved diagnostic methods and perhaps the influence of any likely causative environmental and/or occupational factors (Hughes and Herrick, 2012, Royle et al., 2018).

It has been reported that SSc has an overall prevalence of 1 – 15/100.000 (Sticherling, 2012). Prevalence rates do vary across the globe (Table 1.1). In the United States of America, Australia and Argentina prevalence of 150-300 cases/million are suggested with lower estimates in Scandinavia, Japan, United Kingdom, Taiwan and India (Barnes and Mayes, 2012). Based on a study of the United Kingdom scleroderma group, the prevalence of SSc in the UK is estimated to be 8/100.000 of the population (Hansi et al., 2014). However, recent reports estimated that there are currently 1180 new cases of SSc each year in the UK and 19,390 people living with SSc. Moreover, due to the predicted growth and ageing of the population, there is a prediction of a 24% increase in incident cases and 26% increase in prevalent cases over the next 20 years' time (Royle et al., 2018). The complex nature of this illness can often cause misdiagnosis, hence the true number of people with the disease is unknown.

1.2.2 Age

Systemic sclerosis tends to manifest in the middle to late life with the peak age of onset between 30-50 years of age. However, the disease can arise in the second or third decades of life. Patient ethnic background may influence the risk of SSc within individuals. African-American ethnic background developing the disease at an earlier age than whites (Ranque and Mouthon, 2010, Gelber et al., 2013, Hansi et al., 2014).

1.2.3 Gender

Systemic sclerosis has a female predominance being 3-8 times more common in females than males. In addition, females are more likely to develop SSc in early life compared with males (Hughes and Herrick, 2012). Male patients may have a greater risk of cancer development than female patients this reflecting the aetiology related to tobacco smoking, alcohol and immune and haematological malignancies (Olesen et al., 2010).

Table 1.1 Incidence and Prevalence according to regions

Region	Study period	Incidence per million	Prevalence per million	Publication
USA				
Minnesota	1947 - 68	2.7	-	(Medsger and Masi, 1971)
Minnesota	1953 - 67	1.2	105	(Kurland et al., 1969)
Minnesota	1950 - 79	10	138	(Michet et al., 1985)
USA	1963 - 68	2.3	19.8	(Medsger and Masi, 1978)
Pennsylvania	1963 - 82	13.9 - 18.7	-	(Steen et al., 1997)
South carolina	1989	-	290 - 1130	(Maricq et al., 1989)
Michigan	1985 - 91	14.1	-	(Laing et al., 1997)
Michigan	1989 - 91	21	276	(Mayes et al., 2003)
Oklahoma	1996	-	658.6	(Arnett et al., 1996)
All states	2001 - 02	-	300	(Robinson et al., 2008)
Quebec	2003	-	443	(Bernatsky et al., 2009)
Argentine				
Buenos Aires	1999 - 2004	21.2	296	(Rosa et al., 2011)
Australia				
Southern Half	1950 - 73	1.96	-	(Wigley and Borman, 1980)
New Zealand	1970 - 79	6.3	30	(Eason et al., 1981)
Sydney	1974 - 88	12	45.2 - 86.2	(Englert et al., 1999)
South Australia	1987 - 93	-	208	(Chandran et al., 1995)
South Australia	1993 - 99	15.1 - 22.8	200 - 233	(Roberts-Thomson et al., 2001)
South Australia	1993 - 02	20.4	232.2	(Roberts-Thomson et al., 2006)
Japan				
Tokyo	1987	7.2	38 - 53	(Tamaki et al., 1991)
Taiwan				
Taiwan	2002 - 2007	10.9	56	(Kuo et al., 2011)
India				
North India	2006 - 2007	-	120	(Minz et al., 2012)
UK & Europe				
England (West Midlands)	1986	3.7	31	(Silman et al., 1988)
England (Newcastle)	2000	-	88	(Allcock et al., 2004)
Hungary (South West)	2001	-	910 - 2370	(Czirjak et al., 2005)
Estonia (South)	1996 - 97	-	350 - 2280	(Valter et al., 1997)
Iceland	1975 - 90	3.8	71	(Geirsson et al., 1994)
Finland	1990	3.7	-	(Kaipiainen-Seppanen and Aho, 1996)
France (Seine St Denis)	2001	-	15.8	(Le Guern et al., 2004)
Greece (Northwest)	1981 - 02	11	154	(Alamanos et al., 2005)
Spain (Northwest)	1988 - 06	23	277	(Arias-Nunez et al., 2008)
Italy (Northeast)	1991 - 2007	43	341	(Lo Monaco et al., 2011)

Adapted from (Ranque and Mouthon, 2010, Barnes and Mayes, 2012)

1.2.4 Ethnicity

Systemic sclerosis arises in all ethnic groups and seems to be more common in certain ethnic groups. In the United States, SSc is more common in African Americans than American Whites. African American develop disease at an earlier age than Whites and have an increased frequency of diffuse cutaneous disease and poorer prognosis (Gelber et al., 2013). The difference between black and white ethnic groups in the United States may involve multiple predisposing factors such as socioeconomic status and health care access, and recently it has been suggested that genetic factors might explain more the racial disparities such as the overexpression of profibrotic factors and the under-expression of antifibrotic factors (Nashid et al., 2011, Silver et al., 2012).

1.2.5 Survival and mortality

Mortality varies widely among different patient populations and their organ involvement, and it is increased in male patients (Nikpour and Baron, 2014). The five-year survival rate is estimated to be 85%, and the 10-year survival rate is under 70% (Sticherling, 2012). Similar results have been reported in a systematic review and meta-analysis that included 17 studies and 9239 patients and revealed that the main cause of death is related to the pulmonary involvement of the disease (Rubio-Rivas et al., 2014). In a comprehensive study of 700 patients, African-Americans had a 43 – 60% increased risk of mortality in comparison to White Americans (Gelber et al., 2013). Recent studies have reported that patients with SSc have survival rates 16 – 34 years less than appropriate gender and age-matched populations due presumably to cardiopulmonary involvement and renal impairment (Nikpour and Baron, 2014, Rubio-Rivas et al., 2014).

1.3 Classification Criteria

Classification criteria for SSc were not developed until 1980 when the American Rheumatism Association (now known as the American College of Rheumatology (ACR)) developed specific criteria to differentiate systemic sclerosis disease from other connective tissue diseases. This included four items (SSc proximal to the metacarpophalangeal joints, sclerodactyly, digital pitting scars and bilateral basilar pulmonary fibrosis). This classification was judged to have been low sensitivity and specificity in the identification of early or mild disease. The further classification was developed in 1988, which divided the disease into two main categories (localised and diffuse). Localised was characterised by localised skin fibrosis limited to the distal aspects of the fingers and face without systemic involvement while diffuse disease type was generalised skin involvement with rapid progressive internal organ involvement (van den Hoogen et al., 2013).

In 2001, LeRoy and Medsger developed new criteria for early SSc with some new elements of the presence of relevant autoantibodies, Raynaud's phenomenon, skin fibrosis and nail fold capillaroscopy. This modification gave a high score of sensitivity (Ranque and Mouthon, 2010, Pope, 2015).

In 2013, a classification system was developed principally to aid research but also to help clinical practice and diagnosis (Table 1.2). The new American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) criteria considered three main features:

1- Fibrosis of the skin and/or internal organs.

2- Production of specific autoantibodies.

3- Presence of vasculopathy.

In the new diagnosis of SSc it is likely if the patient has skin thickening of the fingers that extends proximally to the metacarpophalangeal joints. Seven factors including skin thickening of the fingers, fingertip lesions, telangiectasia, abnormal nailfold capillaries, interstitial lung disease and/or pulmonary arterial hypertension, Raynaud's phenomenon and SSc-related autoantibodies are considered if the cutaneous features are not present. Each of these factors has a certain value, but overall a score of 9 points or more is considered to be a definitive diagnosis of SSc (Table 1.2) (van den Hoogen et al., 2013).

The sensitivity and specificity of the new classification criteria have been assessed and have excellent results achieving 91%, 92% respectively across different populations. However, the ACR/EULAR criteria should not be misinterpreted as a diagnostic tool as some recent reports indicate that there are patients for example who have Raynaud's phenomenon, positive SSc-related antibodies and nailfold capillaroscopy but do not fulfil the new criteria (Pope, 2015, Pope and Johnson, 2015). Despite the overall acceptance of this classification system further studies of different populations may help to allow the determination of the possible power of the criteria to predict disease progression and overall prognosis (Jordan et al., 2015, Pope and Johnson, 2015).

Table 1.2 ACR-EULAR 2013 classification criteria for systemic sclerosis

Category	Subitems	Weight/score
Skin thickening of the fingers of both hands is extending proximal to the metacarpophalangeal joints.	-	9
Skin thickening of the fingers	Puffy fingers Whole finger, distal to MCP	2 4
Fingertip lesions	Digital tip ulcers Fingertip Pitting scars	2 3
Telangiectasia	-	2
Abnormal nail fold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease	Pulmonary arterial hypertension Interstitial lung disease	2 2
Raynaud's Phenomenon (RP)	-	3
SSc-related autoantibodies (anticentromere, anti-topoisomerase-I [anti–Scl-70], anti–RNA polymerase-3)	-	3

Adapted from (van den Hoogen et al., 2013)

The use of different diagnosis or classification system over the past 40 years does, at times, prevent a detailed review of the clinical features of SSc from being presented. Thus, the following sections that describe the clinical aspects of SSc are based upon accepted clinical types of SSc that may not entirely reflect the currently accepted diagnostic criteria.

Systemic sclerosis can, in general, be divided into two main types of the disease - localised and systemic. SSc does not progress from localised to systemic, but both types can co-exist. All affected patients with SSc have certain shared features:

- Progressive scarring of blood vessels beginning in the fingers but with the risk of extending to internal organs.
- Scarring of tissues outside the blood vessels, including skin thickening and lung involvement.
- Varying levels of tissue inflammation and evidence of an overactive immune system.

Localised form of the disease consists of two main subtypes: morphea and linear SSc. Systemic disease includes three subclasses: limited cutaneous (lcSSc); that previously referred to CREST syndrome, diffuse cutaneous (dcSSc) and sine SSc.

1.3.1 Localised systemic sclerosis

About 70% of all patients with SSc have been diagnosed with localised disease. Localised SSc has two main subtypes (morphea and linear SSc) and rarely progresses into systemic disease as it commonly affects the skin and subcutaneous tissues. About 10% of patients may have muscle spasm, deformities or disfiguration due to excessive scar formation (Lachner, 2016).

Morphea SSc is a rare form of SSc that is sometimes referred to as circumscribed SSc. It can develop during childhood commencing as violaceous skin patches of variable size that may then progress to form fibrotic coloured skin plaques that later evolve from a sclerotic stage to non-indurated lesions that may appear as hypo- or hyper-pigmentation and may extend to the underlying cutaneous layers and manifest as a depressed area below the skin level. Morphea can be differentiated from systemic sclerosis by the absence of sclerodactyly, Raynaud's phenomenon and nailfold capillary changes. Morphea SSc can be limited to the hands and called acrosclerosis however patients with morphea can present some systemic symptoms such as malaise, fatigue, arthralgia and myalgia accompanied with a generalised form of morphea (Bali et al., 2013).

Linear SSc is more likely to manifests in children than adults and generally manifests as a band-like thickening that usually affects one side of the body and can extend to the underlying skin tissue and may extend to the muscles and bones. Linear SSc in some severe circumstances can give rise to arthritis, growth impairment and contractures of the associated joints causing significant deformity (Lachner, 2016).

Linear SSc has two subtypes (*En coup de sabre* and Parry-Romberg syndrome). *En coup de sabre* commonly affects the head and neck area resembling the stroke of a sabre and causing hyper-pigmented skin lesions and also in severe instances can give rise to fibrosis of the skin, subcutaneous tissues, muscles and extend to bones leading to a sword thrust shape. The lesion is typically located paramedial on the forehead and runs to the hairline, but it can occur on the chin and can extend intraorally. A linear depression area or groove of the skin can be apparent and can cause loss of hair (alopecia) if present on the scalp or eyelids and craniofacial development can be affected in severe cases and cause hemifacial atrophy (Horberg et al., 2015, Tolkachjov et al., 2015). In occasional patients, the defect can extend to the peridentine and has been reported to cause root abnormalities of teeth in affected areas (de Figueiredo et al., 2008, Horberg et al., 2015, Arroyo-Bote et al., 2017).

Progressive hemifacial atrophy or Parry-Romberg syndrome is a very rare orofacial form of the disease characterised by involvement of both muscles and bone rather than superficial skin layers. It can affect the body in a symmetrical manner, although cutaneous involvement can occur, and lesions can extend to tongue, gingiva, teeth and palate. Neurological complications such as seizures, headaches and trigeminal neuralgia after cranial nerve neuropathies may be features. Of concern, ocular disorders can result in a mild impairment to permanent blindness due to both muscular and neural pathological involvement. Patients with Parry-Romberg syndrome can have dental abnormalities such as delayed eruption, dental root exposure and/or resorption, temporomandibular joint disorder, trismus and muscle spasm and atrophy of the affected soft tissues such as the lips and tongue (Horberg et al., 2015, Tolkachjov et al., 2015, Distler and Cozzio, 2016). The severity and pattern of the disease vary between patients.

Both subtypes of linear SSc commonly manifest between 5 to15 years of age and are more predominant in females than males with a ratio of (3:1). A number of factors have proposed to clinically and histologically distinguish between *en coup de sabre* and progressive hemifacial atrophy, as indicated in Table 1.3. Occasional patients can have an overlap of clinical and histological observations, perhaps suggesting that they lie within a spectrum of both disorders. Although the precise cause of localised SSc remains unknown, a combination of autoimmune and vascular dysfunction is suggested to be of relevance (Tolkachjov et al., 2015).

Table 1.3 Comparison of *en coup de sabre* and progressive hemifacial atrophy (Parry-Romberg syndrome)

Items	**En coup de sabre**	**Progressive hemifacial atrophy**
Average Age (years)	10	13.6
Gender (F:M)	2:1 – 3:1	3:1
Dominant clinical features	- Cutaneous induration/sclerosis - Scalp to forehead and facial area - Hyperpigmentation - Alopecia (scalp/eyebrow)	- Paramedian atrophy - No overlying skin induration - Atrophy may extend down entire face
Histopathologic features	- Dermal Sclerosis - Adnexal atrophy - Mononuclear cell infiltrates	- Dermal sclerosis - Fat atrophy - Decrease in adnexal structures - Mononuclear cell infiltrates
Extracutaneous associations	-	- Atrophy subcutaneous tissue, fat, muscle, and osteocartilaginous structures - Atrophy and deformities of the tongue, teeth and gingivae - Cranial neuropathies - Visual impairment - Seizure disorders

Adapted from (Tolkachjov et al., 2015)

1.3.2 Systemic sclerosis

In contrast to localised SSc - where the affected tissues are predominantly cutaneous without the involvement of blood vessels or viscera - systemic sclerosis comprises cutaneous and vascular disease with the likelihood of visceral involvement. Systemic sclerosis can have life-threatening complications affecting the gastrointestinal, pulmonary, cardiovascular and renal systems. Systemic sclerosis can be divided into two main groups (limited and diffuse cutaneous SSc).

Limited cutaneous systemic sclerosis is characterised by low-grade skin involvement that is commonly limited to extremities such as the hands, forearms and feet with the possibility of head and neck involvement. It is the most common type of systemic sclerosis, accounting for around 60% of patients. 90 - 95% of patients with limited cutaneous SSc have Raynaud's phenomenon for a long time before the development of other manifestations of the disease (Lachner, 2016).

As noted earlier, limited cutaneous SSc was previously termed CREST as a common manifestation was this combination of cutaneous Calcinosis, Raynaud's phenomenon, Oesophageal dysfunction, Sclerodactyly and Telangiectasia as denoted in Table 1.4.

Table 1.4 Description of the CREST Syndrome

Calcinosis	Raynaud's Phenomenon	Oesophageal dysfunction	Sclerodactyly	Telangiectasia
Accumulation of calcium salts under the skin and causes hard painful raised areas that can open and cause ulcerations of the skin. Typical sites of deposition are mainly on elbows, knees and fingers.	Vasoconstriction with intermittent loss of blood flow to fingers, toes and nose that occurs with exposure to cold and stress and causes numbness, tingling and pain. Disease progression can lead to gangrenous lesion of tissue and erosion of the terminal extremities	Weakened lower oesophagus causing reflux and swallowing difficulties. This commonly leads to heartburn, inflammation and scarring of oesophageal tissues.	Excess collagen in the skin layers causing thickening, tighten and shiny appearance and difficulty moving fingers/toes. In severe cases there is notable contraction of the fingers and toes.	Dilation of capillaries causing small blanching red spots on hands, face, chest and mouth. While harmless they may cause disfigurement and social embarrassment.

Adapted from (Lachner, 2016)

Patients with limited cutaneous systemic sclerosis may have a significant degree of associated pain (e.g. Raynaud's), infection, fatigue and disfigurement. Other disease features that can present in about 33% of affected individuals include digital pitting ulcers and scars. Anticentromere antibodies (ACA) are present in 70-80% of affected individuals. Mortality and morbidity among these patients' populations are linked mainly to the high incidence of pulmonary arterial hypertension and interstitial lung disease (10-15%) that might include shortness of breath and significantly limited the exercise ability and tolerance (Desbois and Cacoub, 2016).

In contrast to lcSSs, diffuse cutaneous systemic sclerosis usually manifests as more generalised skin thickening that can extend to the trunk and other body areas rather than proximal limbs and have a rapid progression onset that leads to mobility impairment of associated joints and musculature structures.

Diffuse cutaneous systemic sclerosis is usually accompanied by early internal organ involvement, particularly the heart, lungs and kidneys. These common associated complications of the disease may include myocardial involvement, interstitial lung disease, renal failure and diffuse gastrointestinal impairment ranged from oesophageal dysmotility to small bowl hypomotility with commonly presence of Anti-Scl-70 (30%) and anti-RNA polymerase-I, II, or III (12-15 %) antibodies (Lachner, 2016, Desbois and Cacoub, 2016).

Both systemic disease subtypes have several shared clinical and serological features with a variable degree of clinical involvement and severity (Table 1.5).

Table 1.5 The main clinical features of systemic sclerosis

Items	lcSSc	dcSSs	ACA	ATA	ARA
Digital ulcers	33 – 38%	43%	18 – 42%	40 – 45%	20%
Interstitial lung disease	35%	53%	13 -21%	30 – 60%	20%
Renal crisis	1%	4 – 11%	1%	2 – 4%	20%
Pulmonary arterial hypertension	9%	6%	5 – 10%	13 – 17%	10%
Oesophageal involvement	67%	68%	64 – 71%	68%	60%
Cardiac involvement	6%	8%	9%	17%	15%
Muscular involvement	22%	37%	23 – 40%	32 – 50%	50%

Adapted from (Desbois and Cacoub, 2016)

1.4 Clinical features

1.4.1 Cutaneous features

Cutaneous disease is the most common manifestation of SSc. It is consists of thickening and induration of the skin mainly of the hands and face. Hand involvement often begins with non-pitting oedema that gradually hardens and leads to atrophic lesions and ulceration. The prognosis of the disease can be based upon the degree of skin involvement as the higher the initial skin score, the worse the prognosis. Cutaneous features of SSc in hands commonly include Raynaud's phenomenon, sclerodactyly, acral soft tissue thinning, digital pitting and ulcers. Other manifestations include acroosteolysis, calcinosis, tendon friction rubs, flexion/ contractures, arthralgias, hypo- and/or hyper-pigmentation, telangiectasia and loss of sebaceous glands (Hughes and Herrick, 2012).

Cutaneous involvement also can involve parts of the body other than the extremities and characterise by thickening of the skin of the chest, abdomen and other pressure areas. There can be hypo- and/or hyper-pigmentation of the affected sites (Volkmann and Furst, 2015).

1.4.2 Vascular features

Raynaud's phenomenon (RP) is the earliest and most common disease feature in 95% of patients with SSc. This is bilateral and can also affect feet, nose, ears and, very rarely, the tongue. It consists of white (ischaemia), blue (deoxygenation) and painfully red decolouration (reperfusion) as a result of vascular spasm and ischemia (Desbois and Cacoub, 2016). In most cases, the presence of RP along with both nailfold capillary changes and SSc-specific antibodies indicating a high probability of developing SSc with the association of irreversible tissue injury, ulceration and critical ischaemia. In addition to ischaemia, patients may have paraesthesia, discomfort and pain during episodes (McCray and Mayes, 2015).

The presence of RP may differ across patients with SSc. In those with limited SSc it typically begins many years before the first onset of cutaneous disease, while in patients with diffuse SSc, the RP usually occurs in parallel with, or even after, the onset of the other cutaneous events (Elhai et al., 2015).

1.4.3 Gastrointestinal features

The gastrointestinal tract is the second most common site of involvement, occurring in 75% - 90% of patients with SSc (Elhai et al., 2015). It is one of the leading causes of morbidity in SSc and the third most common cause of mortality after cardiopulmonary and renal involvement (Hansi et al., 2014). All parts of the gastrointestinal tract can be affected although gastro-oesophageal involvement is most common with SSc-related disease accounting for 90% of the symptoms of heartburn, regurgitation and dysphagia in SSc (Hansi et al., 2014). Other gastrointestinal manifestations include poor appetite, motility abnormalities (e.g. diarrhoea, constipation, bloating, actual and pseudo-obstruction of the bowel due to poor peristalsis). Severe gastro-oesophageal reflux can lead to oesophageal stricture formation and narrowing, Barrett's

oesophagus and risk of adenocarcinoma (McCray and Mayes, 2015). 50% of patients with GIT involvement of SSc have gastroparesis. This delayed gastric emptying can cause early satiety, bloating, nausea, vomiting, weight loss and subsequent undernourishment. Other gastrointestinal disease features include rectal prolapse, tenesmus, and pain during defecation, spontaneous colonic perforation and colonic infarction (Barsotti et al., 2014, Gyger and Baron, 2015).

1.4.4 Cardiopulmonary features

Pulmonary involvement can affect 70 - 80% of all patients with SSc. Interstitial lung disease and pulmonary arterial hypertension (PAH) are the most frequent features of lung involvement (Lachner, 2016). Interstitial lung disease is considered as one of the major causes of death in SSc patients while PAH is considered as one of the leading causes of death in SSc patients, particularly in a late stage of the disease and when associated with interstitial lung disease. The prevalence of PAH in all patients with SSc is about 9-12% (Elhai et al., 2015).

Cardiac involvement in SSc carries a poor prognosis and is the leading cause of death. Both the pericardium and myocardium can be affected. A wide spectrum of pericardial diseases occurs in SSc including acute pericarditis, chronic pericarditis, pericardial fibrosis and constrictive pericarditis (Bissell et al., 2016).

Myocardial involvement is commonly associated with vasospasm of the small vessels and ischaemia of the coronary microcirculation that may lead to myocardial fibrosis. Systolic and diastolic ventricular dysfunction can occur as a result of myocardial involvement and can lead to post-capillary pulmonary hypertension. Recent reports have found that pulmonary involvement together with factors including age, male gender and myositis are independent risk factors for acute myocardial infarction in

patients with SSc. In addition, immunosuppressive therapy does not lessen the risk of myocardial infarction (Barsotti et al., 2014).

1.4.5 Renal features

Renal involvement in SSc is relatively rare occurring in about 4-6% of patients. Nevertheless, the severe manifestation can occur even in early disease. Patients with renal involvement can have a renal crisis, normotensive renal crisis, anti-neutrophil cytoplasmic antibody-associated glomerulonephritis, penicillamine-associated renal disease and reduced renal function. The renal crisis is the most significant renal complication with a prevalence of 5% in diffuse subtype and 2% in limited-SSc. Renal crisis commonly presents as severe hypertension 90%, hypertensive encephalopathy or cardiac failure, rapid deterioration of renal function and thrombotic microangiopathy 40%. Although the prognosis of renal involvement has been improved by using the angiotensin-converting-enzyme inhibitors as the first line of treatment for the renal crisis, the mortality rate remains high with overall five-year survival rates being only 30-50% (Elhai et al., 2015).

1.4.6 Neurological features

Various neurological disorders can arise in SSc. Central nervous system (CNS) involvement includes headache 23.7%, seizures 13.5%, cognitive impairment 8.4%, depression 73% and anxiety 23.9%. While peripheral nervous system (PNS) involvement can manifests as myopathy 51.8%, trigeminal neuropathy 16.5%, peripheral sensorimotor polyneuropathy 14.2% and carpal tunnel syndrome 6.5% (Amaral et al., 2013). Although the cause of neurological involvement is not fully defined, different possible theories are suggested including vascular-dependant mechanisms due to vasculitis and/or vessel wall damage, compression-dependent mechanisms due to oedema and/or fibrosis then progressive demyelination and

autoimmune-dependent mechanisms associated with anti-neuronal antibodies (Amaral et al., 2013, Ludwig et al., 2017).

1.5 Association of malignancy

The precise association of SSc with the risk of cancer remains undetermined. However, recent studies report that the risk of malignancy is increased in SSc. Several reports have demonstrated an increased incidence of cancer lesions in SSc populations with a concern about the long-term morbidities of the disease especially among older patients with the diffuse cutaneous SSc (Barnes and Mayes, 2012, Zeineddine et al., 2016). The reported standardised incidence ratio (i.e. the ratio of observed to expected instances) for cancer among men was higher than women 2.2 (95% CI 1.7-2.8), 1.3 (95% CI 1.1-1.6) respectively. However, the most frequent malignancies in SSc were found to be either smoking or alcohol-related cancers. Other studies reported the relative risk of overall cancer among SSc patients to be 3.15 (95% CI 1.77-5.20) with highest for haematologic and lung malignancies.

The cancer risk in some patients with systemic sclerosis may be associated with the presence of anti-RNA polymerase III antibodies (14.2%) rather than anti-topoisomerase I antibody and anti-centromere antibodies. In patients with positive anti-RNA polymerase III antibodies, the risk of developing cancer (e.g. breast cancer, melanoma, colorectal cancer, lymphoma and lung cancer) may be four to six times greater in the 3 years since the first onset of clinical signs of SSc (Desbois and Cacoub, 2016, Zeineddine et al., 2016). It has been suggested that severe and progressive fibrosis, chronic inflammation and B-cell stimulation may increase the risk of carcinogenesis with contributions by environmental factors, DNA oxidative damage, genetic background and immunosuppressive therapy (Zeineddine et al., 2016).

1.6 Sine systemic sclerosis

Sine SSc is a rare form of the disease accounting for 2-8% of affected individuals and can resemble either limited or diffuse systemic sclerosis. The diagnosis is challenging as it commonly manifests as internal organ involvement without skin sclerosis with early systemic changes occurring in the oesophagus (56% - 83%), lungs (25% - 57%), kidneys (2.5% - 3.7%) and blood vessels. Patients with sine SSc may have some features of other disease types such as mild telangiectasia, digital ulcers and circulating autoantibodies (Desbois and Cacoub, 2016, Lachner, 2016).

Recent studies suggest that patients with sine disease form may have the same laboratory features as other disease categories however they should be classified as a separate subset and diagnosed as early as possible to lessen the risk of significant morbidity and mortality associated with visceral disease (Simeon-Aznar et al., 2014).

1.7 Juvenile systemic sclerosis

It has recently been suggested that SSc be further classified into adulthood and childhood disease as its childhood disease may differ from that in adults. New classification criteria have now been proposed to differentiate between the localised and systemic forms of juvenile SSc. Recent reports suggest an estimated prevalence of less than 1 in 5000. The incidence rate per million children per year for both jSSc and jlSSs in United Kingdom and Ireland are 0.27 (95% CI 0.1 - 0.5) and 3.4 (95% CI 2.4 - 4.1) respectively with a median time diagnosis of juvenile SSc of 0.2 to 18.8 years delay being greater than jlSSc (Foeldvari, 2013, Foeldvari, 2015, McCann and Pain, 2016).

The new proposed classification of jSSc (Table 1.6) may be helpful to improve early diagnosis and hence management of the disease. It consists of one major criterion (proximal skin fibrosis/induration) and secondary factors associated with different body

organs. However, a further classification system considers jlSSc as a separate type of the disease, but this has yet to be widely validated (Table 1.7) (Foeldvari, 2013).

Juvenile localised SSc is the more common form of the disease in children (93%) with mean age onset 7.3 years old, and is characterised by skin and subcutaneous tissue fibrosis and rarely in 20% associated with extracutaneous manifestations including multiple internal organ involvement. Both forms of localised SSc (linear and morphea) frequently occur in childhood-onset and may lead to significant aesthetic and function impairment especially in growing periods which can give rise to joint contractures, bone length malformation and facial atrophy (Trainito et al., 2012, McCann and Pain, 2016).

Juvenile systemic sclerosis is the less common variant and affects children with a mean age around (8.1 years old). Patients with juvenile dcSSc commonly present with a wide range of skin involvement and rapid widespread fibrosis of internal organs. Vascular features such as Raynaud's phenomenon, nailfold capillary changes, digital ulcers and scars can arise in juvenile localised SSc but the visceral disease of jSSc depending upon the severity and activity scores of the jSSc, can be considered to be a life-threatening condition with a significant mortality rate (12%) with approximately 5 – 8% of patients dying within five years following disease diagnosis (Foeldvari, 2015, McCann and Pain, 2016).

Table 1.6 A new proposed classification criteria for Juvenile systemic sclerosis

Major criterion (*required*): Proximal skin sclerosis/induration of the skin	
Minor criterion (*at least two required*):	
Cutaneous	Sclerodactyly
Peripheral vascular	- Raynaud's phenomenon - Nailfold capillary abnormalities - Digital tip ulcers
Gastrointestinal	- Dysphagia - Gastroesophageal reflux
Cardiac	- Arrhythmias - Cardiac failure
Renal	- Renal crisis - New-onset arterial hypertension
Respiratory	- Pulmonary fibrosis (high-resolution computed tomography/radiography) - Decreased diffusing capacity of carbon monoxide - Pulmonary arterial hypertension
Neurologic	- Neuropathy - Carpal tunnel syndrome
Musculoskeletal	- Tendon friction rubs - Arthritis - Myositis
Serologic	- Antinuclear antibodies - Systemic sclerosis–selective autoantibodies (anticentromere, anti–topoisomerase I [Scl-70], antifibrillarin, anti-PMScl, antifibrillin, or anti–RNA polymerase I or III)

Adapted from the Paediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism (Foeldvari, 2013)

Table 1.7 Preliminary proposed classification for juvenile localised systemic sclerosis

Main Group	**Subtype/Definition**
1- Circumscribed morphea	- Superficial - Deep
2- Linear SSc	- Trunk / Limbs - Head (En coup de sabre, Progressive hemifacial atrophy)
3- Generalized morphea	- Four or more plaques (>3 cm) and involves at least 2 of 7 anatomic sites.
4- Pan sclerotic morphea	- Circumferential involvement of the limbs affecting all tissue layers including the bone.
5- Mixed morphea	- Combination of 2 or more previous types.

Adapted from (Foeldvari, 2013)

1.8 Overlap syndromes

Systemic sclerosis often overlaps with other autoimmune connective tissue diseases. The diagnosis of SSc overlap syndrome is usually made upon fulfilment of specific criteria of SSc and the presence of related clinical features and/or serological autoantibodies (Table 1.8). The most common variants are an overlapping syndrome with Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis or polymyositis. Approximately up to one-fifth (10-38%) of the patients with SSc may have elements of these other disorders (Denton, 2016). This overlap may reflect a genetic element as 16.3% of patients with overlap disease can have a family history of autoimmune disease, this being more likely in affected children (23.8%) than adults (10.6%) (Kreuter et al., 2016).

Table 1.8 Diagnostic features of systemic sclerosis-overlap syndrome

Diagnosis	Clinical criteria of SSc plus
SSc–polymyositis overlap syndrome	Muscle weakness with elevated creatine kinase and two of the following: - Inflammatory myositis from muscle biopsy - Abnormal electromyography (EMG) - Positive for anti-PM-Scl or anti-Ku
SSc–dermatomyositis overlap syndrome	Dermatomyositis skin lesions such as (heliotrope, Gottron's sign, Gottron's papule) plus three of the following: - Muscle weakness - Elevated creatine kinase - Inflammatory myositis from muscle biopsy - Abnormal electromyography (EMG) - Positive anti-Mi2
SSc–systemic lupus erythematous overlap syndrome	≥ four of the following criteria with at least one clinical and one laboratory criteria according to Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria 2012 for SLE or kidney biopsy proven-lupus nephritis with ANA or anti-DNA positive. Clinical criteria composed of: - Acute cutaneous lupus - Chronic cutaneous lupus - Oral or nasal ulcers - Non-scarring alopecia - Arthritis - Serositis - Renal involvement - Neurological involvement - Haemolytic anaemia - Leukopenia - Thrombocytopenia Laboratory criteria compose of (ANA, Anti-DNA, Anti-Sm, Antiphospholipid antibodies, Low complement, Direct Coombs' test in the absence of haemolytic anaemia)
SSc-rheumatoid arthritis overlap syndrome	Total score ≥ 6 according to 2010 ACR-EULAR classification criteria for RA Joint distribution: - 1 large joint (score = 0) - 2–10 large joints (score = 1) - 1–3 small joints (score = 2) - 4–10 small joints (score = 3) - > 10 joints (score = 5) Serology: - Negative RF and negative anti-CCP (score = 0) - Low positive RF or low positive anti-CCP (score ==2) - High positive RF or high positive anti-CCP (score = 3) Duration of symptoms: - < 6 weeks (score = 0) - ≥ 6 weeks (score = 1) Acute phase reactants: - Normal CRP and normal ESR (score = 0) - High CRP or high ESR (score = 1)
SSc–polymyositis – systemic lupus erythematous overlap syndrome	PM plus clinical features of SLE and the specific serology for PM or SLE

Adapted from (Foocharoen et al., 2016)

“Sicca” symptoms (i.e. oral and ocular dryness) are suggested to be common (71.2%) in SSc, but some patients (33.9%) might have an overlap with SS with Ro and/or La positive antibody profiles (Kobak et al., 2013). The co-existence of systemic lupus erythematosus (SLE) in SSs is more often reported in association with localised rather than systemic disease and may be more likely in young populations (Nazarinia et al., 2016).

SSc-rheumatoid arthritis overlap syndrome has been described and accounts for about 13.2% of all overlap disease. The SSc-polymyositis overlap syndrome may be the most common type (70.6%) as patients have features including vasculopathy, skin fibrosis and internal organ involvement such as gastrointestinal, cardiopulmonary and renal impairment. Multiple sclerosis had been found in some patients with SSc (Foocharoen et al., 2016).

In addition to the aforementioned overlap conditions, other rare cutaneous disorders have been listed as a differential diagnosis of systemic sclerosis such as eosinophilic fasciitis, scleredema and scleromyxoedema. Eosinophilic fasciitis is very uncommon and has symmetric skin manifestations characterised by the fibrosis of the underlying fascia with an absence of autoantibodies, Raynaud’s phenomenon and nailfold changes.

Moreover, sclerodema as a collagen deposition disorder can lead to a similar appearance of SSc skin lesions, but it usually does not involve extremities. Scleromyxederma has a common involvement of face and hands with other features including oesophageal dysmotility, arthralgia, myopathy and Raynaud’s phenomenon. It differs from SSc as there is no involvement of lung disease or calcinosis with the absence of autoantibodies (McCray and Mayes, 2015).

The term *mixed connective tissue diseases* (MCTD) was proposed to describe the overlap between systemic sclerosis with other autoimmune disorders with the presence of serum antibody to ribonucleoprotein (Jasinska and Boczon, 2015). The concept of MCTD has been established to classify the combination of having more than one connective tissue disease with regards to ARA classification criteria (Hoffmann-Vold et al., 2015). However, mixed connective tissue disease is defined as a multisystem disorder with overlapping clinical manifestations of systemic lupus erythematosus, systemic sclerosis and polymyositis or dermatomyositis and the definite diagnosis is mainly determined upon the serological lab investigations and the related specific antibody titers (Martínez-Barrio et al., 2018).

Common clinical features of MCTD can be summarised as patients have Raynaud's phenomenon, arthritis, sclerodactyly and myositis (Ungprasert et al., 2016). However, the involvement of cardiac, renal and respiratory systems is common. The neurological involvement of the MCTD may include headaches, sensorineural hearing, cerebral haemorrhage, transverse myelitis, cauda equine syndrome, retinal vasculitis, progressive multifocal encephalopathy and demyelinating neuropathy (Jasinska and Boczon, 2015).

In one recent study, Melkersson-Rosenthal syndrome was suggested to be an early neurological manifestation of the MCTD with its common symptoms including facial nerve palsy, fissured tongue and facial oedema (Jasinska and Boczon, 2015), but there is little evidence to strongly support this notion.

In a recent survey, the incidence of MCTD found to be 1.9/100,000 population with an overall mortality rate ratio of 1.1 (95% CI, 0.4-2.6). The most prevalent symptoms were arthralgia 86%, Raynaud's phenomenon 80%, swollen hands 64%,

leukopenia/lymphopenia 44% and heartburn 38%. The evolution of SSc found to be 6.3% with 10 years rate of evolution (Ungprasert et al., 2016).

1.9 Environmentally-induced systemic sclerosis

Environmental risk factors have been reported to be linked with some SSc-like disorders when there is a history of exposure to an environmental agent suspected of causing SSc and chemical potential precipitant agents such as silica dust, hydrocarbons, organic solvent materials, quartz salts, vinyl chloride, epoxy resins and pesticides (Mayes et al., 2003). Moreover, some authors tended to consider systemic sclerosis as an occupational disease in regard to some industrial exposure to chemicals such as trichloroethylene, chlorinated solvents, aromatic solvents, ketones and welding fumes (Barnes and Mayes, 2012, Niklas et al., 2016). Although, recent studies concluded that there is no association between SSc and silicone breast implants (Hong et al., 2015).

Further studies could investigate the suggested link between the different potential agents and SSc as there is a lack of strong evidence for the majority of these case reports to be associated with SSc (Ranque and Mouthon, 2010, Sticherling, 2012, Dumoitier et al., 2014).

1.10 Diagnostic criteria

The diagnostic features of systemic sclerosis are mainly based on the identification of the disease features that patients mostly have such as Raynaud's phenomenon, puffy swollen fingers, abnormal nail fold capillaroscopy and the presence of serum specific antibodies.

Early diagnosis of SSc is usually challenging as patients might not show any extracutaneous features at this early stage of the disease, or they might not have visible skin lesions for example in the case of having sine SSc. Raynaud's

phenomenon is often the first disease manifestation however it is present in 3-5% of general population as a primary RP that may not lead to development of SSc although 79.5% of the patients having RP with other feature and/or serum antibodies might indicate the diagnosis of SSc (Sakkas et al., 2015, Desbois and Cacoub, 2016).

In the case of patients having sine SSc the diagnosis usually made upon the presence of the other disease manifestations such as Raynaud's phenomenon, oesophageal dysmotility, nail fold microvascular changes and other suspected organs involvement including heart, lungs and kidneys. Autoantibodies are considered a highly valuable diagnostic tool in SSc as it found in about 90-95% of SSc population however in some rare cases 6.4%, SSc autoantibodies were negative (Diab et al., 2014, McCray and Mayes, 2015).

Skin biopsy is not very helpful in the diagnosis of SSc as it might represent similar features with other SSc-like disorders that are differentiated from each other by the clinical features and the nature of involvement. Although, it might be considered for other conditions such as eosinophilic fasciitis, sclerodema and scleromyxedema (Hachulla and Launay, 2011). In making the diagnosis, it is essential not only to confirm the presence of SSc but also to determine its extent and severity particularly with regards to the involvement of the organs thus the diagnosis is usually made by the physician through a combination of medical history, past and present symptoms, a thorough examination, blood tests and capillaroscopy.

The diagnosis of SSc can be challenging particularly in its early stages, therefore, the concept of Very Early Diagnoses clinic for Systemic Sclerosis (VEDOSS) initiative in Europe 2009 aiming for early diagnostic tests for systemic sclerosis in any patient with Raynaud's and finger swelling, using nail fold capillaroscopy and anti-nuclear antibody tests (Jordan et al., 2015).

1.11 Aetiopathogenesis

A detailed discussion of the aetiopathogenesis of SSc is out with the remit of this present work, but certainly, SSc has a strong immunological basis. Although the precise aetiology of SSc remains unknown, several factors are thought to be considered as risk factors such as age, sex, genetic background, environmental elements and infectious agents (Stern and Denton, 2015).

Both autoimmune factors and vascular injury have been proposed to play a major part in the disease pathology, while defects in cell-mediated immunity lead to fibrosis. The abnormal activation of the fibroblast and increased production of the collagen and extracellular matrix in the dermis layers usually results in symmetrical thickening, tightening and induration of the skin appearance associated with other pathological processes including narrowing of blood vessels and ischaemia. Also, the association of high levels of non-specific and specific autoantibodies proposed the pathogenesis autoimmune mechanism of the disease (Bali et al., 2013).

The role of the environmental and occupational risk factors in the aetiology of SSc remains a controversial issue. As discussed previously, exposure to a variety of different chemicals can cause SSc-like disease (Hughes and Herrick, 2012). Similarly, certain occupations that increase the opportunity to expose to chemicals such as trichloroethylene, chlorinated solvents, aromatic solvents, ketones and welding fumes may increase the risk of SSc-like disease. Nevertheless, such exposures do not account for the great hazards of individuals with SSc (Sticherling, 2012, Desbois and Cacoub, 2016).

