

Quality of life in Sjögren syndrome patients

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Quality of life in Sjögren Syndrome Patients

GRADUATE THESIS



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This graduation paper was made at the Division of Clinical Immunology, Pulmonology and Rheumatology; Department of Internal Medicine, Clinical Hospital Centre "Sisters of Mercy", School of Medicine, University of Zagreb, under the supervision of Prof. Jasenka Markeljevic, MD, PhD, and it was submitted for evaluation in the academic year of 2014/2015.

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Abbreviations:

SS - Sjögren's syndrome

pSS - primary Sjögren's syndrome

sSS - secondary Sjögren's syndrome

HRQOL - Health related quality of life

AECG-criteria - American and European Consensus Group classification

SLE - systemic lupus erythematosus

NSAID - non steroidal anti inflammatory drug

FSS - fatigue severity scale

FACIT-F - functional assessment of chronic illness therapy - fatigue

VAS-F - fatigue visual analogue scale

WHOQOL-BREF - World Health Organization Quality of Life Assessment-BREF

PHQ-9 - Patient Health Questionnaire

HADS - Hospital Anxiety and Depression Scale

SUMMARY

Quality of life is an essential component of the way Sjögren's syndrome should be evaluated, indicating that management of such patients is not a simple task one would think, but the life that the patient leads, and the quality of it must be engaged as a whole. Sjögren's syndrome is a chronic inflammatory autoimmune illness, slowly progressing and targeting the body's exocrine glands. Ranging from xerophthalmia and xerostomia to more systemic and severe manifestations, Sjögren's syndrome may also co-exist with other diseases of autoimmune origin and also progress to more malignant scenarios. Somewhat subtle presentation leads to delays in all aspects, causing severe impairment of the life that this individual leads, both physically and mentally. Diagnosis remains one of the major difficulties, as it overlaps with other autoimmune diseases, making diagnosis usually a long and tedious process, burdening the patient and impairing their quality of life. The health related quality of life is a multifactorial assessment, and can be evaluated using different models to assess mental and physical well being, such as the Short-Form Health Survey questionnaire 36 (SF 36) and other patient centered questionnaires. The therapeutic management includes the separation into glandular and systemic manifestations and their respective treatment modalities. Symptomatic therapy dominates for the glandular manifestations, including replacement and stimulation of fluids, while various disease modifying drugs are used for these systemic or extraglandular manifestations. Impaired function is associated with reduced quality of life and symptoms such as pain, fatigue, and depression, as well as disease activity, illustrating the importance of optimal management of all aspects of the disease.

Key words: Sjogren's syndrome, quality of life, xerophthalmia, xerostomia

1. INTRODUCTION

Sjögren's syndrome has a great impact on the life of a person suffering from it, with tolls being taken throughout life on both the physical side and mental side, thus indicating how important the quality of life that these people lead is. A tremendous burden will be placed on these individuals if Sjögren's syndrome is looked at simply as a disease when the patient visits the physician, and not as a disease that persists throughout the patient's life and influences the way it lived. The introduction of this paper is to highlight and display the key elements of Sjögren's syndrome and how it affects the life that these individuals lead. The main goal is to review literature focused on the more known facts about Sjögren syndrome in terms of disease etiology, epidemiology, predisposing and risk factors, signs and symptoms, diagnostic tests, and as well as the quality of life that is led when one has the illness and the treatment options and care that should be performed. Sjögren's syndrome is a chronic inflammatory autoimmune disorder. The syndrome may be primary or secondary, which is associated with connective tissue diseases such as rheumatoid arthritis or systemic sclerosis. The first to describe such a syndrome was Swedish ophthalmologist Henrik Sjögren, in the year 1933. The reason for this was because he noted a connection between dry eyes, arthritis, and dry mouth. Assessing patients with chronic scenarios of these complaints, as well as fatigue, can lead to and be helpful for an early diagnosis. Sjögren's syndrome is characterized by lymphocytic infiltration and fibrosis of exocrine glands, especially of the salivary and lacrimal glands. This subsequently leads to a subtle range of signs and symptoms which ultimately results in a difficult and taxing way of life. This impaired quality of life is brought up mostly by

dry eyes, decreased salivation and dry mouth, vaginal dryness, dry cough, dysphagia, and if systemically involved, there may be manifestations through arthralgia, vasculitis, lymphadenopathy, lung, kidney and liver involvement, peripheral neuropathy, myositis, and fatigue. There is also an increased association with other autoimmune diseases and increased risk of lymphoma. This wide range of signs and symptoms that encompass this syndrome highlights the necessity for proper management. A multidisciplinary team is essential, including from ophthalmologists, rheumatologists, dental practitioners, nurses, and many others, to decrease the burden that people with this syndrome endure. As with other chronic diseases, permanent cures are uncertain, and the patient must learn to deal and ultimately live with such an illness.

2. SJÖGREN'S SYNDROME

2.1 Classification

Sjögren's syndrome is an autoimmune disease highlighted by systemic and broad organ specific manifestations, of which the most dominant is decreased salivary and lacrimal gland function, keratoconjunctivitis sicca, parotid gland swelling, and xerostomia. As noted previously, primary Sjögren syndrome presents alone, while secondary presents itself in connection with other connective tissue diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. Overall, Sjögren's syndrome can present as an isolated entity, limited to complaints related to decreased glandular function, or encompassing a more systemic presentation, both of which can be subtle and chronic. It

is precisely this complexity of presentations that has led to elaborate diagnostic and classification criteria.