A variety of different infectious agents have been suggested to be potential trigger factors for SSc such as EBV, CMV, HPV, Parvovirus B19, HBV, retrovirus, Toxoplasmosis, *Helicobacter pylori* and chlamydia. This may arise as a consequence

of molecular mimicry with the induction of cross-reactivity between several antigens with cellular autoantigens which might lead to autoreactive immune responses and the initiation of the disease (Sticherling, 2012, Farina and Farina, 2016).

Many studies have demonstrated that there is an increased susceptibility to develop SSc among family members of affected individuals with a relative risk as high as 13 (10 -16 across cohorts) and recurrence risk of 1.6% versus 0.026% in the general population. The relative risk between siblings maybe 15 (10 - 27 across cohort) (Dumoitier et al., 2014, Stern and Denton, 2015), although studies have reported that the relative risk of developing SSc in families among first-degree relatives is 3.07 (95% CI, 1.25-7.57), and 2.14 (95% CI, 1.16-3.95) in third-degree relatives (Luo et al., 2013). Genome-wide association studies have been reported that there is a contribution between SSc and different components of the major histocompatibility complex (MHC), and non-HLA genes that are strongly associated with SSc (Luo et al., 2013, Dumoitier et al., 2014, Murdaca et al., 2016).

The common pathological events of SSc are microvascular changes, inflammation and immune system activation leading to connective tissue repair and fibrosis of affected organs (Stern and Denton, 2015). Vascular abnormalities and endothelial dysfunction are early events that lead to progressive obliteration of the microvessels and ischaemia of the associated tissues. Fibrogenesis and collagen production occur as via subsequent activation of T and B lymphocytes and secretion of the inflammatory cytokines and chemokines causing chronic fibroblast activation, myofibroblast formation and fibrotic accumulation (Hua-Huy and Dinh-Xuan, 2015).

1.12 Serological features of SSc

Systemic sclerosis is associated with several specific and non-specific autoantibodies some of which are of diagnostic and/or prognostic value. The present classification criteria of the American College of Rheumatology/European League against Rheumatism in 2013 includes the presence of SSc-related autoantibodies such as (Anti-centromere, Anti-topoisomerase I and Anti-RNA polymerase III) as a diagnostic item for SSc. However, ANA is found to be positive in approximately 90-95% of SSc patients with different frequencies being reported in the different disease subtypes and populations. About 6.4% of patients with SSc may have no detectable autoantibodies hence making early disease challenging (Hughes and Herrick, 2012, McCray and Mayes, 2015).

1.12.1 SSc associated antibodies

Anti-centromere antibody (ACA):

The most frequent found autoantibodies among white individuals and females are anti-centromere antibodies (ACA). The frequency of ACA among SSc patients with limited cutaneous disease is 15 – 43%. Patients with positive ACA often have pulmonary hypertension but are unlikely to have other disease features such as digital ulcers, parenchymal lung disease, myocardial and kidney involvement. ACA positive SSc patients tend to have a better prognosis and lower mortality rate than those with other SSc autoantibodies (Sticherling, 2012, Desbois and Cacoub, 2016).

Anti-topoisomerase I antibody (ATA) / (anti-ScL-70):

Systemic sclerosis with positive ATA is mainly that of diffuse cutaneous type disease (30 – 40%) but some studies reported positive values of ATA in limited cutaneous disease (14%), and/or when there is lung fibrosis or digital ulcers. ATA positivity suggests a poor prognosis with high mortality rate. Patients with ATA positive SSc

tend to develop Raynaud's phenomenon at an early stage and to have more severe skin disease (Hughes and Herrick, 2012, Desbois and Cacoub, 2016).

Anti-RNA Polymerase III:

Anti-RNA polymerase III antibodies are mainly associated with diffuse cutaneous systemic sclerosis (11-19%) and rarely (3-5%) occur in limited cutaneous disease. Overall, they are found in about 11% and their prevalence can vary across different ethnic groups. Anti-RNA polymerase III positive patients can have an increased risk of visceral complications such as SSc-renal crisis (OR 3.8), tendon contracture (OR 2.5) and cancer (OR 4.2) in the first five years from time of diagnosis of SSc (Desbois and Cacoub, 2016).

A variety of other autoantibodies have been found in or associated with SSc and other overlap-SSc syndromes. While these autoantibodies may not be of notable diagnostic help, they can be rarely associated with certain clinical features.

Anti-Th/To antibodies:

They are present in 0.2-6% of patients with SSc and are typically associated with the limited cutaneous type disease and those with a risk of renal crisis, pulmonary arterial hypertension and pericarditis (but not digital ulcers). The presence of these antibodies is usually associated with low survival rate (Nihtyanova and Denton, 2010, Desbois and Cacoub, 2016).

Anti-fibrillarin/U3 RNP antibodies:

Anti-U3 RNP antibodies occur in about 4-18% of patients with SSc and are strongly found in African/American males. These autoantibodies can be associated with both main types of the disease with a greater tendency for the diffuse subtype. Their presence indicates an increased risk of pulmonary arterial hypertension, muscular involvement, digital ulceration, pericarditis and severe involvement of the lower

gastrointestinal system. Reports show conflicting results about the impact on survival rates with Anti-U3 RNP, but the association with a younger age at onset has been documented (Silver et al., 2012, Desbois and Cacoub, 2016).

Anti-U11/U12 RNP antibodies:

The prevalence of these antibodies and their clinical associations are not well documented, although they may be found in about 3% of patients with SSc. It has been reported that there is a high risk of developing pulmonary fibrosis among patients with positive anti-U11/U12 RNP antibodies (Nihtyanova and Denton, 2010).

1.12.2 SSc overlap-associated antibodies

Anti-Pm/Scl antibodies:

Anti-Pm/Scl antibodies can occur in (2-3%) of SSc patients, and their positivity has been linked to a variety of clinical features of overlap connective tissue diseases (e.g. Raynaud phenomenon, calcinosis, sicca syndrome and myositis). Anti-Pm/Scl antibodies are also present in 55% of other autoimmune diseases such as polymyositis/dermatomyositis, systemic lupus erythematosus and Sjogren's syndrome. Up to 85% of positive anti-Pm/Scl antibodies patients developed pulmonary fibrosis and digital ulceration (Nihtyanova and Denton, 2010).

Anti-Ku antibodies:

Anti-Ku antibodies are not specific to SSc and have been found in only 2% of patients with SSc and other undifferentiated connective tissue disease, overlap syndromes with features of systemic lupus erythematosus, polymyositis/dermatomyositis and Sjogren's syndrome. These antibodies have been strongly associated with musculoskeletal involvement in SSc with a suggested protective role against severe digital ulceration (Nihtyanova and Denton, 2010).

Anti-U1 RNP antibodies:

Anti-U1 RNP antibodies are found in about 90% of mixed connective tissue diseases and commonly associated with the presence of other antibodies such as anti-Ro/SSA, anti-La/SSB and anti-smith antibodies. They are more likely in patients with a limited form of SSc and have a poor prognosis in instances of pulmonary arterial hypertension (Nihtyanova and Denton, 2010, Desbois and Cacoub, 2016).

Anti-phospholipid antibodies:

Both anti-cardiolipin antibodies and anti- β2 glycoprotein I antibodies are the most clinically significant anti-phospholipids antibodies. Positive results of these antibodies have been associated with an increased risk of pulmonary arterial hypertension, Raynaud's phenomenon and digital ulceration. However, the frequency of these antibodies has been reported to be 13.3% among SSc patients (Nihtyanova and Denton, 2010, Rai and Swetha, 2015).

1.13 Haematological features of SSc

A spectrum of haematological abnormalities can arise in patients with SSc such as raised erythrocyte sedimentation rate (ESR), mild anaemia of chronic disease, iron deficiency anaemia, megaloblastic anaemia and autoimmune haemolytic anaemia (Ranque and Mouthon, 2010, Hughes and Herrick, 2016). Circulating apoptotic fragmented red blood cells might give rise to microangiopathic haemolytic anaemia while passing though obstructed microvessels.

Thrombocytopenia can occur in SSc as a consequence of prolonged platelet activation and deposition in the association of endothelial injury. Neutropenia is common in SSc patients either as a result of associated anti-neutrophil autoantibodies or the

dysfunction in the physiological phagocytic system. Thrombotic thrombocytopenia purpura that comprises thrombocytopenia, thrombosis and microangiopathic haemolytic anaemia is a significant, but rare, scenario among SSc patients with the renal crisis (Keeler et al., 2015).

1.14 Management

A detailed discussion of the different agents used in managing systemic sclerosis is out with the scope of this review. However, as discussed previously, patients with SSc frequently have more than one disease manifestation that might occur at the same time. Thus, the management of SSc is often challenged. However, therapeutic strategies have, therefore been developed that are directed towards the organ systems involved (Table 1.9).

Among patients with Raynaud's phenomenon, treatment should be aiming at reducing the symptoms and preventing further progression to digital ulceration. General measures including avoiding cold exposure, wearing warm clothes and stopping smoking could be beneficial. Drug treatment such as calcium antagonists is recommended as first-line therapy. Another options including Angiotensin II receptor antagonist, angiotensin-converting enzyme inhibitors, alpha blockade and selective serotonin-reuptake. In severe cases and the presence of digital ulcerations intravenous prostanoids (e.g. iloprost and epoprostenol), endothelin-1 receptor antagonist (e.g. bosentan and ambrisentan) are associated with improved haemodynamics and significant reduction in the frequency and duration of RP attacks, and antibiotics should be prescribed in case of recurrent ulcers and possible infections (Hughes and Herrick, 2016). Sildenafil and other phosphodiesterase inhibitors are recommended agents for therapy in vasculopathy related SSc as it can decrease the expression of several pro-fibrotic factors and promote vascular smooth muscle

relaxation (Higuchi et al., 2015). Non-healing digital ulcerations can be treated with digital sympathectomy to prevent amputation (Hughes and Herrick, 2012, Desbois and Cacoub, 2016). In some cases, low doses of prednisolone or topical corticosteroid creams can be beneficial. Other immunosuppressive agents such as mycophenolate mofetil or methotrexate can be administered as well as local phototherapy (Teske and Jacobe, 2016).

Cyclophosphamide is recommended as first-line therapy in SSc patients with interstitial lung disease. Other options for immunosuppression are azathioprine and mycophenolate mofetil sometimes in combination with anti-fibrotic agents such as imatinib, nintedanib and nilotinib for improving and stabilising the lung disease. However, the advanced disease in which patients are unresponsive to either treatment, lung transplantation may be required, although surgical treatment approaches tend to have high risk and mortality in relation to the multi-organ nature of the disease. Patients with PAH are usually treated first by applying general measures including rehabilitation and exercise training within symptoms limits. Other options include anticoagulant agents, diuretics and oxygen use with receiving of calcium channel blockers for patients with the vasoactive disease (Desbois and Cacoub, 2016).

Patients with SSc are considered at high risk of renal disease; thus, prevention should include using angiotensin-converting enzyme inhibitors (ACE) or angiotensin receptor blockers as an alternative. Glucocorticoids should be avoided or if necessary, given at low doses as they associated with the renal crisis (Desbois and Cacoub, 2016). SSc renal crisis is a serious complication with a hypertensive emergency. Early detection with prompt initiation of treatment is crucial. For severe cases, other drugs are added

to ACE inhibition therapy (e.g. prostacyclin, dopamine and sympathetic blockers) with close monitoring and regular follow-up (Lee and Pope, 2016).

Cardiac involvement in SSc patients is common, including conducting system, myocardial and/or pericardial leading to left ventricular dysfunction and heart failure. However, ACE inhibitors and/or diuretics are considered as standard treatment (Hughes and Herrick, 2012).

Cases with SSc-related gastrointestinal involvement, treatment with proton-pump inhibitors can be beneficial for oesophageal dysmotility. However, lifestyle modifications are recommended including not eating at certain times especially before sleeping, elevating the head position of the bed, decreasing the caffeine consumption and other exacerbating food groups like spicy food and carbonated beverages (Hansi et al., 2014).

Rapidly developing an understanding of the underlying pathological mechanisms of SSc and other connective tissue diseases has aided to the development of new novel therapies entering clinical trials such as the specific targeted biologic medicines and molecular therapies. These therapeutic modalities are mainly targeting the profibrotic pathway and the B-cell depletion aiming to minimise the damage from early inflammation and autoimmunity, restore the vascular homeostasis, promote repair of structural connective tissue and modulate scarring. These new therapeutics trends are targeting biological agents, intracellular signalling inhibitors, stem cell biology and epithelial regeneration (Hughes and Herrick, 2012, Denton and Ong, 2013).

Table 1.9. Therapeutics strategies and treatment agents in the management of SSc

Clinical features	Diagnostic procedure	Therapeutic strategies
	Vascular system	
Raynaud's phenomenon	- RP provocation - Nailfold capillaroscopy - Serology	- Calcium channel blockers (e.g. nifedipin, amlodipin, felodipin) - Angiotensin II receptor blocker (e.g. losartan) - Serotonin reuptake inhibitor (e.g. luoxetin) - Phosphodiesterase inhibitor (e.g. sildenafil) - Prostacycline infusion (e.g. iloprost)
Digital ulceration	- Clinical assessment for infection and necrosis - Radiograph or MRI	- Prostacycline infusion (e.g. iloprost - Phosphodiesterase inhibitor (e.g. sildenafil - Dual ET receptor antagonist (e.g. bosentan) - Antibiotic treatment
	Skin	
Skin thickening	- Clinical assessment - Durometer - Biopsy	- Moisturising cream - Physiotherapy - Phototherapy - Steroids or calcineurin inhibitors - Ciclosporin - Methotrexate - Cyclophosphamide
Calcinosis	- Clinical assessment - Imaging (X-ray, MRI, CT)	- Corticosteroid injections - Laser therapy - Surgery - Minocycline - Oral bisphosphonate
Telangiectasia	- Clinical assessment	- Laser therapy - Camouflage
	Gastrointestinal involvement	
Gastroesophageal reflux disease (GORD)	- Gastro-oesophageal endoscopy	- Proton pump inhibitor (e.g. lansoprazole, omeprazole) - Prokinetics (e.g. domperidone) - H2 receptor antagonists (e.g. ranitidine)
Dysphagia	- Oesophageal scintigraphy	- Prokinetics (e.g. domperidone, metoclopramide)
Diarrhoea Constipation	- Colonoscopy	- Prokinetics (e.g. domperidone) - Laxative
	Cardiopulmonary involvement	
Lung fibrosis	- Lung function test - Imaging (X-ray/HRCT) - Bronchioalveolar lavage	- Cyclophosphamide - Glucocorticosteroids - Azathioprine - Mycophenolate mofetil
PAH	- Lung function test - Electrocardiography - Echocardiography - Cardiac catheterisation	- Bosentan - Sildenafil - Epoprostenol - Oxygen
Cardiac myopathy	- Electrocardiography - Echocardiography - MRI	- Cyclophosphamide - Glucocorticosteroids - Azathioprine - Mycophenolate mofetil - Pacemaker
	Renal involvement	
Renal crisis	- BP control - Ultrasound - Serological renal profile - Proteinuria analysis	- ACE inhibitors - Iloprost

1.15 Orofacial features

Orofacial manifestations occur in about 80-91% of patients with SSc, and it can give rise to a range of extra-oral and intra-oral features (Marmary et al., 1981, Jagger et al., 2006b, Bajraktari et al., 2015, Vitali et al., 2015, Hadj Said et al., 2016b, Veale et al., 2016). The common extra-oral manifestations of SSc include hardening and tightness of facial skin (mask-like appearance) also known as “bird’s face” or “Mona Lisa face”, facial asymmetry, telangiectasia, small nose (peak nose), narrow eyes, parotid salivary gland enlargement, trigeminal neuralgia and firm stretched lips.

Systemic sclerosis can give rise to a wide range of intra-oral features that include microstomia, xerostomia, mucosal ulceration and atrophy, increased risk of caries and dental erosion, periodontal and gingival inflammation, occasional oral infections and rigidity of the tongue (“chicken tongue”) and lips (“fish mouth”) (Nagy et al., 1994, Maddali-Bongi et al., 2011, Chapin and Hant, 2013).

Affected patients usually have more than one feature of the disease, and this may lessen both the functional and aesthetic aspects of the patients and lead to a negative impact on their emotional and social lives (Kwakkenbos et al., 2015).

Interincisal distance is determined by asking the patients to open the mouth widely and measuring the distance between the incisal edges of both the upper and lower incisors in millimetres (Wood and Lee, 1988). Also, the maximum mouth opening can be determined by measuring the distance between the nearest points of the two vermillion borders of the lips. Unsurprisingly in one study the mean interincisal distance for patients with SSc has been found to be less than (37.68mm ± 8.36) compared to unaffected individuals (mean 44.30mm ± 6.59) (p=0.0001) (Baron et al., 2014).

It is one of the most comprehensive studies across Europe that examined a broad range of symptoms (40 symptoms) of patients with SSc. It has been reported that more than 70% of SSc patients complained of fatigue, Raynaud's phenomenon, joint and muscle pain. Some of the oral impairments of systemic sclerosis including xerostomia, decreased mouth opening and dysphagia have been included in this study among 537 patients from five European countries (France, Netherlands, Spain, Switzerland, and United Kingdom) (Willems et al., 2014).

The survey was translated into different languages as a self-reported questionnaire assessing both frequencies of the symptoms in the last year and the impact of each symptom on their daily life activities (Table 1.10 and 1.11). Most of the patients, 55% had lcSSc, 36% had dcSSc, and 9% did not report. All three symptoms (decreased mouth opening, dry mouth and difficulty swallowing) have been reported by all patients with different values across countries (Willems et al., 2014).

In addition approximately 80% of patients with SSc have oral manifestations of the disease (Del Rosso and Maddali-Bongi, 2014), another study clinically assessed 163 participants (12 patients with SSc, 151 control group), the result showed a significant impact of SSc on the oral functions and reported oral-related decreased quality of life as up to 30% of the patients considered having severely decreased mouth opening of less than 30mm (Baron et al., 2014, Baron et al., 2015b). A high degree of tongue involvement was found with a 42% reduction of the protrusion of the tongue, 23% decreased strength and 92% lessened endurance (ability to sustain maximum pressure on a specific period of time) which might affect a wide range of normal functions such as speaking, chewing, saliva control and maintenance of swallowing which can be associated with other complications such as changing in facial appearance and resorption of the lips (Maddali Bongi et al., 2012, Vitali et al., 2015).

Table 1.10 Frequency and impact of oral symptoms experienced by patients with SSc in five European countries

Symptoms	France (n=111)	Netherlands (n=229)	Spain (n=61)	Switzerland (n=50)	UK (n=86)
Dry mouth	74%	69%	55%	69%	79%
Difficulty swallowing	53%	56%	56%	77%	70%
Difficulty opening mouth	39%	44%	40%	39%	44%

Adapted from (Willems et al., 2014)

Table 1.11 Impact on everyday activities of oral symptoms among patients with SSc in five European countries

Symptoms	France (n=111)	Netherlands (n=229)	Spain (n=61)	Switzerland (n=50)	UK (n=86)
Dry mouth	69%	50%	64%	46%	53%
Difficulty swallowing	79%	65%	72%	53%	73%
Difficulty opening mouth	84%	60%	67%	50%	61%

Adapted from (Willems et al., 2014)

1.15.1 Microstomia

Microstomia is considered to be the most common oral feature of patients with SSc (52.0 – 80%). Reduced mouth opening plays a significant role in lessening the quality of life of patients as it is strongly related to multiple functions such as speaking, eating, aesthetic appearance and even maintenance of good oral hygiene. This is mainly resulting from the pathological nature of the disease as an increased amount of collagen deposition in orofacial tissues (Marmary et al., 1981, Fischer and Patton, 2000, Bajraktari et al., 2015).

With respect to measuring the mouth opening, different methods have been applied as following:

- Inter-commissural distance: while the teeth are in occlusion, recording of the distance between two points from one commissure to the other.
- Maximum oral aperture: by opening the mouth as much as possible, the measurement done by tracing of all-around vermilion borders of both lips by a non-stretchable cord.
- Inter-incisal distance: after registration of the overbite during the maximum intercuspation, the mouth is opened wide and the distance between the upper and lower incisal edges is measured plus the amount of overbite.
- Maximum mouth opening: by using the Willis Bite Gauge, the distance between both upper and lower incisal edges measured while opening the mouth widely.

By applying these different methods of measuring the mouth opening, several studies demonstrated that mouth opening was significantly reduced in patients with SSc (Wood and Lee, 1988, Vitali et al., 2015, Baron et al., 2014). As reported by Cox et al., the average mean of the normal maximum mouth opening among 700 healthy individuals (98%) was 47.1mm (33.7 – 60.4mm) (Cox and Walker, 1997). However, the mean reduced mouth opening for SSc patients found to be 34.9mm (Mouthon et al., 2007). It has been reported that maximum mouth opening of less than 40mm can be considered as reduced mouth opening with up to 30% of SSc patients showing a severe form of decreased mouth opening as less than 30mm (Vitali et al., 2015).

Reduced mouth opening is suggested to be a co-factor for mandibular erosions as it may be a cause of increased strain of the associated muscles and tightness of the skin of the face (Baron et al., 2015a). Microstomia may be associated with an increased risk of tooth loss and periodontal disease and even the overall disease severity (Nagy et al., 1994, Baron et al., 2015b).

1.15.2 Salivary gland hypofunction and xerostomia

Symptoms of mouth dryness in SSc patients varies from 32-70% and is considered as one of the most frequent oral manifestations of SSc (Wood and Lee, 1988, Bajraktari et al., 2015). Dry mouth is found to be associated with salivary gland fibrosis, the presence of Sjogren's syndrome (SS) and increased deposition of collagen in the oral mucosa. Objective estimate of the unstimulated salivary flow (using the Saxon test; an oral equivalent of Schirmer's tear production test) in 163 SSc patients with disease duration 13.9 years (8.5), found saliva production to be reduced (147.52mg/min). Both resting and stimulated whole saliva production may be reduced in SSc (Baron et al., 2014).

Loss of salivary glands function may increase the risk of dental caries, gingival and periodontal disease and perhaps oral malodour as well as causing some degree of dysphagia, dysarthria and dysgeusia. It is recommended that all patients with SSc might be investigated for Sjogren's syndrome as it was reported that the prevalence of SS among SSc patients ranged from 17-29% (Chu et al., 2011).

The presence of histological features of fibrosis of salivary glands in patients with SSc has been reported in 23-48% while the histopathological features of SS occur in 65% of examined specimens. A recent study of 118 patients with SSc against SS-related antibodies found that sicca symptoms were present in 71.2% of patients with SSc and 33.9% were diagnosed with SS (Kobak et al., 2013). Hence, salivary hypofunction in SSc disease is linked to SS as one of the expected underlying causes (Baron et al., 2015b). It has been proposed that both microstomia and salivary gland dysfunction may coexist as a consequence of common pathological fibrosis of the tissues (Nagy et al., 1994).

1.15.3 Gingival and periodontal ligament disease

A number of studies have been reported that gingival and periodontal ligament disease found to be common in patients with SSc (76%) with an increased likelihood of deep periodontal pockets and high gingivitis scores (Chu et al., 2011).

A relatively recent study of patients with SSc concluded that periodontitis was more likely and severe in SSc than appropriate control subjects. High plaque indices were associated with sclerodactyly and more severe SSc disease status. The higher gingival index was linked with disease duration and severity while bleeding on probing only correlate with duration of the SSc (Elimelech et al., 2015).

The relationship between periodontal disease and SSc might reflect reduced salivary production but periodontitis was not found to be directly related to neither the number of missing teeth nor the SSc disease severity (Baron et al., 2015b). Other studies have concluded that there is a significant level of periodontal disease in patients with SSc (Wood and Lee, 1988, Baron et al., 2014). It is potentially possible that this is the consequence of fibrotic changes and hypovascularity (Yuen et al., 2014b). Although as patients may have reduced manual dexterity, there is a risk of this symptom reflecting the difficulty in being able to maintain good oral hygiene (Fischer and Patton, 2000, Poole et al., 2013).

Progressive (presumably non-dental plaque-induced) gingival recession and/or resorption of alveolar bone has been documented in SSc. A 19-year-old female patient having had SSc (*En coup de sabre)* for 3 years was found to have localised 4mm recession of the upper incisor together with a linear atrophic lesion traced from the nose to the upper lip on the same side and extended to the gingival tissue mesial to the affected tooth with periapical radiograph showing widening of PDL and pulp stone (Van der Veken et al., 2015). Recently, another 10-year-old female patient was

diagnosed with localised SSc (morphea). On intra-oral examination revealed a white plaque extending from the centre of upper lip mucosa to the oral vestibule with 12-13mm PD pocket depth found to be associated with both maxillary left central and lateral incisors. Radiographical findings revealed alveolar bone resorption between the affected teeth. However, there are no specific recommendations for the management of the intraoral disease involvement and so conservative intervention and maintaining optimum oral health care is mandatory to prevent further gingival and periodontal inflammation (Van der Veken et al., 2015, Wang et al., 2015).

1.15.4 Temporomandibular joint and trismus

Involvement of the temporomandibular joint can further increase the risk of trismus. This can be due to fibrosis of masticatory muscles, muscles of facial expression, oral and perioral tissues and the resorption of the articular bones. However, as a consequence of this, the movement of the mandible is restricted, and there may be articular pain and swelling due to synovitis and tendinitis. Also, as a consequence of the masticatory muscles atrophy, due to the low blood supply and the fibrosis of the blood vessels, this can cause trismus and increase the risk of inflammation within the associated joint structures (Chu et al., 2011, Alantar et al., 2011, Baron et al., 2015a). TMJ involvement in SSc can develop early in the disease onset and then give rise to malocclusion, limited movement, speech impairment, tenderness, pain and discomfort. Wood et al., indicated a high risk of TMJ dysfunction among patients with severe and more active disease (Wood and Lee, 1988).

With regards to SSc patients with TMJ involvement, a recent study of 27 patients with SSc (12 diffuse and 15 limited) revealed that 74.1% had TMJ clicking, 66.7% had reduced mouth opening, and 77.8% had pain with muscle and TMJ tenderness with 55% reported pain lasting for six months or more. Crepitation has been reported

among 70.4% of the total sample. However, magnetic resonance imaging findings were 51.8% abnormal disks without displacement, and 81.5% had disk displacement with reduction and TMJ osteolytic bone lesions 66.6%. Moreover, flattening of the temporal eminence function surface 48.1%, flattening of condyle 66.7%%, osteophytes 44.4% and synovitis 37% (Matarese et al., 2016).

Bilateral TMJ involvement has been reported in SSc and recognised as a consequence of mandibular bone resorption (MacIntosh et al., 2015). In advance stages of bone resorption and TMJ involvement, 4 -13% might present with trigeminal neuropathy with up to 83% involvement of mandibular and maxillary nerves (Fischoff and Sirois, 2000, Doucet and Morrison, 2011).

1.15.5 Neurological involvement

Neurological disease can arise secondary to SSc in about 40%. Various forms of neurological complications have been described in association with different subtypes of SSc such as cranial entrapment, peripheral, cutaneous and autonomic neuropathies, myopathy and rarely associated with the central nervous system (Amaral et al., 2013).

Cranial neuropathy has been described in SSc with the most common being trigeminal neuropathy that affects 5-15% of patients with SSc (Cazal et al., 2008, Vincent et al., 2010, Amaral et al., 2013, Bajraktari et al., 2015). Although, the exact pathophysiology of trigeminal neuropathy related to SSc, it is still unknown, some studies reported that it can occur as a consequence of vascular-dependant neuropathy (due to vasculitis and/or vessel wall damage), compression-dependant neuropathy (related to oedema or fibrosis and as a consequence of progressive demyelination) or autoimmune-dependant neuropathy (associated with antineuronal antibodies) (Fischoff and Sirois, 2000, Jagger et al., 2006b, Amaral et al., 2013).

Several reports have generally documented multiple neurological symptoms which might correlate either to disease severity or as an iatrogenic cause with 83% prevalence of maxillary and/or mandibular nerves involvement with (4 - 13%) sensory neuropathy. Symptoms of trigeminal neuropathy can manifest bilaterally and are frequently associated with pain that is described as throbbing, aching, scalding, burning or lancinating with involvement of the intraoral tissues that may be provoked by jaw movement (Farrell and Medsger, 1982, Lee et al., 1984, Fischoff and Sirois, 2000, Vincent et al., 2009, Doucet and Morrison, 2011).

It has been reported that neurological involvement in 224 patients with SSc included seizures (13.56%), headache (23.73%) and trigeminal neuropathy (16.52%). Moreover, depressive and anxiety symptoms are highly prevalent as the estimated prevalence of depression (73.15%) and (23.95%) for feeling anxiety. Other very rare features included dropped head (4%), facial weakness (4%) and (0.40%) for having suicidal ideation (Amaral et al., 2013).

1.15.6 Tongue rigidity and ankyloses

Hardening of the oral soft tissue structures is common in SSc. Tongue rigidity of up to 25% prevalence has been documented and could greatly impact oral functions such as speech, eating and swallowing (Fischer and Patton, 2000, Jagger et al., 2006b, Cazal et al., 2008, Hajimahmoudi and Mostafavi, 2014). In one small study of 12 SSc patients 42% had a reduction of tongue protrusion, 23% a reduction of tongue strength, and 92% a reduction of tongue endurance (Vitali et al., 2015). A shortened lingual frenulum was found in 0.4% of 75 patients with SSc (Bajraktari et al., 2015).

1.15.7 Oral mucosal atrophy and ulceration

Thinning (atrophy) of oral mucosa can occur in SSc and might reflect fibrosis and/or local ischaemia (Poole et al., 2013). Oral ulceration due to disease-modifying drugs

(e.g. methotrexate, azathioprine and cyclophosphamide) can arise. Oral ulceration may also be an adverse consequence of malnutrition, vitamins deficiency, exocrine pancreatic insufficiency or small bowel involvement associated with bacterial overgrowth (Nagy et al., 1994, Alantar et al., 2011). It has been suggested that ulceration can occur due to gastroesophageal reflux disease (GORD), but there is little supportive evidence; however oral ulceration giving rise to dysphonia and dysphagia has been reported (Jagger et al., 2006b).

1.15.8 Dental erosion and decay

Patients with SSc exhibit enamel erosion that may be related to gastroesophageal reflux disease (GORD) and less likely xerostomia (Chapin and Hant, 2013). It has been reported that both xerostomia and GORD are responsible for a decreased salivary pH that compromises the buffering capacity of the saliva and can induce enamel and dentine erosion (Jung et al., 2016). The Canadian systemic sclerosis oral health study, which describes the largest SSc cohort (163 patients with SSc), reveals that patients with SSc had significantly more decayed teeth compared to healthy controls (0.88 vs 0.59, $P = 0.0465$) (Yoshikawa et al., 2012, Baron et al., 2014, Baron et al., 2015b). According to a study of 42 patients with SSc, examining the oral health status in relation to SSc disease, all the study sample had dental caries with 65% untreated decay (Chu et al., 2011). However, a trend towards increasing number of dental decay has been reported and it would be expected that it is related to oral dryness and difficulties with oral hygiene routine associated with reduced manual dexterity and limitation in mouth opening (Jung et al., 2016).

1.15.9 Oral infections

Increased susceptibility to microbial infection would be expected in consequence to other oral manifestation of SSc disease such as (decreased mouth opening, salivary

gland hypofunction and drug adverse side effects). Candida infection has been correlated to SSc patients with low saliva flow rate (Fischer and Patton, 2000). Furthermore, patients using immunosuppressant agents such as corticosteroids and cyclophosphamide and/or antibiotics have a high risk of developing oral candidiasis (Martin et al., 1997).

1.15.10 Treatment-related adverse side effect

A wide range of medications are often prescribed for the treatment of SSc and its complications. Use of medicine including immunosuppressive and cytotoxic drugs (cyclophosphamide, cyclosporine, methotrexate), antihypertensive, antidepressant and anticoagulant drugs can give rise to some oral complications such as (mucosal ulceration, xerostomia, gingival bleeding and hyperplasia) (Elimelech et al., 2015). Calcium channel blockers used to treat vascular features, may give rise to gingival hyperplasia (Seymour and Heasman, 1988, Shah and Wigley, 2008, Yuen et al., 2011, Yuen et al., 2014b).

Using corticosteroid agents for a long time can give rise to candida infection while cyclophosphamide has been used for cases with lung involvement and caused oral infections and even oral ulceration if taken in high doses (Martin et al., 1997).

For treatment of joint and muscles involvement, methotrexate has been indicated and was found to be recommended for use with folic acid supplements to decrease the risk of mucosal ulceration. Patients with SSc have a great impact on their quality of life and may present a wide range of psychological distress symptoms, therefore they may use antidepressant medications with anticholinergic effects which might cause symptomatic dry mouth (Scully, 2003, Thombs et al., 2007). Furthermore, anti-vitamin K anticoagulants agents, mostly prescribed for SSc patients in regards to preventing thrombosis, might results in an increased tendency to gingival bleeding and

inflammation and hence those patients particularly must maintain good oral hygiene (Alantar et al., 2011).

Medication-related osteonecrosis of the jaw can be seen among patients with SSc who are taking bisphosphonate therapy (zoledronic acid and/or pamidronate) or other medications such as bevacizumab or sunitinib to lessen skeletal-related diseases or metastatic cancer. MRONJ may give rise to oral infections, mucositis and impaired wound healing. Among those patients, it has been recommended that a thorough oral examination should be performed before starting to take the medications. Also, all invasive dental treatment should be completed, and preventive measures should be considered to reduce the risk of jaw osteonecrosis. Furthermore, MRONJ needs long-term management, including a combination of systemic and topical antimicrobial agents and surgical debridement of necrotic bone (Sigua-Rodriguez et al., 2014, Mawardi et al., 2016).

1.15.11 Telangiectasia and oral mucosa

Dilatation of blood vessels, also called “Telangiectasia” can manifest in extra and intra-oral tissues (Ramazani et al., 2015). Oral mucosal telangiectasia can occur in the palate, lips, lateral borders of the tongue and buccal mucosa in about 56.3% and other studies reported 70 - 80% (Nagy et al., 1994, Vincent et al., 2009, Chu et al., 2011). Telangiectasia may cause some level of cosmetic disfigurement and psychological impact as it may present peri-orally as well as on the face, neck and hands. Patients can use make-up, or it can be treated conservatively by laser application (Lachner, 2016).

Assessing oral mucosal fibrosis have been done using an ultrasonography imaging technique and found a significant increase of fibrotic components in the buccal mucosa

among patients with SSc with a case report of fibro-epithelial polyp on the buccal mucosa (Jackowski et al., 1999, Chapin and Hant, 2013).

1.16 Orofacial radiological features

The radiological findings of the maxillofacial area are mainly due to the involvement of the musculoskeletal structures in the pathological sclerosis of SSc and/or due to the vascular ischemia possibly caused either by the deposition of abnormal collagen or as a result of tightening of the associated soft tissue and its pressure effect (Jung et al., 2016, Veale et al., 2016). Recently, different assessment measures are used to determine the radiological findings in relation to systemic sclerosis such as magnetic resonance imaging and high-frequency ultrasonography (Chapin and Hant, 2013).

Overall mandibular resorption prevalence 50% with incidence of 20-30% has been reported in a review by Haers and Sailer of 22 publications with a sample of 52 patients, the mandibular angle was affected by 37.6%, resorption of the coronoid process 20%, condylar head 20.8% and the resorption of the ascending ramus was found in 14.4% and 13.7% as a bilateral condylysis (Seifert et al., 1975, Haers and Sailer, 1995, Doucet and Morrison, 2011, Chapin and Hant, 2013, Delantoni and Matziari, 2015).

A recent study of 159 patients with SSc find 14.5% of mandibular erosion with regards to the range of other reports (6.6% - 46.7%) (Table 1.12) and there was up to 60.9% of the patients had multiple sites of erosion in the mouth (Dagenais et al., 2015). Resorption of the zygomatic arches has been reported in SSc patients in association with other parts of bone resorption such as mandibular angles and ascending ramus (Hopper and Giles, 1982, Wood and Lee, 1988).

Other patterns of mandibular erosions have been reported as osseous resorption of the digastric region 2.53%, resorption of the posterior ramus 5.06% (Dagenais et al., 2015). However, apart from the presence of rheumatoid factor that is found to be positive in about 33% of SSc cases, the overall resorption pattern of the maxillofacial bones in SSc patients especially the bilateral bone resorption in mandibular angles, digastric region and both coronoids and condyles processes might be caused by the long term (5-7 years disease duration) effect of increased physical pressure from the overlying tight skin and also due to the associated sites of attachments of masticatory muscles such as masseter, temporal, lateral pterygoid and anterior belly of digastric muscles which may affect the blood supply to the bone itself. Also, another explanation included in the pathological process of the disease which might cause ischemia as a result of vasculitis and perivascular fibrosis, and this could affect the blood supply vessels of related bone structures such as the maxillary artery to the condyle, coronoid process, mandibular angle and both masseteric and pterygoid muscles (Ramon et al., 1987, Jagger et al., 2006a, Jagger et al., 2006b, Rahpeyma et al., 2013, Delantoni and Matziari, 2015, MacIntosh et al., 2015).

MRI has been used to measure the masseter musculature in a group of 15 SSc patients in relation to mandibular osteolysis. A high ratio of fat replacement and atrophy of the muscular tissues appeared in association with the disease (Chapin and Hant, 2013). The reported incidence of mandibular erosion in SSc is 20%, and the overall prevalence is 50% with almost 28.6% considered as a mild degree of osteolysis. However, it has been suggested that the more severe mandibular erosion, the more severe the sclerosis (MacIntosh et al., 2015).

As a consequence of TMJ involvement in individuals with SSc, MRI showed that 51.8% of the sample consisted of 27 patients with SSc (12 diffuse and 15 limited)

revealed abnormal disks without displacement and 81.5% diagnosed as disk displacement with reduction. The reported symptoms are mainly TMJ clicking 63%, crepitation in 70.4%, reduced mouth opening 66.7%, TMJ and muscle tenderness in 55.6% and 55% reported pain lasting for 6 months or more (Matarese et al., 2016).

Degenerative bone changes were reported in 66.6% with the highest percentage in flattening of condyle anterior surface was (66.7%), followed by joint surfaces erosion and irregularities (55.6%). Furthermore, flattening of temporal eminence functional surface 48.1%, osteophytes (44.4%), synovitis (37%), subchondral cysts (11.1%) and idiopathic condyle resorption (11.1%) with a significant correlation of the frequency of bone changes and the duration of the disease ($P< 0.05$). However, the re-adsorption theory might take place in different sites such as mandibular angle, condyle and/or coronoid process as a result of atrophic ischemia and this may increase the risk of a pathological fracture of the affected site (Matarese et al., 2016).

Also, an ultrasonographic scanner has been applied to 10 patients with SSc evaluating the extra-oral and intraoral changes by looking specifically to a range of criteria such as reduction in the range of facial expression, telangiectasia in both oral mucosa and facial skin, perioral folds, changes in lip redness, impaired tongue movement, flattening of the palate and shortening of the uvula, myosclerosis in the vestibule of the mouth, decreased inter-incisal distance and gingival inflammation. Two patients showed an increased amount of fibrotic deposition and sclerosis. However, considering ultrasonography as a non-invasive investigative tool might be useful for monitoring the disease activity and therapeutic effectiveness. Also, it has been reported that colour Doppler ultrasound has benefits of measuring dermal blood flow as it might indicate underlying active disease (Chapin and Hant, 2013, Tolkachjov et al., 2015).

More recent studies demonstrated that the widening of the PDL is the most common oral radiographic feature. A study sample of 159 individuals with systemic sclerosis, 38% indicated a widening of the PDL and a strong association was found between the number of teeth included and the severity of the disease. However, widening of the PDL in patients with SSc could be due to the generalised overproduction of collagen, but there is no clear correlation to other periodontal diseases as it is not showing any significant level of gingival attachment loss. Although, it has been found that there is a strong association between smoking, widening of PDL and the severity of SSc (Baron et al., 2015a).

In Jung et al., periodontal ligament widening in patients with SSc usually presented in both anterior and posterior teeth with more tendency to be found around the posterior teeth (Jung et al., 2013). Furthermore, widening of PDL has been described as a uniform widening in up to 10% of SSc cases (Chapin and Hant, 2013) and it was located in 163 patients with SSc adjacent to coronal and periapical areas of the roots by using either periapical or panoramic radiographs (Dagenais et al., 2015).

As a rare case, cone-beam computerised tomography and panoramic radiograph images have been used to report an uncommon calcification in both widening PDL and pulp canals, which might be related to the dystrophic calcinosis pattern of the disease. A case report with 13 years diagnosis of diffuse SSc, a history of persistant maxillary pain lasting for several weeks, involvement of systemic organs including the lungs, gastrointestinal and myocardial involvement and digital ulcers. Clinical examination reported tightness of facial skin, telangiectasia, thin and sclerotic lips and decreased mouth opening. The radiological evaluation shows generalised PDL widening, and by utilising the CBCT, it has been found that multiple maxillary teeth revealed calcifications in associated PDL spaces. Additionally, those affected teeth,

specifically the incisors and premolars also contained pulp stones and were at risk of root canal obliteration. In this case, the calcification was associated with areas of PDL widening and the lamina dura was intact. However, it is suggested that this clinical scenario might be related to the nature of the sclerotic features of SSc (Jung et al., 2013).