In 1993, the Preliminary European Classification criteria was published. This criteria was then reviewed and re-examined in 2002 by a joint European and American Committee. The final result of this revision was that it yielded the AECG-criteria (American and European Consensus Group classification), which introduced more clearly defined rules for classifying patients with primary or secondary Sjögren's syndrome and provided more accurate exclusion criteria (1). This criteria is not perfect, as it has its benefits and negative aspects, illustrating the difficulty in establishing a proper classification for diagnosis. One of the major differences that the AECG-criteria implemented was the obligatory need for serology or biopsy to confirm the diagnosis, therefore making it mandatory for an invasive procedure to be done to fulfill the criteria. Another factor that must be taken into account is that criteria does not have any influence on the prognosis of disease and that there are no prognostic factors included at all, which is something that makes the classification fall under criticism. The joint AECG-criteria is as follows:

Table 1 (C. Baldini et al. / Journal of Autoimmunity 39 (2012) 9e14)

American-European Consensus Group Criteria. Revised international classification criteria for Sjögren's syndrome.

I. Ocular symptoms: a positive response to at least one of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrently or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1. Schirmer's I test, performed without anaesthesia (<5 mm in 5 min)
2. Rose bengal score or other ocular dye score (>4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm² of glandular tissue

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (<1.5 ml in 15 min)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitory or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer

VI. Autoantibodies: presence in the serum of the following autoantibodies:

1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

Revised rules for classification

For primary SS

In patients without any potentially associated disease, primary SS may be defined as follows:

- a.* The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
- b.* The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)
- c.* The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

For secondary SS

In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SS

Exclusion criteria:

Past head and neck radiation treatment
Hepatitis C infection
Acquired immunodeficiency disease (AIDS)
Pre-existing lymphoma
Sarcoidosis
Graft-versus-host disease
Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

An early and accurate diagnosis is of utmost importance to try and prevent and ultimately aim to prevent complications. It can also ensure treatment to be administered on time to aid in prevention. One of many complications that will be further touched upon is dental candidiasis. This occurs due to decreased salivation and oral dryness. If there is early restoration of salivary function then this can slow down and maybe even prevent the development of such an oral complication. Oral candidiasis is one of the more benign complications, early diagnosis and proper treatment can contribute to identifying possibly more dangerous systemic complications, such as lymphoma. One more factor that should be stressed is that the longer the disease remains undiagnosed, the longer a patients mental well being can suffer such as the anxiety of not knowing, as well as the their physical well being.

2.2 Etiology

Sjögren's syndrome is a progressive autoimmune disease, characterized by lymphocytic infiltration and a difficult pathogenesis that requires an involving immune cell production and activation, autoantibody production, and a predisposing genetic background. The etiology is unclear and unknown thus far, susceptibility to the disease can be ascribed to the connection and linkage between environmental, hormonal, and genetic influences (2). Of these factors, the constant stimulation of the immune system is said to be the most prominent variable, as noted through the production of various autoantibodies, particularly anti-Ro/SS-A and anti-La/SS-B. Further touching upon the genetics aspect, there is a familial association with other autoimmune diseases. It is documented that it is common for a patient with Sjögren's syndrome to have relatives with autoimmune

diseases, this association can reach up to 30% (3). For the development of autoimmune diseases, the major histocompatibility complex is the most well documented genetic risk factors. For Sjögren's syndrome, the most prominent haplotypes for the formation of anti-Ro/La are DRB1 0301-DQB1 0201-DQA1 0501 (3). A consistent finding in patients with the syndrome is that there is B-cell activation, leading to infiltration of organs in the body. From an infectious perspective, trials show that certain viruses such as cytomegalovirus and hepatitis C can be postulated to cause Sjögren's syndrome (4). Whether these infectious agents truly cause the disease or simply mimic it through symptomatology is yet to be determined. Overall, the cause is yet to be determined, but it is deemed to be multifactorial, combining genetic, environmental, infectious, hormonal, and autoimmune factors.

2.3 Epidemiology

Sjögren's syndrome, having the perplexing clinical picture as described above, leads to a somewhat skewed number in terms of concluding how many people are actually affected. The criteria/classification listed above has led to some clarification, but ultimately many of the signs and symptoms are subtle and chronic, which leads to a partially subjective view and interpretation.

Sjögren's syndrome is the second most common autoimmune rheumatic disease, with an estimated prevalence ranging between 0.1-4.2% of the population. Approximately 60% of Sjögren's syndrome patients have the disease secondary to an accompanying autoimmune disorder such as rheumatoid arthritis, systemic sclerosis, or SLE (5). It

mainly affects middle aged women, accumulating a female to male ratio of 9:1 (6). Average age occurrence is between 40-60 years of age. Due to its subtle and difficult symptomatology, affected individuals are often misdiagnosed and treated inadequately and not properly, leading to years of debilitating living standards. More than half of affected individuals remain undiagnosed, illustrating the difficulty in diagnosing Sjögren's syndrome.

3. QUALITY OF LIFE

Quality of life is a multidimensional structure, encompassing ones mental, physical, and social well being. As the population of world continues to rise in the category of age, it is therefore expected to not only assess and treat illnesses, but to evaluate the way of life thereafter. Adding to global factors such as morbidity and mortality, quality of life, and especially health related quality of life can provide great insight and can help build on the relationship between mental, medical, and social services.

3.1 Importance

This is an aspect that should not be overlooked for sufferers of chronic diseases. The overall burden can be one of important significance in the way these people lead their lives. This segment not only describes the importance of quality of life in Sjögren's syndrome, but also of other chronic diseases, highlighting the fact that this affects a great deal of people, and proper awareness and education about the topic should be stressed. Quality of life can be interpreted in a number of ways, whether it be through the social

circle one enjoys, the amount of riches one possesses, ones health, or various other variables, of which will be touched upon further throughout this paper. All these factors go hand in hand with one another, and that is precisely why a broad view approach must be done, and not just viewing an illness as simply an illness. The importance of health related quality of life is because is very different compared to the disease the individual is suffering from. It cannot be deduced based on a clinical diagnosis but must be thoroughly evaluated. In a great deal of situations, patients often come to their physician looking to solve their symptoms and the way these symptoms are taking a toll on their everyday living. Patients can be bothered by their symptoms, worried about the future of their health, complain about not being able to perform daily activities, all of which can be addressed by the physician. Many time the physician treats the illness in this case, but this is in fact not why the patient came to seek help in the first place. Just as with the delays in diagnosing a disease such as Sjögren's syndrome, there are also delays in this entirely different aspect of the disease. It should thus be deduced that assessing and treating ones illness does not directly give knowledge about ones quality of life, which is why proper evaluations have been developed throughout the years.