Rarely there may be a few reported cases with external dental root abnormalities (resorption, dilacerations, underdevelopment) as it has been reported to be associated with the disease with considerable high prevalence in childhood cases 27.3% (Trainito et al., 2012). One study revealed a patient with intraoral features of SSc such as significantly decreased mouth opening (20mm), telangiectasia on both the hard palate and lateral border of the tongue with radiological findings of left side mandibular erosion coincident with the external distal root resorption of the lower left third molar. However, the resorption of the apical third of the root was found to be adjacent to the area of the bone resorption of the mandible, and after excluding other causes, it was suggested that it had happened as a consequence of both the erosive pathological process of the disease and the high magnitude of the external pressure from the adjacent muscular structure (de Figueiredo et al., 2008). However, a recent study has reported that patients with SSc may present with an external pattern of root resorption located cervically instead of apically (Arroyo-Bote et al., 2017).

A study of 16 patients with juvenile localised SSc showed a rare presentation of the disease in 9 patients (81.8%) as the cephalometric analysis was applied and revealed an overgrowth of the lower third of the face as an increased anterior face height. The same study reported that 81.8% had skeletal malocclusion, and 18.7% had TMJ asymmetry (Trainito et al., 2012).

Table 1.12 Radiographic oral findings of systemic sclerosis

Author / Year	Sample size	Mandibular erosions	PDL widening
(Dagenais et al., 2015)	159	14.47%	37.96%
(Leung et al., 2011)	36	NR	Mean width of PDL was greater in SSc cases but not reported
(Vincent et al., 2010)	30	6.67%	33.3%
(Marcucci and Abdala, 2009)	15	46.7%	NR
(Rout et al., 1996)	21	9.5%	33%
(Wood and Lee, 1988)	24	29%	Mean width of PDL was greater in SSc cases but not reported
(Janssens et al.)	47	NR	59%
(Alexandridis and White, 1984)	26	NR	65%
(Butts et al., 1977)	35	8.6%	37%
(Rowell and Hopper, 1977)	30	NR	70%
(Marmary et al., 1981)	21	19%	100%
(Seifert et al., 1975)	16	31%	NR

1.17 Head and neck malignancy

As discussed previously, patients with SSc have an increased risk of malignancy. Similarly, there is some evidence that patients with SSc may have an increased risk of head and neck cancers with areas most commonly involved (oral cavity, oropharynx and oesophagus) (Takeda, 2004, Derk et al., 2006). Gastroesophageal reflux disease (GORD), causing chronic inflammation may increase the risk of malignancy of the oesophagus similar to the effect of Barrett's oesophagus (Nagaraja et al., 2015). However, multiple other risk factors have been identified to predispose to oesophageal cancer in SSc including tobacco smoking, immunotherapies and having a family history of cancer with higher prevalence among male patients (Onishi et al., 2013, Zhang et al., 2013). It is recommended that all SSc patients should have a regular endoscopic examination of the oesophagus (Wipff et al., 2005).

The risk of oral squamous cell carcinoma in patients with SSc has been reported particularly of the tongue and lower lips (Derk and Jimenez, 2003, Petrov et al., 2009, Acarturk et al., 2015). The exact underlying causes of this increased risk are not known. Regarding the poor prognosis of both systemic sclerosis and cancer lesions, early diagnosis is highly valuable among SSc patients.

1.18 Oral treatment and rehabilitation

1.18.1 Oral Hygiene

As noted previously, patients with SSc have an increased risk of common plaque-induced dental disease. Patients can have difficulty maintaining good oral hygiene in view of a limited range of mouth opening and reduced manual dexterity. Any oral dryness will increase the risk of plaque retention, the stiffness and rigidity of oral mucosa and peri-oral soft tissues, restricted tongue movement and fibrosis of the lingual frenum may reduce normal oral movements and self-cleaning mechanisms leading to increased the susceptibility to dental caries and periodontal disease (Yuen et al., 2014b).

Regular dental attendance and prophylaxis have been suggested to be of benefit for SSc patients such as the regular application of 5% sodium fluoride varnish which may decrease the risk of carious lesions (Chu et al., 2011, Gyger and Baron, 2015).

Oral hygiene tools may be required to be modified if patients have limited hand or arm mobility. Helper-assisted tooth brushing can be useful, but clearly requires the assistance of a partner or carer. A variety of toothbrushes are available to allow patients to better clean their teeth such as angled brushes, altered filament length brushes, easy-grip brushes, extended handle brushes, electric brushes and soft small-headed toothbrushes. Recent studies recommend the use of appropriately adapted

flossing and/or interdental cleaning tools to prevent periodontal disease and interdental lesions (Poole et al., 2010, Yuen et al., 2014a).

Other suggested, but little proven, therapeutic modalities include connective tissue massage, joint mobilisation, finger stretching exercise, manual lymph drainage of the hands and ultrasound therapy (Maddali Bongi et al., 2009, Yuen et al., 2014a, Willems et al., 2015b).

Patients with SSc may require referral to a dietitian as they have difficulties in eating solid food or dietary choices. Furthermore, patients with a significant level of dry mouth and/or gastroesophageal reflux may tend to consume more frequent meals that are softer and contain refined carbohydrates which increase the risk of caries (Alantar et al., 2011).

Additionally, the psychological status of the patients should be monitored as those with depression can lose interest in maintaining a high standard of oral hygiene (Yuen et al., 2014a).

1.18.2 Dry mouth

Xerostomia has been linked to an increased number of missing teeth, carious lesions and periodontal diseases among SSc patients due to low salivary flow rate and salivary pH value. Also, it might give rise to an altered taste sensation, oral malodour and loss of retention of dentures.

The treatment of oral dryness in relation to SSc is no different from the treatment of other causes of oral dryness. This has been summarised in table 1.13.

Table 1.13 The principals of the management of oral dryness

Methods	Therapies
Oral care measures	- Determine the cause (clinical, radiologic and laboratory-based tests) - Oral hygiene (fluoride toothpaste and mouthwash) - Oral moisturisation (water, olive oil and lubricants) - Dietary supplementation (soft food, vitamins, linseed extract salinum) - Antifungals (nystatin pastilles, amphotericin lozenges and miconazole gel)
Topical therapies	- Sugar-free gum (Biotene dry mouth gum and BioXtra chewing gum) - Lubricating gels and lozenges (Oralbalance and BioXtra) - Salivary stimulant pastilles (Salivix, Provalis) - Mucin based-product (Saliva Orthana) - Carboxymethylcellulose based-product (Glandosane, Luborant, Salivace, Saliveze)
Systemic therapies	- Pilocarpine (Salagen) - Cevimeline - Bethanechol - Interferon α - Carbacholine - Bromhexine - Corticosteroids - Hydroxychloroquine - Vitamin supplementation
Other measures	- Electrostimulation - Acupuncture - Acupressure

Amended from (Porter et al., 2004, Al Hamad et al., 2019)

1.18.3 Reduced mouth opening

The management of limited mouth opening associated with SSc remains challenging. There are few studies of the non-surgical management of microstomia but techniques such as the patients placing both thumbs in both corners of the mouth and applying stretching movement bilaterally for 15 minutes two times per day, or inserting wooden spatulas between the premolars and then moving it back to the molar area once a day have been reported to improve mouth opening by up to 10.7 mm, with patients having less difficulty eating, speaking and an improved ability to clean their teeth or wear dentures (Pizzo et al., 2003).

A study of 20 patients with SSc that comprised a 9 weeks comprehensive programme of massaging techniques of the soft tissues, facial physiotherapy and facial muscle exercises found a significant improvement in mouth opening. Another method of trying to increase mouth opening consists of neuromuscular stimulation of the facial muscles in conjunction with passive and active physiotherapy to the temporomandibular joint. However, the long-term benefits of such intervention have not been published (Maddali-Bongi et al., 2011, Poole et al., 2013, Baron et al., 2015b).

Surgical interventions for microstomia such as bilateral commissurotomies might increase the size of the labial opening, but these run the risk of impaired healing and further fibrosis (Fischer and Patton, 2000, Albilia et al., 2007). Bilateral commissurotomies may be indicated for patients who require major general surgical operations as severely limited mouth opening might impede general anaesthesia and oral intubation.

Perhaps the most promising treatment for orofacial tightness in SSc is autologous fat grafting (AFGT). In a study of 20 patients with dcSSc, 2 mm of autologous fat grafting were injected into 8 different areas around the lips. At 3-month follow-up, all patients had a significant degree of mouth opening improvement and improved orofacial function. Perioral skin elasticity significantly improved in this 3 month period and there was a reduction of fibrosis (Del Papa et al., 2015).

A later study compared the two methods of AFGT with autologous adipose-derived stromal cell (ADSC) therapy in 2 groups of patients with SSc. Both methods led to an improvement in mouth opening and patient satisfaction. However, ADSC method was concluded to be the more technically challenging technique as it necessitated laboratory processing to isolate the stem cells (Onesti et al., 2016).

AFGT was suggested to be more effective for severe fibrotic lesions. However, in contrast to ADSC the results of AFGT are unpredictable as it may give rise to an asymmetrical appearance of the two sides of the face. Furthermore, AFGT requires administration by cannula rather than the ADSC method that requires the injection of cells using a thin needle. Hence the AFGT is more likely than the ADSC method to cause operative scarring (Onesti et al., 2016).

Intralesional injection as a combination of decamycin corticosteroid (dexamethasone sodium phosphate 4 mg) and hyaluronidase (Hynidase 1500IU) with the multi-antioxidant capsule (Ricinia-LP) for 5 months has recently been found to improve mouth opening. Intralesional injections of the lips and face were given over multiple visits. It has been suggested that this technique may lessen hyperactivity of fibroblasts (Kumar et al., 2016).

1.18.4 Prosthetic dental care

Patients with SSc commonly show some degree of reduced mouth opening, tongue rigidity, dry mouth and impaired manual dexterity so special therapeutic modifications should be considered as the disease nature and progression may limit the treatment options (Baron et al., 2015b).

The increased acidity of the oral cavity as a result of decreased salivary flow rate and GORD may greatly affect the dentition and increase the risk of developing caries and/or erode the teeth structures. Thus, during the treatment planning, it is essential to consider the most appropriate restorative dental material as the suitability and longevity is arguably more important than aesthetic aspects.

Glass ionomer-based restorations have multiple advantages such as the long-term fluoride release, the inherent adhesive properties and the similar coefficient of expansion to enamel with low setting shrinkage. However, it might be suggested that

using resin-modified glass ionomer restorations is more beneficial in regard to overcoming the physical characteristics and the dual-cure effect that allows longer working time and rapid hardening during the clinical setting. Also, the shortened dental arches concept indicates that the dental arches compromising the anterior teeth and premolars can meet the requirements of a functional dentition hence compromised treatment planning may consider the shortened dental arches concept, in so far as it does not contradict the current theories of occlusion. However, considering the patients' ability to cooperate, adapt and maintain the dentition with the possible treatment options, this may help achieve therapeutic goals and desired outcomes (Armellini and von Fraunhofer, 2004).

Comprehensive prosthetic dental treatment may be considered for patients with SSc with great attention to the limitations and necessity of modifications. Common challenges while making dental treatment decisions are the degree of reduced mouth opening, the rigidity of the tongue, dry mouth status and the manual dexterity (Yenisey et al., 2005, Gozde Turk and Ulusoy, 2015).

With regards to overcoming the difficulties for the clinical setup, fabrication and construction of the removable prostheses some studies have recommended using different modifications such as sectional, collapsible or combined sectional-collapsible designs with various connection systems such as clasp retainers, stud attachments, telescope systems, swing-lock attachments, magnetic attachments and pins (Singh et al., 2014, Gozde Turk and Ulusoy, 2015).

Benefits of utilising the overdenture prostheses include preserving abutment teeth that help to lessen the alveolar bone loss, enhance the stability and comfort, provide favourable crown-root ratio, maintain the PDL proprioception and enhance the well-being sensation (Benetti et al., 2004). It is recommended maintaining good oral

hygiene and cleaning dentures with a soft brush with a mild detergent can considerably reduce the risk of developing microbial and/or fungal infection especially on the fitted surface of the denture (Singh et al., 2014).

The impression taking procedure is one of the most critical clinical steps during prosthetic treatment. Sectional tray impression technique has been employed with either locking segments along the midline or using hinges, plastic building screws, orthodontic expansion screws, locking levers, stepped butt joints or resin blocks with indexing technique (Prithviraj et al., 2009, Hajimahmoudi and Mostafavi, 2014, Gozde Turk and Ulusoy, 2015).

Implant treatments are not necessarily contraindicated in SSc. Two main areas are commonly indicated for implant placement either in the canine area of the mandible for stabilisation and/or in the maxillary incisors and canine area for aesthetics (Oczakir et al., 2005). However, dental implants are contraindicated among patients with severe gingival and periodontal disease as they commonly manifest a significant degree of tissue fibrosis and microvascular impairment (Alantar et al., 2011).

Due to the nature of the disease, it is important to consider the disease's impact on all of the associated tissue structures and the related patient's quality of life by considering all other available alternative treatment modalities including simplicity, future repair services and financial concerns (Baptist, 2016).

1.19 Impact of systemic sclerosis upon the quality of life

Systemic sclerosis is a chronic disorder that can adversely impact upon an individuals physical and psychological wellbeing. According to the World Health Organisation, the quality of life (QoL) concept goes back to the 1947 (WHO) definition of health as a "state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity (WHO, 1947). The use of the term "well-being" in this definition of health has contributed significantly to the conceptual confusion about what is health and what is QoL. Quality of life encompasses (physical, mental and social wellbeing). Within these, there are the physical, mental and social impacts of any orofacial disease that an individual may have. The Canadian Dental Association has defined oral health-related quality of life as "a state of the oral and related tissues and structures that contribute to physical, mental and social well-being and enjoyment of life's possibilities, by allowing the individual to speak, eat and socialise without feeling pain, discomfort or embarrassment" (Gift and Atchison, 1995, Petersen, 2003). Over the past two decades, there has been an acknowledgement that the management of disease must consider the oral health-related quality of life. An assessment of the quality of life is now considered an essential aspect of the evaluation of treatment and management of health-related conditions. There are many good reviews of this subject area (Ni Riordain and McCreary, 2010a), but the measurement of quality of life remains challenging. A variety of different instruments can be employed to record QoL, these basically fall into generic and specific. Generic instruments (typically questionnaires) may demonstrate a change in the quality of life, but they do not detect small clinical changes relevant to a specific disease. Specific measures may more accurately determine changes within a particular disease - but do not allow for comparison between diseases (Ni Riordain et al., 2011).

It has been recommended that a combination of both generic and specific measures can be of clinical relevance in order to gain insight into as many dimensions of a patient's well-being as possible. However, it is essential to determine the appropriateness of each instrument to ensure that they are valid, reliable and detect responsiveness (Locker et al., 2007, Lopez-Jornet and Camacho-Alonso, 2008, Oviedo-Joekes et al., 2010) as detailed below.

Construct validity assesses the ability of an instrument to reflect theories in relation to the relevant disease (Ehrs et al., 2001). Convergent validity shows the degree to which a new instrument might relate to similar ones that it is supposed to be related (Butt et al., 2009). Internal consistency reliability refers to the degree to which items in an instrument correlate with one other (Aaronson et al., 2002). Also, in assessing the reliability over time, test-retest reliability can be applied at two different points in time with a recommended interval range from 12 to 14 days (Henson et al., 2001). Responsiveness as the 'ability of an instrument to measure a meaningful or clinically important change in a clinical state' (Liang, 2000), hence more simply responsiveness can be considered as a measure of the magnitude of any treatment (therapeutic effects) (Terwee et al., 2003).

1.19.1 Health-related quality of life measures in systemic sclerosis

Perhaps unsurprisingly, in view of its relative rarity, there are few studies of the impact of SSc, or indeed the orofacial aspects of SSc upon the QoL of affected individuals.

Certainly, SSc can affect the mental status of affected individuals. For example, anxiety and fear have been reported by 49% of 50 patients, with social and generalised anxiety disorders being most common. This may reflect the unpredictable course of the disease and the patient's (and carer's and partner's) worry about the future (Baubet et al., 2011, Kwakkenbos et al., 2015).

Fatigue in SSc can adversely impact on the daily life activity. 89% of 464 patients reported that they experienced fatigue at least some of the time due to the disease. 70% of a group of 537 European patients reported fatigue, Raynaud's phenomenon, muscle and joint pain (Willems et al., 2014).

Sleep disruption is a common complication among SSc patients due to dyspnoea, pain, fatigue and depressive symptoms (Almeida et al., 2015). 60% to 83% of examined SSc patients may report experiencing pain from Raynaud's phenomenon, gastrointestinal, joint and musculoskeletal or cutaneous disease. Pruritus was cited by 43% of 959 patients as being an upset. Unhappiness with facial appearance due to SSc can also adversely impact upon the quality of life (Kwakkenbos et al., 2015).

Sexual dysfunction was reported by 62% of 165 female sexually active patients. Vaginal pain can lessen the quality of life (Levis et al., 2012), although one study did not find that sexual dysfunction has larger concern in another group of female patients. Thickening and tightening of the skin, vaginal sclerosis and oral dryness together with ulcers of the hands may be contributing to sexual dysfunction (Maddali Bongi et al., 2013). Sexual dysfunction in males has been reported, with 38% of a group of 130 men reporting severe erectile dysfunction due to severe cutaneous, muscular or renal involvement of SSc, elevated pulmonary pressures and restrictive lung disease (Foocharoen et al., 2012). A more recent study found that erectile dysfunction was the most common "sexual" problem in males while in females genital tract alteration are the dominant contributors to sexual impairment and a lessening of the quality of life (Bruni et al., 2015).

Living with a disorder such as SSc require repeated clinical attendance to professional services, including clinical psychology units, patient support groups and self-management programmes which are helpful in lessening any decline in the ability of

patients to ‘cope’ with the physical and psychological consequences of the disease lifestyle changes (Kwakkenbos et al., 2015).

Nevertheless, in one recent study, 36% of 280 patients with SSc reported that they are not interested in or have no perceived need of support groups, while 35% reported that they had no access to such groups, 13% were not aware of the existence of these support groups, 6% were facing a practical barrier to attend, 4% did not attend due to emotional factors, 4% were uncertain about whether to attend or not and 3% have negative perceptions about support groups (Delisle et al., 2016).

The present discussion thus reveals that there are many ways in which SSc can lessen the quality of life of an affected individual, indeed any single physical complication of SSc has the potential to lessen the enjoyment of life.

Expanding upon earlier discussion physical, social, psychological, emotional, cognitive, spiritual, work-related and financial impact are all aspects of an individual’s life which can each be affected.

A variety of generic and specific assessment measures of HRQol have been employed or developed to be relevant to SSc (Table 1.14) covering global health-related quality of life and life satisfaction, global disability and pain, assessment of work-related factors and daily activities, assessment of fatigue, sleep disturbance, depression, sexual dysfunction, assessment of specific physical disability, aesthetic and skin impairment. Assessment of both the gastrointestinal, nutritional and pulmonary aspects of SSc has been undertaken (Almeida et al., 2015).

Table 1.14 Health-related quality of life assessment measures that have been used in SSc

QoL measures	Specificity to SSc	Validity for SSc
Patient-Reported Outcome Measurement Information System-29	No	Yes
Short-form 36 questionnaire Version 2	No	Yes
The patient overall health assessment	No	No
The physician assessment of overall health	No	No
Manchester Short Assessment of Quality of Life	No	Yes
Health Assessment Questionnaire Disability Index	No	Yes
Scleroderma Health Assessment Questionnaire	Yes	Yes
McMaster Toronto Arthritis Patient Preference Disability Questionnaire	No	Yes
Pain assessment/Visual analogue scale	No	Yes
SSc-associated symptoms assessment	Yes	Yes
Symptom Burden Index	Yes	Yes
Patient-generated Index	Yes	Yes
The modified Work Productivity Survey—Rheumatoid Arthritis	No	No
Work Ability Index	No	No
Scleroderma Functional Score	Yes	Yes
Satisfaction with Daily Occupations instrument	No	Yes
Functional Assessment of Chronic Illness Therapy-Fatigue	No	Yes
Medical Outcomes Study Sleep Scale	No	Yes
Centre for Epidemiologic Studies Short Depression Scale—10	No	Yes
Patient Health Questionnaire—8 or —9	No	Yes
Female Sexual Function Index	No	No
Female Sexual Distress Scale	No	No
The Cochin Hand Function Scale	No	Yes
Mouth Handicap in Systemic Sclerosis Scale	Yes	Yes
Satisfaction with Appearance Scale	No	Yes
Dermatology Life Quality Index questionnaire	No	No
Raynaud's Condition Score	Yes	Yes
The University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Scale 2.0	Yes	Yes
Mahler's Baseline Dyspnoea Index (BDI) and Transition Dyspnoea Index (TDI)	No	No
Cambridge Pulmonary Hypertension Outcome Review	No	No

Adapted from (Almeida et al., 2015)

Recently, a study has explored the relationship between different QoL measures of skin manifestations in SSc and the skin histopathological features with clinical examination. The informally developed new measurement, called The Skin Symptom Assessment (SSA), evaluates six cutaneous symptoms (tight, painful, red, hard, rigid/stiff and itchy) with a score of five-level Likert Scale (not at all, a little bit, somewhat, moderately and severely). Among 41 patients, the SSA correlated well with histopathological features of the biopsies of the 29 patients who had provided biopsy material. The new SSA questionnaire requires further assessment, but it might aid the evaluation of SSc skin disease and improve the ability to measure the effectiveness of different treatment modalities (Ziemek et al., 2016).

Using the paper profiles of 150 patients, a new outcome measurement tool was developed – called the Composite Response Index in SSc (CRISS). The new composite index (CRISS) was tested in a randomised control trial of methotrexate versus placebo (p=0.02). CRISS is a two-step process employed in a 12 months interval period between primary and secondary measures. At present, however, this new composite index is considered to be only at the provisional stage of use and may require further assessment for use in clinical studies (Khanna et al., 2016).

1.19.2 Oral health-related quality of life measures in systemic sclerosis

As reviewed previously despite the potential impact of its orofacial features no quality of life measure has been specifically constructed to assess the impact of SSc upon the oral quality of life other than the Mouth Handicap scale (MHISS) (Mouthon et al., 2007).

The MHISS was developed to assesses the degree of restriction of mouth opening, dryness of the mouth and the aesthetic appearance. It consists of 12 items (each with five levels of answers) divided into 3 subscales. Subscale 1 examines impact related

to reduced mouth opening, subscale 2 examines impact related to dryness of the mouth and subscale 3 records aesthetic concerns. The possible total score ranges from 0 to 48, the higher the number indicating the greater impact of mouth limitations (Table 1.15).

Oral health-related quality of life using the MHISS scale has been investigated in a number of studies of patients in several countries (Table 1.16). MHISS has been applied for the first time among 71 Caucasian patients in France (61 female); 32 (45.1%) had dcSSc, 38 (53.5%) had lcSSc and one (1.4%) had lSSc. The mean MHISS score was 20.3 (SD 9.7) and scored 36.5% of the total variance in global disability. The MHISS was found to have excellent reliability by scoring an ICC=0.96 and good construct validity (Mouthon et al., 2007).

Table 1.15 Mouth Handicap in Systemic Sclerosis scale

MHISS Questions	Never	Rarely	Occasionally	Often	Always
I have difficulties opening my mouth	0	1	2	3	4
I have to avoid certain drinks (sparkling, alcohol, acidic)	0	1	2	3	4
I have difficulties chewing	0	1	2	3	4
My dentist has difficulties taking care of my teeth	0	1	2	3	4
My dentition has become altered	0	1	2	3	4
My lips are retracted and/or my cheeks are sunken	0	1	2	3	4
My mouth is dry	0	1	2	3	4
I must drink often	0	1	2	3	4
My meals consist of what I can eat and not what I would like to eat	0	1	2	3	4
I have difficulties speaking clearly	0	1	2	3	4
The appearance of my face is modified	0	1	2	3	4
I have trouble with the way my face looks	0	1	2	3	4

Adapted from (Mouthon et al., 2007)

The MHISS has been translated into different languages including (English, French, Italian and Dutch). The Italian version of MHISS was validated with 40 SSc patients (7 had dcSSc, 33 had lcSSc). The total MHISS score was 17.65 (SD 5.20) with good reliability (ICC=0.93) and validity. Good external consistency was found with mouth opening (-0.3869, p=0.0137) and good internal consistency by (Cronbach's alpha = 0.93) (Maddali Bongi et al., 2012). A Dutch version has been employed in a study of 52 SSc patients from the Netherlands, 27 (52%) of whom had dcSSc. The mean total score was 17.5 (SD 10.0). Good convergent validity was demonstrated, and excellent reliability with (ICC = 0.94), Cronbach's alpha was (0.88) (Schouffoer et al., 2013).

It has been suggested that the MHISS may be useful in assessing any improvement of the face and mouth after physiotherapy and evaluating the outcomes after the dental therapeutic intervention (Maddali-Bongi et al., 2011), although there is little evidence that this has been undertaken.

The MHISS has been employed with other HRQoL measures including Short Health Survey (SF-36), Hospital Anxiety and Depression (HADS), HAMIS (Hand Mobility In SSc) and Health Assessment Questionnaire (HAQ), to assess a group of 46 female patients with SSc (29 had lcSSc and 17 had dcSSc) assessing hand and mouth disability in association with sexual function and, unsurprisingly, it was found that hand and mouth involvement may lessen the sexual function of patients due to hardening of face skin, digital ulceration and skin sclerosis with total MHISS (p=0.038) (Maddali Bongi et al., 2013).

A cross-sectional survey of 381 patients with SSc from France, 187 (50.5%) had lcSSc, 149 (40.3%) had dcSSc and 34 (9.2%) had lSSc assessed by different measures, including the MHISS, found that mouth handicap was significantly higher in patients with symptoms of anxiety and depression (Nguyen et al., 2014). Another

study of 248 SSc patients from France, 146 (58.9%) had lcSSc, 90 (36.3%) had dcSSc, 12 (4.8%) had lSSc aimed to compare hospitalised patients with those from patient associations using MHISS with other health-related quality of life measures. Mouth impairment was significantly greater in the patient association group than the group of hospitalised patients with MHISS mean scores of 20.65 (SD = 10.91) and 13.25 (SD = 9.26) $p = 0.0001$ respectively. It was considered that this might reflect the non-hospitalised patients being older and having had the condition longer than hospitalised patients. (Mestre-Stanislas et al., 2010).

Certainly, the MHISS is likely to be greater in those individuals who have more orofacial involvement than those who do not. This was indeed found in a study of 119 patients from Italy in correlation with the global disability measures including Short Health Survey (SF-36), Hand Mobility In SSc (HAMIS) and Health Assessment Questionnaire (HAQ), in which the total score of MHISS was found to be higher in dcSSc patients with reduced mouth opening score than the lcSSc group (Maddali-Bongi et al., 2014).

Despite not being specific for SSc a number of other health-related quality of life measures have been employed to investigate the impact of the oral aspects of SSc upon the quality of life. For example, the Oral Health Impact Profile (OHIP) and Short Health Survey (SF-36).

The Oral health impact profile (OHIP) is a questionnaire designed to measure oral health-related QoL in adults with oral disease. The OHIP-49 consists of 49 items representing seven aspects including (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap) and has been found to be reliable and valid to evaluate changes and to exhibit suitable cross-cultural consistency, based on a conceptual oral health model

outlined by Locker et al. (Slade and Spencer, 1994). The short form of OHIP (OHIP-14) consists of two questions in each of the seven OHIP aspects. Both OHIP questionnaires have been found to be useful tools for use in clinical practice with good reliability, validity and precision. Each question is rated on a 5-point Likert scale, and patients are invited to answer questions by choosing from a 0-4 scale while 0=never and 4=very often (Allen and Locker, 1997, Slade, 1997).

OHIP was used to assess the OHRQoL of 163 patients with SSc and 231 controls. The SSc patients had a significantly increased number of carious and missing teeth, more periodontal inflammation, less saliva production and less interincisal distance than the control subjects. However of relevance to OHRQoL the patients with SSc had significantly higher scores in all seven subscales of the OHIP (p<0.01) with an overall mean score 41.58 vs 26.67 (p<0.0001) respectively (Baron et al., 2014).

A study of 39 patients with SSc (22 in the intervention group and 17 as a control group) completed the two OHIP versions at three different time points. An acceptable stability was found with ICC (0.50 – 0.86) but due to the large standard error of measurement and the large coefficient of repeatability, this indicated that OHIP was precise nor sensitive tool to assess change (Yuen and Nelson, 2014).

Measuring pain in SSc is one of the most common global assessments in SSc. There are, however, no standardisation measurements, although the visual analogue scale (VAS) is commonly employed.

The Visual Analogue Scale consists of a 10-cm line with verbal anchors labelling both ends. It is a straight line with the left end of the line, or 0, meaning no pain (none) and the right end of the line, or 10, representing the worst pain that can happen. Patients are invited to mark the line according to the intensity of their pain (Ni Riordain et al., 2011). Feeling pain among SSc patients is found to be associated with other disease

impairments such as sleep problems, fatigue, depression and physical disability. Thus, pain in SSc, unsurprisingly, is associated with a reduced HRQoL and being greater in those with dcSSc than lcSSc (Pope, 2011, Kwakkenbos et al., 2015).

The 36-item short-form health survey (SF-36) is designed as a generic assessment of health status used in a wide range of types and severity of conditions. The 36 items includes eight concepts of health (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health). However, after answering the questionnaire, all scores have to be added together and transformed on a scale from 0 (worst health) to 100 (best health) (Ni Riordain et al., 2011). However, the SF-36 instrument is not a specific measure, but it has already been used in SSc with good validity and responsiveness (Nguyen et al., 2014, Almeida et al., 2015).

Patients with diffuse cutaneous SSc may have some degree of body image dissatisfaction in relation to the disease changes. The satisfaction with appearance scale (SWAP) was developed to assess the body image disfigurement among a variety of disorders, including SSc. It is a 14 items questionnaire designed to focus on two aspects of the disease (subjective body image satisfaction and social impact). It has four subscales assessing the social distress, facial features, non-facial features and social impact. A brief version of the SWAP was developed and consists of 6 items with the same two subscales previously identified for SSc (Jewett et al., 2010). Both forms of SWAP present a good to excellent level of internal consistency, reliability and validity. However, it has been suggested that the brief SWAP might be more specific for SSc, being useful for the identification of support (for example psychological) for patients with SSc (Mills et al., 2015, Almeida et al., 2015).

Although not a measure of the quality of life, the interincisal opening is often used to objectively assess the effects of fibrosis upon the mouth.

Table 1.16 Reported impact of systemic sclerosis upon oral quality of life by using MHISS scale

Author and Year	Country	Number of Patients	Age (range) years	Mean disease duration	Male/Female	Mouth opening
(Mouthon et al., 2007)	France	71	57.6 (11 years)	13.7 (12.3 years)	10 / 61 83.6% female	34.9 (7.6) mm
(Mestre-Stanislas et al., 2010)	France	248	57.45 (12.5 years)	9.9 (8.4 years)	43 / 205 82.6% female	NR
(Maddali Bongi et al., 2012)	Italy	40	57.27 (11.41 years)	9.4 (4.4 years)	6 / 34 85% female	40 (10.8) mm
(Schouffoer et al., 2013)	Netherlands	52	55 (21 years)	7.2 (7.3 years)	11 / 41 79% female	38.7 (10.1) mm
(Maddali Bongi et al., 2013)	Italy	46	56.1 (12.4 years)	9.85 (5.9 years)	46 females	40 (11.2) mm
(Maddali-Bongi et al., 2014)	Italy	119	59.46 (13.87 years)	10.74 (7.42 years)	14 / 105 88.2% female	38.9 (1.00) mm
(Nguyen et al., 2014)	France	381	57 (47-65 years)	7 (3-13 years)	62 / 379 83.6% female	36 (30-40) mm

AIMS AND OBJECTIVES

In view of the paucity of information regarding the oral disease of systemic sclerosis in patients resident in the UK, the aims of this thesis are:

1. To determine the orofacial features and oral complications in a large cohort of individuals with SSc in the UK.
2. To determine the impact of SSc upon access to dental care and oral health care needs of SSc patients in the UK.
3. To assess the quality and readability of available online information regarding oral health in SSc disease.
4. To determine the impact of SSc disease upon health-related quality of life (HRQoL) and oral health-related quality of life (OHRQoL).
5. To explore the psychometric properties of the Mouth Handicap in Systemic Sclerosis (MHISS) specifically exploring aspects of validity and reliability of MHISS in UK SSc patients.

CHAPTER 2: A retrospective analysis of orofacial features of systemic sclerosis

1 Introduction

As reviewed in chapter 1 systemic sclerosis (SSc) is a relatively rare autoimmune connective tissue disease of middle-aged and elderly persons that may adversely impact upon the quality of life of affected persons (Almeida et al., 2015). SSc is characterised by three pathophysiological features: i. obstructive vasculopathy of the small blood vessels, ii. immunological dysfunction followed by iii. cellular inflammation (Baron et al., 2015b). Inflammation and fibrotic changes characteristically lead to thickening of the skin and fibrosis of internal organs particularly the lungs, gastrointestinal tract and kidneys and/or associated with high morbidity and mortality (Rubio-Rivas et al., 2014, Royle et al., 2018). As indicated in chapter 1 patients with SSc are suggested to have a wide range of orofacial problems such as fibrosis of the facial skin, mask-like facial appearance, telangiectasia, stiffening of the tongue and oral mucosa, microstomia, salivary gland dysfunction and xerostomia, dysphagia as well as a potential risk of caries, periodontal disease and head and neck malignancy (Jung et al., 2016, Veale et al., 2016, Crincoli et al., 2016a, Smirani et al., 2018b). Despite its potential impact upon the mouth, little is known about the frequency of orofacial features experienced by patients with SSc resident in the UK.

There are few detailed reports of the nature and impact of oral features of SSc, and most studies were undertaken outside the United Kingdom. Therefore, knowledge about the orofacial features of SSc and the related oral health care needs is needed to clarify the oral treatment that affected individuals may require.

2 Material and Methods

2.1 Study Group

The current analysis incorporates data of 138 patients with SSc who attend or previously attended, the Oral Medicine Unit of UCLHT Eastman Dental Hospital for the care of their mouths between June 1994 and December 2018. The case records of all patients were reviewed carefully to obtain details of the patients' address, age, gender, ethnicity, past medical history, details of their referral source and any treatment received in UCLHT Eastman Dental Hospital. Data of the dental and oral status was extracted systematically, coded and recorded on predetermined Excel data sheets for subsequent statistical analysis.

It is appreciated that different diagnostic criteria for SSc have been applied over time due to increased knowledge and changing diagnostic criteria. However, the diagnosis has some consistency as most patients in this study had been referred with a diagnosis of SSc confirmed by a specialist team in the Rheumatology Department of the Royal Free Hospital – London. All patients were subsequently found to have clinical, and usually histo-pathological features of SSc.

The disease categorisation divided the patients into three groups: those with diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc) or mixed/overlap SSc. lcSSc was defined as skin involvement distal to the elbows and knees, with or without face involvement. dcSSc was defined as skin involvement proximal to the elbows and knees, with or without truncal involvement. Mixed and/or overlap SSc was proposed to describe the existance of SSc and other autoimmune connective tissue diseases with the presence of related clinical features and/or serological autoantibodies (Desbois and Cacoub, 2016, Denton, 2016). Orofacial features related to SSc were

reported based on detailed clinical examination by clinicians experienced in the field of oral medicine, Professor Stephen Porter (SRP) or Professor Stefano Fedele (SF).

2.2 Statistical Analysis

Descriptive statistical analysis of data was summarised to describe the demographics and characteristics of patients with SSc. Comparisons of different variables were performed by using classical statistics, including chi-square test for categorical variables, Student's t-test and Mann-Whitney U test for continuous variables. All statistical analysis was performed using SPSS 25 (version), and the significance level was taken when the p-value was less than 0.05.

2.3 Ethical considerations

No ethical approval was required, and data management was conducted with appropriate confidentiality.

3 Results

3.1 Patient demographics

3.1.1 Age and gender

The study group consisted of 138 patients managed by the Oral Medicine Unit of UCLHT Eastman Dental Hospital between June 1994 and December 2018, 116 patients (84.1%) were female, and 22 patients (15.9%) were male. The mean age of the patients at their initial attendance in the Oral Medicine unit was 55.4 years (SD ± 12.7) years, with an age range being between 16 to 87 years. The mean disease duration since diagnosis was 12.3 years (SD± 9.1) years with a range being between 1 to 34 years. (Table 2.1). There were no readily apparent differences in the age, ethnicity, marital and occupational status between the two genders or disease types.

Table 2.1 Age, gender and disease duration of 138 patients with SSc

Age group	Male, n (%)	Female, n (%)	Total
10-19	0 (0)	1 (0.8)	1 (0.7)
20-29	0 (0)	5 (4.3)	5 (3.6)
30-39	2 (9)	5 (4.3)	7 (5.1)
40-49	6 (27.4)	26 (22.4)	32 (23)
50-59	6 (27.4)	32 (27.5)	38 (28)
60-69	4 (18.1)	35 (30.1)	39 (28.2)
70-79	4 (18.1)	8 (7.1)	12 (8.6)
80-89	0 (0)	4 (3.5)	4 (2.8)
Total	22 (15.9)	116 (84.1)	138
Age (year), mean (SD)	54 (11.1)	55.5 (13.1)	55.4 (12.7)
Disease duration (years), mean (SD)	22.3 (6.4)	10.9 (8.8)	(9.1)

3.1.2 Ethnic group:

The majority of patients were White British (81; 58.7%), 10 were Indian (7.2%),6 Black African (4.3%) and other ethnicity backgrounds including 7 black Caribbean (5.1%),12 other white patients (8.7%), 3 Asian patients (2.2%), 2 Pakistani patients (1.4%), 1 Bangladesh patient (0.7%) and 16 patients belong to another unspecified racial group (11.6%) (Table 2.2).

Table 2.2 Ethnicity of patients with SSc

Ethnic group	Number of patients	% of group
British White	81	58.7
Other White	12	8.7
Indian	10	7.2
Black Caribbean	7	5.1
Black African	6	4.3
Pakistani	2	1.4
Asian	3	2.2
Bangladesh	1	0.7
Another ethnicity	16	11.6

3.1.3 Marital status:

Marital status was stated under four categories; married - which included married patients and patients with civil partnership; single, divorced and widowed. Eighty (58%) patients were married or living with a partner. 36 (26.1%) were single, 12 (8.7%) were widowed, 10 (7.2%) were divorced (Table 2.3).

Table 2.3 Marital status of patients with SSc

Marital status	Number of patients	% of group
Married	80	58
Single	36	26.1
Widowed	12	8.7
Divorced	10	7.2

3.2 Tobacco use and alcohol consumption:

Only 16 patients (11.6%) stated that they smoked tobacco, while 122 (88.4%) were not considered current smokers. 79 patients (57.2%) stated no history of alcohol consumption and 59 patients stated that they were presently drinking alcohol (42.8%) with 19% of these patients stating that they drink less than two units per week (Table 2.4).

Table 2.4 Tobacco use and alcohol consumption of patients with SSc

Item	Number of patients	% of group
Smoking	16	11.6
Alcohol	59	42.8

3.3 Occupational status:

18.1% of the patients were employed, 19.6% were unemployed, and perhaps unsurprisingly 8.7% were retired. Almost 53.6% of the study group patients could not be classified accurately as their details were unavailable or inappropriate and recorded with unknown work status (Table 2.5).

Table 2.5 Employment status of patients with SSc

Employment status	Number of patients	% of group
Employed	25	18.1
Unemployed	27	19.6
Retired	12	8.7
Unknown	74	53.6

3.4 Dental registration status and source for referral:

Most (100; 72.5%) of the patients had a general dental practitioner (GDP), the records of the remaining patients did not provide any details of registration with a general dental practitioner. The majority (80.4%) of the patients had been referred directly from the Royal Free Hospital-Rheumatology clinics, 17 patients were referred by their GDP

(12.3%), five patients were referred from Oral and Maxillofacial Surgery clinics (3.6%), 4 patients were referred from a General Medical Practitioner (2.9%), and one patient was referred from an Orthodontic specialist (0.7%) (Table 2.6).

Table 2.6 Dental registration status and source of referral for patients with SSc

Item	Number of patients	% of group
Registered with a dentist	100	72.5
Source of referral		
Rheumatology	111	80.4
General dental practitioner	17	12.3
Oral maxillofacial surgeon	5	3.6
General medical practitioner	4	2.9
Orthodontics	1	0.7

3.5 Pattern and reasons for referral:

Most referrals were primarily directed to Oral Medicine clinics 114 (82.6%), 22 cases were referred seeking dental treatment (16%), and two cases were referred for periodontal treatment (1.4%) (Table 2.7). Reasons for referrals were usually linked to patients' complaints and treatment needs including "poor dentition" (50 patients 36.3%), microstomia (30 patients 21.7%), "oral medicine consultation" (23 patients 16.7%), dry mouth (20 patients 14.5%), sore mouth (11 patients 8%) with single patients having complaints of oral ulceration, temporomandibular joint dysfunction, micrognathia, altered taste and a burning sensation of the mouth (Table 2.8).

Table 2.7 Clinical speciality for referral of patients with SSc

Item	Number of patients	% of group
Oral medicine clinics	114	82.6
Dental treatment	22	16
Periodontal treatment	2	1.4

Table 2.8 Reasons for referral of patients with SSc to oral health care services

Item	Number of patients	% of group
Poor dentition	50	36.3
Microstomia	30	21.7
Oral medicine consultation	23	16.7
Xerostomia	20	14.5
Sore mouth	11	8
Mouth ulcers	1	0.7
Temporomandibular joint dysfunction	1	0.7
Micrognathia	1	0.7
Dysgeusia	1	0.7

3.6 Mobility of patients with systemic sclerosis

When considering the ability to access clinics, the ability of the patient to easily walk was recorded. 107 (77.5%) patients did not have a musculoskeletal impairment that affected the ability to walk while 31 (22.5%) patients reported some impaired mobility such as muscle weakness, joint pain and/or limited joint movement (Table 2.9). Some patients had more than one manifestation affecting mobility.

Table 2.9 Mobility difficulties of patients with SSc attending for oral health care

Item	Number of patients	% of group
Muscle weakness	11	7.9
Joint pain	12	8.6
Other limitations	11	7.9
Total reported mobility impairment	31	22.5

3.7 Manual dexterity

Manual dexterity was not assessed formally, but Raynaud's phenomenon 95 (68.8%), sclerodactyly 34 (24.6%) and digital ulceration 11 (7.9%) were reported by patients or observed by the attending clinicians. Most patients had more than one manifestation affecting dexterity.

3.8 Distance travelled

Distance travelled was estimated from the patient's home address to UCLHT Eastman Dental Hospital. Although some of the study participants were resident in London, the category of 13 plus miles was the largest with around 30% of patients travelling an estimated round trip in excess of 60 miles to access their dental care at the Hospital (Table 2.10).

Table 2.10 Distance travelled to obtain dental care at the Eastman Dental Hospital

Distance	Number of patients	% of group
1-4 miles	9	6.5
5-9 miles	21	15.2
10-19 miles	45	32.6
20-39 miles	32	23.1
More than 40 miles	31	22.6

3.9 Systemic involvement and past medical history

Cutaneous disease was the dominant non-oral feature of SSc for this group of patients as almost two-thirds (67.4%) of the patients had or had had different types of dermatological diseases including dermatomyositis, digital ulceration, Raynaud's phenomenon, sclerodactyly, calcinosis and nail fold abnormalities. Respiratory manifestations of SSc, including pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD), were recorded in 53.6% of patients. Half of the patients had problems related to the gastrointestinal tract such as oesophageal dysmotility, abdominal discomfort, constipation, diverticulitis, gastric ulcers and gastroesophageal reflux disease (GORD). However, cardiovascular and dermatological diseases were more common among patients with dcSSc (p=.01). Additional details of past medical history are provided in Table 2.11. Most patients had more than one feature of systemic involvement.

Table 2.11 Past medical history of patients with systemic sclerosis

Condition	Examples	Number of patients	% of group
Cardiovascular	Hypertension, MI, angina, DVT, peripheral vascular disease and others	58	42
Respiratory	Asthma, pneumonia, lung fibrosis, pulmonary hypertension, interstitial lung disease, COPD and others	74	53.6
Haematology	Anaemia, thalassemia, thrombocytopenia, IgA gammaglobulinopathy, hypercholesterolaemia and others	18	13
Endocrine	Diabetes mellitus, thyroid dysfunction, primary biliary cirrhosis and others	21	15.2
Gastrointestinal	Oesophageal dysmotility, discomfort, constipation, diverticulitis, gastric ulcers, irregular bowel movement, irritable bowel syndrome, Crohn's disease, GORD, dysphagia and others	69	50
Neurology	Migraines, sciatica, dizziness, vertigo, epilepsy, facial palsy and others	13	9.4
Dermatology	Dermatomyositis, digital ulcers, Raynaud's Phenomenon, sclerodactyly, calcinosis, genital dryness, eczema, cutaneous panniculitis, calcinosis cutis, vitiligo, dystrophic nail plate abnormalities,	93	67.4
Psychological/Mental	Depression, anxiety and other psychiatric problems	3	2.2
Nephrology	Renal failure, UTI, renal crisis	16	11.5
Others	OLP, Sjogren's syndrome, systemic lupus erythematosus, Rheumatoid Arthritis, osteoarthritis, stiff joints, osteoporosis, inflammatory arthritis, myasthenia gravis, sarcoidosis, fibromyalgia, vulval lichen sclerosis, vaginal atrophy, chronic fatigue syndrome, endometriosis and Seckel syndrome	55	39.9

3.10 Concurrent medication and past drug history

Patients were receiving a wide range of medication at the time of their clinical consultation. As expected, the most common agents used were prescribed for the treatment of gastrointestinal problems (70.3%), followed by 66.7% of drugs being prescribed for the treatment of cardiovascular disorders. Patients with dcSSc were using medication for gastrointestinal problems more than patients with lcSSc (p=.03) while patients with lcSSc were found to be using nutrition and metabolic agents more than patients with dcSSc (p=.005). The different agents used to manage the patients'

various systemic disorders are summarised in Table 2.12. All patients had more than one prescribed medication for their medical illnesses.

Table 2.12 Past drug history of patients with systemic sclerosis

Drug or drug group	Examples	Number of patients	% of group
Cardiovascular	Calcium-channel blockers, Beta-adrenoceptor blockers, Potassium-channel activators, Angiotensin-converting enzyme inhibitors and others	92	66.7
Respiratory	Corticosteroid, selective beta 2 agonist, anticholinergic and others	35	25.4
Endocrine	Thyroid hormones, Antidiabetic, Vitamin D and others	27	19.6
Gastrointestinal	H2-receptor antagonist, aminosalicylate, proton pump inhibitor, compound alginates, drugs affecting biliary composition and flow and others	97	70.3
Neurology	Benzodiazepine, tricyclic antidepressant, serotonin re-uptake inhibitor, antiepileptic and others	26	18.8
Corticosteroids	Betamethasone, Clobetasol propionate, Fluticasone propionate (flixonase spray), Betamethasone esters, Mometasone furoate, Fluocinolone acetonide, Prednisolone and others	79	57.2
Vitamins, Nutrition and Blood	Ferrous Sulphate, Folic Acid, Iron supplements, Ferrous gluconate, Vitamin B-12, Vitamin E, Vitamin K, Pharmaton (multivitamins and minerals)	26	18.8
Bone metabolism	Alendronic acid and Etidronate disodium	13	9.4
Others	Acetylsalicylic acid, Acetaminophen, NSAIDs, compound analgesic preparations, opioid analgesics, antimalarials, antifungal, antiviral drugs, antibacterial, antifungal, dry mouth treatment, anti-gout, ocular lubricants, treatment of glaucoma, antihistamines, anticholinergic agents for urinary and bladder dysfunctions and others	45	32.6

3.11 Classification of systemic sclerosis

58 (42%) patients reported having diffuse cutaneous SSc, 43 (31.2%) had limited cutaneous SSc while 37 (26.8%) had another type of disease including mixed/overlap connective tissue disease (Table 2.13).

Table 2.13 Classification of patients with systemic sclerosis referred to UCLH Eastman Dental Hospital

Disease type	Number of patients	% of group
Limited cutaneous SSc	43	31.2
Diffuse cutaneous SSc	58	42
Mixed/overlap SSc	37	26.8

3.12 Presenting extra-oral disease features

At the initial clinical examination, the patients were found to have a wide range of extra-oral features (Table 2.14). The most frequent recorded extra-oral feature was fibrosis of facial skin - occurring in 52 (37.7%) of patients - followed by perioral skin tightening in 48 (34.8%) patients. Other extra-oral features (or reported facial symptoms) included dry eyes, the absence of lines of facial expression, perioral wrinkling, pinched-out nose, loss of vermillion borders and enlargement of either the parotid or submandibular salivary glands. Of note, none of the patients were found to have clinically detectable cervical lymphadenopathy.

Table 2.14 Extra-oral clinical findings at presentation of patients with SSc

Features	Number of patients	% of group
Facial skin fibrosis	52	37.7
Peri-oral skin tightening	48	34.8
Ocular dryness	33	23.9
Submandibular gland enlargement	1	0.7
Parotid gland enlargement	4	2.9
Facial telangiectasia	37	26.8
Reduced vermillion borders	27	19.6
Perioral skin wrinkling	8	5.8
Fissured lips	3	2.1
Angular cheilitis	4	2.9
Facial swelling	2	1.4
Cervical lymphadenopathy	0	0

Microstomia of undefined nature was recorded in 101 (73.2%) patients. Formal measurements of maximum mouth opening were not consistently recorded. In the 69 (50%) of patients where measures were recorded, 16% had a maximum mouth opening between 40mm and 31mm, half of the patients (49%) had maximum mouth opening between 30mm and 21mm and 35% had maximum mouth opening less than 20mm. 15.2% of patients had temporomandibular joint disorder (TMD) with other disease features such as speech impairment, limited mouth movement and malocclusion (Table 2.15 and 2.16).

Table 2.15 Limited mouth opening and TMD at presentation of patients with SSc

Features	Number of patients	% of group
Microstomia	101	73.2
TMD	21	15.2
Limited mouth movement	4	2.9
Speech impairment	7	5.1
Malocclusion	8	5.8

Table 2.16 Measurements of maximum mouth opening of 69 patients with SSc

Scale	Number of patients	% of group
10-20mm	24	35
21-30mm	34	49
31-40mm	11	16

3.13 Presenting intra-oral disease features

3.13.1 Gingival and periodontal disease

Formal examination of the gingival or periodontal tissues was not undertaken in 53 (38.4%) patients, although 47.1% of the group were recorded as having generalised chronic periodontitis. Non-specific plaque-induced acute gingivitis (alone) occurred in 9.4%. Other related features were reported such as acute necrotising ulcerative gingivitis (ANUG), desquamative gingivitis and localised chronic periodontitis (Table 2.17).

Table 2.17 Gingival and periodontal features observed in patients with SSc

Features	Number of patients	% of group
Generalised chronic periodontitis	65	47.1
Gingivitis (Non-plaque induced acute disease)	13	9.4
Desquamative gingivitis	3	2.2
Acute necrotising ulcerative gingivitis (ANUG)	3	2.2
Localised chronic periodontitis	1	0.7

3.13.2 Oral hygiene status

Seventy-four (53.6%) patients were considered to have poor oral hygiene by virtue of the appearance of obvious deposition of supragingival plaque and debris. The majority of patients (97.8%) received oral hygiene advice during their appointments, and 36.2%

of patients were prescribed toothpaste (usually high concentration fluoride agents) and/or mouthwashes (usually Chlorohexidine). Furthermore, 43.5% of patients with hypo-salivation (of known or unknown cause) were prescribed a variety of saliva substitutes and/or oral lubricants. 64.5% of patients were referred for oral hygiene therapy, and 26.1% were referred for specialist periodontal treatment (Table 2.18).

Table 2.18 Oral hygiene status of patients with systemic sclerosis

Item	Number of patients	% of group
Oral hygiene instructions and advice	135	97.8
Fluoride toothpaste and/or anti-microbial mouthwashes prescription	50	36.2
Saliva substitutes and/or lubricants	60	43.5
Hygiene therapy	89	64.5
Specialist periodontal treatment	36	26.1

3.13.3 Dental status

Unfortunately, no precise records of the present dental status of a substantial number of patients were available as no formal record of the decayed, missing or filled teeth (DMFT) was undertaken from the patient's notes or referrals to the oral medicine unit. The number or status of teeth decayed, missing, mobile or restored have not been clearly indicated. However, 104 (75.4%) patients did have one or more decayed teeth, 107 (77.5%) had teeth with dental restorations, and 79 (57.2%) had missing permanent teeth. 15.9% of patients had at least one clinically mobile tooth (the degree of mobility was never assessed) and dental erosion was found in 8.7% of patients. None of the patients were edentulous (Table 2.19).

Table 2.19 Decayed, mobility, missing and filled teeth of patients with systemic sclerosis

Feature	Number of patients	% of group
Poor oral hygiene	74	53.6
Decayed teeth	104	75.4
Filled teeth	107	77.5
Mobile teeth	22	15.9
Missing teeth	79	57.2

3.13.4 Oral mucosal involvement

Just over half of the patients had apparently healthy oral mucosae (51.4%). 23.2% had “dry lining mucosa”, 17.4% had erythematous mucosa, and a small number were reported to have tight or “atrophic” mucosa 7.2% and 0.7% respectively. Mucosal alterations were mostly manifested as a generalised involvement (87.7%) while only 12.3% of patients had localised involvement of buccal mucosae. Oral ulceration was observed in 15.2% of patients while indentation of buccal mucosa occurred in 10.1% of cases. Oral telangiectasia occurred in 29.7% of patients in a variety of locations including the palate, buccal mucosa and tongue (Table 2.20).

Table 2.20 Oral mucosal involvement of patients with systemic sclerosis

Features	Number of patients	% of group
Dry lining mucosa	32	23.2
Erythematous mucosa	24	17.4
Tight mucosa	10	7.2
Atrophic mucosa	1	0.7
Denture stomatitis	4	2.9
Lichenoid hyperkeratosis	1	0.7
Ulceration	21	15.2
Submucosal fibrosis	1	0.7
Oral telangiectasia	41	29.7
Indentation of the buccal mucosa	14	10.1

3.13.5 Salivary gland disease and oral infection

A sensation of dry mouth was reported in 47.1% of patients, and 23.9% of this group were complaining of dryness of their eyes. However, 30.4% of patients had already been diagnosed as having Sjogren's syndrome and 28.3% reported with objectively mouth dryness. 22.5% of patients complained of dysphagia, and 43.5% were diagnosed with GORD. Moreover, increased susceptibility to microbial infection would be expected in consequence to dry mouth and other disease manifestations. Acute candida infection (e.g. pseudomembranous) or chronic (e.g. erythematous) was diagnosed in about 15.9% of patients with SSc (Table 2.21). A comparison between the different disease subtypes showed that patients with lcSSc had a significantly more coincident diagnosis of Sjogren's syndrome (p<.001), more symptoms of dry eyes (p=.004) and candida infection (p=.004).

Table 2.21 Salivary gland disease and oral infection of patients with systemic sclerosis

Features	Number of patients	% of group
Xerostomia	65	47.1
Hypo-salivation	39	28.3
GORD	60	43.5
Dysphagia	31	22.5
Candida infection	22	15.9
Sjogren's syndrome	42	30.4

3.13.6 Tongue rigidity and ankyloses

Symptoms or signs of abnormalities of the tongue were reported by 27 patients, this being of greater prevalence in patients with lcSSc (p=.02). Tongue rigidity was reported in 6.5% of patients. 8.7% of patients had an atrophic disease of the tongue, and 4.3% had restricted movement of the tongue. Depapilation of the dorsum was

observed in 3.6% of patients, and 2.9% were reported to have a lobulated tongue (Table 2.22).

Table 2.22 Tongue involvement of patients with systemic sclerosis

Features	Number of patients	% of group
Tongue atrophy	12	8.7
Tongue rigidity	9	6.5
Tongue ankylosis	6	4.3
Depapillated dorsum	5	3.6
Lobulated tongue	4	2.9

3.13.7 Orofacial pain involvement

Burning mouth syndrome was diagnosed in seven patients (5.1%), and trigeminal neuralgia was diagnosed in four patients (2.9%) (Table 2.23).

Table 2.23 Orofacial pain manifestations of patients with systemic sclerosis

Features	Number of patients	% of group
Burning mouth syndrome	7	5.1
Trigeminal neuralgia	4	2.9

3.14 Radiographic features

The orthopantomographic views of the jaws of 101 (73.2%) patients were available and reviewed by the attending clinicians. 19.5% of the patients had signs of generalised alveolar bone loss. Resorption of the mandibular angle (1.4%), mandibular ramus (0.7%), coronoid process (2.2%), condylar process (0.7%), or bilateral condylysis (0.7%) were recorded by attending clinicians.

3.6% of patients were found to have a possible widening of the periodontal ligament space, this was around the posterior teeth adjacent to the coronal area. One patient had signs of pulpal calcification of the premolars as well as hypercementosis (Table 2.24).

The incidence of resorption of a mandibular angle, ramus of the mandible and condylar process were only observed in patients with dcSSc, while other features including bilateral condylysis, pulp calcification and hypercementosis were only reported in the lcSSc group.

Table 2.24 Radiographic findings of 101 patients with systemic sclerosis

Features	Number of patients	% of group
Generalised alveolar bone loss	20	19.5
Mandibular angle resorption	2	1.4
Mandibular ramus resorption	1	0.7
Coronoid process resorption	3	2.2
Condylar process resorption	1	0.7
Bilateral condylysis	1	0.7
Widening of periodontal ligament space	5	3.6
Pulp calcification	1	0.7
Hypercementosis	1	0.7

3.15 Oral health care interventions

Following their initial consultation in oral medicine, 57.2% of patients were referred to specialists of Special Care Dentistry for further treatment including preventative and/or conservative restorative treatment. Subsequently, 22.5% required dental extractions, while 23.9% had different types of restorative dentistry (e.g. fixed or removable prosthodontics and conservative dentistry). Further follow-up visits to oral medicine clinics were usually arranged every 6 months depending upon oral health care needs. However, five patients needed later referral to other specialities such as Otorhinolaryngology (ENT) and Oral and Maxillofacial Surgery (OMFS). One case was referred for reconstructive surgery for a facial fat stem cell transplant, and one was referred for speech therapy (Table 2.25).

Table 2.25 Subsequent treatment of orofacial disease of patients with systemic sclerosis

Interventions	Number of patients	% of group
Special Care Dentistry	79	57.2
Surgical treatment	31	22.5
Restorative treatment	33	23.9
OMFS	3	2.1
ENT	2	1.4
Speech therapy	1	0.7
Facial stem cell transplant	1	0.7

4. Discussion

The primary aim of this part of the study was to determine the key orofacial manifestations and explore the nature of the oral health problems of a large cohort of individuals with SSc and thus present the possible oral health care needs of such patients. The present group of participants comprised 138 patients with different types of SSc and thus represented the largest group of patients with SSc resident in the UK to have ever been examined for aspects of their oral health.

The demographics of the present patient cohort confirm recent reports that SSc is primarily a disease affecting middle to late age females (Chu et al., 2011, Willems et al., 2014, Jung et al., 2016, Veale et al., 2016, Smirani et al., 2018b). Although SSc is most commonly diagnosed in the middle to late age group, it can affect younger people (Ranque and Mouthon, 2010, Hughes and Herrick, 2012, Gelber et al., 2013, Hansi et al., 2014) as also demonstrated in the present study group. Although most of the patients' records did not specify employment status, a considerable number of the patients were unemployed or retired. These data could be related to the morbidity of the disease and/or physical disability in SSc patients (Decuman et al., 2015, Poole et al., 2016, Morrisroe et al., 2018).

There have been several reports of the oral manifestations of SSc, and a recent large multisite study of the Canadian systemic sclerosis oral health study group examined several aspects of the disease characteristics, orofacial features and oral health-related quality of life (Baron et al., 2014). The Canadian researchers analysed 163 patients with SSc. 90% were female, and the mean age of the group was 56 years, 72% had limited cutaneous subtype and 28% with diffuse cutaneous SSc (Baron et al., 2015b). As expected, for a group of residents in the UK the patients were predominantly female and predominantly white British (58.7%), also reflecting the

epidemiology of SSc in the UK (Kuo et al., 2011, Barnes and Mayes, 2012, Ingegnoli et al., 2018). Different values have been recorded in this study with regards the disease subtypes, 42% had a diffuse cutaneous subtype, 31.2% had limited cutaneous SSc, and 26.8% had other mixed/overlap connective tissue diseases. Although the data on the prevalence of SSc in the UK is limited, previous reports have shown that the ratio of limited cutaneous SSc to diffuse cutaneous SSc was (4.7:1) (Allcock et al., 2004, Willems et al., 2014). However, similar values have been reported recently where dcSSc was slightly more common than other subtypes (26/50, 52%) (Gomes da Silva et al., 2019). Differences in the distribution of disease subtype across countries have been identified and may be attributed to different disease profiles or different access to services. However, it is unclear to what extent the observed differences in the disease subtypes reflect any differences in disease features or is a consequence of sampling differences as the current results incorporate data of patients who attend or previously attended one tertiary health care centre (the Oral Medicine Unit of UCLHT Eastman Dental Hospital).

The majority of patients in the present study had general dental practitioners, but most of them were referred from a (single) Rheumatology Centre in North London – Royal Free Hospital, that provides a nationally recognised clinical service for the treatment of SSc – managing 2000 out of approximately 12000-19000 patients living with SSc in the UK (Royle et al., 2018). Although most of the patients were registered with general dental clinics, the reasons for referral to the specialists clinics were generally for the supposed difficulty in obtaining routine dental care and/or for further consultation and treatment needs that mainly included poor dentition 36.3%, reduced mouth opening 21.7%, oral medicine consultation 16.7% and feeling dry mouth 14.5%. An alternative, and possibly more likely reason for the present referral pattern is that it reflects the

rheumatology team having knowledge that the Oral Medicine unit of the EDH has an interest in managing patients with complex connective tissue disease.

Despite supposedly having a general dental practitioner, 53.6% of the patient group of 138 patients were considered by the oral medicine team to have poor oral hygiene, and indeed 64.5% subsequently received oral hygiene care. More than half of the patients were later referred to Special Care Dentistry (SCD) as well as other specialities for further treatment. The dominant referral to SCD probably reflected the levels of associated impaired mobility, difficult dental access due to reduced mouth opening and abnormal manual dexterity making effective oral hygiene difficult and hence subsequent plaque-related disease likely (Poole et al., 2010, Yuen et al., 2014a, Alantar et al., 2011). As suggested by the present pattern of referral, and subsequent oral health care, the oral health needs of patients with SSc may sometimes require the skills and experience of clinicians from a variety of dental specialities (Leader et al., 2014).

In the present study, a possible mask-like facial appearance (due to fibrosis) was observed in 37.7% of cases. 34.8% of the patients had tightness of the perioral skin, some within this group, and others had features such as the absence of lines of facial expression, a perioral wrinkling, a pinched-out nose, a reduced vermillion borders and/or facial telangiectasia. While such orofacial manifestations have been described in about 80-90% of SSc cases (Bajraktari et al., 2015, Burchfield and Vorrasi, 2019), it is possible that such obvious signs will impact adversely upon an individual's confidence in social interaction.

The present group of patients with SSc had reduced mouth opening in 73.2%, and 84% of them had objective evidence of reduced interincisal distance less than 30mm. Similar findings have been reported in other large cohorts of patients with SSc, and

the mean interincisal distance was 37.7mm with more severely limited mouth opening (mean=34.4mm) among patients with diffuse cutaneous subtype (Baron et al., 2014, Jung et al., 2016). Microstomia has the potential to interfere considerably with oral function, and also cause challenges with oral hygiene self-care and dental treatment, due to the limited access (Alantar et al., 2011, Del Rosso and Maddali-Bongi, 2014). The degree of decreased mouth opening has been found to correlate with overall disease activity, the extent of skin involvement and specific SSc antibodies (Baron et al., 2014). Of note, the majority of the present patients with limited oral opening had dcSSc. Severely limited mouth opening might be more related to disease severity and diffuse subtype of SSc.

The intra-oral clinical features of SSc have been described in several large cohorts (Leung et al., 2011, Elimelech et al., 2015, Jung et al., 2016, Pischon et al., 2016). In the present study, SSc gave rise to a variety of mucosal and periodontal manifestations. 47.1% of the patients were found to have generalised chronic periodontitis, while other gingival and soft tissue alterations included desquamative gingivitis and localised chronic periodontitis. It has been reported that patients with SSc can have a significant level of periodontal disease and higher periodontal attachment loss compared with healthy controls (Baron et al., 2014, Pischon et al., 2016). Previous reports have suggested that an increased risk of periodontal disease may be related to the microvascular abnormalities of the disease and/or increased collagen deposition (Chu et al., 2011). However, the cause of the periodontal disease in the present group of patients with SSc is likely to be multifactorial in its nature and is likely to be dominated by poor oral hygiene. Other suggested risk factors include tobacco smoking, level of education, daily alcohol consumption and body mass index (Isola et al., 2017). However, this is unlikely to be related for this patient group.

Although certain intra-oral manifestations such as thinning and atrophy of oral mucosa can be related to the generalised fibrosis and tissue ischaemia involving both overlying skin and gastrointestinal system 66 – 90% (Poole et al., 2013, Jung et al., 2016), the present patients have little dryness, erythematous and tightening oral mucosa (23.2%, 17.4% and 7.2%) respectively. Mucosal alterations were mostly generalised involvement which might be correlated to other manifestations of the disease including malabsorption, drug-related adverse side effects or GORD (Alantar et al., 2011, Jung et al., 2016).

Changes to the tongue, such as fibrosis leading to restricted movement of the tongue or lingual fraenum (Chu et al., 2011, Vitali et al., 2015) have previously been observed in patients with SSc. In the present study atrophy, ankylosis and rigidity of the tongue were noted in a small number of patients. Atrophic tongue was significantly associated with the lcSSc. Tongue involvement can adversely impact upon speech, eating and swallowing (Fischer and Patton, 2000, Vitali et al., 2015, Crincoli et al., 2016b) and hence, although uncommon, can ultimately lessen general health and quality of life.

Perhaps, as might be expected given the oral hygiene status of the patients, 75.4% of the group had at least one carious tooth, 77.5% had filled teeth, and 57% had missing teeth. These findings of perhaps high levels of present and past dental disease agree with previous reports which revealed that patients with SSc have significantly worse dental health including more missing teeth and periodontal disease than those without SSc (Chu et al., 2011, Baron et al., 2014, Baron et al., 2015b). Also, it has been reported that these patients are more likely to have salivary gland hypofunction and reduced mouth opening (Baron et al., 2014, Crincoli et al., 2016b).

Interestingly, it was reported that the number of missing teeth among patients with SSc was associated with salivary dysfunction, as for every 10 mg/min increase of

saliva production the number of missing teeth decreased by 3%. Furthermore, a significant association was found between missing teeth and gastroesophageal reflux disease (Baron et al., 2015b). These data might explain the high level of missing teeth among the present sample as 43.5% of the patients were diagnosed with GORD. However, it would seem that the possible difficulties in being able to clean their teeth due to reduced mouth opening and reduced manual dexterity and/or oral dryness due to Sjogren's syndrome, or possibly drug therapy, resulted in these patients with SSc having a substantial dental disease burden.

53.6% of patients were considered to have poor oral hygiene. Almost all patients initially required oral hygiene instruction and advice and 64.5% of patients were referred to have oral hygiene therapy, while 26.1% required advanced periodontal treatment. The ability to maintain a good level of oral hygiene may reflect microstomia, reduced manual dexterity and/or associated co-morbidity of the disease (Poole et al., 2013, Del Rosso and Maddali-Bongi, 2014).

Of relevance, fatigue, Raynaud's phenomenon, stiffness of the hands and joint pain have been found to adversely impact upon the ability to carry out everyday activities, as well as, somehow, lessening the opening of the mouth, and the ability to swallow (Bassel et al., 2011, Willems et al., 2014).

Several studies have shown that patients with SSc do have difficulties in the maintenance of oral hygiene care, while the microstomia of SSc may compromise oral hygiene care by patients (Poole et al., 2004). Measures to enable individuals with SSc to maintain good oral hygiene have been suggested and include regular follow-up visits, patient education and using adaptive oral hygiene devices (e.g. angled brushes, altered filament length brushes, easy-grip brushes, extended handle brushes, electric brushes and soft small-headed toothbrushes (Alantar et al., 2011, Jung et al., 2016).

47.1% of the present group of patients with SSc reported having a feeling of dry mouth and 22.5% having dysphagia. Indeed, salivary gland hypofunction was reported in 28.3% of patients with SSc but unfortunately not objectively measured in all the present group of patients with SSc. These present results are in line with those of other studies that reported that salivary gland hypofunction in patients with SSc was 33.9% and associated with the presence of Sjogren's syndrome-related antibodies (Kobak et al., 2013). 29.9% of the present group of patients had been diagnosed as having Sjogren's syndrome. The presence of Sjogren's syndrome in systemic sclerosis is well known (14-33.9%), and certainly it would be important to assess all patients with SSc and oral dryness for Sjogren's syndrome in view of the risk of non-Hodgkin's lymphoma (Chu et al., 2011, Jung et al., 2016). Indeed it has been recommended that all patients with SSc should be investigated for Sjogren's syndrome as it was reported that the prevalence of SS among patients with SSc is ranged from 17-29% (Kobak et al., 2013).

The patients were receiving a wide spectrum of drugs for the management of SSc and other disorders. Some of these agents will cause or worsen oral dryness (Elimelech et al., 2015). Previous evidence has been reported that the use of such drug therapies was thought to be related to increasing pre-existing xerostomia in 76.3% of the study sample (Baron et al., 2014, Baron et al., 2015b) and hence increasing the risk of plaque-related oral disease as well as dental decay. Treatment adverse side effects among patients with SSc are common as certain medications (e.g. immunosuppressive, cytotoxic drugs, antihypertensive, antidepressant and anticoagulant drugs) can give rise to some oral complications such as (mucosal ulceration, xerostomia, gingival bleeding and hyperplasia) (Alantar et al., 2011, Elimelech et al., 2015, Porter et al., 2017). Other therapeutic agents (e.g. Calcium

channel blockers, corticosteroids and Medication-related to osteonecrosis) may be responsible for specific symptoms such as increased risk of oral infections, mucositis, impaired wound healing and risk of jaw osteonecrosis (Yuen et al., 2014b, Mawardi et al., 2016, Jung et al., 2016). Considering the many adverse effects that can be observed, such therapies should be used carefully, and all patients should undergo clinical and radiographic examination prior to commencing any dental treatment.

Maxillofacial radiographic features of SSc have been reported among patients with SSc in different cohort studies (Marcucci and Abdala, 2009, Dagenais et al., 2015, Crincoli et al., 2016b, Burchfield and Vorrasi, 2019). Periodontal ligament (PDL) widening is a reported radiographic feature of SSc that might be due to excessive pathological collagen deposition. However, the present results showed that only 3.6% of patients have signs of PDL widening. This value is significantly lower than results from other studies that ranged from 10% - 38% of patients with SSc (Baron et al., 2015a, Jung et al., 2016). Present results might be related to a relatively small sample size having radiographic records and the measurements that have been performed, were on panoramic radiographs that are known to be prone to image distortion. Although no evidence of a clear correlation between PDL widening and other periodontal diseases have been reported, careful assessment of similar radiographic features and awareness of this specific disease manifestation can prevent misleading diagnosis among patients with SSc.

Bone resorption is considered common (6.6% - 46.7) in patients with SSc (Jung et al., 2016). However, there is no clear correlation between disease severity and the incidence of bone resorption (Vincent et al., 2009, Baron et al., 2015a). Present results showed that up to 19.5% of patients have a generalised pattern of alveolar bone loss. Furthermore, a different pattern of mandibular bone resorption has been reported with

most frequently affected sites; coronoid process 2.2%, angle of the mandible 1.4%, condylar process, ramus of the mandible and bilateral condylysis 0.7%. Higher values have been reported from previous studies with a different range of severity that rarely can result in facial asymmetry, malocclusion and pathological fracture (Veale et al., 2016). Findings such as bilateral condylysis, pulp calcification and hypercementosis were only reported in patients with lcSSc 0.7% while other features including resorption of the angle of the mandible, ramus and condylar process were only reported among patients with dcSSc. This heterogenicity of the pathogenesis of bone resorption is not well understood and may be related to the nature of the disease subtype and/or duration of disease.

Temporomandibular joint dysfunction is frequently associated with SSc disease and can manifest as (pain, clicking, deviation, trismus, crepitation) (MacIntosh et al., 2015, Matarese et al., 2016, Crincoli et al., 2016a). Present results showed that up to 15.2% of patients with SSc have TMJ involvement while 5.8% present with different sort of malocclusion, 5.1% speech impairment and 1.4% trismus. However, bilateral TMJ involvement has been reported in multiple cases, and it has been recognised as a consequence of mandibular bone resorption (MacIntosh et al., 2015). In the advanced stages of bone resorption and TMJ involvement, 4 -13% might present with trigeminal neuropathy with 83% involvement of mandibular and maxillary nerves (Fischoff and Sirois, 2000) (Doucet and Morrison, 2011). Thus, giving a comprehensive clinical assessment of facial involvement in the course of SSc should be performed on a routine basis.

Current data revealed that almost all patients who participated in this study received advice regarding their oral health, and 64.5% received dental scaling and polishing, while 26.1% needed to undertake advanced periodontal treatment. Similarly, half of

the patients were referred to a special care dental unit for further treatment due to their medically compromised health status and impaired dental access. These figures support the previous evidence that highlights the limited access to dental treatment along with the dental treatment challenges among patients with SSc (Alantar et al., 2011, Poole et al., 2014, Leader et al., 2014). Thus, patients' education and advice should be detailed regarding the associated risk factors of oral disease and the importance of maintaining preventative measures. The need to implement therapeutic modalities should be explained, such as regular follow-up with appropriate preventive measures (e.g. topical fluoride application, fissure sealing restorations, scaling and root planning) and routine radiographic evaluation aiming to achieve early diagnosis and management of related disease manifestations.

On the other hand, dental health care providers should be aware of the features of SSc disease, the challenges that SSc patients have in obtaining dental care and integrated into the multidisciplinary team. Dental health care providers play an important role in the management of this condition and should be involved in the diagnostic process and know the specific orofacial manifestations of SSc. However, medical health care providers need to reinforce and acknowledge that patients need to be regularly monitored by their dentists and familiar with the alternative oral hygiene aids to maintain the recommended level of oral hygiene.

5. Conclusion

Retrospective observational studies such as the present study have many limitations that include; missing data, high variability in the quality and quantity of the data and differences in reporting clinical features and outcomes. Going forwards, there is also a need to address the importance of detailed data recording when attempting a retrospective study. The more detailed information collected, the more likely the data are to contribute to expanding our knowledge in the future. Despite these limitations, this study provides useful information on the oral health status of the UK people with SSc, and it allows a rational understanding of the oral health status and dental care needs of people with SSc in the UK. However, the results of this study reveal that UK patients with SSc are typically middle to late age group and complain of variable degrees of orofacial symptoms of the disease. Concerning oral management, early multidisciplinary management based on the collaboration between different health care providers is essential. The majority of patients will have long-term SSc, and perhaps a high risk of more severe adverse side effects of SSc-related features that might impact upon their ability to maintain a good standard of oral hygiene and/or access to oral health care. Indeed some orofacial manifestations might aid for the early diagnosis of SSc thus it is essential that such individuals are carefully monitored by appropriately trained clinicians using standardised evaluation of orofacial involvement during routine clinical reviews

CHAPTER 3: Orofacial features of systemic sclerosis and the impact of disease upon oral health and access to dental care

1 Introduction

As previously discussed orofacial manifestations of SSc have been reported to arise in sometimes up to 80-90% of patients including skin fibrosis, microstomia, xerostomia and dysphagia, as well as the potential increased risk of caries, periodontal disease and oral malignancy (Jung et al., 2016, Veale et al., 2016, Smirani et al., 2018b). Affected individuals usually have more than one feature of the disease, and this may lessen both the functional and aesthetic aspects of patients and lead to a negative impact on a patient's emotional and social life (Kwakkenbos et al., 2015). Despite its impact upon the mouth, there are little data regarding the patients perceived adverse oral health and access to oral health care.

The clinical course can be variable and unpredictable (Pope and Johnson, 2015, Lachner, 2016), and the oral and facial features of SSc may vary with each type of disease. Patient self-maintenance of oral health and the delay of professional oral health care have the potential to be compromised as a consequence of systemic features of the disease such as fatigue, joint and muscle pain, dysphagia, reduced manual dexterity and cardiopulmonary involvement and perhaps limit the ability of patients to attend for routine or essential oral health care (Alantar et al., 2011, Willems et al., 2014).

It might thus be expected that individuals with SSc may have, or have had, oral features that caused them or their oral health care providers concerns. In addition, the relative rarity of SSc could perhaps affect the ability or willingness of oral health teams to provide care (Leader et al., 2014, Willems et al., 2015a). Patients with rare diseases such as SSc might experience challenges including gaps in knowledge of attending

clinician about the disease, difficulty obtaining an accurate diagnosis and limited ability to treat affected individuals (Delisle et al., 2018). Certainly patients with SSc have reported substantial unmet needs regarding general health care services, management of their physical and psychological symptoms, health information and social support (Rubenzik and Derk, 2009, Schouffoer et al., 2011, Cossu et al., 2017). There is no information as to the perception of individuals with SSc as regards whether SSc has impacted upon their oral health nor any published knowledge of the experience of patients with SSc being able to access oral health care services.

The aims of the present chapter were to assess the frequency and type of oral manifestations of SSc that patients self-report and to explore the implications of SSc upon the ability to obtain routine dental care and.

The objectives of the present study were as follows:

1. To identify the perceived oral manifestations as reported by patients or a family member or partner of the patient.
2. To determine dental registration status and type of provider services for adults with SSc.
3. To determine if individuals with SSc believe that their disease status has influenced the availability of dental care for them.

2 Material and Methods

2.1 Study sample

This was an observational cross-sectional study undertaken between May and July 2017. The study group comprised 50 patients with a diagnosis of systemic sclerosis (SSc) who were registered with Scleroderma Society and participated in Scleroderma family day – UK and/or attended the outpatient Rheumatology clinic of the Royal Free Hospital, London; and 18 partners or relatives of these patients.

All patients and partners or relatives were over 18 years old and able to understand and communicate in verbal and written English language. All patients were invited to participate in the study following a verbal explanation of the aim of the study and were asked to invite their partners or relatives to participate in the study. All completed a self-administered questionnaire concerning their opinions of access to dental care and the impact of SSc upon their oral and general health status.

2.2 Questionnaire design

Two questionnaires were designed and employed in this study. The first questionnaire (A) was designed for individuals with SSc, including details of registration status with a dentist, difficulties in accessing dental services and self-perceived oral problems due to SSc.

The second questionnaire (B) was designed for partners or relatives of the individuals with SSc, to obtain similar information as the patient' questionnaire. Both questionnaires were 8 pages; single-sided on A4 pages.

Copies of the questionnaires are provided in the appendices.

Questionnaire A was based on closed questions which should be answered “yes” or “no”. If the patient replied with an affirmative answer, s/he was invited to give additional details.

The questions were designed for individuals with SSc and the main topics of the questions were related to the following:

1. Personal data and demographic information.
2. Date of diagnosis and sub-type of disease as reported to them by their attending specialists.
3. General and oral health status (function and dentition).
4. Dental history, attitude and pattern of dental attendance (current mouth problems, details of registration status with a dentist, the reason for attending the dental surgery).
5. Access to dental care (including any perceived difficulties in accessing dental services and availability of dental care).
6. Oral hygiene self-maintenance (including any perceived difficulties in performing oral care and its relation with the SSc).
7. Orofacial features related to SSc (self-perceived orofacial disease in relation to SSc).
8. Any additional information related to the mouth or the dental care that they believed to be relevant.

Questionnaire B was designed to obtain similar information to that of the patient-directed questionnaire, but from a partner or friend of each patient with SSc. The questions were based on closed questions which should be answered “yes” or “no”. If the participant replied with an affirmative answer, s/he was asked to give additional details.

The main topics were:

1. Personal data and demographic information.
2. Confirmation of not having SSc.
3. Oral health status (function and dentition).
4. Dental history, attitude and pattern of dental attendance (current mouth problems, details of registration status with a dentist, the reason for attending the dental surgery).
5. Access to dental care (including any perceived difficulties in accessing dental services, the influence of SSc on their partners with SSc in relation to the availability of dental care and the status of their mouth).
6. Oral hygiene self-maintenance (including any perceived difficulties for performing oral care by their partners with SSc and its relation with the SSc).
7. Orofacial features similar to SSc features (a self-perceived orofacial disease in relation to SSc).
8. Any additional information related to the mouth or the dental care that they believed to be relevant.

2.3 Data collection and statistical analysis

The participants were asked to return the completed questionnaire on-site or in a provided stamped addressed envelope. After completion of the data collection, all data was transferred to Excel spreadsheets, tabulated and later interpreted where appropriate using the SPSS statistical software package version 25.

The descriptive statistical analysis was undertaken for demographics and disease features. Means, standard deviations and ranges were calculated for continuous variables while frequency counts (number and percentage) were calculated for categorical (ordinal and nominal) variables. In patients and controls, further statistical analysis was performed for comparisons of different variables using the Chi-squared test, Fisher's exact test for categorical variables, independent t-test and Mann-Whitney U test for continuous variables. For all statistical analyses, the threshold of significance was set at a *P*-value < 0.05.

Some data concerning the dental status, access to NHS dentistry, number of teeth and frequency of dental check-up of the study group were compared with the South of England regional data of the Adult Dental Health Survey (2009) for age-matched individuals and with the results of a study conducted by Ipsos MORI on behalf of Citizen's Advice Bureau in 2008.

Ethical approval was sought for this study; however, as this was considered to be an evaluation of service, ethical approval was not deemed necessary.

3 Results

3.1 Demographics of patients with SSc and their partners

The participants in the study consisted of 50 individuals (the patient group) with likely SSc and 18 partners or relatives (the partner/relative group). The patient group consisted of 48 females (96%) and 2 males (4%), with a group mean age of 62.5 years (SD = 10.8), with an age range between 29 and 81 years. The the partner/relative group consisted of 14 males (78%) and 4 females (22%) with a group mean age of 67 years (SD = 8.8), with an age range between 46 and 78 years. The disease group had a disease duration of 13.2 years (SD = 10.9). A slight majority of the patients were married (54%). 70% were British white, and 88% had an educational level at degree level or above.