3.2 Quality of Life in Sjögren's Syndrome

Factors that influence the quality of life in patients with Sjögren's syndrome can vary from symptoms that the patients suffers from, limitations in performing day-to-day activities, financial burden, emotional status, and social troubles. Signs and symptoms will be touched upon further in this paper, while this segment is to describe what actually

affects the quality of life in these individuals. Proper evaluation methods have been developed in the past, and these have given insight on the lifestyle of these patients. One major flaw in these methods of evaluation is that two separate individuals are attempting to quantify something. What the patient perceives as troubling or problematic is sometimes not felt with the same attitude from the physician, and vice versa. As a situation with multiple perspectives, different perspectives of the same objective situation can vary in interpretation. The effect of primary Sjögren's syndrome on a broad spectrum of quality of life including economic resources, work status, leisure activities and interpersonal relationships has not been well studied. Because primary Sjögren's syndrome is predominantly diagnosed in peri-menopausal women, there is very limited data concerning the health status of younger women particularly those of child bearing age, as well as limited data concerning the health status of men with primary Sjögren's syndrome (7). There have been various studies trying to compare the physical, mental, and social aspects of Sjögren's syndrome to its fellow autoimmune diseases such as SLE and RA, with certain differences and similarities. Fatigue is one topic that is touched upon through various studies, as it can be detrimental for the patient. Alluding to the same conclusion, patients with Sjögren's syndrome have substantially lowered quality of life based on questionnaires such as SF-36 described in the next segment of this paper. Sjögren's syndrome shares this similarity with its other autoimmune diseases such as SLE and rheumatoid arthritis, the latter being even lower in terms of physical fatigue, while the former matching Sjögren's syndrome in other aspects of fatigue such as mental fatigue (8). It has also been postulated that there is also an inflammatory component

causing fatigue in Sjögren's syndrome, although data has been inconclusive showing this (9).

Oral problems such as the lack of saliva predisposing to a somewhat immunodeficient state leads to certain oral infections and difficulties with swallowing. These pathological changes can be obvious, but if we delve deeper into such problems a conclusion can be reached with the problems that arise from difficult swallowing. What was once easy and effortless to swallow now becomes a burden for these people suffering from Sjögren's syndrome. This can be of great psychological concern, especially in the elderly with inadequate dentures, once again indicating that proper oral health is of great importance. It has also been documented that patients with Sjögren's syndrome also have an abnormal chemosensory perception, thus leading to difficulties with taste and smell. It might be anticipated that progressive exocrine gland damage with loss of secretions would affect the special senses of smell and taste, which contribute so much to daily functions and enjoyment of life (10). In conclusion, oral distress has proven to be a serious issue, with patients consistently scoring significantly lower than patients with low levels of oral distress in five of the SF-36 subscales, indicating that oral conditions have a marked impact on general quality of life (11).

Continuous fatigue can be detrimental to one's health, and when combined with the other complaints of Sjögren's syndrome, can take a toll on one's mental being. Depression and anxiety can begin to manifest, and patients may begin to wonder why they have such a disease, what the consequences of their signs and symptoms will be, and will they ever be

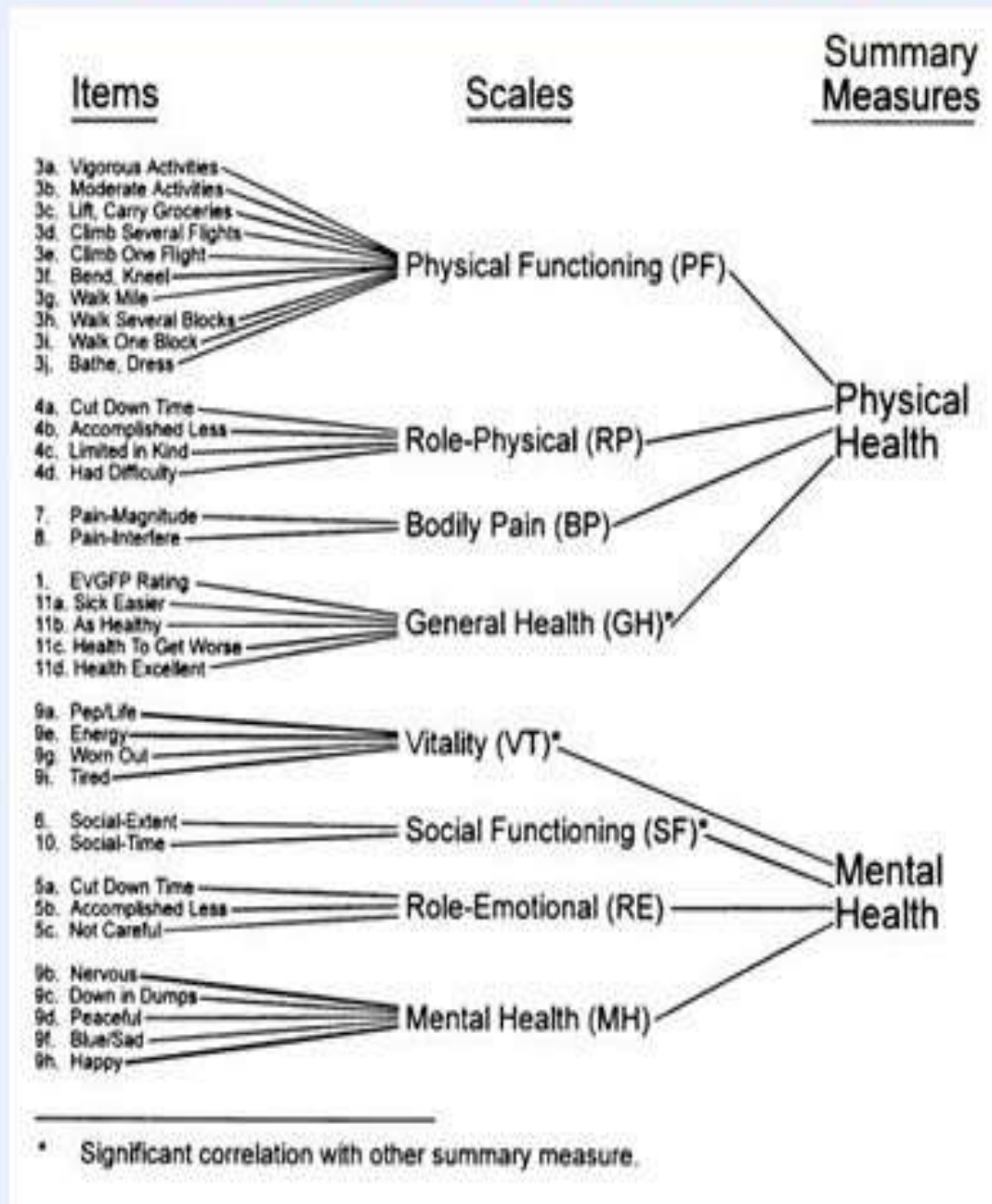
able to lead normal lives. This psychological burden can be very negative when it come to the quality of life (12). Fortunately, cognitive impairment has not been noted in Sjögren's patients, although a healthy mental state may play a great role (13). One interesting study attempted to assess the defensive profile of primary Sjögren's syndrome patients and to investigate the independent associations of psychological distress and personality variables with health-related quality of life, concluding that there were difficulties for these patients, and that physicians should consider and address these issues as consequences of Sjögren's syndrome (14). The combination of fatigue and salivary abnormalities may even lead to sleep disturbances and excessive day time sleepiness, once again showing a very wide range of complications outside the usual 'pathology' that first comes to mind.

3.3 Assessing Quality of Life

Sjögren's syndrome is very rarely a threat to ones life and it does not present in an acute fashion. As the disease is one of chronic manifestations, targeting the glands in primary Sjögren's syndrome and affecting the body in a systemic way in secondary Sjögren's, it is most certainly a threat to ones well being and lifestyle, and therefore ones quality of life. Health related quality of life (HRQOL) is a broad multidimensional concept that usually includes self-reported measures of physical and mental health (15). There are multiple ways of evaluating ones quality of life, many of them based on questionnaires. The Medical Outcomes Short-Form Health Survey questionnaire 36 (SF-36) is thus used as a model to evaluate and monitor the quality of life in patients in a clinical setting, and it has

shown to be a reliable and valid measure (16). The model of how this SF-36 questionnaire is structured is displayed below (17):

SF-36[®] Measurement Model



SF-36 is just one of the many models that have been designed for measuring the quality of life, and more importantly the health related quality of life. Many assessments exist to only examine a single problem, while other assessments encompass various domains, such as the SF-36 measurement model.

A very general approach used to assess population quality of life incorporated by the Centers for Disease Control and Prevention encompasses 4 general questions about ones health; Would you say that in general your health is excellent, very good, good, fair or poor, Now thinking about your physical health, which includes physical illness and injury, how many days during the past 30 days was your physical health not good, Now thinking about your mental health, which includes stress, depression, and problems with emotions, how many days during the past 30 days was your mental health not good, During the past 30 days, approximately how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation (18).

The Health Assessment Questionnaire (HAQ), is among the first patient reported outcome instruments designed to represent a model of patient-oriented outcome assessment. The HAQ is based on five patient-centered dimensions: disability, pain, medication effects, costs of care, and mortality (19).

The World Health Organization Quality of Life Assessment-BREF (WHOQOL-BREF) questionnaire is yet another assessment used to evaluate the quality of life. Using such

broad evaluations such as this one, in combination with a selective assessment for a certain complaint such as fatigue, it can be properly evaluated whether ones quality of life is truly lowered, as shown through various studies (20).

Fatigue is a frequent complaint and from both the mental and physical side can impair ones life. There are many evaluations that exist today to measure and assess fatigue, the majority of them being through questionnaires. The fatigue severity scale (FSS), the fatigue visual analogue scale (VAS-F), and the functional assessment of chronic illness therapy - fatigue (FACIT-F) are all ways of assessing fatigue individually, whether it be in relation to autoimmune diseases such as Sjögren's syndrome or not. One study used these measures to investigate fatigue change in pSS in a longitudinal study, and explore whether any clinical or laboratory variables at baseline, including serum cytokines, were associated with a change in fatigue scores over time (9).

Oral health is another aspect of Sjögren's syndrome that requires attention as it requires extreme care so it does not impede the quality of life and even more importantly, so it does not progress to more severe complications. The Oral Health Impact Profile (OHIP-49) can be used to assess oral quality, and in combination with other assessments of quality of health such as SF-36, can provide a great deal of information (21).

Psychological issues play a large role in autoimmune diseases, the reasoning being that over time the patient endures dilemmas about how they perceive their illness. Whether they truly comprehend their disease or simply correlate their symptoms with their disease

are just a few of the issues that can become taxing over long periods of time. Depression and other mental illnesses may then show, further lowering the quality of life, and thus posing as a large problem in addition to already present physical complaints. The Patient Health Questionnaire (PHQ-9) and Hospital Anxiety and Depression Scale (HADS) are two assessments that have been used in the evaluation of the mental state of individuals with Sjögren's syndrome. These findings indicate that psychological factors are important correlates of health related quality of life in these disease groups and encourage the design of psycho-educational therapies targeting disease-related cognitions in pSS in an attempt to improve patient's physical health related quality of life (12).