The type of systemic sclerosis was based upon the diagnosis as reported by the patient. There was no attempt to elucidate the clinical type by additional clinical examination or alternative investigations. Twenty-four patients described themselves as having diffuse cutaneous SSc (dcSSc) while 30 patients reported that they had limited cutaneous SSc (lcSSc). Six patients described having mixed/overlap SSc. However, seven patients with SSc did not report their likely type of the disease.

No significant difference in age, marital status, work status, education level and ethnicity were found among participants' groups. Demographics and disease characteristics related to SSc are summarised in Table 3.1.

Table 3.1 Baseline characteristics of patients with SSc (n = 50) and partner/relative group (n = 18)

Variables		SSc subjects	Partner/ relative group	*P*-value
Age (year), mean (SD)		62.5 (10.8)	67 (8.8)	.093
Disease duration (years), mean (SD)		13.2 (10.9)	-	-
Female, n %		48 (96)	4 (22.2)	<0.0001
Marital status, n %	Single	10 (20)	2 (11.1)	.265
	Married	27 (54)	15 (83.3)	
	Divorced	10 (20)	1 (5.6)	
	Widowed	2 (4)	0 (0)	
	Unknown	1 (2)	0 (0)	
Education level	No degree-level	6 (12)	2 (11)	.756
	At degree-level or above	44 (88)	16 (89)	
Work status, %	Working/Not working	42/58	50/50	.558
Work-time (Full/Part-time), %		28/72	78/22	.708
Smoking, n %		0 (0)	2 (11)	.017
Alcohol, n %		23 (46)	14 (78)	.020
Ethnicity, n %	British White	35 (70)	17 (94.4)	.404
	Other White	5 (10)	0 (0)	
	Indian	4 (8)	1 (5.6)	
	Black Caribbean	2 (4)	0 (0)	
	Pakistani	1 (2)	0 (0)	
	Other ethnicity	3 (6)	0 (0)	
Disease subtype, n %	Diffuse cutaneous SSc	24 (48)	-	-
	Limited cutaneous SSc	13 (26)	-	-
	Mixed/Overlap SSc	6 (12)	-	-
	Unknown	7 (14)	-	-

3.2 Perceived general health status

When asked about current general health status, 46% of patients with SSc reported having fair general health status while others 14% reported having health status as

bad to very bad. Only 40% of patients reported that they considered their health status to be good or very good. In contrast, 14 of 18 (78%) partners expressing having a good to fair general health status with 16.7% reported having very good health status, and only 5.6% reported having bad general health status. A continuity corrected *p*-value for perceived general health status indicates that there was no statistically significant difference between the two groups ($P < 0.05$), (Table 3.2).

86% of patients reported that SSc had affected their general health, while 72.2% of partners have reported that they believed that SSc has negatively affected their partner's general health (Table 3.3).

Table 3.2 Perceived general health status for patients and partners/relatives

General health status	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
Very good	5 (10)	3 (16.7)	.187
Good	15 (30)	7 (38.9)	
Fair	23 (46)	7 (38.9)	
Bad	5 (10)	1 (5.6)	
Very bad	2 (4)	-	

Table 3.3 Perceived influence of systemic sclerosis on patients' general health

	Patient group, n (%)	Partner/relative group, n (%)
Yes	43 (86)	13 (72.2)
No	7 (14)	5 (27.8)

3.3 Orofacial features

The orofacial features reported by the patients with SSc in their own words by choosing it from a list (as shown in Table 3.4). The SSc participants had higher scores than partners for all orofacial manifestations related to SSc except for bleeding and recession of gums. 48% (*P* = .001) of the SSc participants reported experience of facial skin tightness and telangiectasia, 44% (*P* = .003) reported having dysphagia, 42% (*P* = .005) reported having microstomia.

Table 3.4 Orofacial features related to systemic sclerosis that experienced by patients (n=50) and partners/relatives (n = 18)

Orofacial features	SSc subjects, %	Partners/relatives, %	*P*-value
Microstomia	42	5.6	.005
Bleeding/recession gums	32	50	.174
Loose/mobile teeth	30	22.2	.528
Loose/mobile denture	12	11.1	.920
Bruising/ulceration of the lining of the mouth (oral mucosa)	30	11.1	.113
Tightness of facial skin/oral mucosa	48	5.6	.001
Altered breath smell (halitosis)	12	0	.124
Difficult root canal treatment (endodontics)	16	0	.071
Difficulties with dental extractions	22	0	.030
Oral infection	18	16.7	.899
Speech impairment (dysarthria)	10	0	.163
Swallowing difficulty (dysphagia)	44	5.6	.003
Altered taste sensation (dysgeusia)	12	0	.124
Tongue atrophy / Ankyloses / rigidity	16	0	.071
Salivary gland swelling/hypofunction	20	5.6	.154
Facial/oral telangiectasia (pigmentation)	48	5.6	.001
Fissured/cracked lips	28	0	.012

3.4 Oral health status (function and dentition)

48% of the patient group and 33.3% of the partner/relative group reported having fair oral health status. Although 32% of patients reported having good to very good oral health status, 20% of them have reported that they had an oral health status that they considered to be bad to very bad. In contrast, 61.1% of the partner/relative group reported having good to very good oral health status while only 5.6% reported having bad oral health status. A continuity corrected p-value for the oral health status indicates that there is a statistically significant difference between the two groups ($P < 0.05$), (Table 3.5).

Table 3.5 Perceived oral health status for patients and partners

Oral health status	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
Very good	4 (8)	4 (22.2)	.018
Good	12 (24)	7 (38.9)	
Fair	24 (48)	6 (33.3)	
Bad	6 (12)	1 (5.6)	
Very bad	4 (8)	-	

Moreover, there was a significant difference between both groups when asked about current mouth problems, 70% of those with SSc reported having had problems in their mouth, while only 33.3% of partners expressing having mouth problems. 48% of the patients and 55.5% of the partner/relative group had more than 21 teeth in their mouth. Accordingly, when asked about thoughts of having any treatment needs if attending their dentists in the near future, 54% of patients reported that they thought they would need treatment while only 27.8% of the partner/relative group reported that they believed they would need treatment during next visit (Table.3.6).

Table 3.6 Presence of "mouth problems" and number of teeth reported by patients and partners

Item	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
"Mouth problems"	35 (70)	6 (33.3)	.007
More than 21 teeth	24 (48)	10 (55.5)	.738
Dental treatment needs	27 (54)	5 (27.8)	.058

3.5 Dental History, Attitude and pattern of dental attendance

96% of SSc patients and all of the partner/relative subjects were registered with a dental practitioner. There was no statistically significant difference in the proportion of dental registration between the two groups. The majority of patients with SSc 80% were registered with a National Health Service (NHS) dental practice; 10% attended NHS dental clinics with a private dental service, while a small group attended hospital dental care and private dental clinics respectively (8%, 2%). In the partner/relative group, 61.1% attended an NHS dental practice, 11.1% attended NHS dental clinics with a private dental service, and 27.8% were registered with a private dental service (Table 3.7).

The frequency of dental attendance and the reasons for recent dental attendance are summarised in Tables 3.8 and 3.9. The most commonly cited reason for the last dental visit in both patients and partner/relative subjects was for a routine dental check-up (62% in SSc group and 72.2% in the partner/relative group), although twice as many patients with SSc as other participants did cite that they had "problems with the mouth" (70% vs 33.3%).

The frequency of dental attendance is summarised in Table 9. For patients with SSc and control subjects, the greatest frequency of visiting dentists was between 1 month to 6 months. In SSc group, 16% reported that they had attended a dentist within the

last year. In the partner/relative group, 11.1% reported that they attended a dentist within the last year. 6% of the SSc group reported that they only attended a dentist when having trouble with their teeth as compared to 5.6% in the partner/relative group. There was no significant difference in the pattern of attendance between the two groups.

Table 3.7 Dental registration status of patients with systemic sclerosis and partner/relative group

Item	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
Registered with a dentist	48 (96)	18 (100)	.393
Private dental care	1 (2)	5 (27.8)	.891
NHS dental care	40 (80)	11 (61.1)	
NHS dental care as a private dental patient	5 (10)	2 (11.1)	
Hospital dental care	4 (8)	-	
Another type of care	-	-	

Table 3.8 Reasons for dental attendance by patients with systemic sclerosis and partner/relative group

Item	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
Routine check-up	31 (62)	13 (72.2)	.555
Emergency treatment	6 (12)	1 (5.6)	
Non-emergency treatment	13 (26)	4 (22.2)	

Table 3.9 Frequency for dental attendance by patients with systemic sclerosis and partner/relative group

Item	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
Once every 6 months	34 (68)	15 (83.3)	.214
Once every year	8 (16)	2 (11.1)	
Once every two years	5 (10)	-	
Less than every 2 years	-	-	
Only when having trouble with my teeth	3 (6)	1 (5.6)	

3.6 Access to dental care

Different measures have been reported from patients and partner/relative groups when travelling to obtain dental care from their dental health care providers. Although the majority of the patients were using private transportation when travelling to their dentist, 24% thought that they do require someone to assist them while travelling to their dentist hence 42% of SSc patients and 27.8% of partner/relative group believe that access to dental care could be improved (Table 3.10).

Table 3.10 Distance travelled to obtain dental care

Item	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
1-4 miles	31 (62)	12 (66.7)	.892
5-9 miles	10 (20)	3 (16.7)	
10-19 miles	5 (10)	1 (5.6)	
20-39 miles	2 (4)	-	
More than 40 miles	2 (4)	2 (11.1)	
Way of travel to the dentist			
Public transport	18 (36)	2 (11.1)	.035
Private transport	32 (64)	16 (88.9)	
Need for assistant travelling to the dentist	12 (24)	-	.023
Believe that access to dental care could be improved	21 (42)	5 (27.8)	.215

Patients with SSc seemed to have had more difficulties in registering with dental care (16%) compared to the partner/relative group (5.6%), and similarly, the SSc group had had more difficulties in obtaining dental care in the past 5 years than their partners (20% vs 5.6%), nevertheless, while there was no statistically significant difference in individuals with SSc and their partners in obtaining dental care in the last 5 years, 24% of the patient group and 27.8% of their partners believed that their SSc had influenced the availability of dental care for them or affected the ability to receive dental care (Table 3.11).

Table 3.11 Frequency in perceived difficulties in accessing dental care

Item	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
Have difficulty in registering with GDP	8 (16)	1 (5.6)	.266
Have difficulty in obtaining dental care	10 (20)	1 (5.6)	.157
Believe that SSc influenced dental care	12 (24)	5 (27.8)	

Patients provided written reasons as to why SSc had affected their ability to attend a dentist in the last two years and why they might search for another dental care provider, the most common reasons being summarised in Tables 3.12 and 3.13.

Table 3.12 Reasons not been to the dentist in the last 2 years

Item	Patient group, n (%)
Difficult to get to the dentist	16 (32)
Have had bad experience with a dentist	10 (20)
Don't see the point in going to the dentist	1 (2)
Cannot find a NHS dentist	6 (12)
Cannot afford the NHS charges	1 (2)
Afraid of going to the dentist	6 (12)
Have not got time to go to the dentist	1 (2)
Other reasons	9 (18)

Table 3.13 Reasons for searching for another dental care provider

Item	Patient group, n (%)
Lack of availability of private dentist	8 (16)
Lack of availability of NHS dentist	13 (26)
Better quality of care	13 (26)
More accessible location	2 (4)
Lower waiting times	3 (6)
Better reputation	4 (8)
More specialised dentist	3 (6)
Affordability	2 (4)
No reason	2 (4)

3.7 Oral Hygiene and behaviour

Table 3.14 details the regular hygiene, the source and frequency of professional oral hygiene received by both groups. 76% of the SSc patient group and 66.7% of the partner/relative group reported that they received regular oral hygiene. Both groups received their oral hygiene (e.g. “scale and polish”) by a dentist or a dental hygienist equally. Both groups reported the frequency of oral hygiene to be mainly either 1 - 6 months or 6 months – 1 year. The t-test result showed the *P*-value to be = 0 .036, which suggests that the SSc group received hygiene therapy more frequently than their partners.

Table 3.14 Professional oral hygiene received for patients with systemic sclerosis and partners

Item	Patient group, n (%)	Partner/relative group, n (%)	*P*-value
Having regular oral hygiene care	38 (76)	12 (66.7)	.392
Source of oral hygiene care			
Dentist	16 (42)	5 (42)	.158
Dental therapist	-	-	
Dental hygienist	22 (58)	7 (58)	
Frequency of oral hygiene care			
Once every 6 months	20 (52.6)	8 (66.6)	.036
Once every year	14 (28)	2 (16.6)	
Once every 2 years	2 (4)	2 (16.6)	
Less than every 2 years	1 (2)	-	
Only when having trouble with my teeth	1 (2)	-	

52% of patients reported having difficulties in being able to maintain oral hygiene, the main cited reasons being manual dexterity problems (e.g. cannot hold floss nor interdental brushes or use a normal toothbrush). 44% of SSc patients and 66.7% of their partners reported that inter-dental flossing was the most difficult aspect of oral

hygiene procedures followed by using interdental brushes and toothbrushes (Table 3.15). 56% of the patients believed that their condition had affected the way in which they perform oral hygiene while 55.6% of their partners believed that SSc adversely affected the ability of their partners to perform oral hygiene (data not shown).

Table 3.15 Reported difficulties in performing oral hygiene care

Item	Patient group, n (%)	Partner/relative group, n (%)
Have difficulty performing oral hygiene, n %	26 (52)	-
Brushing	14 (28)	2 (11.1)
Flossing	22 (44)	12 (66.7)
Interdental brushes	14 (28)	3 (22.2)

3.8 Additional comments provided by patients

The final part of the questionnaire allowed patients or their partners/relatives to provide any additional comments/information that was relevant to dental care or oral health. Twenty-eight patients (56%) provided an opinion, of which 35.7% reported having had orofacial symptoms (e.g. gingival bleeding and recession, limited mouth opening, sore and dry mouth, teeth decay and mobility, ulcers related to the faulty prosthesis and chronic cheek and tongue biting, TMJ disorder and muscle pain). Moreover, 35.7% indicated that they faced difficulties accessing dental care services while 32.1% reported they were concerned about the lack of the appropriate level of knowledge of dentists regarding their conditions indicating that they sometimes felt neglected. Fortunately, 17.8% of the patients were attending Eastman Dental Hospital for receiving dental care and were happy and feeling satisfied with the level of care and treatment provided. Finally, 32.1% of patients expressed worries about their future dental needs and where to seek treatment in emergency situations.

3.9 Comparison to MORI study 2009 and ADHS 2009

Access to NHS dentistry is an issue in the UK, and it is even harder for those with a complex medical history, with a mental or physical disability to access NHS dentistry for various reasons. A survey on access to NHS dentistry was conducted by Ipsos MORI on behalf of the Citizens Advice Bureau between 7th to 13th of December 2007; the survey interviewed 1813 adults aged 15 and over throughout England and Wales (MORI, 2008). It highlighted significant problems accessing NHS dentistry. 34% of participants indicated that they had not been to a dentist for the last three years. The most common reasons given were 'lack of access to an NHS dentist' (31%) and 'not needing treatment' (30%). Amongst those who had attended a dentist, 64% had NHS treatment, and 31% had private treatment.

The registration status with a dentist and the source of dental treatment provided for patients and partners/relatives were compared with the Access to NHS dentistry study 2008 that was conducted by MORI for Citizens Advice Bureau. There was no statistically significant difference between the present SSc patients and their partners in dental registration (P=0.393), indeed more of the SSc patients and their partners were registered with a dentist (96-100%) than that in the MORI group study (65%). There was no statistically significant difference between the two groups as both SSc patients and the partner/relative group in the type of dental service provider (P = .891). However, amongst all participants (this study or MORI) NHS services were the most common providers of dental care (Table 3.16).

Table 3.16 Access to dental services by patients with systemic sclerosis and partner/relative group compared to the MORI 2008 study

Item	Patients group, n (%)	Partner/relative group, n (%)	MORI study, n (%)
Registered with dentists			
Yes	48 (96)	18 (100)	1178 (65)
No	2 (2)	-	616 (34)
No answer/ Don't know	-	-	19 (1)
Type of dental service provider			
NHS	40 (80)	11 (61.1)	710 (64)
Private	1 (2)	5 (27.8)	334 (31)
Both/ don´t know	5 (10)	2 (11.1)	56 (5)

The Adult Dental Health Survey (ADHS) was the fifth in a series of national dental surveys that have been carried out every decade since 1968. The ADHS 2009 is the latest survey, which was conducted by the Office for National Statistics (ONS) on behalf of the National Health System (NHS) between 1st to 31st of December 2009; the survey interviewed 5,622 adults who were included in final examination and data was published on 24 March 2011 (ADHS, 2009). The survey collected information about the condition of adults' teeth and dental hygiene and investigated dental experiences, knowledge of and attitudes towards dental care and oral hygiene for the whole UK.

Table 3.17 illustrates the comparison of the reported dentate status, the frequency of routine dental check-up and dental visits between the individuals with SSc, their partner/relatives and the Adult Dental Health Survey 2009. 48% of SSc individuals and 55.5% of the partner/relative group reported having more than 21 teeth as compared to 86% in the Adult Dental Health Survey 2009. With regards to routine dental check-up visits, 62% of SSc individuals attended their dental service for routine check-up appointments as compared to 72.2% of their partners and 61% of the individuals who reported in the in Adult Dental Health Survey 2009. However, the time frame of the

routine check-up was not detailed either by the participants in the study group or the Adult Dental Health Survey 2009.

Furthermore, 68% of SSc individuals and 83.3% of the partners attended their dental service between 1 and 6 months as compared to 49% reported in the Adult Dental Health Survey 2009. 16% of SSc individuals, 11.1% of the partners attended their dental service between 6 months and 1 year as compared to 21% reported in the Adult Dental Health Survey 2009 (Table 3.17).

Table 3.17 Dentate status, Frequency of routine dental check-up and dental visits for patients with systemic sclerosis, their partners in this study compared to the Adult Dental Health Survey of 2009

Item	Patient group, n (%)	Partner/relative group, n (%)	ADHS data, (%)
Number of teeth			
More than 21 teeth	24 (48)	10 (55.5)	(86)
Frequency of routine dental check-up			
Routine check-up	31 (62)	13 (72.2)	(61)
Frequency of Dental visits			
1-6 months	34 (68)	15 (83.3)	(49)
6 months-1 year	8 (16)	2 (11.1)	(21)

4 Discussion

Systemic sclerosis (SSc) can give rise to a number of oral problems as a consequence of the disease (Hughes and Herrick, 2012, Desbois and Cacoub, 2016), thus an individual could potentially experience difficulties in access to dentistry as a result of dentists either being unfamiliar with SSc or concerned about their ability to provide oral care for patients with severe disease (Leader et al., 2014, Willems et al., 2015a). Although there are no studies to confirm this, it might be expected that people with SSc may encounter difficulties in accessing dental health care services. Individuals with SSc may have impaired mobility and they may depend on others to travel for hospital and dental appointments (Liem et al., 2017). The multisystem involvement of the disease may affect an individual's prioritisation of dental care and regular dental attendance. The emotional effect of the disease along with fear, embarrassment, poverty and fear of prejudice could also be significant barriers to accessing dental care (Yuen et al., 2014a, Kwakkenbos et al., 2015, Mouthon et al., 2017). Lack of suitable dental service provision could be a barrier to access. The dentist or dental team may be unwilling to treat challenging disease (Leader et al., 2014). However, the provision of special care dentistry services in the community dental service could lessen any inequality to dental care. Since the implementation of the Disability Discrimination Act 2005, the service providers have had to make reasonable adjustments in their premises to remove physical barriers stopping or impeding disabled access and increased provision of domiciliary care.

By virtue of its many effects upon the skin, viscera and mouth, SSc has the potential to adversely impact upon the oral health of and delivery of dental health care to affected individuals (Alantar et al., 2011). The present study sought to explore the implications of SSc upon the oral health and provision of dental care in a large group

of patients who have the likely diagnosis of SSc and are living in the UK. The present study is, of course, limited by the fact that no detailed oral and/or systemic examination was undertaken to confirm that all of the participants with SSc were indeed affected by this disorder and had relevant orofacial features, hence there is only a presumption that all do have SSc. Nevertheless, as is evident from the results, in which many of the participants report oral features such as limited mouth opening and tightness of facial skin, it would seem that these individuals are likely to have SSc-like disease.

The present group of participants comprised 50 individuals with different types of SSc and 18 partners or relatives who were either attending a national patient group (scleroderma society) or a nationally recognised clinic (Rheumatology clinic – Royal Free Hospital – London) for the management of SSc and thus represents the largest group of UK patients of SSc to have ever been asked about aspects of their oral health or their experience of UK dentistry. As patients were all adults and had had the diagnosis of SSc for a mean time of over 13 years with this ranging from less than one year to more than forty years, it is likely that the opinions of this group are valid.

Despite all the limitations, this study provides a snapshot of the perceived oral health problems and oral health care experience of a large number of individuals with SSc and indeed represents the first such investigation of its type in the UK.

The sample included adult patients and their partners/relatives who were able to speak and comprehend English and to complete the provided questionnaires. The study group had a greater proportion of females (96%) than that of males (4%) which are consistent with the previous reports such as the research carried out by Hughes and Herrick in 2012, suggesting the 8:3 female predominance of SSc (Hughes and Herrick, 2012). The ethnicity distribution of the study group was predominantly White British in contrast to several studies which have shown higher incidence of SSc in black

populations in American, French and other European population samples along with the reported high prevalence of SSc in Caucasians (Nashid et al., 2011, Silver et al., 2012, Gelber et al., 2013, Yuen et al., 2014a).

The geographic region of residence of individuals with SSc was mainly London in contrast to a study done by Allcock et al. in 2004 had reported that in the United Kingdom, SSc appears to be more common in the northeast of England (Allcock et al., 2004). Although many participants come from London, the patients were resident in all parts of England (data not shown) thus this does allow some broad comparisons to be made with the last Adult Dental Health Survey of England (ADHS 2009) and the Access to NHS dentistry study 2008 that was conducted by MORI for Citizens Advice Bureau (MORI 2008). However, no attempts have been made to examine deprivation scores of the patients or partners.

In view of the impact of SSc upon health, it might have been expected that patients could have encountered difficulties in accessing dental care services. However, access to oral health care services was higher in a sample of patients with SSc and partners as compared to the MORI study. The majority of patients (96%) and all partners were registered with a dentist as compared to MORI 2008 figures, 65% of people were registered with a dentist. In the SSc group, this could be due to the fact participants of this study were members of the Scleroderma Society, which provides a detailed information leaflet on dental care for individuals with SSc. Therefore, the high percentage of registration with a dentist could be a result of the sample group being aware of the importance of oral health.

The most commonly reported type of service was NHS dental services, with 80% of patients with SSc and 61.1% of their partners compared to data obtained from the MORI study (64%). However, paid for NHS dental care was reported as the third most

common service by partners of people with SSc (11.1%). Data obtained from the ADHS 2009 indicated that 70% of the dentate adults who participated attend to paid NHS dental service (45%) and free NHS dental service (25%) (data not shown).

Private dental care was reported by only 10% of patients with SSc, 27.8% of their partner as compared to the MORI study 2008, which showed 31% had access to private dental service. Hence patients with SSc would seem to access dental services with the same general pattern as those of their partners. Only 2% of the patient group was not registered with a dentist as compared to 34 % as indicated in the MORI study. Most of the patient group in this study had access to NHS dentist (80%). 2% received private dental care, none were registered with another type of dental care such as community dental service, and 8% received their dental care from hospital dental care. The most commonly used dental service in the partner's group was also NHS general dental practice with 61.1% registration, followed by 27.8% registration with the private dental service and none of the partner's group was registered with another type of dental care such as community dental service nor specialist hospital dental care. It is reassuring that the majority of patients were able to attend an NHS or private dental service as this presumably means that their service is local to their site of residency. The high rate of attendance at a GDP, as opposed to the other type of dental care such as community dental service and hospital dental care, may reflect the willingness of general dental practitioners to provide treatment, limited availability of community dental service or patients not having the appropriate clinical criteria for acceptance by the community dental services.

The continued provision (at least at present) of special care dentistry service in the community dental service in England and Wales and the increase in specialist training

posts in special care dentistry based both in hospital and community dental service should be able to enhance the dental health care of patients with SSc.

Both the patient and the partner groups generally attended a dentist regularly, and there was no significant difference in the frequency of attendance between the patient and the partner/relative group (68% and 83.3% respectively). However, a lower value has been reported in the Adult Dental Health Survey of 2009 (49%). The reason for regular attendance was also highlighted to be mainly for a routine dental check-up in both groups consistent with the Adult Dental Health Survey of 2009.

It would, therefore, seem that SSc does not affect the ability to attend for and receive regular dental care as confirmed by 84% of the individuals with SSc having attended a dentist in the preceding year (data not shown).

As might be expected, the dental status of patients with SSc did seem to have been consequently adversely affected. When the number of patients (48%) having more than 21 teeth was compared with either partner (55.5%) or results from the ADHS 2009 study (86%), it was evident that patients with SSc had significantly more missing teeth than the individuals of the ADHS study. It would seem that the possible difficulties in being able to maintain good oral hygiene due to their disorder resulted in these patients with SSc having a substantially increased risk of hard tissue disease of the mouth. However, the reason for loss of teeth in those with SSc could be due to a combination of inability to keep the posterior teeth cleaned by the patients themselves as indicated in the current result and previous study (Yuen et al., 2014a) and restricted mouth opening, limiting the access for dentist to provide complex restorative treatments hence causing loss of teeth. Both could have caused the prognosis of teeth to become poor.

Life expectancy, in general, is increasing in the UK, and more people are also retaining more teeth at an older age. As reported by Mayes in 2003, the life expectancy for individuals with SSc has increased in the last few decades (Mayes et al., 2003). Ionnidis et al. in 2005 conducted a meta-analysis and concluded that the risk of death was not significantly different for individuals with SSc from that for the general population in three cohorts unless there were significant internal organ involvement and anti-topoisomerase I antibodies involvement (Ioannidis et al., 2005). Hissaria et al. in 2011 conducted a retrospective analysis of clinical notes between 1993 and 2007 and reported that the mean age of death for patients with limited SSc (lcSSc) was 74.1 years, diffuse SSc (dcSSc) 62.9 years and overlap disease 57.8 years. They also report that survival has improved over the 15-year study period (Hissaria et al., 2011). However, recent studies have been reported that SSc patients have high risk of mortality as they might have survival rates 16 – 34 years less than the sex- and age-matched populations due to their active disease and other risk factors including (extensive skin disease, cardiopulmonary involvement, renal impairment, gastrointestinal involvement, older age and male gender) (Nikpour and Baron, 2014, Rubio-Rivas et al., 2014, Richard et al., 2018).

The increase in life expectancy of patients with SSc implies that the dental care demands of people with SSc are likely to increase. The present results point towards a need to ensure that the access that patients presently have to dental care is maintained and that strategies to allow patients to maintain good oral hygiene are established.

Just over 60% of those with SSc indicated that the reason for the last dental visit was for a routine check-up, although this dropped to 54% when those patients reported that they think they would need treatment if visited dentist in the near future. Almost

72.2% of the partner's group reported a check-up to be the reason for their last dental attendance. 61% of the dentate adults interviewed in the ADHS 2009 indicated that the reason for their last dental attendance was for a check-up. Thus, again the SSc group do not seem to have any different pattern of dental attendance as others without this disease.

However, while 26% of patients with SSc indicated that their last attendance was because of a treatment needed, while 22.2% of partners reported this as a reason. This does not, however, imply that SSc does necessitate more frequent dental examination or treatment sessions, as 27% of the group of ADHS 2009 participants attended when they had a dental problem.

The difficulties that patients reported in accessing dental health care in the previous 5 years did not appear to be related to SSc. Instead cited reasons included their dentist migrating to a private service, difficulties in being able to find an appropriate dental service or a lack of NHS dentist in their area of residence. Seven out of 10 (14% of the total group) who reported access difficulties did report that they believed that their dentist had a lack of knowledge of SSc and that this may have led to difficulties in receiving dental care – presumably under the NHS. Three out of 10 (6% of the total group) cited failed treatment as an indication of lack of access, but this seems contradictory as they must already have received dental care (data not shown).

It would thus seem that patients with SSc do not encounter significant difficulties in obtaining regular dental care, as confirmed by 84% having attended a dentist in the year preceding the study. Furthermore, although the partner/relative group comprised fewer individuals to that of the SSc group, there were no significant differences in the trends with regard to the type of dental service attended or recent attendance patterns between the two groups. The present data indicate that SSc does not impact

significantly upon access to dental services. When comparing these results with Ipsos MORI, Access to NHS Dentists Study (2008), patients with SSc and their partners have a higher level of registration and attendance to dental services (96%, 100%) respectively (both NHS and private) than the adults who participated in the latter study, where 65% reported having attended a dentist between April 2006 and December 2007 (a 20 month-period).

The present 24% of SSc patients who reported that SSc may have affected the availability of dental care for them cited reasons such as lack of understanding or knowledge about SSc by dentists, psychological barriers (e.g. previous bad experience with a dentist and feeling afraid of going to the dentist), difficulties in access (e.g. physical limitations, cost), oral complications of SSc (limited mouth opening, fatigue, pain and TMJ dysfunction) and the need to migrate to a private dentist. Seventy-two per cent of the partners or relatives of SSc patients did not believe the disease has influenced the availability of dental care for individuals with SSc. Those who reported patients with SSc having difficulties indicated the same reasons as the patient group: lack of understanding or knowledge about SSc by dentists, difficulties in access, oral complications of SSc and the need to migrate to a private dentist or referred to hospital dental services with the long waiting time.

Despite first being described over 100 years ago, this continues to be an unknown disorder for a considerable number of healthcare workers, due perhaps to its low prevalence. There would seem to be a need to enhance the knowledge of dental care workers on relevant aspects of SSc to perhaps lessen the risk of patients (all be it a small group) with SSc being unable to access dental care services.

Pokrajac-Zirojevic, Slack-Smith and Booth (2002) investigated the level of dental attendance in a Rheumatoid arthritis (RA) and Osteoarthritis (OA) population

(Pokrajac-Zirojevic et al., 2002). They reported that 41% of patients with RA (51.1% of non-RA subjects) and 42% of OA patients (51.3% of non-arthritic individuals) visited a dentist during a previous 12 months period. These figures are lower than those of the present group of SSc patients (84%) and their partners (94.4%). The main finding reported by Pokrajac-Zirojevic, Slack-Smith and Booth (2002) was that chronic diseases affect dental attendance; however, this does not seem to be necessarily the case for individuals with SSc.

There are no published reports concerning the ability to attend a dental service in relation to SSc. The present data indicate that SSc does not significantly influence the ability to attend a dental practice, but this does not imply that all patients do not encounter difficulties.

The maintenance of good oral hygiene is a fundamental component of oral disease prevention in all groups of individuals (Yuen et al., 2014a). 76% of the SSc group and 66.7% of the partner/relative group reported regular oral hygiene care was provided by their dental service provider. This could suggest that the dental health provider and the patient group are aware of the implications of SSc upon their mouths. However, as 24% of patients did not receive regular oral hygiene care, there is a concern that they will be at risk of caries and periodontal disease especially if they also have secondary Sjogren's syndrome (Chu et al., 2011, Baron et al., 2015b).

76% of SSc individuals and 72.2% of the partners reported that SSc did not have an adverse effect on the availability of dental care. Only 24% of individuals with SSc believed that SSc had adversely influenced the availability of dental care as compared to 27.8% in the partner/relative group. The present data indicate that there is no significant impact of SSc upon access to dental services. However, the reason for the lack of availability even in the small group could be due to restricted mouth opening,

a dentist's lack of experience in dealing with SSc and patient's own reluctance to attend dental service due to physical disabilities.

There is an obligation for a special care dentist to understand the attitudinal barriers people can encounter and are expected to demonstrate an appropriate level of disability etiquette. This has been established to ensure that the clinical care of people with a medical or physical disability is carried out with a progressive and positive approach to their disability-related issues. The findings of the present study indicate that patients with SSc are only sometimes encountering some difficulties in receiving dental care, nevertheless, there do seem to remain some barriers to be overcome.

52% of the patients with SSc considered that their oral hygiene technique was adversely affected by SSc involvement of hands and fingers. Problems such as hand pain, sclerodactyly, Raynaud's phenomena, digital ulceration and loss of manual dexterity necessary for different methods of oral hygiene (flossing, use of a manual toothbrush or interdental brushes) were reported by patients with SSc. A direct relationship between reduced manual dexterity and an inability to maintain oral care has previously been reported (Felder et al., 1994, Yuen et al., 2014a) hence the present results are of concern as it may be that patients with SSc may be prone to develop plaque-related oral diseases such as caries or periodontal disease as a consequence of difficulties in oral hygiene procedures.

Although other non-orofacial disease features were not evaluated in this study, about 44% of patients with SSc indicated that the most difficult aspect of oral hygiene procedure was related to interdental flossing hence this might be due to the disease-related disorders of the hands (e.g. sclerodactyly, Raynaud's phenomena, digital ulceration and reduced manual dexterity). Patients with SSc (32%) reported that periodontal problems such as gingival bleeding and recession might affect their ability

to maintain an effective oral hygiene, however, periodontal involvement may be affected if a patient does not carry out or cannot undertake an effective oral hygiene technique (Fischer and Patton, 2000, Poole et al., 2013, Yuen et al., 2014b, Baron et al., 2015a). Dentists and dental hygienists should thus consider educating patients on an appropriate method of oral hygiene and should explain that there is always an implicit risk of periodontal problems due to the associated poor oral hygiene status.

52% of individuals with SSc reported that they encountered difficulty in performing oral hygiene procedures. The suggested reasons for the difficulty included tightness of skin around the mouth, difficulty in opening mouth, SSc of hands and difficulty in flossing posterior teeth. The frequency of reported limited mouth opening, tightening of skin of face and SSc of hands affecting the manual dexterity is consistent with the previous literature by others (Wood and Lee, 1988, Fischer and Patton, 2000, Poole et al., 2004, Chu et al., 2011, Baron et al., 2014, Elimelech et al., 2015). There is thus a need to develop strategies that will ensure that patients with SSc are able to maintain an efficient standard of oral hygiene. Such a strategy/protocol should be patient-driven to ensure that their opinions are acknowledged, for example, developing a simple method of interdental cleaning.

Limited mouth opening and tightness of the facial skin were the most commonly cited perceived oral manifestation in the SSc group 42% and 48% respectively. This is consistent with the literature in which it is indicated that approximately 52-80% of individuals with SSc have orofacial involvement and the most striking feature to be fibrosis of the facial skin (Marmary et al., 1981, Fischer and Patton, 2000, Bajraktari et al., 2015).

20% of individuals reported the presence of dry mouth, the cause of this is unclear. The study did not include any oral examination nor a reference to the patient's medical

history. However, if the patients do indeed have salivary gland dysfunction, there will be a need for them to maintain low levels of plaque to lessen any risk of caries or gingivitis (Wolff et al., 2012, Gyger and Baron, 2015).

Oral ulceration was reported by 30% of the SSc individuals as an oral manifestation of the disease. This might reflect anaemia due to gastrointestinal involvement of SSc, pernicious anaemia, pancreatic insufficiency or as an adverse side effect of therapeutics (Alantar et al., 2011, Baron et al., 2015b). Oral ulceration in the oral cavity has also been reported due to changes in collagen structure in the mucous membrane, making them thin and prone to ulceration (Fischer and Patton, 2000, Elimelech et al., 2015, Mawardi et al., 2016). The patients in this study have also reported limited tongue movement to be one of their main oral manifestations of SSc (16%) which is also consistent with the previous literature as SSc can cause the tongue to become fibrotic and have reduced mobility (Fischer and Patton, 2000, Vitali et al., 2015).

With regard to other Connective Tissues Disorders (CTDs), although perhaps at the other extreme of mobility patients with Ehlers-Danlos Syndrome (EDS) have reported difficulties in the maintenance of oral hygiene care (De Coster et al., 2005, Abel and Carrasco, 2006). While the hypermobility and involvement of different joints (e.g. wrists, elbows or shoulders) may compromise oral hygiene care by patients. (Poole et al., 2004), suggested a series of measures to enable individuals with CTDs to maintain good oral hygiene, for example, the toothbrush should have handles with a thumb stop and soft rubber inserts, to provide a good grip and effective control. A small head and soft bristles may also aid plaque removal. When a manual toothbrush cannot be easily used, an electric toothbrush is advisable. Large diameter floss may be used to easily allow cleaning of interdental areas.

Poole et al. (2010) developed an intervention programme for patients with SSc, involving a dental examination, analysis of upper extremity functioning and a home programme with patient education on brushing and flossing methods, hand and facial exercises, adapted dental appliances and supplementation of dental products. The researchers found that such a regimen improved the oral hygiene and periodontal status of patients with SSc. It would thus seem logical that an appropriate patient guidance “kit” be developed for the oral hygiene care of patients with CTDs. Of course, this will require the active participation of patients in the developing of the “kit” (Poole et al., 2010). Hence, Patients’ education and advice should be detailed regarding the associated risk factors of the disease and the importance of maintaining preventative measures with consideration of manual dexterity as a major limitation among SSc population and the need to implement other therapeutic modalities such as connective tissue massage, joint mobilisation, fingers stretching exercise, manual lymph drainage of the hands and ultrasound therapy (Maddali Bongi et al., 2009, Poole et al., 2013, Willems et al., 2015b, Thuraisingham and Sinniah, 2016).

SSc can give rise to a range of orofacial manifestations. Most will be obvious signs or symptoms, although features such as the widening of periodontal space ligament (PDL) are unlikely to give rise to symptoms (Baron et al., 2015a). The present group of patients with SSc reported tightness of facial skin and/or oral mucosa and facial and/or oral telangiectasia (48%), swallowing difficulty (44%), microstomia (42%) and gingival recession and bleeding (32%) to be their most common orofacial concerns. These common self-reported features accord with those expected orofacial manifestations of SSc, however, gingival involvement is probably more likely to be due to plaque-related gingivitis rather than directly the consequence of SSc (Baron et al., 2015a). Some of the other reported features may reflect xerostomia (e.g. loose

denture, oral infection, halitosis, dysphagia, mucosal soreness and cracked lips) but it is of interest to note that despite 48% of patients having tightness of facial skin and/or oral mucosa and 42% having microstomia, only 10% of the patients reported symptoms of possible dysarthria (e.g. chewing difficulties and/or speech impairment).

Of note, 24% of SSc patients who reported that SSc might have affected the availability of dental care have cited that they had had difficulties with past therapeutic dental procedures such as failure of endodontic therapy (16%). However, as expected having, for example, a severe degree of reduced mouth opening might be challenging for dentists to carry out different types of dental interventions, without a more detailed history it is not possible to determine how real this was and what the precise causes were for the failure of endodontic therapy. However, as dental root abnormalities (e.g. calcification, resorption, dilacerations and underdevelopment) are dental features of SSc, it might not be unexpected for these to compromise dental treatment outcome such as in endodontic therapy (de Figueiredo et al., 2008, Trainito et al., 2012, Jung et al., 2013).

Many patients with SSc commented that they felt misunderstood by health care workers in terms of their general pain or physical difficulties which arise as a consequence of SSc. A considerable number (32.1%) indicated that they were depressed due to lack of understanding by dental staff about their condition. Other concerns have been reported such as difficulties to find a dentist or the need to travel long distances to attend a dental clinic, worries about their future dental needs and where to seek treatments in emergency situations. Some reported being concerned that they would have to keep their mouths open for long periods despite having significantly limited mouth opening and/or facial skin tightness. It seemed that some

patients were angry about issues related to dentistry, particularly if they had been “rejected” because of the SSc. While this study did not explore the psychological impact of dentistry upon SSc (or vice versa), it is known that patients with SSc have psychological upset, such as mild to moderate levels of anxiety, depression or anger (Almeida et al., 2015). Regardless of the possible psychological implications of dentistry and SSc, it is important that all workers of the dental team demonstrate empathy and understanding concerning the problems that SSc will cause for affected individuals (Delisle et al., 2018). It is important to note that only 17.8% of the present group of patients, indicated they had been treated by a “good dentist” with an awareness of SSc.

The majority of patients with systemic sclerosis who participated in this study were registered with a dentist, and the main provider service they attend is an NHS dental service. The majority of patients did not believe that their disease has influenced the availability of dental care for them, nor their ability to attend dental services, however, they have encountered slightly fewer difficulties in obtaining dental care in the past 5 years than their partners/relatives believed that they had. Patients with SSc indicated that a lack of understanding or knowledge about SSc by dentists is one of the difficulties they have encountered when attending a dental service.

Individuals with SSc have encountered problems when performing oral hygiene, interdental cleaning being the most challenging aspect of this. The most common orofacial features reported by patients were the tightness of facial skin and/or oral mucosa and facial and/or oral telangiectasia, swallowing difficulty, microstomia and gingival recession and bleeding. Patients reported having had a bad experience with

dental services that sometimes might be related to difficulties with past therapeutic dental procedures and a high rate of unsuccessful outcomes.

Although this study is limited by lack of definitive diagnosis of SSc and that all participants were not examined clinically, the relatively high numbers of participants and generally strong trends would suggest that SSc can adversely impact upon oral health and the provision of oral health care to affected individuals. A much more detailed study is warranted to confirm the present observations, but there is perhaps sufficient evidence to consider developing a specific tool to provide patients with appropriate information and skills to maintain good oral hygiene, thereby hopefully reducing the risk of common, usually plaque-related, oral disease.

5 Conclusion

Although the present study is limited by its cross-section design, the current results suggest that oral health care providers can learn from our findings and benefit from routine assessment of patients with SSc to develop and evolve support regarding their oral health care needs. It is evident that although uncommon, SSc has the potential to adversely affect oral function and compromise access to and the delivery of oral health care. To date, there remains no study that describes the impact of SSc upon access to dentistry in the UK.

This is the first study to show the perceived oral implications and access to dental care service SSc patients as compared to their partners. Despite the SSc, most of the individuals were able to access NHS dentists. The main oral implications of the SSc were tightness and telangiectasia of facial skin and oral mucosa, dysphagia and microstomia. The oral hygiene procedures which individuals with SSc find difficult were brushing and flossing especially of posterior teeth. Almost half of the individuals with SSc have reported having more than 21 teeth in the mouth. The increase in life expectancy of patients with SSc implies that the dental care demands of people with SSc are likely to increase. The present results point towards a need to ensure that the access that patients presently have to dental care is maintained and improved and that strategies to allow patients to maintain good oral hygiene are established.

This study has indicated that access to dental health care is not greatly affected by SSc. However, patients with SSc may experience the expected oral consequences of SSc and can have difficulties in maintaining effective oral hygiene. There is a need to extend this work to determine more precisely the impact of SSc upon oral health, to elucidate the influence of SSc upon the quality of life of people with SSc and to develop simple patient-centred protocols for oral self-care.

CHAPTER 4: Web-based information on the treatment of the mouth in systemic sclerosis

1 Introduction

As detailed in chapter 1, although rare, systemic sclerosis (SSc), can give rise to a wide spectrum of manifestations that affect the skin and internal organs that may negatively impact upon a patient's quality of life (Almeida et al., 2015). The extra-oral and intra-oral manifestations of SSc can be challenging to manage effectively and can limit oral function, negatively impact upon facial aesthetics and adversely affects a patients' emotional and social life (Marmary et al., 1981, Nagy et al., 1994, Alantar et al., 2011, Kwakkenbos et al., 2015).

The recent emphasis on shared decision making in a clinical setting places increased importance upon patient education (Powell et al., 2011, Lee et al., 2014). To effectively participate in clinical decisions regarding their healthcare patients need to be familiar with the risks and benefits of treatment options being considered (Eysenbach and Kohler, 2003, Andreassen et al., 2007, Trotter and Morgan, 2008). The Worldwide Web is considered one of the most rapidly growing sources of healthcare information and patient self-education. Although such online information is easily accessible and plentiful, there are concerns regarding the poor quality, inaccuracy and difficult readability of health-related information (Ni Riordain and McCreary, 2009, Dy et al., 2012). Thus, online information could be misleading or inaccurate and hence hinder informed shared clinical decision making (Murray et al., 2003, Lorence et al., 2006, Singh et al., 2012, Alcorn and Madhok, 2012). In addition, poor quality information can limit the ability of a patient with chronic illness to cope with their disease (Bremer et al., 1997, Trento et al., 2008, Alnafea et al., 2017).

Due to the chronic and variable nature of the disease, individuals with SSc are likely to require or wish to have the appropriate knowledge to help them to cope with the impairments of the disease. Individuals with oral and/or facial disease of SSc are likely to search for information concerning the features of the disease, their treatment options and perhaps the complications of therapy (Almeida et al., 2015, van der Vaart et al., 2013). There is, however, no data on how helpful online information regarding the orofacial aspects of SSc may be for patients (or carers).

The aim of the present chapter was to categorise the content and evaluate the quality and readability of the available web-based information concerning the treatment of the oral aspects of SSc.

2 Materials and Methods

2.1 Search

An online search using the most popular international search engine (Google.com) was conducted in November 2018 using three different search terms (“Treatment of the mouth in scleroderma”; “Treatment of the mouth in systemic sclerosis”; “Treatment of the mouth in scleroderma/systemic sclerosis”). The first 100 websites of each term were assessed for duplications and screened for any non-operative link. Inclusion criteria were included only unique websites in the English language relevant to the employed search terms. The following exclusion criteria were then applied; scientific articles, book reviews, websites with non-related content, non-working links, non-English language links, membership-based websites, promotional product websites, discussion groups, video feeds and online medical dictionaries.

The remaining websites were categorised as defined by Ni Riordain and McCreary (2009), based upon affiliation (commercial, non-profit organisation, university/medical centre and government), specialisation (exclusively or partly related to treatment of the mouth in scleroderma/SSc), content type (medical facts, clinical trials, question and answers and human interest stories) and content presentation (image, video and audio).

2.2 Quality assessment

The quality of the online material was assessed by two reviewers (IA and RNR) using the DISCERN instrument (Charnock et al., 1999), and the Journal of the American Medical Association (JAMA) benchmarks for website analysis (Silberg et al., 1997). The presence of the HON seal was also recorded.

The DISCERN instrument is a 16-point questionnaire developed and validated to examine the reliability of online content and its specific information on treatment options and overall quality scoring (Charnock et al., 1999). The JAMA benchmarks were used to analyse the quality of websites. These benchmarks include clarity of authorship of medical content including (authors, contributors, affiliations and relevant credentials), inclusion of attributions (references and sources), statements of disclosure (ownership, conflicts and interest) and indication of currency (dates of content posted and updates) (Silberg et al., 1997). Health on the Net (HON) is a non-profit organisation established in 1995 to guide in the evaluation of the reliability of online information and sources in the medical field. The HON seal can be displayed on websites that comply with eight elements ranging from the indication of authors' qualifications to clearly distinguishing advertising from editorial content.

2.3 Readability assessment

Readability is defined as the determination by systematic formulae of the reading comprehension level a person must possess to understand written texts (Albright et al., 1996). The readability assessment was undertaken by using the Flesch Reading Ease Score. This score is based upon a formula that incorporates the average sentence length and the average number of syllables per word and the outcome score is a number ranging from 0 to 100. The higher the score - the easier the passage is to read (Flesch, 1948). For example, Flesch Reading Ease Scores above 90 are considered easily understandable by an average 5^{th}-grade student while scores between 60 and 70 are supposed to be easily readable for 8^{th} and 9^{th}-grade students. Finally, scores less than 50 represented an academic grade level and considered as difficult level of readability.

2.4 Statistical analyses

Standard descriptive statistical analysis was performed by using SPSS (version 25) and tabulated as mean ± standard deviation of the mean.

3 Results

3.1 Available websites

The search strategy for the term “treatment of the mouth in scleroderma/systemic sclerosis” generated 432 000 websites, 440 000 websites for “treatment of the mouth in scleroderma” and 338 000 by searching “treatment of the mouth in systemic sclerosis” on the Google search engine. Of the first 300 websites of the three search terms, 105 were scientific articles, 6 were book reviews, 12 were online medical dictionaries, 34 were non-related websites, 10 were links of online discussion groups, two were commercial and 24 were duplicated (Figure 4.1). Only 107 selected websites met the inclusion criteria, however, a total of 57 unique websites remained for final review after eliminating the duplicates between the three search terms (Figure 4.2). Among these selected 57 sites, only 16 sites (28.1%) were exclusively dedicated to the treatment of the mouth in SSc.

Figure 4.1 Number of excluded websites

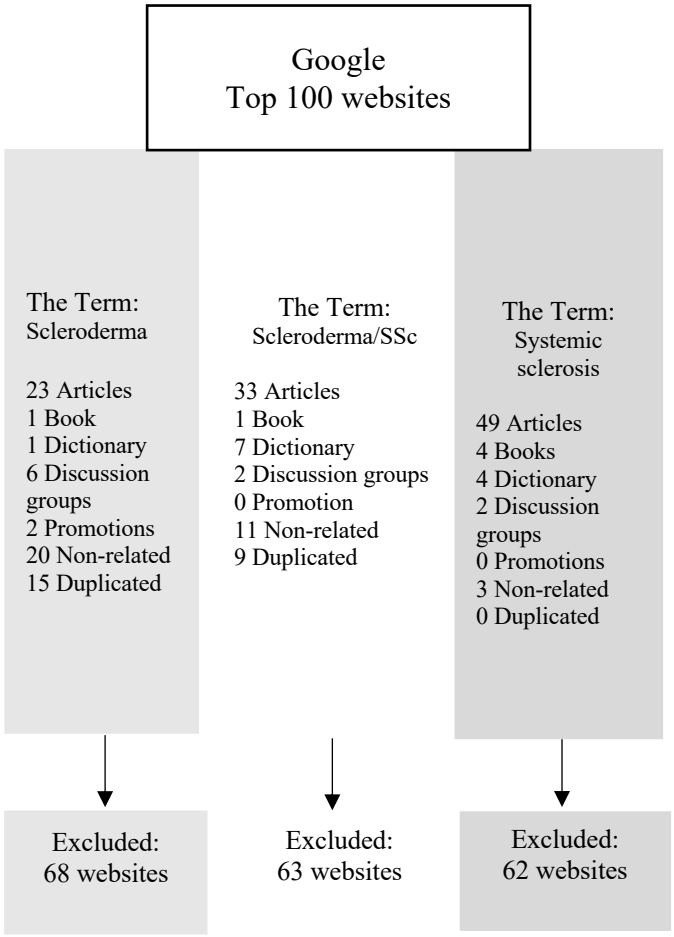
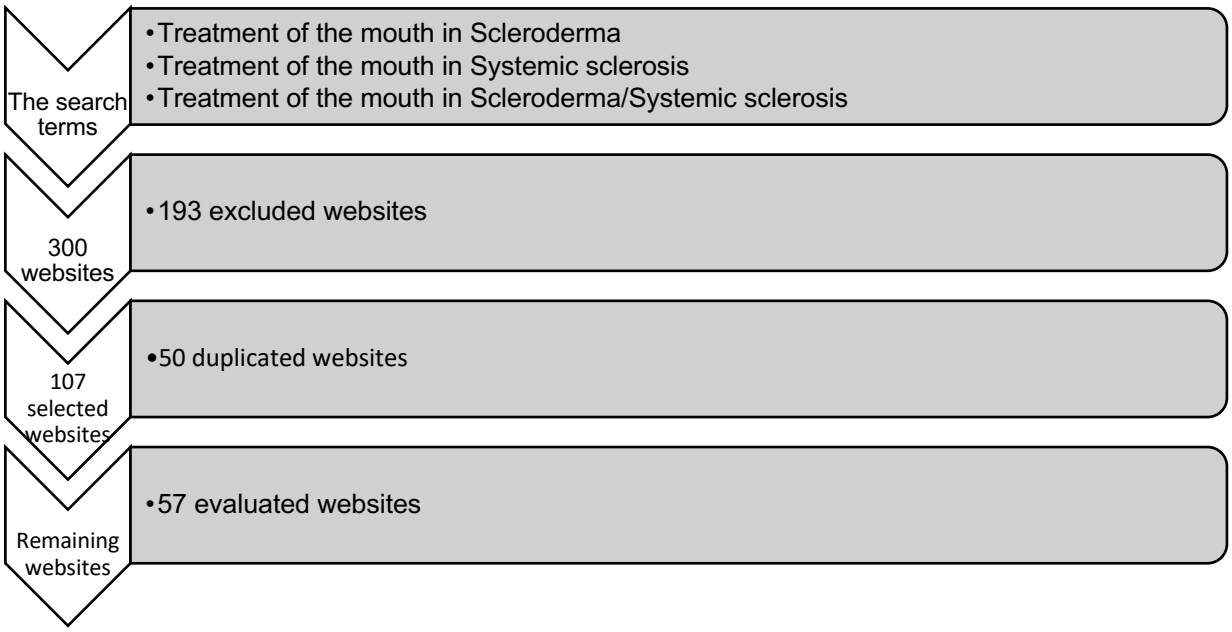


Figure 4.2 Flowchart of the sample selection strategy



Regarding the affiliation of the websites, 25 websites (43.9%) were commercial, 23 (40.4%) were non-profit websites, 5 (8.8%) were considered as governmental, and only 4 (7%) were either universities or hospitals. The majority of the websites (82.5%) included medical facts. However, 10 (17.5%) of the sites included clinical facts, 6 (10.5%) included human-interest stories, and only 5 (8.8%) included questions and answers. The content presentation varied as 17 (29.8%) websites included images, and only one website (1.8%) included an audio illustration. None of the websites included videos. (Table 4.1) provides a summary of website categorisation.

Table 4.1 Categorisation of websites based on affiliation, specialisation, content type and content presentation

Category	Criteria	Number of websites (%)
Affiliation	Commercial	25 (43.9%)
	Non-profit organisation	23 (40.4%)
	Governmental	5 (8.8%)
	University/medical centre	4 (7.0%)
Specialisation	Exclusively related to SSc	16 (28.1%)
	Partly dedicated to SSc	41 (71.9%)
Content type	Medical facts	47 (82.5%)
	Clinical trials	10 (17.5%)
	Human interest stories	6 (10.5%)
	Question and answer	5 (8.8%)
Content presentation	Image	17 (29.8%)
	Video	0 (0%)
	Audio	1 (1.8%)

3.2 Quality assessment

The mean overall DISCERN score across the 57 selected websites was 2.37 (± 1.01). No website achieved the maximum rating, and 13 (22.8%) received the minimum overall rating. The majority of the websites had scores that ranged between 2 and 3. The questions with the poorest DISCERN scores related to the effect of no treatment ("Does it describe what would happen if no treatment were used?"), additional sources of support or information ("Does it provide details of additional sources of support and information?") and the explicit date of the material published ("Is it clear when the information reported in the publication was produced?") with mean scores of 2.16 (± 0.75), 2.25 (± 1.5) and 2.26 (± 1.28) respectively (Table 4.2). Only twelve of the 57 websites (21.1%) displayed the HON seal.

Table 4.2 Means and standard deviation scores for DISCERN

Domain	DISCERN question	Mean (SD)
Reliability	Q1. Explicit aims	2.30 (±0.865)
	Q2. Aims achieved	2.74 (±0.768)
	Q3. Relevance	3.79 (±0.840)
	Q4. Explicit sources	2.46 (±1.377)
	Q5. Explicit date	2.26 (±1.289)
	Q6. Balanced and unbiased	2.61 (±0.701)
	Q7. Additional sources	2.25 (±1.550)
	Q8. Areas of uncertainty	2.74 (±0.992)
Treatment options	Q9. How treatment works	2.61 (±1.013)
	Q10. Benefits of treatment	2.72 (±1.048)
	Q11. Risk of treatment	2.39 (±0.940)
	Q12. Effects of no treatment	2.16 (±0.751)
	Q13. Effects on quality of life	2.81 (±0.953)
	Q14. All alternatives described	3.47 (±1.002)
	Q15. Shared decision	2.74 (±0.720)
Overall rating		2.37 (±1.011)

With regard to the JAMA benchmarks, the majority of the websites (71.9%) fulfilled the authorship benchmark, and nearly half of the websites (54.4%) achieved the attribution benchmark. However, only 24 (42.1%) websites achieved the currency benchmark and only 15 (26.3%) achieved the disclosure benchmark (Table 4.3).

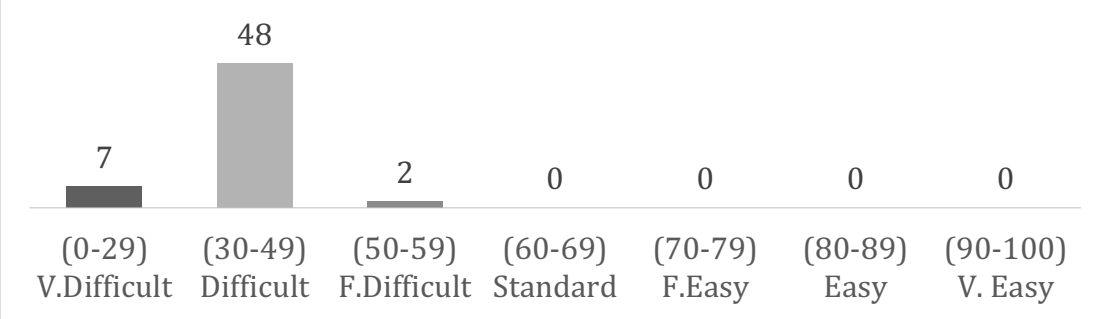
Table 4.3 Websites content based on JAMA benchmarks

JAMA benchmarks	Number	(%)
Authorship	41	71.9
Attribution	31	54.4
Disclosure	15	26.3
Currency	24	42.1

3.3 Readability

Flesch Reading Ease ratings varied from 7.48 to 54.18, with a mean total readability score of 37.5 (± 8.7). The majority of the websites (n=55) had readability levels ranging from difficult to very difficult, while only two websites had readability level as fairly difficult (Figure 4.3).

Figure 4.3 Flesch Reading Ease Score



4 Discussion

Patients with chronic diseases such as those managed in a rheumatology setting use the world wide web to seek health-related information more than other groups of patients (e.g. patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis) (Rubenzik and Derk, 2009, Schouffoer et al., 2011, Singh et al., 2012, van der Vaart et al., 2013). As systemic sclerosis is a chronic disease, which may lead to physical impairment and morbidity, patients commonly search for online information in relation to the disease itself and available therapies (Morrisroe et al., 2016). Up to 70% of patients with SSc commonly experience a broad range of symptoms of the disease such as fatigue, Raynaud's phenomenon, joint pain and muscle pain that might negatively impact upon health-related quality of life (Willems et al., 2014). In addition, SSc can give rise to a variety of orofacial features such as skin fibrosis, microstomia, increase the susceptibility to dental caries and periodontal disease, xerostomia and pathological bone resorption all of which can have a negative impact on patients' oral health-related quality of life (Baron et al., 2014). According to van der Vaart et al., about 85% of patients with SSc use the internet to seek information regarding their condition, with 58-63% of these patients searching for information specifically about treatment options and lifestyle management (van der Vaart et al., 2013). Patients with SSc use the Internet more frequently and spend more time searching for disease-related information than other patients' groups, such as those with autoimmune rheumatic diseases (Schouffoer et al., 2011, van der Vaart et al., 2013). Due to the aforementioned extensive oral and peri-oral manifestations of SSc and the almost ubiquitous use of the Internet as a source of medical information by this patient cohort, it is crucial to evaluate the quality and readability of information available online regarding the treatment of the mouth in patients with SSc.

When considering the content of the websites reviewed in this study only 28.1% of the examined websites were exclusively dedicated to the treatment of the mouth in SSc with 82.5% of the sites identified in this study containing medical facts. With over four-fifths of the material being deemed as medical facts, it is unsurprising that the Flesch readability level in this study ranged from “difficult” to “very difficult”. Patients searching for material specifically dedicated to the management of the oral manifestations of SSc will not only have to delve into the website content to find content pertaining to the oral cavity but will also have to try to interpret the extensive medical content. Concern has previously been expressed regarding the ability of patients to accurately interpret medical information (Ayonrinde, 1998, Sacchetti et al., 1999). Ayonrinde highlights that although the access to high-quality specialist medical texts online is beneficial to the medical community in the pursuit of the practice of evidence-based medicine, the general public lacks the crucial appraisal skills to appreciate the quality of the published material or interpret the data provided (Ayonrinde, 1998). In other studies that have evaluated online health information-seeking behaviour of patients with chronic or debilitating diseases a number of barriers have been reported, which include patients being unable to find specific information and an inability of patients to evaluate the material found (Baker et al., 2007, Lee and Hawkins, 2010, Samal et al., 2011). Based on the findings of this study, these barriers may be relevant to patients with oral manifestations of SSc, therefore, providing guidance to this cohort of patients on easily accessible and comprehensible online information pertaining to the management of the oral manifestations of SSc is worthwhile.

An alternative means of providing the material that is easily understood to patients is to use human-interest studies or patient-based vignettes. These vignettes contain medical content but use lay terminology and present the material often using the

patient voice. These human-interest vignettes have been reported to be considered as a form of social and emotional support to patients (van Uden-Kraan et al., 2009). Hay et al. reported that up to 9% of patients attending a rheumatology clinic searched online, trying to find people with matching disease features and experiences (Hay et al., 2008). In spite of the merits of this form of patient information, only 10.5% of the websites reviewed in this study contained human-interest studies. With the permission of patients under their care, a collaborative initiative between Rheumatologists and Dental Practitioners could provide a series of vignettes to be included in online material, thereby eliminating the need for critical appraisal skills needed for medical texts and providing a form of emotional support for patients with the oral manifestations of SSc.

In considering the reliability of the online material the overall mean DISCERN score of the assessed websites was 2.37 (± 1.01), indicating that the quality of the available information was low to moderate (Charnock et al., 1999). Similar results have been reported among several studies dealing with different oral health-related conditions (Lopez-Jornet and Camacho-Alonso, 2010, Ni Riordain and Hodgson, 2014, Wiriyakijja et al., 2016). These poor results in the overall DISCERN score were mirrored in the study findings for the JAMA benchmarks. Only 7% of the websites met the full JAMA benchmarks, while the highest number of websites (30%) achieved two benchmarks. Less than half of the websites achieved the currency benchmark (42.1%), and only 26% achieved the disclosure benchmark while almost half of the sites achieved the attribution benchmark (54.4%).

Recent similar findings were seen across different online sources dealing with other oral health-related conditions, and the absence of such information could be considered to be suspicious since patients cannot trust these online sources

(Wiriyakijja et al., 2016, Alnafea et al., 2017, Alsoghier et al., 2018). The American Food and Drug Administration (FDA, 2005) suggested that the highest quality of online information is usually administrated by governmental, non-profit and academic institutions. However, the current results showed variations of quality among these available online sources which might be related to a potential commercial bias as the highest number of included websites were categorised as commercial sites (43.9%).

5 Conclusion

This study highlights the poor quality and questionable reliability of the content of the associated online sources in relation to the treatment of the mouth in SSc. However, when considering the significant impact of SSc upon both physical and psychological aspects of patients, it is worrying that more high-quality patient-centred material is not available to those searching online. Current results also suggest that the readability level of the available online information did not meet the recommended levels to be read and understood easily by the general population. Thus at present patients with SSc who are seeking health-related online information should be aware of the substantial unmet needs regarding the available information about the treatment of the mouth and its related conditions. Based on the results of this study, further work is required to ensure accurate, comprehensible and relevant online content is accessible to patients with SSc.

CHAPTER 5: Oral health-related quality of life and self-reported anxiety and depression in systemic sclerosis compared with the UK general population

1 Introduction

Systemic sclerosis (SSc) can give rise to a high level of physical and psychological symptoms (e.g. pain, fatigue, depression, anxiety and fear) (Baubet et al., 2011, Del Rosso et al., 2013). Patients with SSc have a standardised mortality ratio of 3.5 and higher rates of psychological morbidity compared to the general population (Willems et al., 2014, Sumpton et al., 2017, Royle et al., 2018). As a consequence with the aforementioned adverse side effects of the disease, its chronicity and the lack of a definitive cure, patients with SSc frequently have a reduced health-related quality of life (HRQoL) in comparison to general population controls (Smirani et al., 2018a).

Patients with SSc usually have more than one feature of the disease, and this may lessen both the functional and aesthetic elements that negatively impact on an individual's emotional and social life (Kwakkenbos et al., 2015). Despite its impact upon the mouth, there are little data regarding the perceived adverse oral health and impact on the oral health-related quality of life of individuals with SSc in the UK.

According to the World Health Organisation, quality of life (QoL) is defined as "the absence of disease or physical or mental weakness as well as person's ability to lead a productive and enjoyable life" (WHO). By stating this, WHO outlined three specific areas dealing with the HRQoL (physical, mental and social). The Canadian Dental Association defines the oral health-related quality of life (OHRQoL) as "a state of the oral and related tissues and structures that contribute to the physical, mental and social well-being and enjoyment of life's possibilities, by allowing the individual to speak, eat and socialise without feeling pain, discomfort or embarrassment"(Gift and Atchison, 1995, Petersen, 2003).

Patient-reported outcome measures (PROMS) are standardised measures directly reported by the patient that characterise the patient's perception of the impact of disease and treatment on health and functioning. Several patient-reported quality of life measures have been developed to measure the impact of SSc on a patient's health-related quality of life (Pope, 2011). PROMS can be designed to comprehensively assess the overall HRQoL and can be a generic instrument or alternatively designed with a specific focus on a particular aspect, disease or population and commonly known as specific instruments. However, quality of life is considered as a multidimensional construct that covers different impact domains of physical, social, psychological, emotional, cognitive, spiritual, work-related and financial aspects. Thus, it is recommended that both generic and specific QoL measures are employed to assess relevant functioning and psychological well-being (Almeida et al., 2015, Callahan, 2016).

With respect to the mouth, a number of different patient-reported outcome measures (PROMS) have been used over the last decade to measure the impact of different diseases upon the OHRQoL of patients (Lopez-Jornet et al., 2009, Ni Riordain and McCreary, 2010a, Liu et al., 2012, Ni Riordain et al., 2016). Various reports have explored the impact of SSc upon both HRQoL, and OHRQoL using different PROMS such as (the oral health impact profile, the 36-item short-form health survey, hospital anxiety and depression scale and oral impact on daily performance) and have demonstrated a significant level of negative impact upon patients' general and oral health-related quality of life (Maddali Bongi et al., 2013, Maddali-Bongi et al., 2014, Baron et al., 2014, Baron et al., 2015c, Smirani et al., 2018a).

Patients with SSc can have a spectrum of oral and maxillofacial features that may interfere with both function and aesthetic appearance and can lessen the OHRQoL as

compared to the general population (Bajraktari et al., 2015, Jung et al., 2016). The Mouth Handicap in Systemic Sclerosis (MHISS) was developed to evaluate the limitations of the oral condition in SSc individuals by measuring the degree of restriction of mouth opening, dryness of the mouth and aesthetic orofacial appearance. It is the only specific PROMS for OHRQoL in SSc (Mouthon et al., 2007) and has been employed in several studies and validated in different populations in France, Italy and Netherlands with excellent test-retest reliability and good construct and divergent validity (Maddali Bongi et al., 2012, Schouffoer et al., 2013, Maddali-Bongi et al., 2014).

There are no data on the impact of SSc upon the OHRQoL among patients in the UK, thus the aim of this study was to assess the impact of SSc upon OHRQoL and general well-being using a number of specific and non-specific employed quality of life instruments such as the SSc oral health-specific questionnaire (MHISS), oral health-related questionnaires (OHIP-14, OIDP), a generic health-related questionnaire (SF-36) and the general psychological health-related questionnaires (HADS, MDAS). Such information should provide an understanding of whether there is a need to develop perhaps personalised management strategies for individuals with SSc affecting the orofacial tissues.

2 Material and Methods

2.1 Study design and participants

This was an observational cross-sectional study to evaluate the self-perceived general and OHRQoL in patients with SSc in the UK. The study group comprised of 50 patients and 18 partners or relatives who attended the Outpatient Rheumatology Clinic of the Royal Free Hospital – London and Scleroderma family day – UK between May and

July 2017. All patients had a diagnosis of SSc confirmed by a Rheumatology team, were over 18 years of age and had an adequate command of the spoken and written English language to comprehend the study questionnaires. All participants were invited to answer relevant questionnaires regarding their health and medical condition including (SF-36, OHIP-14, MHISS, HADS, MDAS and OIDP).

Disease duration was measured as the time between the diagnosis and the time of recruitment to the study. The disease categorisation divided into three groups: diffuse cutaneous SSc (dcSSc), limited cutaneous SSc (lcSSc) and mixed/overlap SSc. lcSSc was defined as skin involvement distal to the elbows and knees, with or without face involvement. dcSSc was defined as skin involvement proximal to the elbows and knees, with or without truncal involvement. Mixed and/or overlap SSc was proposed to describe existing SSc and other autoimmune connective tissue diseases with the presence of related clinical features and/or serological autoantibodies (Desbois and Cacoub, 2016, Denton, 2016). Orofacial features related to SSc were reported in relation to patients' perceptions and not as a consequence of any formal clinical examination.

2.2 Outcome measures

All participants were given detailed written information concerning the study and requested to answer all the included questionnaires. Information collected included sociodemographic data including age, sex, ethnicity, marital status and clinical diagnosis. Participants were given HRQoL, OHRQoL and psychological self-administered questionnaires including (SF-36, OHIP-14, MHISS, HADS, MDAS and OIDP).

The 36-item short-form health survey (SF-36) is designed as a generic assessment tool to measure functional health and well-being from the patient's point of view. The 36 items are summarised into psychometrically-based physical component that includes questions about physical functioning, role limitations due to physical health, bodily pain and general health perceptions while mental component includes questions about vitality, social functioning, role limitations due to emotional problems and mental health. All health domain scales contribute to the scoring of both the physical and mental component summary measures and transformed on a scale from 0 (worst health) to 100 (best health) with higher values reflecting better HRQoL (Del Rosso et al., 2004).

The Oral Health Impact Profile (OHIP-14) is a modified short version instrument to measure OHRQoL in adults with oral diseases. OHIP was originally developed as a 49-item tool representing seven domains including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. This was subsequently refined to the 14 item OHIP-14 by including two questions in each of the seven OHIP aspects (Locker and Allen, 2002). Each question is rated on a 5-point Likert scale to record the frequency of the oral problems. Patients are invited to answer questions by choosing from 0-4 scale while 0=never and 4=very often. The total score ranges from 0 to 56 by summing the score for all items.

The Mouth Handicap in Systemic Sclerosis (MHISS) was developed by Mouthon et al. in 2007 to identify and evaluate the limitations of the oral manifestations of SSc on affected individuals. It consists of 12 items (with five levels of answers), divided into three subscales as subscale one examines impact related to reduced mouth opening, subscale 2 examines impact related to dryness of the mouth and subscale 3 examines

aesthetic concerns (Mouthon et al., 2007). The total score ranges from 0 to 48 by summing the score for all items.

The Hospital Anxiety and Depression Scale (HADS) is a psychological assessment tool used to identify and evaluate psychological distress. It consists of 2 main domains concerning anxiety and depression, respectively. The HADS includes seven questions for each domain with a score range from 0 to 21 with 0 implying no depression, or anxiety while 21 reflects the highest level of depression or anxiety. Scores ranging between 0 – 7 are considered as normal, 8 – 10 as borderline based on a cut-off point more or equal to 8 and sores more than 10 represent abnormal values (Honarmand and Feinstein, 2009).

The Modified Dental Anxiety Scale (MDAS) is an assessment tool regarding anxiety related to receiving dental care. It includes questions assessing fears associated with visiting dentists as well as four other scenarios comprising anticipated anxiety in relation to sitting in a dentist's waiting room, having a scale and polish dental procedure, having a tooth drilled or having a local anaesthetic injection. A five-point response format is employed ranging from 1 (not anxious) to 5 (extremely anxious) with the lowest possible score being five and the maximum possible score of 25. Scores of 19 and above are considered to reflect extreme dental anxiety (Humphris et al., 2013).

The Oral Impact on Daily Performance (OIDP) is an assessment tool of oral quality of life that attempts to determine oral impacts that can significantly affect a person's daily life. The OIDP is based on Locker's adaptation of the World Health Organisation's (WHO) classification of impairments, disability and handicap concepts model and tends to measure the most significant oral impacts (Locker et al., 2000). The OIDP scale assesses the frequency and severity of oral impacts among nine daily

performances in the past 12 months using a scale from 0 – 5, where 0 is no effect, and 5 is a very severe effect. The total score is calculated by adding all subscores, then divided by the maximum score (45) and multiplied by 100; the range of values is therefore from 0 – 100. Higher total OIDP scores indicate the more severe effect of oral impacts on daily life and represent the poorer quality of life.

2.3 Data collection and statistical analysis

Participants were asked to return the completed questionnaires on-site or in a stamped addressed envelope to one of the authors (SRP). After completion of the data collection, all data were transferred to Excel spreadsheets, tabulated and adjusted for later interpretation where appropriate. Descriptive statistical analysis was calculated for demographics and disease features. Mean, median, standard deviation and interquartile range were calculated for continuous variables and frequency counts (number and percentage) were calculated for ordinal and nominal variables. In patients and controls, further statistical analysis was performed for comparisons of different variables using Chi-squared tests, Fisher's exact test, independent t-tests and Mann-Whitney U tests as appropriate. For all statistical tests, the threshold of significance was set at a *P*-value < 0.05. All statistical analysis was performed using the SPSS statistical software package (version 25).

Ethical approval was sought for this study; however, as this was considered to be an evaluation of service, ethical approval was not deemed necessary.

3 Results

3.1 Baseline characteristics of patients with SSc and controls

The SSc group comprised 48 females (96%) with a group mean age of 62.5 years (SD = 10.8). The partner/relative group comprised only 4 females (22.2%) with a group mean age of (67 ±8.8) years. Participants with SSc had disease duration (13.2 ±10.9)

years. The majority of participants in both groups were married. More than two-thirds (70%) of the SSc patients and (94.4%) of the partner/relative group were British white. Almost 88% of participants had an education level at degree level or above. Twenty-four patients had diffuse cutaneous SSc (dcSSc), 13 patients had limited cutaneous SSc (lcSSc), and six patients had mixed/overlap SSc, while 7 patients did not report their disease type. When asked about their oral disease in the enduiring questionnaire, 48% (*P* = .001) of the participants reported the experience of facial skin tightness and telangiectasia, 44% (*P* = .003) reported having dysphagia and 42% (*P* = .005) reported having microstomia. Patient demographics, disease characteristics and self-reported orofacial features are summarised in Table 5.1 and 5.2.

3.2 Oral health-related quality of life measures

In all OHRQoL measures (OHIP-14, MHISS and OIDP), strong statistically significant trends in impairment were observed between patients and partners or relatives except for the OIDP component related to problems enjoying contact with others. The total mean OHIP-14 score was significantly lower in the patients with SSc (16.5 ±12.4) compared with partners or relatives (6.06 ±7.6, *P* .001). Indeed, all the mean scores of OHIP-14 components were significantly lower in patients with SSc than the partner/relative subjects (Table 5.3).

The MHISS scores highlighted similar results. The total mean MHISS score was significantly higher in patients (21.26 ±12) compared with partner/relative group (4.8 ±7.3, *P* <.0001). Also, and perhaps unsurprisingly, patients reported significantly higher scores in all MHISS components (mouth opening restriction, mouth dryness, aesthetic concerns) than partner/relative group, *P* <.0001 (Table 5.3).

With regard to the oral impact of SSc upon daily performances, the total mean score for patients was (10 ±8.7) compared with partner/relative group (1.72 ±3.4, *P* <.0001). The mean scores of nine components of the OIDP reflecting the presence of the last 12 months were significantly poorer in the patients compared with partner/relative group. The only exception was that enjoyment of contact with others was not reduced. However, oral impacts were very frequent for most patients compared to partner/relative group, as 88% of SSc patients reported difficulty performing at least one element of the OIDP compared to 44.4% in partner/relative group. Overall, the more prevalent oral impacts among SSc patients were difficulty eating (76%), difficulty relaxing and sleeping (52%), problems smiling without embarrassment and difficulty cleaning teeth (50%). Among partner/relative group, although the prevalence was very low compared to patients, the most prevalent oral impacts referred to finding problems smiling without embarrassment (6%), difficulty relaxing and sleeping (4%) and difficulty eating (3%) (Table 5.3).

3.3 General health-related quality of life measures

Although this study was focused upon the oral aspects of SSc, general health-related quality of life also revealed low scores. The general health mean score of SF-36 was significantly lower in patients with SSc (43.3 ±27.2) compared with that of partner/relative group (69.3 ±18.8, *P* <.0001). All subscales scores other than that of mental health were significantly lower in patients than partner/relative group (Table 5.4).

3.4 Anxiety and depression measures

There were no significant differences between patients and partner/relative group for both HADS and MDAS scales. However, there was a trend for patients with SSc to have higher scores for both depression and anxiety of HADS and MDAS total score. Patients with SSc had a higher mean score for HADS depression (4.8 ±3.3) and anxiety (6 ±4.6) compared to their partners or carers (3.7 ±3.1) (4.7 ±3.9) respectively. In patients with SSc, the rates of abnormal depression and anxiety were (6% and 18%) respectively, higher when compared to partner/relative group (5.5%) for both depression and anxiety. 16% of patients had borderline rates of both depression and anxiety compared to their partners or relatives (5.5% and 16.6%) respectively. Similarly, the mean of total MDAS score was higher among patients compared to their partners or relatives (11.7 ±5.3), (9.5 ±4.4) respectively which indicates a moderate trend of dental anxiety level. Overall, twelve per cent of patients had an MDAS score of 19 or more, which suggests extreme dental anxiety and phobia compared with no extreme level of dental anxiety among the control group. Almost half of the patients with SSc (46%) reported a moderate level of dental anxiety compared to 38.9% in partner/relative group. However, 38% of patients had an MDAS score of between 5 and 9, indicating low/no dental anxiety compared with 61.1% of the partner/relative group (Table 5.5).

Table 5.1 Baseline characteristics of patients with SSc (n=50) and partners or relatives (n=18)

Variables		Patients with SSc	Partner/relative group	*P*-value
Age (year), mean (SD)		62.5 (10.8)	67 (8.8)	.093
Disease duration (years), mean (SD)		13.2 (10.9)	-	-
Female, n %		48 (96)	4 (22.2)	<0.0001
Marital status	Single	10 (20)	2 (11.1)	.265
	Married	27 (54)	15 (83.3)	
	Divorced	10 (20)	1 (5.6)	
	Widowed	2 (4)	0 (0)	
	Unknown	1 (2)	0 (0)	
Education level	No degree-level	6 (12)	2 (11)	.756
	At degree-level or above	44 (88)	16 (89)	
Work status	Working/Not working, %	42/58	50/50	.558
Work-time (Full/Part-time), %		28/72	78/22	.708
Smoking, n %		0 (0)	2 (11)	.017
Alcohol, n %		23 (46)	14 (78)	.020
Ethnicity	British White	35 (70)	17 (94.4)	.404
	Other White	5 (10)	0 (0)	
	Indian	4 (8)	1 (5.6)	
	Black Caribbean	2 (4)	0 (0)	
	Pakistani	1 (2)	0 (0)	
	Other ethnicity	3 (6)	0 (0)	
Disease subtype	Diffuse cutaneous SSc	24 (48)	-	-
	Limited cutaneous SSc	13 (26)	-	-
	Mixed/Overlap SSc	6 (12)	-	-
	Unknown	7 (14)	-	-

Table 5.2 Orofacial symptoms related to SSc reported by patients with SSc (n=50) and partner or relative subjects (n=18)

Orofacial features	Patients with SSc, %	Partner/relative group, %	*P*-value
Microstomia	42	5.6	.005
Bleeding / recession gums	32	50	.174
Loose / mobile teeth	30	22.2	.528
Loose / mobile denture	12	11.1	.920
Bruising / ulceration of the lining of the mouth (oral mucosa)	30	11.1	.113
Tightness of facial skin / oral mucosa	48	5.6	.001
Altered breath smell (halitosis)	12	0	.124
Difficult root canal treatment (endodontics)	16	0	.071
Difficulties with dental extractions	22	0	.030
Oral infection	18	16.7	.899
Speech impairment (dysarthria)	10	0	.163
Swallowing difficulty (dysphagia)	44	5.6	.003
Altered taste sensation (dysgeusia)	12	0	.124
Tongue atrophy / ankylosis / rigidity	16	0	.071
Salivary gland swelling / hypofunction	20	5.6	.154
Facial / oral telangiectasia (pigmentation)	48	5.6	.001
Fissured / cracked lips	28	0	.012

Table 5.3 Comparison of OHRQoL between patients with SSc (n=50) and partner or relative subjects (n=18)

Instrument	Scale	Patients with SSc		Partner/relative group		*P*-value
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
OHIP-14	Functional limitations	2.48 (1.8)	2 (1-4)	0.89 (1.5)	0 (0-2)	.001
	Physical pain	3.44 (2.3)	3 (2-5)	1.89 (1.9)	1.5 (0-3)	.015
	Psychological discomfort	3..18 (2.8)	2 (0-6)	1.56 (1.9)	1 (0-3)	.044
	Physical disability	2.32 (2.5)	2 (0-4)	0.5 (1.33)	0 (0)	.002
	Psychological disability	2.18 (2.2)	1 (0-4)	0.72 (1.2)	0 (0)	.010
	Social disability	1.34 (1.6)	1 (0-2)	0.33 (0.68)	0 (0)	.015
	Handicap	1.52 (1.8)	0.5 (0-3)	0.17 (0.38)	0 (0)	.004
	OHIP total	16.5 (12.4)	13 (6-28)	6.06 (7.6)	2.5 (0-9)	.001
MHISS	Mouth opening restriction	9.38 (7.1)	9.5 (2-16)	1.72 (3.1)	0 (0-3)	<.0001
	Mouth dryness	8.44 (4.1)	10 (7-11)	2.5 (3.8)	0.5 (0-4)	<.0001
	Aesthetic concerns	3.52 (2.9)	4 (0-6)	0.61 (1.33)	0 (0)	<.0001
	MHISS total	21.26 (12)	22.5 (11-30)	4.8 (7.3)	3 (0-7)	<.0001
OIDP	Difficulty eating	2.08 (1.5)	2 (1-3)	0.33 (0.84)	0 (0)	<.0001
	Difficulty speaking	0.29 (1.1)	0 (0-2)	0.22 (0.94)	0 (0)	.004
	Difficulty cleaning teeth or dentures	1.42 (1.6)	0.5 (0-3)	0.17 (0.5)	0 (0)	.002
	Difficulty going out	0.46 (0.9)	0 (0)	0 (0)	0 (0)	.024
	Difficulty relaxing and sleeping	1.46 (1.7)	1 (0-3)	0.28 (0.5)	0 (0)	.009
	Problems smiling without embarrassment	1.6 (1.8)	0.5 (0-3)	0.5 (0.85)	0 (0)	.054
	Difficulty carrying out major role or work	0.74 (1.1)	0 (0)	0 (0)	0 (0)	.005
	Problems with emotional instability	0.76 (1.08)	0 (0)	0.11 (0.32)	0 (0)	.013
	Problems enjoying contact with others	0.52 (0.9)	0 (0)	0.11 (0.32)	0 (0)	.088
	Total score	10 (8.7)	8 (2-16)	1.72 (3.4)	0 (0)	<.0001

Table 5.4 Comparison of HRQoL measures between patients with SSc and (n=50) and partner or relative subjects (n=18)

Tools	Variables	Patients with SSc		Partner/relative group		*P*-value
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
SF-36	Physical Functioning	52.7 (29.3)	50 (28-75)	73.6 (31.7)	95 (42-100)	.011
	Role-physical	33 (40.8)	12.5 (0-75)	66.6 (42.8)	100 (18-100)	.007
	Role-emotional	64.9 (41.5)	100 (33-100)	88.8 (28)	100 (100-100)	.027
	Vitality	42.6 (30.3)	37.5 (23-61)	61.9 (21.3)	65 (51-80)	.004
	Mental health	69 (19.8)	70 (56-88)	77.7 (11)	76 (71-88)	.107
	Social functioning	63 (27.6)	62.5 (50-88)	87.5 (21.4)	100 (84-100)	.001
	Bodily pain	59.6 (26.5)	62.5 (35-80)	78.06 (28.6)	90 (45-100)	.016
	General health	43.3 (27.2)	39.3 (23-61)	69.3 (18.8)	72.5 (53-82)	<.0001

Table 5.5 Comparison of anxiety and depression measures between patients with SSc (n=50) and partner/relative group (n=18)

Tools	Variables	Patients with SSc		Partner/relative group		*P*-value
		Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
HADS	Depression	4.8 (3.3)	5 (2-7)	3.7 (3.1)	4 (0-6)	.213
	Anxiety	6 (4.6)	5 (2-8)	4.7 (3.9)	5 (0-7)	.364
MDAS	Total	11.7 (5.3)	10.5 (7-15)	9.5 (4.4)	8 (5-13)	.110

4 Discussion

Systemic sclerosis is a complex autoimmune disorder that gives rise to small vessel disease and fibrosis of the mucocutaneous surfaces and viscera, particularly the lungs and gastrointestinal tract. Co-morbidity of the disease is considered high among affected individuals due to the multisystem involvement, the unpredictability of disease and variable response to therapy (Stern and Denton, 2015, Royle et al., 2018). As with all disease, management is centred upon maintaining function as well as quality and longevity of life.