The majority of individuals suffering from Sjögren's syndrome present with xerophthalmia, which then results in painful, erythematous, and itchy eyes. Associated with xerophthalmia is xerostomia, which is due to inadequate saliva. Insufficient saliva thus results in increased risk of cavities, taste disturbances, speech impeding, dysphagia and cough. The third classic symptom to complete this triad is tenderness and enlargement of the parotid glands. These are generally referred to the hallmark or classic signs and symptoms of Sjögren's syndrome and/or sicca syndrome. These signs and symptoms, although few, in addition with such systemic manifestations such as pain and fatigue, are the chief factors responsible for the decreased quality of life in patients with the disease. This segment contains a wide scope of signs and symptoms to evaluate, and this illustrates the few among many assessments necessary to complete such evaluations.

4. HEALTH RELATED QUALITY OF LIFE - COMPLICATIONS ARISING FROM SJÖGREN'S SYNDROME

4.1 Oral Complications

The oral distress that accompanies the disease can be very troubling for patients, not only to due to its constant effect, but also due its chronic one, thus resulting is serious implications on the health related quality of life. Studies have shown, and it has been proven that patients with Sjögren's syndrome have shown deteriorating salivary and lacrimal secretions. The rate of xerostomia increased from 41% at the initial diagnosis to 84% 10 years after the diagnosis, again noting the negative fact that a person gone undiagnosed for a long period of time is prone to suffer a great deal more as opposed to being diagnosed early and treated appropriately (22). Saliva has a number of benefits, playing the role of lubrication of the oral cavity, as well as containing immunoglobulins, glycoproteins, and lysozymes to further aid in a protective fashion. The saliva that is produced helps limit the growth, production, and adherence of bacteria, thus also protecting against dental caries. Saliva is not only a protective factor against infection, but it also aids in lubrication of the oral cavity. Leading to a somewhat immunodeficient state, the oral cavity becomes prone to opportunistic infections such as *Candida albicans*. Oral dryness is not usually a painful complaint as it is a uncomfortable one, leading to many physicians to dismiss it as a quite common and irrelevant symptom unfortunately. An association with *Candida* organisms can result in angular cheilitis, which is indeed painful and further hampers the ability of the oral cavity (23). Other organisms such as

Streptococcus mutans and Lactobacillus are also reported with increased frequency. Prevalence of C.albicans is >68% in patients with Sjögren's syndrome compared to the prevalence in the normal population, which ranges between 23 to 68% (24). Decreased saliva production thus leads to increased irritability, erythematous swelling, inflammation, ulcer formation, and even in advanced cases, depapillation of the tongue. Difficulties in eating also ensues, as the food particles remain in the oral cavity due to inadequate clearance with saliva.

Therefore, just as the most frequent complaint can be xerostomia, the patients may also complain of unpleasant taste, dysphagia, particularly while eating dry food, soreness and irritation. An article published by the University of Oslo in 2011 illustrates how the oral distress suffered by patients suffering from Sjögren's syndrome can severely impede their lives from day to day (25). The SF-36 was used to evaluate the health related quality of life and another survey was used to evaluate and measure the oral distress, the Oral Health Impact Profile 14. Compared to normal individuals not suffering from the disease, the patients with Sjögren's syndrome and oral distress scored significantly lower on the SF-36 survey. This indicates that there is a severe impact on the health related quality of life. This becomes an alarming fact, as oral conditions are one of the chief influences on the quality of life of these individuals. A greater deal of attention and focus must be directed on this issue with the aim of improving the quality of life for these patients.

4.2 Ocular Manifestations

Xerostomia, xerophthalmia, and the symptoms related to these are the main complaints causing an impediment on the quality of life of these patients. Even more problematic is that they are quite common and thus can be dismissed quite readily. Another problem is that they are subjective complaints, and can thus be misinterpreted and mistaken for other general disorders such as anxiety or a sort of dermatitis.

Dry eye is the most prominent ocular feature of Sjögren's syndrome, and it can encompass additional signs and symptoms such as a disturbing sensation, an itchy feeling, soreness, eye fatigue, photosensitivity, erythema, and decreased visual acuity. These features can even present themselves as the eye appears normal, further complicating efforts in diagnosis. Further complications in diagnosis is that although a hallmark of the disease is decreased tear production, it does not accurately correlate with ocular complaints and discomfort. It is therefore crucial when assessing the dry eyes of a patient, the aim should be to discover whether the objective signs are in proportion with the signs and symptoms of the patient.

Further examination can reveal a decreased tear film and abnormal mucus component, leading to thick secretions and discharge. Complications can as well present themselves in the manner of conjunctivitis due to infection, opacification, ulceration of the cornea, and even perforation.

4.3 Female Sexual Function

Unfortunately, diagnostic criteria do not specifically address vaginal dryness in patients with Sjögren's syndrome. Vaginal manifestations can result in severe discomfort for a woman, leading her to already known physical impairments and as well as mental suffering. Prevalence of dyspareunia and dryness in woman is high with primary Sjögren's syndrome. Surveys done in an article published very recently, in 2015, display dramatically lower scores in the areas such as sexual desire, lubrication, excitement and arousal, and orgasm. Compared to healthy controls, women with vaginal dryness reported sexual dissatisfaction, depressive symptoms, problems with their relationships and overall lower mental quality of life (26).