The clinical consequences of SSc can lessen the quality of life of patients through activity limitations, impairments and/or disability, thus understanding the impact of systemic sclerosis upon HRQoL may help to address the healthcare needs aiding healthcare providers to better-overcome any unmet patients needs for this rare condition. Previous evidence has reported that SSc can radically affect oral health and impact negatively on oral and general HRQoL compared with the general population (Veale et al., 2016, Smirani et al., 2018b). Aside from dysfunction of lungs, kidneys, heart, gastrointestinal tract and musculoskeletal system, there is an increased risk of malignancy (Elhai et al., 2015, McCray and Mayes, 2015, Lachner, 2016, Zeineddine et al., 2016). The orofacial manifestations of SSc have been ranked by patients as amongst the most worrying aspects of their disease as they may alter the patient's OHRQoL and hinder multiple functions such as eating, speaking and interfere with daily hygiene and dental treatment procedures (Alantar et al., 2011, Del Rosso and Maddali-Bongi, 2014, Jung et al., 2016). Despite their high frequency, the precise impact of the oral manifestations of SSc patients upon the patient's quality of life has rarely been investigated. Certainly, HRQoL can be significantly impaired in SSc patients as demonstrated using (SF-36, OHIP-14, MHISS and OIDP) and OHRQoL is

associated with global HRQoL (Baron et al., 2015c). Due to the heterogeneity of SSc, different disease-specific PROMS have been developed such as Scleroderma Health Assessment Questionnaire (Steen and Medsger, 1997, Johnson et al., 2005, Pope, 2011), UK Scleroderma Functional Score (Silman et al., 1998), Symptom Burden Index (Kallen et al., 2010), Scleroderma Gastrointestinal Tract Scale and UCLA SCTC GIT (Khanna et al., 2007, Khanna et al., 2009) and Raynaud's Condition Score (Merkel et al., 2002, Pope, 2011) but there remains only one SSc-specific PROM that measures the mouth-related disability – the MHSS (Mouthon et al., 2007). Another study has assessed the psychometric properties, including validity and reliability of MHISS scale in the same cohort of patients with SSc making it the first study to validate the MHISS in the UK population. Both SF-36 and OHIP-14 have been reported to be used commonly among different OHRQoL studies of different oral disorders perhaps of relevance to SSc with excellent measurement properties (Ni Riordain and McCreary, 2010a, Baron et al., 2015c) and hence the inclusion of these in the present study has some relevance.

In this study, the generic and specific HRQoL was measured in a cohort of patients with SSc compared to non-SSc participants as a control group using a number of PROMS including (SF-36, OHIP-14, MHISS, HADS, MDAS and OIDP). The current results indicate that SSc disease and associated orofacial features radically affect the HRQoL and may affect psychological factors including depression and anxiety. Although using generic instruments such as SF-36 might be less responsive to changes due to the focus on general aspects of the related-condition, it assesses the influence of the disease on overall well-being rather than specific manifestations and may detect an unexpected clinical event which would otherwise be missed by measures that are more specific.

According to present results, SSc patients present a significantly high level of disability in all subscales scores of SF-36 other than that of mental health compared to partner/relative group. These results reflect those of a recent meta-analysis that suggests that physical health measured by SF-36 was more likely to be affected than mental well-being in systemic sclerosis (Li et al., 2018). The present results also demonstrate that the effect of emotional impact, mental health and social functioning are remarkable with the highest scores in the SF-36 questionnaire. Previous studies have reported similar results with a high impact of psychological disability on the HRQoL of the SSc patients including pain, anxiety and depression (Mestre-Stanislas et al., 2010, Maddali Bongi et al., 2013, van der Vaart et al., 2013, Maddali-Bongi et al., 2014, Bragazzi et al., 2019). Moreover, in this group of patients with SSc psychological discomfort and disability as recorded in the OHIP-14 questionnaire had high scores, patients felt 'self-conscious', 'tense', 'distressed', 'not able to relax' and/or 'embarrassed' as an outcome of their oral condition as well as experiencing increased physical pain and functioning limitation. Baron et al. similarly reported that SSc had impacted greatly upon functional limitation, physical pain and disability, psychological discomfort and disability in the OHIP (Baron et al., 2014).

Apart from the multisystemic nature of the disease, patients with SSc are commonly affected by a variety of orofacial features that can impact upon OHRQoL including increased susceptibility to dental decay and perhaps periodontal disease, decreased saliva production, limited mouth opening and tightening of the facial skin (Veale et al., 2016, Smirani et al., 2018b). Thus patients with SSc can have significant mouth disability of the orofacial tissues (Schouffoer et al., 2013, Maddali-Bongi et al., 2014), as well as a reduction in global well-being (Nguyen et al., 2014, Kwakkenbos et al., 2015). The present results have revealed that patients with SSc do report significantly

higher scores in all MHISS components (mouth opening restriction, mouth dryness, aesthetic concerns) and thus have significantly impaired overall OHRQoL. As perhaps expected the present patients often reported facial disability and reduced mouth opening – as recorded in the MHISS. Indeed, tightness of facial skin and/or oral mucosa and reduced mouth opening were among the most commonly reported SSc-specific features (48% and 42%). However, several studies have found that patients reported experiencing dry mouth as the second most common feature with comparatively lower scores for aesthetic change related to their disease. (Maddali Bongi et al., 2012, Maddali-Bongi et al., 2014, Smirani et al., 2018b, Basta et al., 2019). According to the most recent Adult Dental Health Survey (ADHS) of the UK, 33% of participants report having difficulty with at least one item on the OIDP compared to 88% of patients with SSc. However, the most prevalent oral impacts among SSc patients were difficulty eating (76%), difficulty relaxing and sleeping (52%), problems smiling without embarrassment and difficulty cleaning teeth (50%) reflecting much higher values comparing to Adult Dental Health Survey (ADHS, 2009). Patients with SSc scored a significant level of impact in all scores except for “problems enjoying contact with others”. This perhaps may be related to the benefits of perceived help and support from either relatives and friends and/or support groups (Milette et al., 2019). However, these findings are in line with results among other groups of patients with chronic disease particularly some of the rheumatological disorders (Gumuchian et al., 2016, Gumuchian et al., 2017, Poole et al., 2018).

Other aspects, such as anxiety and depression, were assessed using the hospital anxiety and depression scale (HADS). A direct relationship has been reported between depression and anxiety and reduced HRQoL among patients with SSc (Kwakkenbos et al., 2015, Almeida et al., 2015, Lisitsyna et al., 2018). Similar to the

results in an Italian population, the present data show that up to 16% of patients with SSc had ‘borderline’ depression and anxiety while 18% have had an ‘abnormal’ anxiety scores and 6% have had an ‘abnormal’ depression score (Del Rosso et al., 2013, Nguyen et al., 2014). These results of the HADS are lower compared to a previous French study, where depression and anxiety were detected in 40%, 58%, respectively whereas 66% displayed symptoms of anxiety and/or depression (Nguyen et al., 2014). The high prevalence of anxiety and depression among patients with SSc may be related to various factors (e.g. pain, fatigue, body image dissatisfaction) and may be associated with increased disability and poorer HRQoL. Therefore, psychological and emotional impact upon patients’ quality of life should not be underestimated. Dental anxiety is considered to be one of the most important psychological barriers to patients accessing dental care (Hill et al., 2013). Current results highlighted that up to 12% of SSc patients have extreme dental anxiety, while 46% reported a moderate level of dental anxiety.

Interestingly, results from the latest dental health survey (ADHS, 2009) indicated a relationship between dental anxiety and dental attendance. Participants with extreme dental anxiety were found to be less likely to attend unless having problems with their teeth 22% than attending for a routine dental check-up 8%. Therefore dental anxiety may act as a psychological barrier to seeking dental care and might lead to a negative impact on OHRQoL.

Some oral features are more painful while others have only an aesthetic burden, but together they build a complex figure of impairments to patients OHRQoL. Oral disorders may impact daily living through work disability, reduced productivity and decreased social interaction (Poole et al., 2016, Morrisroe et al., 2018). Although patients with SSc reported higher levels of impact upon all physical and functional

domains, the present results indicated no significant difference between patients and controls in relation to work status and employment. This might be related to the relatively small sample size. A precise evaluation of the disease severity is important to determine whether health care can easily be accessed and performed. Due to the chronic and progressive nature of the disease patients with SSc might need to be continuously assessed by their health care providers (Rubenzik and Derk, 2009). Compared to other chronic diseases, patients with rare conditions such as SSc tend to receive more help and support regarding their chronic illnesses (Joachim and Acorn, 2003). Therefore, more efforts is needed towards disease-specific evaluation and support that could help to improve the quality of life of affected patients' groups.

5 Conclusion

Systemic sclerosis has a negative impact on both general and OHRQoL of the affected individuals that might not be routinely captured by healthcare assessment of disease severity. Although, as mentioned above, not all HRQoL measures have been validated specifically in SSc, the present data suggest that patients with SSc have significantly impaired global and oral health-related quality of life. Indeed, there is a high level of anxiety and depression compared to their partners or relatives. This study is not without limitations as it has a cross-sectional design without detailed clinical evaluation. However, the strengths of this study include the assessment of both oral and global health-related quality of life at the same time along with the evaluation of associated psychological impact, including anxiety and depression symptoms. Given the impact of poor HRQoL, OHRQoL and psychological distress on the lives of patients, health care providers should make efforts to collaborate and develop early multidisciplinary targeted interventions to improve the disease comorbidity in patients with SSc. Research is required to better understand, monitor and evaluate patients with SSc in any health care setting and clinical trial.

CHAPTER 6: Validity and reliability of the Mouth Handicap of Systemic Sclerosis (MHISS) questionnaire in a UK population

1. Introduction

Due to the nature of the disease and the lack of a definitive cure, the management of SSc can be challenging, and patients may face significant physical, social and psychological impacts on daily life (Almeida et al., 2015). SSc is commonly associated with anxiety, fear and depression that might be related to the unpredictable course of the disease and the concern about the future (Baubet et al., 2011) not only due to the disease manifestation but also due to the increased mortality reported in this cohort of patients (Lee, 2018). Living and coping with the disease itself and its subsequent complications usually need both pharmacological and non-pharmacological therapeutic efforts and referral to multiple healthcare clinicians. The goal of treatment is to improve health-related quality of life (HRQoL) and reduce the morbidity of the disease.

As previously discussed quality of life is a multidimensional concept incorporating areas such as physical function, social function, psychological, emotional, cognitive, spiritual, work-related and financial aspects of health and disease (Callahan, 2016). Since early 1990, the utility of patient-reported outcome measures (PROMS) in the medical field, both in clinical practice and in research has grown significantly. Efforts have been made over the last two decades to enhance the acceptance of PROMS in routine clinical practice and research (Callahan, 2016, Ni Riordain et al., 2016). However, more than 250 PROMS exist in the field of rheumatology (Pellar et al., 2016). Although the use of PROMS is thought to be helpful in recording the impact of the disease from the perspective of the patient, further research is needed to refine disease-specific PROMS in SSc and to investigate psychometric properties.

As highlighted in the literature and the previous chapter, the majority of patients with SSc have impairment of health-related quality of life (HRQoL) and oral health-related quality of life (OHRQoL) that should not be underestimated when considering the spectrum of systemic manifestations of the disease (Baron et al., 2014). Generic and specific oral health-related quality of life measures have been used to assess various aspects of SSc (e.g. OHIP and SF-36). Although these have been used frequently, they may not successfully assess the magnitude and impact of the oral features of the disease as they were not developed in a population with SSc.

The Mouth Handicap in Systemic Sclerosis questionnaire (MHISS) was developed in a French population with SSc and has proven to be a valid and reliable oral health-specific QoL instrument on psychometric testing (Mouthon et al., 2007). However, given the necessity to explore the cross-cultural sensitivity of health-related quality of life measures researchers have examined the psychometric properties of MHISS in Italian and Dutch populations with supporting outcomes (Maddali Bongi et al., 2012, Schouffoer et al., 2013).

The MHISS had not been assessed in the UK population, hence the aims of this chapter were to explore the psychometric properties of MHISS, namely validity and reliability, in an English-speaking UK population.

2. Material and Methods

2.1 Recruitment and data collection

This observational study had a cross-sectional design. A total of 150 questionnaires were distributed at 3 sites: Oral Medicine Department of UCLHT Eastman Dental Hospital, the Outpatient Rheumatology Clinic of the Royal Free Hospital and Scleroderma Family, between May and July 2017. Patients over the age of 18 years with a diagnosis of SSc and who had an adequate command of the English language to comprehend the questionnaires were invited to complete the study questionnaire pack. This pack included SF 36, OHIP-14 and MHISS.

The Mouth Handicap in Systemic Sclerosis questionnaire (MHISS) was developed by Mouthon et al. in 2007 to identify and evaluate the limitations of the oral manifestations of the condition of SSc on individuals and aims to improve the oral health care mainly by measuring the degree of restriction of mouth opening, dryness of the mouth and the aesthetic appearance (Mouthon et al., 2007). It consists of 12 items (with five levels of answers), divided into 3 subscales as subscale one examines impact related to reduced mouth opening, subscale 2 examines impact related to dryness of the mouth and subscale 3 examines aesthetic concerns. The total score ranges from 0 to 48 by summing the score for all items.

The Oral Health Impact Profile (OHIP) is a questionnaire designed by Slade and Spencer to measure OHRQoL in adults with oral disease (Slade and Spencer, 1994). It was originally developed as a 49-item tool representing seven domains including functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap. This was subsequently refined to the 14 item OHIP-14 by including two questions in each of the seven OHIP aspects (Locker and Allen, 2002). Each question is rated on a 5-point Likert scale to record the

frequency of the oral problems. Patients are invited to answer questions by choosing from a 0-4 scale while 0=never and 4=very often. The total score ranges from 0 to 56 by summing the score for all items.

The 36-item Short-Form Health Survey (SF-36) is designed as a generic assessment of health status with a wide range of types and severity of conditions. The 36 items measure eight aspects of health which includes physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. All scores are added together and transformed on a scale from 0 (worst health) to 100 (best health) as a higher score (Del Rosso et al., 2004).

Participants were asked to return the completed questionnaire on-site or in a stamped addressed envelope. After completion of the data collection, all data were transferred to Excel spreadsheets, tabulated and later interpreted where appropriate using the SPSS statistical software package (version 25).

Ethical approval was sought for this study; however, as this was considered to be an evaluation of service, ethical approval was not deemed necessary.

2.2 Psychometric testing

Convergent validity, a type of construct validity, was assessed. Construct validity explores whether the instrument can reflect theories and traits of SSc. Convergent validity is the extent to which MHISS relates to other instruments of a similar construct to which it is proposed to be related (Butt et al., 2009). The initial proposal explored in this study was that patients with poor general HRQoL, as measured by SF-36, would have poorer scores as recorded by MHISS. Secondly, we anticipated that patients with poor OHRQoL, as measured by OHIP-14, would have poorer scores as recorded by MHISS. Spearman's rho correlations were used to assess the relationship between MHISS and SF-36 and between MHISS and OHIP-14. The following grading of the

degree of correlation was applied 0.1 – 0.29 low correlation, 0.3 – 0.49 moderate correlation, 0.5 – 1.0 good high correlation (Anastasi and Urbina, 1997, Schouffoer et al., 2013).

Internal consistency reliability refers to the degree to which items in an instrument correlate with each other and should also correlate with the overall scale score (Aaronson et al., 2002). Cronbach's alpha coefficient was used to determine internal consistency reliability which can range from 0.0 to 1.0. In this study, Cronbach's alpha of 0.6 to 0.69 was considered acceptable, 0.7 or higher is required before an instrument is considered adequate reliability, however, a minimum value of 0.8 is necessary for 'good' internal consistency reliability (Gravetter and Forzano, 2008, Schouffoer et al., 2013).

3. Results

3.1 Patient characteristics

Of the 150 questionnaires distributed to patients, 68 responded, giving a response rate of 45.3%. Of the 68 study participants, 64 were female (94%), and 4 were male. The mean age was 62.5 (±10) years and mean disease duration was 13.2 (±11) years. Most of the study sample were White British (73.5%). All the participants were non-smokers, and 33.8% of the sample consumed alcohol. Approximately a third of the patients had diffuse cutaneous SSc (dcSSc) (35.3%), 19.1% had limited cutaneous SSc (lcSSc), 7.4% had overlap SSc, and 38.2% were reported with unknown disease types as they did not know the subset of their disease. With regard to orofacial manifestations of SSc, 48% of the participants reported experience of facial skin tightness and telangiectasia, 44% reported having dysphagia, 42% reported having microstomia, 32% reported having gingival diseases, and 30% reported having teeth mobility and oral ulceration. Patient demographics, disease characteristics and symptoms are summarised in Table 6.1 and 6.2.

Table 6.1 Sociodemographic and disease characteristics of patients with SSc (n=68)

Variable		Value
Age (year), mean (SD)		62.5 (10)
Disease duration (years), mean (SD)		13.2 (10.9)
Female, n %		64 (94)
Marital status	Single	10 (14.7)
	Married	27 (39.7)
	Divorced	10 (14.7)
	Widowed	2 (2.9)
	Unknown	19 (28)
Education level	No degree-level	6 (8.8)
	At degree-level or above	44 (64.7)
	Unknown	18 (26.5)
Work status	Working/Not working	42/58
	Paid employee/Self-employed	66.7/33.3
Work-time (Full/Part-time)		45.8/54.2
Smoking, n %		0 (0)
Alcohol, n %		23 (33.8)
Ethnicity	British White	50 (73.5)
	Other White	6 (8.8)
	Indian	4 (5.9)
	Black African	1 (1.5)
	Black Caribbean	2 (2.9)
	Pakistani	1 (1.5)
	Other Asian backgrounds	1 (1.5)
	Another ethnicity	3 (4.4)
Disease subtype	Diffuse cutaneous SSc	24 (35.3)
	Limited cutaneous SSc	13 (19.1)
	Overlap SSc	5 (7.4)
	Unknown	26 (38.2)

Table 6.2 Orofacial features related to SSc that experienced by patients (n=68)

Item	%
Microstomia	42
Bleeding/recession gums	32
Loose/mobile teeth	30
Loose/mobile denture	12
Bruising/ulceration of the lining of the mouth (oral mucosa)	30
Tightness of facial skin/oral mucosa	48
Altered breath smell (halitosis)	12
Difficult root canal treatment (endodontics)	16
Difficulties with dental extractions	22
Oral infection	18
Speech impairment (dysarthria)	10
Swallowing difficulty (dysphagia)	44
Altered taste sensation (dysgeusia)	12
Tongue atrophy / ankylosis / rigidity	16
Salivary gland swelling/hypofunction	20
Facial/oral telangiectasia (pigmentation)	48
Fissured/cracked lips	28

The response frequencies to MHISS, OHIP-14 and SF-36 tended towards skewed distributions, with some subscales demonstrating normal distribution. Due to the mixture between normal and skewed data the median, mean, standard deviation, standard error and interquartile range scores for each subscale in MHISS, and the OHIP-14 and for SF-36 have been reported in Table 6.3.

Table 6.3 Descriptive statistics for the SF-36, OHIP-14 and MHISS scales of patients with SSc

Instrument	Scale	Median	IQR	Mean (SD)	Std. Error
SF-36	Physical Functioning	45	20-70	48.05 (28.6)	3.47
	Role-physical	25	0-69	32.72 (40.3)	4.89
	Role-emotional	100	33-100	63.53 (41.4)	5.02
	Vitality	34	15-55	39.34 (28.2)	3.43
	Mental health	72	57-87	70.04 (20.4)	2.48
	Social functioning	62.5	41-88	61.95 (27.5)	3.33
	Bodily pain	56.2	37.5-78	58.04 (24.9)	3.02
	General health	30	20-60	40.59 (26.1)	3.17
OHIP-14	Functional limitations	3	1-4	2.97 (2.1)	0.26
	Physical pain	4	2-5	3.63 (2.2)	0.27
	Psychological discomfort	4	0.25-7	3.97 (2.9)	0.36
	Physical disability	2.5	0-4	2.85 (2.5)	0.31
	Psychological disability	3	0-4	2.81 (2.4)	0.29
	Social disability	1	0-3	1.63 (1.8)	0.22
	Handicap	1.5	0-3	1.79 (1.9)	0.23
	OHIP total	20	7.25-31	19.74 (13.0)	1.57
MHISS	Mouth opening restriction	12	4.25-18	11.31 (7.3)	0.89
	Mouth dryness	10	8-12	9.16 (4.0)	0.48
	Aesthetic concerns	4	1-6	4.03 (2.8)	0.34
	MHISS total	27	12.5-35	24.59 (12.1)	1.47

3.2 Validity

With respect to convergent validity, all Spearman's rho correlation coefficients were significant at the $p<0.05$ and $p<0.01$ levels as seen in Table 6.4 and 6.5. The negative correlation seen in Table 6.4 reflects the fact that the scores of SF-36 and MHISS are inversely related; a higher score in SF-36 reflects a better HRQoL while a higher score in MHISS indicates a worse impact of SSc on the patient. Results show a low correlation between the following - all MHISS domains and SF-36 Role-physical domain; MHISS Mouth opening restriction and SF-36 Social functioning; MHISS Mouth dryness and both SF-36 Vitality and Bodily pain; MHISS Aesthetic concerns and SF-36 Role-emotional and Vitality. A moderate correlation was found between MHISS Mouth opening restriction and SF-36 Role-emotional, Vitality and Bodily pain domains. Also, a moderate correlation was found between MHISS Mouth dryness and both SF-36 Role-emotional and Social-functioning. MHISS total scores were found moderately correlated to all SF-36 except for both Physical functioning and Mental health domains. However, Spearman's rho correlation coefficients indicated that all MHISS subscales were moderately correlated to SF-36 General health domain.

Table 6.4 Matrix of Spearman's rho coefficients between pairs of responses (n=68) to the MHISS and SF-36

Instrument	SF-36 Physical Functioning	SF-36 Role-physical	SF-36 Role-emotional	SF-36 Mental health	SF-36 Vitality	SF-36 Social functioning	SF-36 Bodily pain	SF-36 General health
MHISS Mouth opening restriction	-.158	-.262*	-.307*	-.046	-.300*	-.254*	-.331**	-.362**
MHISS Mouth dryness	-.164	-.276*	-.335**	-.001	-.275*	-.341**	-.250*	-.353**
MHISS Aesthetic concerns	-.136	-.257*	-.247*	-.033	-.283*	-.187	-.092	-.316**
MHISS total score	-.221	-.315**	-.365**	-.058	-.372**	-.351**	-.310**	-.446**

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Table 6.5 Matrix of Spearman's rho coefficients between pairs of responses to the MHISS and OHIP-14 (n=68)

Instrument	OHIP Functional limitations	OHIP Physical pain	OHIP Psychological discomfort	OHIP Physical disability	OHIP Psychological disability	OHIP Social disability	OHIP Handicap	OHIP total
MHISS Mouth opening restriction	.487**	.595**	.618**	.604**	.622**	.455**	.551**	.689**
MHISS Mouth dryness	.573**	.513**	.281*	.548**	.325**	.234	.453**	.489**
MHISS Aesthetics	.383**	.399**	.562**	.407**	.585**	.449**	.438**	.582**
MHISS total score	.575**	.628**	.609**	.652**	.623**	.456**	.602**	.725**

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Most of the MHISS domains were found to positively and highly correlated to the OHIP-14 subscales with Spearman's rho correlation coefficients between 0.543 and 0.725 at the $p<0.01$ level as seen in (Table 6.5). However, data shows some degree of moderate correlation was found between MHISS Mouth opening restriction and both

OHIP-14 Functional limitation and Social disability and between MHISS Mouth dryness and OHIP-14 Psychological disability, Handicap and OHIP-14 total score. MHISS Aesthetic concerns domain was only highly correlated to OHIP-14 (Psychological discomfort, disability and total score). The total MHISS score was highly correlated to all OHIP-14 subscales except the Social disability score that reflects a moderate level of correlation.

3.2 Reliability

With regard to internal consistency reliability, the mouth dryness domain with Cronbach's alpha value of 0.76 demonstrated adequate internal consistency reliability. The other two domains, including mouth opening restriction and aesthetic concerns, indicated good internal consistency reliability level with Cronbach's alpha values of 0.878 and 0.874, respectively. The overall MHISS Cronbach's alpha value of 0.894 indicated very good internal consistency reliability of the 12-item instrument (Table 6.6).

Table 6.6 Internal consistency reliability of the MHISS scales

Items	Scale	Number of items (n=68)	Cronbach's alpha
MO1-MO6	Mouth opening restriction	6	0.878
MD1-MD4	Mouth dryness	4	0.760
AC1-AC2	Aesthetic concerns	2	0.874
All the above	MHISS total score	12	0.894

4. Discussion

SSc is a heterogeneous disease with high morbidity and impacts upon patients' HRQoL (Almeida et al., 2015, Jung et al., 2016). Given the impact of the widespread orofacial manifestations on both HRQoL and OHRQoL, continuous clinical evaluation should be performed routinely in parallel to the continuous assessment of disease-related mouth disability (Veale et al., 2016).

Although the value and merit of PROMS use in chronic disease have long been established, the importance of selecting and administering appropriately valid and reliable instruments cannot be underestimated. It can be challenging for clinicians and researchers to select appropriate tools. Streiner and Norman (2006) recommended the use of both a generic and a disease-specific outcome measure when evaluating the impact of a disease on the daily life of a patient (Streiner et al., 2014). Generic instruments can demonstrate a change in the HRQoL, but they cannot detect small clinical important changes in a specific disease. On the other hand, specific measures can more accurately predict most of the clinical changes but do not allow for comparison between diseases. However, evidence shows that using both generic and specific HRQoL measures when evaluating the impact of a disease is recommended (Ni Riordain and McCreary, 2010a, Baron et al., 2015c).

Oral health-related quality of life measures have been applied among different groups of oral diseases demonstrating valid and reliable outcomes (Lopez-Jornet and Camacho-Alonso, 2008, Ni Riordain et al., 2016, Pacheco-Pereira et al., 2018). Both SF-36 and OHIP were found to be the most frequently used PROMS when assessing the impact of different oral diseases. It is reasonable to consider using these tools when evaluating the impact of the oral manifestations of SSc on patients (Ni Riordain and McCreary, 2010b). However, concerns have been expressed regarding the

suitability of OHIP-14 as an OHRQoL measure in certain patient cohorts (Locker and Allen, 2002, Allen and Locker, 2002). Therefore, using specific disease HRQoL measures could offer more accurate and reliable results in both clinical and research settings as seen in recent reports (Maddali-Bongi et al., 2014, Bennani et al., 2016, Blezien et al., 2017, Gheisari et al., 2018).

MHISS was developed as a disease-specific tool to specifically evaluate the 'Mouth Handicap' in patients with SSc. This may be a viable alternative to OHIP-14 in this patient population. The oral health-related quality of life has been assessed by MHISS scale in many studies (Mestre-Stanislas et al., 2010, Maddali Bongi et al., 2013, Nguyen et al., 2014, Bennani et al., 2016, Gheisari et al., 2018). MHISS has been reported to have acceptable validity and reliability in different languages over different countries (Mouthon et al., 2007, Maddali Bongi et al., 2012, Schouffoer et al., 2013). To the best of our knowledge, there is no study that has investigated the psychometric properties of the MHISS questionnaire among patients with SSc in the UK. Therefore the aim of this study was to explore the psychometric properties of MHISS in a cohort of UK patients with SSc.

Current results demonstrate a moderate correlation between MHISS total score and SF-36 general health (r=-0.446) and other domains. However, the low correlation level that has been reported among different SF-36 subscales highlighted that the SF-36 questionnaire could not comprehensively capture and evaluate specific orofacial impairments related to SSc including mouth opening reduction, mouth dryness and impaired aesthetics. Therefore, OHRQoL should be evaluated using disease-specific HRQoL measures.

Also, the low to moderate level of correlation between the MHISS and the SF-36 different subscales was found to be similar to the previous studies (Maddali-Bongi et al., 2014). However, this lack of correlation might be related to the nature of the generic properties of the SF-36 as it is proposed to evaluate the HRQoL with no specific assessment of the mouth disability in SSc patients. Despite the fact that generic measures might be less responsive due to their focus on general aspects of HRQoL, implementing such generic measures might help to detect an unexpected clinical event that may be out of the scope of other specific tools.

Furthermore, current results demonstrated that the total MHISS score has a high correlation with total OHIP-14 (r=0.725) and most of its domains. However, low to moderate level of correlation has been noticed between different MHISS and OHIP subscales, and this might emphasise the need for using more HRQoL measures related to mouth disability among patients with SSc.

Although these overall values reflect moderate to high convergent validity, variations among different subscales could be further explored in a more general study sample of patients with SSc undertaking qualitative assessment regarding the MHISS instrument and the impact of the disease on their lives and daily activities.

Cronbach's alpha should approach a good level for the instrument to be considered reliable for use in clinical practice. MHISS has shown a good level of internal consistency reliability as the values of Cronbach’s alpha for the MHISS total score was 0.894 and this was also mirrored in the study of the Dutch version of MHISS reporting a good internal consistency reliability level of MHISS with a total MHISS score of 0.88 (Schouffoer et al., 2013). Although these values are considered good they are lower than the values found in a previous study using an Italian translated version of MHISS in patients with SSc which demonstrated excellent reliability (Cronbach’s alpha = 0.99)

(Maddali Bongi et al., 2012). However, these values of reliability could be further investigated in a different setting to obtain precise estimates as it is dependent on the number of items as well as the level of correlation between them.

MHISS is suggested not only to measure the face and mouth handicap among patients with SSc but is also found to be useful in assessing the improvement of the face and mouth after different therapeutic interventions including a facial rehabilitation programme and physiotherapy, laser therapy, autologous fat grafting treatment modalities, and evaluating the outcomes after dental therapeutic intervention (Maddali-Bongi et al., 2011, Bennani et al., 2016, Maddali-Bongi and Del Rosso, 2016, Blezien et al., 2017). Because of this, disease-specific measures are believed to be useful in routine in clinical practice as well as research trials.

In this current study, the validity and internal consistency reliability of MHISS have been tested, and the MHISS has been used to assess the impact of SSc on the HRQoL of English-speaking patients living in the UK. This study has demonstrated that SSc can affect the physical, social, emotional and psychological aspects of the patients. Thus, patients with SSc could require detailed evaluation and specific oral management that might involve a multidisciplinary team with a comprehensive healthcare approach. Therefore additional research is required to refine SSc general and specific PROMS to comprehensively assess the overall HRQoL with a specific focus on particular aspects and manifestations of OHRQoL.

5. Conclusion

Given the impact of the widespread orofacial manifestations of SSc on HRQoL, healthcare providers caring for patients with SSc should be aware of the availability of such a reliable and valid instrument and its essential role to improve OHRQoL. Current results suggest that the MHISS is a valid and reliable instrument to evaluate mouth-related disability in patients with SSc and can be considered potentially useful in daily clinical practice. However, further exploration of related psychometric properties of the questionnaire and its individual domains could facilitate better cross-cultural adaptation among different groups of patients with SSc in different populations.

CHAPTER 7: GENERAL DISCUSSION

Systemic sclerosis (SSc) is a rare autoimmune connective tissue disorder of middle-aged and elderly persons giving rise to wide range of often clinically significant systemic and oral problems that have the capacity to adversely affect the patients' health-related quality of life (HRQoL) and adversely impact upon oral health and the delivery of oral health care (Almeida et al., 2015, Salaffi et al., 2019). Orofacial features can significantly affect the ability to speak, eat and swallow, and ultimately can lessen oral health-related quality of life (OHRQoL). Additionally, SSc can also affect the profile of oral and facial appearance and thus has the potential to cause patient embarrassment, upset and psychological morbidity (Baubet et al., 2011, Bragazzi et al., 2019).

In the past decade, there has been a considerable advance in the knowledge of various aspects of this disorder, but there are still only a few detailed epidemiological studies of SSc which have been carried out, particularly in the UK population. A recent study estimated that there are currently more than one thousand new cases of SSc each year in the UK and approximately 19,000 people living with SSc (Royle et al., 2018). Therefore, the incidence and prevalence of SSc that affects the orofacial region is largely unknown. However, the true prevalence has been suggested to be higher than that suggested previously in the literature. The establishment of a national and international register for this rare disorder would help researchers and practitioners to better study and understand the related clinical features and prevalence of this disease resulting in earlier diagnosis and better management.

The first part of this study retrospectively examined the nature and clinical features of a large cohort of patients with SSc living in the UK. The group comprised of 138 patients with SSc referred to a single London hospital dental clinic, Oral Medicine Unit

of UCLHT Eastman Dental Hospital. It was noted that only one case of childhood SSc was encountered. As expected, the patients were predominantly female in middle to late life and predominantly white British, thus reflecting the epidemiology of SSc (Jung et al., 2016, Smirani et al., 2018b). The proportions of patients with different SSc subtypes varied from previous studies. However the proportions in the present cohort were within the expected ranges as present data demonstrated that 42% of patients had a diffuse cutaneous subtype, 31.2% had limited cutaneous SSc, and 26.8% had other mixed/overlap connective tissue diseases (Willems et al., 2014, Gomes da Silva et al., 2019). Although the results of the present study indicate that most of the patients with SSc were registered with general dental clinics, the reasons for referral of those patients were generally for the supposed difficulty in obtaining routine dental care and/or for further consultation and treatment needs. The present data confirm previous studies that patients with SSc tend to have distinct characteristics of orofacial involvement such as more decayed and/or missing teeth, increased risk of periodontal disease, microstomia, xerostomia, oral infections, dysphagia, oral ulceration and temporomandibular joint dysfunction than systemically well individuals (Nagy et al., 1994, Maddali Bongi et al., 2009, Maddali-Bongi et al., 2011, Chu et al., 2011, Chapin and Hant, 2013, Baron et al., 2014, Del Rosso and Maddali-Bongi, 2014, Jung et al., 2016, Hadj Said et al., 2016a, Burchfield and Vorrasi, 2019). These findings emphasise the need for close working collaboration between specialists as early diagnosis and management of orofacial changes can prevent at least some oral complications of the disease, such as caries and periodontal disease.

The treatment of SSc is likely to be long-term and at present does not lead to complete resolution of most of the orofacial disorders. Previous non-pharmacological therapeutic trials have reported some degree of positive effects regarding

temporomandibular joint dysfunction, reduced mouth opening and decreased manual dexterity in patients with SSc. However, although there have been relatively small numbers of reports on the use of such treatments (Poole et al., 2004, Alantar et al., 2011, Maddali-Bongi et al., 2011, Poole et al., 2013, Willems et al., 2015b, Maddali-Bongi and Del Rosso, 2016, Khanna et al., 2018) there remain no published well-designed randomised controlled trials for the prevention and treatment of oral disease of SSc. New surgical treatment such as autologous fat grafting therapeutic technique (AFGT), autologous adipose-derived stromal cells (ADSCs) and intralesional injections while possibly promising, are costly, necessitate detailed clinical monitoring and carry a risk of significant adverse side effects (Del Papa et al., 2015, Kumar et al., 2016, Onesti et al., 2016, Del Papa et al., 2016).

Oral treatment and rehabilitation for patients with SSc are important as the orofacial disease can adversely impact upon the quality of life. A multidisciplinary team approach is essential as most of the patients were referred to the special needs dental clinic as well as another speciality for further treatment. This might be related to the severity of the disease and the relatively high levels of associated impaired mobility, difficult dental access due to reduced mouth opening and abnormal manual dexterity making effective oral hygiene difficult for them. Due to the nature of the disease, it is important to consider the impact of the disease on all of the associated tissue structures and the health-related quality of life bearing in mind all other available alternative treatment modalities including simplicity, future repair services and financial concerns. Most of the reported studies used to manage patients with oral and/or dental problems have comprised small patient groups; as a result, the management of such disease is largely based on clinical experience not controlled research.

There is a need for detailed, well-designed studies to provide high-quality evidence on the efficacy of treatment of the orofacial consequences of SSc. However, one problem with implementing such research is the limited number of patients that attend individual clinical units and the associated co-morbidity of the disease that makes it difficult for patients to commit to long-term clinical studies.

The present study sought to determine the perceived oral health problems and oral health care experience of a large number of individuals with SSc, and indeed, represents the first such investigation of its type in the UK. The results of the patients were compared to their partners or relatives as well as to the access for NHS dentistry study by MORI 2008 and adult dental health survey (ADHS 2009). Although the majority of individuals in the study group, both patients and partners did have access to dental services, the greatest number of patients believed that SSc has adversely affected their oral and general health. While 20% of patients reported difficulties in obtaining dental care, 42% of patients and 27.8% of partners believed that access to dental care could be improved. However, the present results point towards a need to ensure that the access that patients presently have to dental care is enhanced and that the strategies to ensure that patients are able to maintain good oral hygiene are well established.

It might be expected in the 21st century that patients with SSc, or indeed their carers or relatives or partners would seek information from the World Wide Web. The study has sought to evaluate the related online information for the treatment of oral disability in SSc as part of the patient information needs. This part of the study included categorisation of the content and assessment of the quality and readability of included websites concerning oral health and treatment of the mouth in SSc by using the DISCERN instrument, the Journal of the American Medical Association (JAMA)

benchmarks and the HON seal in a standardised data collection document. However, included websites indicated poor quality and questionable reliability of the content of the associated online sources in relation to the treatment of the mouth in SSc. The readability level of the available online information did not meet the recommended levels to be read and understood easily by a general population. This availability of reliable online sources may be due to the rarity and relatively low prevalence of the disease.

Nevertheless, more efforts should be directed to construct a well informed and knowledgeable level of online sources that can help to facilitate the patients' education and overall healthcare management. Patient education is crucial in the management of rheumatology disorders such as SSc as most of the relevant disorders are chronic, requiring long term treatment and follow-up. Sources include the clinician, support groups, internet sites and brochures. Detailed information on clinical presentation, diagnosis, treatment options and prognosis should be provided as well as information on the presumed adverse therapeutic side effects and/or increased risk of cancer either from the disease or treatment agents and more general advice on any habits (e.g. tobacco smoking cessation, alcohol consumption, maintaining a healthy balanced diet, maintaining good oral hygiene and regular review by a general dental practitioner).

As SSc can sometimes give rise to disease that can compromises orofacial features, it would be anticipated that the quality of life of affected individuals will be compromised. This study has explored the health-related quality of life (HRQoL) and oral health-related quality of life (OHRQoL) of a substantial group of patients with SSc. Aiming to assess the impact of SSc upon health and well-being, different patient-reported outcome measures (PROMs) have been employed (e.g. SF-36, OHIP-14,

MHISS, HADS, MDAS and OIDP) with results indicating that SSc has a negative impact on both general and oral health-related quality of life of the affected individuals. The Mouth Handicap Scale in Systemic Sclerosis (MHISS) was found to be the only tool that specifically measured patient-reported mouth problems in SSc and was found to be both valid and reliable for use in English speaking patients with SSc resident in the UK.

As the patient is considered the centre of the healthcare system, patient-centred care is considered the best approach able to reflect the quality of life of the affected individual (Scambler et al., 2016). According to the Food and Drug Administration (FDA), a patient-reported outcome is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. Indeed, PROMs have been used as effective assessment tools in both clinical practice and research-based trials (Pauling et al., 2017). Systemic sclerosis is known to be chronic in its course and is associated with significant morbidity and mortality as one of the most severe connective tissue disorders (Pearson et al., 2018). Perhaps the most common features of SSc is associated with progressive skin thickening and fibrosis that classically involves the orofacial tissues and may also affect other parts of the body and internal organs causing substantial disfigurement and disability thus impacting patients throughout many domains of their well-being (Denton, 2015, Desbois and Cacoub, 2016). A high level of physical and psychological complications (e.g. pain, fatigue, depression, anxiety and fear) can arise in patients with SSc (Baubet et al., 2011, Del Rosso et al., 2013). Present results highlighted that SSc disease and associated orofacial features radically affected the health-related quality of life. Patients with SSc have a higher prevalence of psychological problems including depression and anxiety.

Oral health-related quality of life has been assessed by a specific tool (MHISS) that provides unique insight into the impact of the disease on mouth involvement. MHISS demonstrate a moderate to high convergent validity and a good level of reliability; thus, it can be considered for use in routine clinical practice in the UK. The assessment of disease status, disease impact, multi-organ involvement and other relevant outcomes such as oral health-related quality of life is particularly challenging in a multi-faceted disease like SSc thus the development and validation of specific tools measuring patient-reported outcomes in SSc are necessary. Scleroderma Clinical Trials Consortium (SCTC), consists of 11 working groups dealing with a variety of aspects of SSc, experts from worldwide and international multicentre disease sites have established its research work aiming to improve clinical trials and observational studies by improving or developing better, more sensitive ways of measuring various aspects of the disease. A recent report has raised concerns regarding SSc morbidity that leads to disability and poor quality of life. It has been concluded that careful attention should be paid to the outcome measures in SSc to improve and enhance the scoring system of various patient-reported outcome measures that deal with SSc disease and its future clinical applications that include; use as an outcome measure and enrichment tool for patient selection in clinical trials, a tool to describe the course of the disease in observational studies and an instrument to quantify disease burden for epidemiological studies and policy-making (Baron et al., 2019).

LIMITATIONS AND SUGGESTED FURTHER STUDIES

There are several factors which may have affected the validity of the data in this study. The analysis of the orofacial features of SSc (Chapter 2) had a retrospective design; hence the results must be interpreted with caution. While retrospective studies are less expensive and time-consuming than prospective studies, can cover extended periods and are often used to report rare diseases they might be limited by bias, lack of agreement on exclusion and inclusion criteria, incomplete data, differences in reporting clinical features and outcomes, variations in diagnostic and monitoring procedures and definition of some terms (Mann, 2003). It is thus important to recognise the importance of detailed data recording when attempting a retrospective study. The more detailed information collected, the more likely these data are to contribute to expanding our knowledge in the future.

Other parts of the study were observational cross-sectional designed investigations, therefore, were limited by the lack of definitive diagnosis of SSc and that all participants were not examined clinically. Furthermore, the sample size was relatively small and may have introduced bias as the individuals who attended the Scleroderma family day event on the weekend were from all across England, may possibly not have mobility issues and be highly motivated as regards their general oral health. This might explain the reason for having a high level of registration status with the dentist. The quality and quantity of the data were variable, and it would be erroneous to draw definitive conclusions from data that lack the statistical power to validate them.

Despite these limitations, this study provides useful information on the oral health status of people with SSc, and it allows a rational understanding of the oral health-related quality of life and dental care needs of people with SSc in the UK. However, suggestions for future work would be to design a much more detailed prospective

longitudinal study with a larger cohort, possibly at more than one centre in the UK to confirm the present observations. Also, a further survey to evaluate and provide an indication of the level of awareness of SSc among general dental practitioners and the willingness of these practitioners to treat patients with SSc is warranted. In view of the present results, there is perhaps sufficient evidence to consider developing packages that provide patients and partners with information about the self-maintenance of oral health and sources of professional oral health care.

CONCLUSION

Although SSc is considered rare multisystem connective tissue disease, patients with SSc as reported in this study, commonly have orofacial involvement such as microstomia, xerostomia, maxillofacial bone resorption, increased risk of caries and periodontal disease. The hallmark signs of this disorder involve excess collagen deposition affecting the connective tissues and vascular hyper-reactivity of the skin and internal organs. Patients with SSc in this study frequently presented with systemic diseases and concurrent medications, making medical assessment and management more complex.

There are many challenges in the management of the orofacial aspects of SSc for both patients and their attendant clinicians. Patients with SSc have reported difficulty accessing dental care, registering with dentists and/or maintaining good oral hygiene due to disease co-morbidity. The results indicate that there is a need to ensure proper access to dental services and improve the management of associated oral disability. Part of this study highlights the poor quality, questionable reliability and difficult readability of the content of the available online information regarding the treatment of the mouth in SSc. Therefore, patients should be aware of the current shortcomings while searching for online health advice of the treatment of the mouth in SSc. However, clinicians should provide guidance to patients regarding the most reliable information sources. Furthermore, the responses of the SSc patients included in this study revealed a high level of psychological disability and a significant negative impact on health-related quality of life. However, the present results indicated good psychometric properties of MHISS among the patients with SSc in the UK, and hence this could be readily introduced into clinical practice in the UK.

CHAPTER 8: REFERENCES

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APPENDIX 1

Oral Health of People with Scleroderma

We would be grateful if you could fill out this anonymous questionnaire.
This questionnaire is designed for individuals with scleroderma.

Please just circle any appropriate answers or complete the free text sections as you might wish.

- **Personal Data:**

Gender (please circle): (Male / Female). **Date of birth: (**……../……../……**)**

Marital status: (……**)**

Town/Postcode (optional**): (**……**)**

Ethnicity (please circle):

1. British White.
2. Other White.
3. Indian.
4. Pakistani.
5. Other black backgrounds.
6. Bangladeshi.
7. Other Asian backgrounds.
8. Black African.
9. Black Caribbean.
10. Other, please specify: (……)

Smoking (please circle): (Yes / No)**, if yes,** (Cigarettes), (Cigar), (Pipe)
Number per day: (……**)**

Alcohol (please circle): (Yes / No),
If yes, Unites per week: (……..…**)**

Do you have any educational, professional, vocational or other work-related qualifications for which you received a certificate? (Yes / No)
If yes, was your highest qualification? (Please circle)

1. At degree-level or above.
2. Another kind of qualification.

Do you do any paid work either as an employee or self-employed? (Yes / No**)**
If yes, do you work as an employee or do you self-employed? (Please circle)

1. Employee.
2. Self-employed.
3. Government scheme.
4. Unpaid work.

In your main job do you working: (Full-time / Part-time)
If part-time, is it because? (Please circle)

1. You are a student/you are at school.
2. You are ill or disabled.
3. You cannot find a full-time job.
4. You do not want a full-time job.

Which kinds of income you personally receive? (Please circle)

1. Earnings from employment.
2. Earnings from self-employment.
3. Pension from former employer.
4. Personal pension.
5. Child benefit.
6. Income support.
7. Tax credits.
8. Other state benefits.
9. Interest from saving
10. Interest from investments
11. Other kinds of regular allowance from outside the household
12. Income from rent
13. Other sources
14. No source of income

Which band represent your total personal income before all deductions? (Please circle)

1. Less than £100 a week.
2. £100 but less than £200.
3. £200 but less than £300.
4. £300 but less than £400.
5. £400 but less than £500.
6. £500 but less than £600.
7. £600 but less than £700.
8. £700 but less than £800.
9. £800 but less than £900.
10. £900 but less than £1000 a week.
11. Over £1000 a week.

- **Date of Diagnosis and Type:**

When you were diagnosed of having Scleroderma? (……..……**)**

If possible, can you indicate the type of Scleroderma that you have? (Please circle)

1. Diffuse cutaneous scleroderma.
2. Localized cutaneous scleroderma.
3. Sine scleroderma.
4. Mixed connective tissue disease/overlap scleroderma.
5. Other type. Please specify (……..……).

- **Oral Health Status (Function and Dentition)**

How is your health in general? (Please circle)

1. Very good.
2. Good.
3. Fair.
4. Bad.
5. Very bad.

How many natural teeth have you got now? (……)

How would you rate your oral health at this time? (Please circle)

1. Very good.
2. Good.
3. Fair.
4. Bad.
5. Very bad.

Apart from your scleroderma condition, do you have any long-standing illness, disability or infirmity – by long-standing I mean anything that has troubled you over a period of time or that is likely to affect you over a period of time? (Yes / No)

If yes, does this illness or disability limit your ability to attend the dentist for routine checkups or treatment in any way? (Yea / No)

Does scleroderma affect your general health? (Yes / No)

If yes, how?

Do these health issues affect the way you receive dental care? (Yes / No)

If yes, how?

Do you think any medications taken for scleroderma have influenced your dental care? (Yes / No)

If yes, how?

- **Dental History, Attitude and Pattern of Dental Attendance:**

Are you currently having any mouth problems? (Yes / No)

If yes, what?

If you went to the dentist tomorrow, do you think you would need any treatment? (Yes / No)

Have you registered with a dentist that you regularly attend? (Yes / No)

If yes, are you registered with? (Please circle)

1. Private dental care.
2. NHS dental care that you paid for.
3. NHS dental care that was free.
4. NHS dental care followed by additional private dental care.
5. Hospital dental care.
6. Some other type of care.
7. Not sure.

Would you say that nowadays you go to the dentist more often, about the same, or less often than you did five years ago? (Please circle)

1. More often.
2. About the same.
3. Less often.

How many times have you been to the dentist in the last five years purely for a checkup? (……..)

How many times have you been to the dentist in the last five years because you have had trouble with your teeth and/or dentures? (……)

In general, do you go to the dentist for? (Please circle)

1. A regular check-up.
2. An occasional check-up.
3. Only when you're having trouble with your teeth/dentures.
4. Never been to the dentist.

How often do you go to the dentist? (Please circle)

1. Once every 6 months.
2. Once every year.
3. Once every 2 years.
4. Less frequently than every 2 years.
5. Only when having trouble with my teeth/denture.

When did you last see a dentist? (Please circle)

1. Within the last 6 months.
2. Within the last 7-12 months.
3. More than 1 year but less than 2 years ago.
4. More than 2 but less than 3 years ago.
5. More than 3 but less than 5 years ago.
6. More than 5 but less than 10 years ago.
7. More than 10 years ago.

What was the reason/Purpose of your visit? (Please circle)

1. For a routine check-up.
2. For emergency or urgent treatment.
3. Other treatment (non-emergency, non-urgent).
4. Some other reason.
5. Don't know / can't remember.

During your last completed course of dental treatment, what did you have done? (Please circle)

1. X-ray taken.
2. Teeth filled.
3. Teeth taken out.
4. Root canal treatment.
5. Crowns re (fitted).
6. Treatment for an abscess.
7. Impression taken.
8. New denture fitted/replaced.
9. Implant to replace a missing tooth/teeth.
10. Other.

Have you ever had (please circle as appropriate)

1. Filling.
2. Wisdom teeth extracted.
3. Any other teeth extracted.
4. Tooth crowned.
5. Dental bridge.
6. Implant replaced missing tooth/teeth.
7. Sedation to relax for dental treatment.
8. Teeth bleached (whitened) by a dentist.
9. Teeth Scaled and polished.
10. Fluoride varnish.

When people go to the dentist, they sometimes have to make more than one visit for a course of treatment. When you last went to the dentist, how many visits did you make? (Please circle)

1. One visit.
2. Two visits.
3. Three visits.
4. Four visits.
5. Five visits or more.

If you went to the dentist with an aching back tooth would you prefer the dentist to take it out (extract it) or fill it (supposing it could be filled)? (Please circle)

1. Take it out (extract it).
2. Fill it.

If the dentist said a back tooth would have to be taken out (extracted) or crowned, what would you prefer? (Please circle)

1. Taken out (extracted).
2. Crowned.

Do you have regular oral hygiene care (e.g. scale and polish)? (Yes / No)
If yes, from whom? (Please circle)

1. Dentist.
2. Dental therapist.
3. Dental hygienist.

How often? (Please circle)

1. Once every 6 months.
2. Once every year.
3. Once every 2 years.
4. Less frequently than every 2 years.
5. Only when having trouble with my teeth/denture.

- **Access to Dental Care:**

Have you ever had difficulties in registering with a dentist? (Yes / No)
If yes, what difficulties did you encounter?

Was it related to your scleroderma condition? (Yes / No)

How do you travel to your dentist? (Please circle)

1. Public transport.
2. Private transport.
3. Ambulance or other health service transport.

Do you require anyone to assist you in travelling to your dentist? (Yes / No)

How many miles do you travel to reach your dentist?

1. (1-4) miles.
2. (5-9) miles.
3. (10-19) miles.
4. (20-39) miles.
5. More than 40 miles.

Do you think that access to dental care could be improved? (Yes / No)

If so, how do you think access could be improved?

Have you encountered any difficulties in the past 5 years in obtaining dental care? (Yes / No)
If yes, what difficulties did you encounter?

Do you believe that your condition has influenced the availability of dental care for you? (Yes / No)
If yes, please give details:

Do you believe that your condition has affected your ability to attend a dentist regularly? (Yes / No)
If yes, please give details:

Which of these, if any, are the reasons why you not been to the dentist in the last 2 years? (Please circle)

1. It's difficult to get to / from the dentist.
2. I've had a bad experience with a dentist.
3. I'm too embarrassed to go to the dentist.
4. I don't see the point in going to the dentist.
5. I can't find an NHS dentist/dentist changed to private.
6. I can't afford the NHS charges.
7. I haven't got the time to go.
8. I am afraid of going to the dentists.
9. Keep forgetting/haven't got round to it.
10. Other reasons, please specify (……).

What, if anything, would you say made you use/search for another dental care? (Please circle)

1. Lack of availability of private dentists.
2. Lack of availability of NHS dentists.
3. Better quality of care (treatment/standards/expertise).
4. Location (more accessible/easier to get to).
5. Lower waiting times.
6. Better reputation of surgery/recommendation from friends or family.
7. More types of treatment available.
8. Affordability.
9. My dentist only sees NHS patients.
10. My NHS dentist has gone private.
11. Insurance provided by employer/job.
12. No reason.
13. Other reasons, please specify (……..).

- **<u>Oral Hygiene and Behaviour:</u>**

How often do you clean your teeth/denture? (Please circle)

1. Never.
2. Less than once a day (i.e. not every day).
3. Once a day.
4. Twice a day.
5. Other, please specify (……..).

Do you use anything other than a toothbrush and toothpaste to clean your teeth? (Yes / No)
If yes, what (Please circle as appropriate)

1. Dental floss, flossing aids.
2. Toothpicks/wood sticks.
3. Interdental brushes.
4. Electric brush.
5. Sugar-free chewing gum.
6. Mouthwash.
7. Denture cleaning solution.
8. Others, please specify (……).

Have you encountered any difficulties performing oral hygiene? (Yes / No)
If yes, please detail these problems:

What would you consider is the most difficult thing for you to do when performing oral hygiene?
(Please circle)

1. Brushing your teeth.
2. Flossing
3. Using Interdental brushes.
4. Other, please specify (……..).

Do you feel that your condition has affected the way in which you perform oral hygiene? (Yes / No)
If yes, please give details:

During your last completed course of dental treatment did you have advice provided to you by the dentist or a member of the dental team about how to look after your teeth (diet, brushing or other)? (Yes / No)

- **<u>Orofacial Features:</u>**

Have you experienced any of the following features? (Please circle as many as you think relevant to you)

1. Decreased mouth opening (microstomia).
2. Bleeding/recession gums.
3. Loose/mobile teeth.
4. Loose/mobile denture.
5. Bruising/ulceration of the lining of the mouth (oral mucosa).
6. Tightness of facial skin/oral mucosa.
7. Altered breath smell (halitosis).
8. Difficult root canal treatment (endodontics).
9. Difficulties with dental extractions.
10. Oral infection.
11. Speech impairment (dysarthria).
12. Swallowing difficulty (dysphagia).
13. Altered taste sensation (dysgeusia).
14. Tongue atrophy / ankylosis / rigidity.
15. Salivary gland swelling/hypofunction.
16. Facial/oral telangiectasia (pigmentation).
17. Fissured/cracked lips.

➢ **Short Health Survey (SF36):**

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1- In general, would you say your **health** is: (Please tick **one** box)

Excellent	☐
Very Good	☐
Good	☐
Fair	☐
Poor	☐

2- **Compared to one year ago**, how would you rate your health in general **now**? (Please tick **one** box)

Much better than one year ago	☐
Somewhat better now than one year ago	☐
About the same as one year ago	☐
Somewhat worse now than one year ago	☐
Much worse now than one year ago	☐

➢ The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?
(Please circle **one** number on each line)

Activities	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited At All**
3- **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4- **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5- Lifting or carrying groceries	1	2	3
6- Climbing **several** flights of stairs	1	2	3
7- Climbing **one** flight of stairs	1	2	3
8- Bending, kneeling, or stooping	1	2	3
9- Walking **more than a mile**	1	2	3
10- Walking **several blocks**	1	2	3
11- Walking **one block**	1	2	3
12- Bathing or dressing yourself	1	2	3

➢ During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Please circle **one** number on each line)

	Yes	**No**
13- Cut down on the **amount of time** you spent on work or other activities	1	2
14- **Accomplished less** than you would like	1	2
15- Were **limited** in the **kind** of work or other activities	1	2
16- Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

➢ During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?
(Please circle one number on each line)

	Yes	**No**
17- Cut down on the **amount of time** you spent on work or other activities	1	2
18- **Accomplished less** than you would like	1	2

20- During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

21- How much **bodily** pain have you had during the **past 4 weeks**? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

22- During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

➢ These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that is closest to the way you have been feeling for each item.
(Please circle **one** number on each line)

	All of the Time	**Most of the Time**	**A Good bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
23- Did you feel full of life?	1	2	3	4	5	6
24- Have you been a very nervous person?	1	2	3	4	5	6
25- Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26- Have you felt calm and peaceful?	1	2	3	4	5	6
27- Did you have a lot of energy?	1	2	3	4	5	6
28- Have you felt downhearted and blue?	1	2	3	4	5	6
29- Did you feel worn out?	1	2	3	4	5	6
30- Have you been a happy person?	1	2	3	4	5	6
31- Did you feel tired?	1	2	3	4	5	6

32- During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives etc.)
(Please tick **one** box)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

➢ How TRUE or FALSE is **each** of the following statements for you?
(Please circle **one** number on each line)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
33- I seem to get sick a little easier than other people	1	2	3	4	5
34- I am as healthy as anybody I know	1	2	3	4	5
35- I expect my health to get worse	1	2	3	4	5
36- My health is excellent	1	2	3	4	5

➢ **Oral Health Impact Profile (OHIP-14):**
(Please circle **one** number on each line)

Functional Limitations	**Never**	**hardly ever**	**Occasionally**	**fairly often**	**very often**
Have you had trouble *pronouncing any words* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you felt that your *sense of taste* has worsened because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Physical pain					
Have you had *painful aching* in your mouth?	0	1	2	3	4
Have you found it *uncomfortable to eat any foods* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Psychological discomfort					
Have you been *self-conscious* because of your teeth, mouth or dentures?	0	1	2	3	4
Have you *felt tense* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Physical disability					
Has your *diet been unsatisfactory* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you had to *interrupt meals* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Psychological disability					
Have you found it *difficult to relax* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you been *a bit embarrassed* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Social disability					
Have you been *a bit irritable with other people* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you had *difficulty doing your usual jobs* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Handicap					
Have you *felt that life in general was less satisfying* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you been *totally unable to function* because of problems with your teeth, mouth or dentures?	0	1	2	3	4

- **Mouth Handicap in Systemic Sclerosis Scale (MHISS):**

(Please circle **one** number on each line)

Restriction in mouth opening	**Never**	**hardly ever**	**Occasionally**	**fairly often**	**very often**
I have difficulties opening my mouth	0	1	2	3	4
I have to avoid certain drinks (sparking, alcohol, acidic)	0	1	2	3	4
I Have difficulties chewing	0	1	2	3	4
My dentist has difficulties taking care of my teeth	0	1	2	3	4
My dentition has become altered	0	1	2	3	4
My lips are retracted and/or my cheeks are sunken	0	1	2	3	4
Mouth dryness					
My mouth is dry	0	1	2	3	4
I must drink often	0	1	2	3	4
My meals consist of what I can eat and not what I would like to eat	0	1	2	3	4
I have difficulties speaking clearly	0	1	2	3	4
Aesthetic concerns					
The appearance of my face is modified	0	1	2	3	4
I have trouble with the way my face looks	0	1	2	3	4

- **Oral Impact on Daily Performance (OIDP):**

We would like to know about the severity of any difficulties or problems caused by your mouth, teeth or dentures.

Using the scale from (0 to 5) on the following questions, where **0** is no effect and **5** is a very severe effect, can you tell us what effect the following difficulties and problems have had on your daily life in the past 12 months? (Please circle one response per question)

Impact of oral health problems	No effect					very severe
1- Difficulty eating?	0	1	2	3	4	5
2- Difficulty speaking?	0	1	2	3	4	5
3- Difficulty cleaning your teeth or dentures?	0	1	2	3	4	5
4- Difficulty going out, for example to the shops or visiting someone?	0	1	2	3	4	5
5- Difficulty relaxing (including sleeping)?	0	1	2	3	4	5
6- Problems smiling, laughing and showing teeth without embarrassment?	0	1	2	3	4	5
7- Difficulty carrying out your major work or role?	0	1	2	3	4	5
8- Problems with emotional instability, for example becoming more easily upset than usual?	0	1	2	3	4	5
9- Problems enjoying the contact of other people, such as relatives, friends or neighbours?	0	1	2	3	4	5

- **Hospital Anxiety and Depression (HADS):**

Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.
(Please circle one answer per question)

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

- **Modified Dental Anxiety Scale (MDAS):**

Many people get anxious about visiting the dentist. I would like to ask you some questions about how anxious you get, if at all, with your dental visit.

Please tell us how anxious you get using the scale on the following questions

(Please tick one response per question)

1. **If you went to your Dentist for TREATMENT TOMORROW, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

2. **If you were sitting in the WAITING ROOM (waiting for treatment), how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

3. **If you were about to have a TOOTH DRILLED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

4. **If you were about to have your TEETH SCALED AND POLISHED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

5. **If you were about to have a LOCAL ANAESTHETIC INJECTION in your gum, above an upper back tooth, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

- Please, provide any additional information that you think is relevant: - for example any issues with your mouth or the dental care that you have received.

_____

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Thank you very much for your participation in this survey.

Please return the completed questionnaire to us at the meeting or posted back to us in the attached stamped addressed envelope.

APPENDIX 2

Oral Health of Partners of People with Scleroderma

We would be grateful if you could fill out this anonymous questionnaire.
This questionnaire is designed for your partner/relative or friend.

Please just circle any appropriate answers or complete the free text sections as you might wish.

- **Personal Data:**

Gender (please circle): (Male / Female). **Date of birth: (**……../……../……**)**

Marital status: (……**)**

Town/Postcode (optional**): (**……**)**

Ethnicity (please circle):

1. British White.
2. Other White.
3. Indian.
4. Pakistani.
5. Other black backgrounds.
6. Bangladeshi.
7. Other Asian backgrounds.
8. Black African.
9. Black Caribbean.
10. Other, please specify: (……)

Smoking (please circle): (Yes / No)**, if yes,** (Cigarettes), (Cigar), (Pipe)
Number per day: (……**)**

Alcohol (please circle): (Yes / No),
If yes, Unites per week: (……..…**)**

Do you have any educational, professional, vocational or other work-related qualifications for which you received a certificate? (Yes / No)
If yes, was your highest qualification? (Please circle)

1. At degree-level or above.
2. Another kind of qualification.

Do you do any paid work either as an employee or self-employed? (Yes / No**)**
If yes, do you work as an employee or do you self-employed? (Please circle)

1. Employee.
2. Self-employed.
3. Government scheme.
4. Unpaid work.

In your main job do you working: (Full-time / Part-time)
If part-time, is it because? (Please circle)

1. You are a student/you are at school.
2. You are ill or disabled.
3. You cannot find a full-time job.
4. You do not want a full-time job.

Which kinds of income you personally receive? (Please circle)

1. Earnings from employment.
2. Earnings from self-employment.
3. Pension from former employer.
4. Personal pension.
5. Child benefit.
6. Income support.
7. Tax credits.
8. Other state benefits.
9. Interest from saving
10. Interest from investments
11. Other kinds of regular allowance from outside the household
12. Income from rent
13. Other sources
14. No source of income

Which band represent your total personal income before all deductions? (Please circle)

1. Less than £100 a week.
2. £100 but less than £200.
3. £200 but less than £300.
4. £300 but less than £400.
5. £400 but less than £500.
6. £500 but less than £600.
7. £600 but less than £700.
8. £700 but less than £800.
9. £800 but less than £900.
10. £900 but less than £1000 a week.
11. Over £1000 a week.

- **Date of Diagnosis and Type:**

Do you have Scleroderma? (Yes / No)

- **Oral Health Status (Function and Dentition)**

How is your health in general? (Please circle)

1. Very good.
2. Good.
3. Fair.
4. Bad.
5. Very bad.

How many natural teeth have you got now? (……)

How would you rate your oral health at this time? (Please circle)

1. Very good.
2. Good.
3. Fair.
4. Bad.
5. Very bad.

Do you have any long-standing illness, disability or infirmity – by long-standing I mean anything that has troubled you over a period of time or that is likely to affect you over a period of time? (Yes / No)

If yes, does this illness or disability limit your ability to attend the dentist for routine checkups or treatment in any way? (Yea / No)

Do you believe that your *loved one's condition* has affected their general health? (Yes / No)

If yes, how?

Do these health issues affect the way *they* receive dental care? (Yes / No)

If yes, how?

Do you think any medications taken for scleroderma have influenced *their* dental care? (Yes / No)

If yes, how?

- **Dental History, Attitude and Pattern of Dental Attendance:**

Are you currently having any mouth problems? (Yes / No)

If yes, what?

If you went to the dentist tomorrow, do you think you would need any treatment? (Yes / No)

Have you registered with a dentist that you regularly attend? (Yes / No)

If yes, are you registered with? (Please circle)

1. Private dental care.
2. NHS dental care that you paid for.
3. NHS dental care that was free.
4. NHS dental care followed by additional private dental care.
5. Hospital dental care.
6. Some other type of care.
7. Not sure.

Would you say that nowadays you go to the dentist more often, about the same, or less often than you did five years ago? (Please circle)

1. More often.
2. About the same.
3. Less often.

How many times have you been to the dentist in the last five years purely for a checkup? (……)

How many times have you been to the dentist in the last five years because you have had trouble with your teeth and/or dentures? (……)

In general, do you go to the dentist for? (Please circle)

1. A regular check-up.
2. An occasional check-up.
3. Only when you're having trouble with your teeth/dentures.
4. Never been to the dentist.

How often do you go to the dentist? (Please circle)

1. Once every 6 months.
2. Once every year.
3. Once every 2 years.
4. Less frequently than every 2 years.
5. Only when having trouble with my teeth/denture.

When did you last see a dentist? (Please circle)

1. Within the last 6 months.
2. Within the last 7-12 months.
3. More than 1 year but less than 2 years ago.
4. More than 2 but less than 3 years ago.
5. More than 3 but less than 5 years ago.
6. More than 5 but less than 10 years ago.
7. More than 10 years ago.

What was the reason/Purpose of your visit? (Please circle)

1. For a routine check-up.
2. For emergency or urgent treatment.
3. Other treatment (non-emergency, non-urgent).
4. Some other reason.
5. Don't know / can't remember.

During your last completed course of dental treatment, what did you have done? (Please circle)

1. X-ray taken.
2. Teeth filled.
3. Teeth taken out.
4. Root canal treatment.
5. Crowns re (fitted).
6. Treatment for an abscess.
7. Impression taken.
8. New denture fitted/replaced.
9. Implant to replace a missing tooth/teeth.
10. Other.

Have you ever had (please circle as appropriate)

1. Filling.
2. Wisdom teeth extracted.
3. Any other teeth extracted.
4. Tooth crowned.
5. Dental bridge.
6. Implant replaced missing tooth/teeth.
7. Sedation to relax for dental treatment.
8. Teeth bleached (whitened) by a dentist.
9. Teeth Scaled and polished.
10. Fluoride varnish.

When people go to the dentist, they sometimes have to make more than one visit for a course of treatment. When you last went to the dentist, how many visits did you make? (Please circle)

1. One visit.
2. Two visits.
3. Three visits.
4. Four visits.
5. Five visits or more.

If you went to the dentist with an aching back tooth would you prefer the dentist to take it out (extract it) or fill it (supposing it could be filled)? (Please circle)

1. Take it out (extract it).
2. Fill it.

If the dentist said a back tooth would have to be taken out (extracted) or crowned, what would you prefer? (Please circle)

1. Taken out (extracted).
2. Crowned.

Do you have regular oral hygiene care (e.g. scale and polish)? (Yes / No)
If yes, from whom? (Please circle)

1. Dentist.
2. Dental therapist.
3. Dental hygienist.

How often? (Please circle)

1. Once every 6 months.
2. Once every year.
3. Once every 2 years.
4. Less frequently than every 2 years.
5. Only when having trouble with my teeth/denture.

- **Access to Dental Care:**

Have you ever had difficulties in registering with a dentist? (Yes / No)
If yes, what difficulties did you encounter?

Was it related to any long-standing illness, disability or infirmity condition? (Yes / No)

How do you travel to your dentist? (Please circle)

1. Public transport.
2. Private transport.
3. Ambulance or other health service transport.

Do you require anyone to assist you in travelling to your dentist? (Yes / No)

How many miles do you travel to reach your dentist?

1. (1-4) miles.
2. (5-9) miles.
3. (10-19) miles.
4. (20-39) miles.
5. More than 40 miles.

Do you think that access to dental care could be improved? (Yes / No)

If so, how do you think access could be improved?

Have you encountered any difficulties in the past 5 years in obtaining dental care? (Yes / No)
If yes, what difficulties did you encounter?

Do you believe that your *loved one's* condition has influenced the availability of dental care for *them*? (Yes / No)
If yes, please give details:

Do you believe that your *loved one's* condition has affected *their* ability to attend a dentist regularly? (Yes / No)
If yes, please give details:

Which of these, if any, are the reasons why you not been to the dentist in the last 2 years? (Please circle)

1. It's difficult to get to / from the dentist.
2. I've had a bad experience with a dentist.
3. I'm too embarrassed to go to the dentist.
4. I don't see the point in going to the dentist.
5. I can't find an NHS dentist/dentist changed to private.
6. I can't afford the NHS charges.
7. I haven't got the time to go.
8. I am afraid of going to the dentists.
9. Keep forgetting/haven't got round to it.
10. Other reasons, please specify (……..…….).

What, if anything, would you say made you use/search for another dental care? (Please circle)

1. Lack of availability of private dentists.
2. Lack of availability of NHS dentists.
3. Better quality of care (treatment/standards/expertise).
4. Location (more accessible/easier to get to).
5. Lower waiting times.
6. Better reputation of surgery/recommendation from friends or family.
7. More types of treatment available.
8. Affordability.
9. My dentist only sees NHS patients.
10. My NHS dentist has gone private.
11. Insurance provided by employer/job.
12. No reason.
13. Other reasons, please specify (……..…).

- **<u>Oral Hygiene and Behaviour:</u>**

How often do you clean your teeth/denture? (Please circle)

1. Never.
2. Less than once a day (i.e. not every day).
3. Once a day.
4. Twice a day.
5. Other, please specify (……..).

Do you use anything other than a toothbrush and toothpaste to clean your teeth? (Yes / No)
If yes, what (Please circle as appropriate)

1. Dental floss, flossing aids.
2. Toothpicks/wood sticks.
3. Interdental brushes.
4. Electric brush.
5. Sugar-free chewing gum.
6. Mouthwash.
7. Denture cleaning solution.
8. Others, please specify (……).

Have you noticed any difficulties in your *loved one's* performing oral hygiene? (Yes / No)
If yes, please detail these problems:

What would you consider is the most difficult thing for your *loved one's* when performing oral hygiene? (Please circle)

1. Brushing your teeth.
2. Flossing.
3. Using Interdental brushes.
4. Other, please specify (……..).

Do you feel that your *loved one's* condition has affected the way in which *they* perform oral hygiene? (Yes / No)

If yes, please give details:

During your last completed course of dental treatment did you have advice provided to you by the dentist or a member of the dental team about how to look after your teeth (diet, brushing or other)? (Yes / No)

- **Orofacial Features:**

Have you experienced any of the following features? (Please circle as many as you think relevant to you)

1. Decreased mouth opening (microstomia).
2. Bleeding/recession gums.
3. Loose/mobile teeth.
4. Loose/mobile denture.
5. Bruising/ulceration of the lining of the mouth (oral mucosa).
6. Tightness of facial skin/oral mucosa.
7. Altered breath smell (halitosis).
8. Difficult root canal treatment (endodontics).
9. Difficulties with dental extractions.
10. Oral infection.
11. Speech impairment (dysarthria).
12. Swallowing difficulty (dysphagia).
13. Altered taste sensation (dysgeusia).
14. Tongue atrophy / ankylosis / rigidity.
15. Salivary gland swelling/hypofunction.
16. Facial/oral telangiectasia (pigmentation).
17. Fissured/cracked lips.

➢ **Short Health Survey (SF36):**

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1- In general, would you say your **health** is: (Please tick **one** box)

Excellent	☐
Very Good	☐
Good	☐
Fair	☐
Poor	☐

2- **Compared to one year ago**, how would you rate your health in general **now**? (Please tick **one** box)

Much better than one year ago	☐
Somewhat better now than one year ago	☐
About the same as one year ago	☐
Somewhat worse now than one year ago	☐
Much worse now than one year ago	☐

➢ The following questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?
(Please circle **one** number on each line)

Activities	**Yes, Limited A Lot**	**Yes, Limited A Little**	**No, Not Limited At All**
3- **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4- **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5- Lifting or carrying groceries	1	2	3
6- Climbing **several** flights of stairs	1	2	3
7- Climbing **one** flight of stairs	1	2	3
8- Bending, kneeling, or stooping	1	2	3
9- Walking **more than a mile**	1	2	3
10- Walking **several blocks**	1	2	3
11- Walking **one block**	1	2	3
12- Bathing or dressing yourself	1	2	3

➢ During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Please circle **one** number on each line)

	Yes	**No**
13- Cut down on the **amount of time** you spent on work or other activities	1	2
14- **Accomplished less** than you would like	1	2
15- Were **limited** in the **kind** of work or other activities	1	2
16- Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

➢ During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (e.g. feeling depressed or anxious)?
(Please circle one number on each line)

	Yes	**No**
17- Cut down on the **amount of time** you spent on work or other activities	1	2
18- **Accomplished less** than you would like	1	2

20- During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

21- How much **bodily** pain have you had during the **past 4 weeks**? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

22- During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

➢ These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that is closest to the way you have been feeling for each item.

(Please circle **one** number on each line)

	All of the Time	Most of the Time	A Good bit of the Time	Some of the Time	A Little of the Time	None of the Time
23- Did you feel full of life?	1	2	3	4	5	6
24- Have you been a very nervous person?	1	2	3	4	5	6
25- Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26- Have you felt calm and peaceful?	1	2	3	4	5	6
27- Did you have a lot of energy?	1	2	3	4	5	6
28- Have you felt downhearted and blue?	1	2	3	4	5	6
29- Did you feel worn out?	1	2	3	4	5	6
30- Have you been a happy person?	1	2	3	4	5	6
31- Did you feel tired?	1	2	3	4	5	6

32- During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

➢ How TRUE or FALSE is **each** of the following statements for you?

(Please circle **one** number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33- I seem to get sick a little easier than other people	1	2	3	4	5
34- I am as healthy as anybody I know	1	2	3	4	5
35- I expect my health to get worse	1	2	3	4	5
36- My health is excellent	1	2	3	4	5

➢ **Oral Health Impact Profile (OHIP-14):**
(Please circle **one** number on each line)

Functional Limitations	**Never**	**hardly ever**	**Occasionally**	**fairly often**	**very often**
Have you had trouble *pronouncing any words* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you felt that your *sense of taste* has worsened because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Physical pain					
Have you had *painful aching* in your mouth?	0	1	2	3	4
Have you found it *uncomfortable to eat any foods* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Psychological discomfort					
Have you been *self-conscious* because of your teeth, mouth or dentures?	0	1	2	3	4
Have you *felt tense* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Physical disability					
Has your *diet been unsatisfactory* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you had to *interrupt meals* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Psychological disability					
Have you found it *difficult to relax* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you been *a bit embarrassed* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Social disability					
Have you been *a bit irritable with other people* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you had *difficulty doing your usual jobs* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Handicap					
Have you *felt that life in general was less satisfying* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you been *totally unable to function* because of problems with your teeth, mouth or dentures?	0	1	2	3	4

- **Mouth Handicap in Systemic Sclerosis Scale (MHISS):**

(Please circle **one** number on each line)

Restriction in mouth opening	**Never**	**hardly ever**	**Occasionally**	**fairly often**	**very often**
I have difficulties opening my mouth	0	1	2	3	4
I have to avoid certain drinks (sparking, alcohol, acidic)	0	1	2	3	4
I Have difficulties chewing	0	1	2	3	4
My dentist has difficulties taking care of my teeth	0	1	2	3	4
My dentition has become altered	0	1	2	3	4
My lips are retracted and/or my cheeks are sunken	0	1	2	3	4
Mouth dryness					
My mouth is dry	0	1	2	3	4
I must drink often	0	1	2	3	4
My meals consist of what I can eat and not what I would like to eat	0	1	2	3	4
I have difficulties speaking clearly	0	1	2	3	4
Aesthetic concerns					
The appearance of my face is modified	0	1	2	3	4
I have trouble with the way my face looks	0	1	2	3	4

- **Oral Impact on Daily Performance (OIDP):**

We would like to know about the severity of any difficulties or problems caused by your mouth, teeth or dentures.

Using the scale from (0 to 5) on the following questions, where **0** is no effect and **5** is a very severe effect, can you tell us what effect the following difficulties and problems have had on your daily life in the past 12 months? (Please circle one response per question)

Impact of oral health problems	No effect					very severe
1- Difficulty eating?	0	1	2	3	4	5
2- Difficulty speaking?	0	1	2	3	4	5
3- Difficulty cleaning your teeth or dentures?	0	1	2	3	4	5
4- Difficulty going out, for example to the shops or visiting someone?	0	1	2	3	4	5
5- Difficulty relaxing (including sleeping)?	0	1	2	3	4	5
6- Problems smiling, laughing and showing teeth without embarrassment?	0	1	2	3	4	5
7- Difficulty carrying out your major work or role?	0	1	2	3	4	5
8- Problems with emotional instability, for example becoming more easily upset than usual?	0	1	2	3	4	5
9- Problems enjoying the contact of other people, such as relatives, friends or neighbours?	0	1	2	3	4	5

- **Hospital Anxiety and Depression (HADS):**

Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.
(Please circle one answer per question)

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	3
Hardly at all	2

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

- **Modified Dental Anxiety Scale (MDAS):**

Many people get anxious about visiting the dentist. I would like to ask you some questions about how anxious you get, if at all, with your dental visit.

Please tell us how anxious you get using the scale on the following questions

(Please tick one response per question)

1. **If you went to your Dentist for TREATMENT TOMORROW, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

2. **If you were sitting in the WAITING ROOM (waiting for treatment), how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

3. **If you were about to have a TOOTH DRILLED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

4. **If you were about to have your TEETH SCALED AND POLISHED, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

5. **If you were about to have a LOCAL ANAESTHETIC INJECTION in your gum, above an upper back tooth, how would you feel?**

Not Anxious ☐	*Slightly Anxious* ☐	*Fairly Anxious* ☐	*Very Anxious* ☐	*Extremely Anxious* ☐

- Please, provide any additional information that you think is relevant: - for example any issues with your mouth or the dental care that you have received.

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Thank you very much for your participation in this survey.

Please return the completed questionnaire to us at the meeting or posted back to us in the attached stamped addressed envelope.

Published papers

Web-based information on the treatment of the mouth in systemic sclerosis.

Validity and reliability of the Mouth Handicap of Systemic Sclerosis questionnaire in a UK population.

Meeting presentation

Web-based information on the treatment of the mouth in systemic sclerosis – IADR/PER July 2018 in London, UK.

Self-reported oral and dental experience of patients with systemic sclerosis - EAOM September 2018 in Gothenburg, Sweden.

Web-based information on the treatment of the mouth in systemic sclerosis – IADR Saudi Arabia Division Annual meeting - April 2019 in Makkah, KSA.

Self-reported oral and dental experience of patients with systemic sclerosis - IADR Saudi Arabia Division Annual meeting - April 2019 in Makkah, KSA.

Validity and reliability of the Mouth Handicap in Systemic Sclerosis (MHISS) questionnaire in a UK population – Scleroderma family day – May 2019 in London, UK.

Measuring the impact of systemic sclerosis on oral health-related quality of life in the UK – World Dental and Oral Health Congress – July 2019 in London, UK.