Sexual function is considered to be vital to physical and mental health, and is associated with the satisfaction and general well being of an individual. Although the etiology of vaginal dryness is unknown, it is a well documented symptom, but the unfortunate matter is that it is viewed simply as that, a symptom. When assessing a patient with Sjögren's symptom, the complaint of vaginal dryness and dyspareunia is well noted, but the information of sexual function is not. Focusing solely on the number of times intercourse occurs or if there are vaginal sicca symptoms as opposed to the whole, broader concept of sexual function has a great effect on the mental and physical well being of the patient. If the primary complaint cannot be successfully dealt with, then physicians must have an open view to the cascade of complaints that may arise further down the line. Unfortunately, data on sexual function is scarce and limited in patients with primary

Sjögren's syndrome. The consequences of vaginal dryness are physical and psychological and must not be overlooked (27). This creates a negative cycle of decreased health related quality of life for the patient as well as a strained patient physician relationship. A great deal of patients do not communicate with their rheumatologist about this issue, either due to the subject never being brought up by the physician, the patient did not have a sexual relationship, or lubrication solved the issue (26). This miscommunication that can arise becomes a disturbing though when there is already enough difficulty in assessing signs and symptoms and the fact that more than half of the patients suffering from Sjögren's disease go unnoticed and undiagnosed for a large period of time. This begs the question as to why female sexual function is not specifically addressed in the diagnostic criteria.

4.4 Mental Well Being

Pain, fatigue, anxiety, depressive symptoms and somnolence in patients suffering from Sjögren's syndrome is quite well documented, but once again, a step further in the understanding is lacking. How these symptoms actually affect and impact the functional ability is generally not very well understood (28). Using another form of questionnaire, the Improved Health Assessment Questionnaire, it has been shown that patients with primary Sjögren's syndrome have a reduced capacity to perform a wide range of normal daily activities, thus heavily impeding their quality of life. The first study to take note of the significance of decreased functional status was the American College of Rheumatology in 2012, which noted a strong correlation between some, but not all of the clinical features of Sjögren's syndrome and decreased functional ability. Fatigue, dryness,

depression, anxiety, pain, and overall burden of disease showed a strong correlation, with fatigue displaying the largest influence (29).

Fatigue somewhat goes hand in hand with functional ability, indicating that it is not an arbitrary attribute or a subjective complaint that should be falsely perceived. It is a debilitating and common symptom of Sjögren's syndrome, with approximately 70% of patients being affected. This is another symptom where self assessment comes into the picture and is needed to be performed to gather data and strategize a model for treatment. The pathogenesis of fatigue is an interesting one, encompassing physiological factors and as well as psychosocial ones. Other occurrences where fatigue plays a role in functional ability is post liver transplantation patients, patients with primary biliary cirrhosis, as well as many other chronic diseases and chronic treatment modalities, indicating that it is not a selective manifestation of Sjögren's syndrome.

Another aspect that is worth mentioning is that inflammatory markers, such as C-reactive protein, seem to play a role in the fatigue that is experienced. This leads to the conclusion that perhaps treatment focusing on the articular systemic aspects of the disease can alleviate the fatigue and therefore help improve the health related quality of life (30). This evaluation and further knowledge on markers in the body could prove useful in the attempts of treating fatigue.

4.5 Pain

Continuing on from our previous segment, fatigue and pain correlate in up to 85% of patients with primary Sjögren's syndrome. Muscle pain and joint pain can become a serious problem resulting in a cascade of negative effects both from a physical perspective as well as a psychological one.

One heavy topic of conversation is that the pain that is accompanied by fatigue, psychological distress, and sleep disturbance is once again subjective and subject to a sort of bias perception. What the patient perceives as painful may be over exaggerated or thought of as more debilitating than it actually is, a distinct phenomenon which is characterized by feelings of helplessness, to ruminate, and excess imagination of cognitions and feelings toward the painful situation, in other words, catastrophizing (31). Many chronic diseases present with catastrophizing, such as cancer and other rheumatoid diseases, and this influences the intensity of chronic pain and can be useful in evaluating the patients' perception of pain. Pain catastrophizing can account for 36% of the variance in pain, 21% for variance in mood, and 27% variance in fatigue (32). As observed, this can be an alarming difference in the perception of the patients' symptoms, the steps taken in treatment, and the evaluation of their overall health. The catastrophizing of pain and its neural mechanisms raise an interesting potential target for therapy that could eventually influence the perception of pain.

4.6 Systemic Manifestations

Adding further to the confusion and complication of establishing a diagnosis, many signs and symptoms of Sjögren's syndrome overlap closely with those of systemic erythematous lupus. Typically the result of chronic inflammation, these manifestations can affect almost the whole body, ranging from skin, arthralgia, myalgia, to more visceral components such as the kidney, lungs, endocrine, gastrointestinal, and nervous system.

Athrititis and arthralgia usually present in a symmetric distribution, and some patients even exhibit a pattern known as erosive arthritis. Development of some additional factor such as asymmetry and swelling could suggest another pathology that is underlying. In addition to myalgia, these are immense factors in the fatigue that these patients experience and the ongoing struggle that they suffer. Myalgia can be associated with fibromyalgia, and frequent analysis of electromyography, muscle enzymes and biopsies may be considered (33).

Skin manifestations include alopecia, vasculitis, vitiligo, xerosis, and even lymphoma as a dire complication. Even the most simple thing like dry skin can cause severe discomfort. More than 10% of patients report a skin rash, while 18% report burning skin sensation in certain studies (5). Lymphoproliferative disease is of particular importance in these patients because their risk of developing it is over 40 times the general population. Clinically identifiable lymphoma occurs in approximately 5% of Sjögren's syndrome patients. Predictors of lymphoma do exist and require the monitoring of such patients. Predictors are of clinical and serological value. The majority of lymphomas are

of B-cell origin and are of low-intermediate grade malignancy, usually localizing in extranodal areas such as the gastrointestinal tract, thyroid gland, kidney, and lung.

When it comes to pulmonary involvement, cough is usually the main presentation, a symptom of xerotrachea, while other complications include lymphocytic alveolitis, fibrosis, pneumonitis, and lymphoma.

Pathology of the kidneys shows nephritis with glomerular sparing. Usually with tubulointerstitial involvement affecting the tubules, resulting in a cascade of problems such as renal tubular acidosis, hypercalcinuria, impaired concentration, and other tubular defects. Further grave complications can be development of nephrotic syndrome, hypertension, and ultimately renal insufficiency.

In a recent study, it is shown that neurological involvement is one of the most common systemic manifestation, ranging from a presentation involving the peripheral or cranial nerves, and sometimes even the central nervous system (34). Peripheral neuropathies are the most common, and these tend to be primarily sensory.

The involvement of the gastrointestinal tract is also profound, being able to affect the entire tract. Dysphagia and esophageal dysmotility are the most common presentations. Organ involvement also plays its role through mild hepatitis and pancreatitis, also adding to differential diagnosis of a wide range of other diseases.

5. MANAGEMENT

Due to Sjögren's syndrome being a pathology of a wide range of signs and symptoms, treatment options can vary, ranging from pharmacology affecting individual and systemic manifestations, as well as non pharmacological treatment options targeting the mental health of the patient to alleviate the difficulty of this burden. Sjögren's syndrome can on a basic level either be a "benign" disease affecting the quality of life, or it can be a more systemic problem with more malignant aspects affecting morbidity and mortality more severely, thus requiring individualized therapy to adequately treat these different problems. Systemic manifestations overlap with other diseases, and to ease this thought, much of pharmacology does as well. An overall principle is that all most therapy should focus some efforts into preventing the dryness that occurs from this illness. How this is accomplished is through various fluids and drugs to try and keep the regions moist and lubricated, and as well as increase the production of natural lubricants. As an overall view, the majority of the drugs that were used in the treatment of autoimmune rheumatic diseases have also been administered to patients with Sjögren's syndrome, with the goal of alleviating symptoms such as the sicca symptoms described. Focusing on the aspect of prevention first and foremost is of utmost importance to ensure that the patient can lead as normal a life as possible, and then attention can shift to treating the various complication of Sjögren's syndrome.

5.1 Dry Eyes

Possibly the most important aspect to focus therapy on, adequately managing ocular manifestations of Sjögren's syndrome is absolutely crucial for the patients well being and ultimately will influence the way they lead their lives (35). Methods that do not include pharmacology include measures such as avoiding prolonged straining of the eyes like extensive reading or staring at a screen for a long period of time, avoiding irritancies such as smoke, dust, and wind, and avoiding actual drugs that may influence the amount of fluid in the eye. These drugs include certain antidepressants, diuretics, cholinergic drugs, beta blockers, as well as antihistamines. If these measures cannot be adequately maintained or are not successful, then pharmacology must be opted for, resulting in attempts to replace fluid in the eyes and applications of certain topical drugs. Replacement of tear volume to limit the dryness in the eye is the priority, using artificial tears to do so. Emulsions that contain hyaluronate and hydroxypropylmethyl-cellulose, hypotonic solutions that decrease osmolality seem to be the best options (3). Other options then to decrease dryness of the eyes include topical drugs, of which corticosteroids, cyclosporine A, and NSAIDs prove to be useful. Emphasis for this was described earlier on throughout this paper, describing the large amount of complications of dry eyes that can greatly then hamper the lifestyle of people with Sjögren's syndrome. The limitations of topical drugs are that they are only permitted to be used for a short period of time, as prolonged use causes side effects that can worsen the condition, an example being decreased corneal sensitivity, predisposing to corneal irritation and ulceration to develop.

5.2 Dry Oral Cavity

Just as with dry eyes, therapy can range from non pharmacological to pharmacological, with the aim being to reduce the complications associated with having a dry mouth. As mentioned previously, decreased salivation can lead to severe complications for the quality of life for a patient and the oral cavity. Most common of all is the development of caries, and also the increased incidence of oral infections. To limit this decreased salivation, fluoride has been used and has been shown to aid in this aspect, whether it be through fluoride containing toothpaste, specific gels, or certain rinses (36). Just as there are ocular tear substitutes, oral secretion substitutes for the purpose of lubrication also play a great role in preventing complications. Methods include the use of mouthwashes, gels, and other fluids such as drinking ordinary sugar free water to lead satisfying results. Chewing gum as a sort of mechanical stimulation has also been reported to yield some moderate success. As previously mentioned, adequate non pharmacological measures must also be attempted in order to preserve lubrication in the oral cavity and to enable the patient to live normally. Adequate hydration is a necessity, as well as avoiding irritants that can dry the mouth such as coffee and nicotine. If there are severe complaints and functions are impaired, then systemic drugs may also be used for therapeutic purposes. Cevimeline and pilocarpine are the two drugs of choice in most cases and as they are muscarinic receptor agonists, then side effects such as sweating, and increased urinary frequency must be looked out for (37). The patient must understand that accepting ones illness will result in a more positive outlook on the situation. In depth and obsessive care of the oral cavity must be undertaken, with frequent dental examination done, swift

treatment if something is noticed, and avoiding small mistakes that can be problematic, such as sleeping with dentures still in the mouth.

5.3 Extraglandular Manifestations

As stated previously, extraglandular manifestations may cause the patient a great deal of complications and problems in their lives, and one must know how to manage these properly. Systemic therapy can range from oldest drugs used in autoimmune therapy such as glucocorticoids, to infectious therapy such as antimalarial drugs, and finally to immunosuppressants and newer biological agents. A point worth noting is that with the use of all of these agents, especially the prolonged use, there is always a risk of severe side effects. Therefore a proper therapeutic plan must be executed, to ensure that the patient can live a fulfilling and rich life, despite the burden of their symptoms and the therapy they are being administered (38). A number of these drugs not only aid in the complications created by extraglandular manifestations, but also for the sicca symptoms that so frequently impair the quality of life of these patients. Drugs against malaria (most often hydroxychloroquine) have been shown to improve on arthromyalgia and fatigue, as well as improving on sicca symptoms through increasing salivary flow. With fatigue, patients must once again aim to live a normal life, with regular exercise being beneficial. and Antimalarials have also to an extent been shown to have antineoplastic properties, which is quite an interesting feature due to the fact that Sjögren's syndrome patients being at increased risk for developing lymphoma. Immunosuppressants seem to have a straightforward role in the treatment of Sjögren's syndrome, being used accordingly for

the specific organ involvement. More studies are necessary to form an adequate conclusion, as agents such as ciclosporin A, methotrexate, azathioprine are all used but with low amount of evidence to support.

As treatment and diagnosis models slowly move into a molecular field, then biological agents logically become a field worthy of exploration. Although the true causes of Sjögren's syndrome are not known, thus rendering biological agents limited in a way, they still prove to be extremely beneficial and efforts are being directed at further research. According to a recent report published in 2012 (39), there are no biological agents approved for the treatment of primary Sjögren's syndrome, although there are studies describing the potential of these drugs in future treatment models.

The relationship between serum pro-inflammatory cytokines and a low quality of life is a strong one, indicating that there is still a great amount options in therapy to be explored. One such topic that has been touched upon in the effect of rituximab. Rituximab (anti CD20) infusions without corticosteroid therapy produced meaningful improvements in health related quality of life (40).

6. CONCLUSION

In conclusion, Sjögren's syndrome not only encompasses the well known signs and symptoms, but also factors in the quality of life that these individuals, signifying the absolute importance of addressing the patient as a whole and attempting to improve their

lives. The quality of life is an essential component of diagnostics and prognosis of people suffering with this illness. Through standard diagnostic and therapeutic methods for not only Sjögren's, but also many other chronic autoimmune diseases, the introduction of adequate support should be a priority. The need for constant evaluation and monitoring is a must, as nothing can be solved from little attempts, especially when dealing with chronic conditions. Although methods for assessment, diagnosis and treatment have improved throughout the years, there is still a long way to go. Diagnostic criteria and classifications still lack in certain aspects, and failure to properly identify a true cause of Sjögren's syndrome gives us a scope of treatments that are still not used to their complete function. Education is essential and the awareness to properly recognize early signs and symptoms is absolutely a must for the well being of the patient. As one of the more common autoimmune rheumatic diseases, it is a positive observation that further research and interest is being undertaken in an effort to fully understand this multifactorial disease. Despite improvement and progress in treatment, treatment will continue to be symptomatic and empirical unless a true etiology is discovered. As focus shifts on a molecular and genetic levels, improvements continue to be made through diagnostics such as salivary proteomics, systemic biology and genomics, there is some promise in unraveling the pathophysiology of Sjögren's syndrome. This will hopefully provide us with a more concentrated view into the underlying mechanisms which could give clues for intervention therapies with biological agents. Without a cure for Sjögren's syndrome, individuals must learn to live with it, and as illustrated above, this can be a difficult task. With a vast amount of problems complicating their lives, patients must accept and live with this burden. With the help of their families in both a physical and mental sense,

hope, and physicians, individuals can readjust their lives without allowing the disease to hinder them. Sjögren's syndrome is an incredibly complex one, and we must understand that individuals with it will suffer, indicating that more focus must be placed on recognizing these people and helping them in the best possible way. Through various articles and papers that have been published, it is recognized that there is a need for continuous aid through psychiatric and psychological support, both through diagnostics and through therapeutic models, as well as a need for a continuous evaluations of quality of life to ultimately improve all aspects of the lives of patients with Sjögren's syndrome.

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REFERENCES

1. Chiara Baldini, Rosaria Talarico, Athanasios G. Tzioufas, Stefano Bombardieri. Classification criteria for Sjögren's syndrome: A critical review. *Journal of Autoimmunity* 2012; 30;39(1-2):9-14.
2. Peri Y, Agmon-Levin N, Theodor E, Shoenfeld Y. Sjögren's syndrome, the old and the new. *Best Practice & Research Clinical Rheumatology* 2012; 26:105–117.
3. Tincani et al. Novel aspects of Sjögren's syndrome in 2012. *BioMed Central Medicine* 2013; 11:93.
4. K Bayetto, RM Logan. Sjögren's syndrome: a review of aetiology, pathogenesis, diagnosis and management. *Australian Dental Journal* 2010; 55 Suppl 1:39-47.
5. Stuart S. Kassan, MD; Haralampos M. Moutsopoulos, MD, FRCP(Edin). Clinical Manifestations and Early Diagnosis of Sjögren's Syndrome. *Archives of Internal Medicine* 2004; 164:1275-1284.
6. Catanzaro J, Dinkel S. Sjögren's Syndrome: The Hidden Disease. *Medsurg Nursing* 2014; 23(4):219-23.
7. Barbara Segal, Simon J Bowman, Philip C Fox, Frederick B Vivino, Nandita Murukutla, Jeff Brodscholl, Sarika Ogale and Lachy McLean. Primary Sjögren's Syndrome: health experiences and predictors of health quality among patients in the United States. *Health and Quality of Life Outcomes* 2009; 7: 46.
8. S.J.Bowman, D.A. Booth, R.G. Platts, and UK Sjogren's interest group. Measurement of fatigue and discomfort in Sjögren's syndrome using a new questionnaire tool 2004; 43(6):758-64.
9. Karstein Haldorsen, Ingvar Bjelland, Anne Isine Bolstad, Roland Jonsson, and Johan Gorgas Brun. A five-year prospective study of fatigue in primary Sjögren's syndrome. *Arthritis Research & Therapy* 2011; 13(5): R167.

10. Usama F. Kamell, Peter Maddison and Rhiannon Whitaker. Impact of primary Sjögren's syndrome on smell and taste: effect on quality of life. *Rheumatology* 2009; 48 (12): 1512-1514.
11. Enger TB, et al. Oral distress in primary Sjögren's syndrome: implications for health-related quality of life. *European Journal of Oral Sciences* 2011; 119: 474–480.
12. Konstantinos Kotsis, Paraskevi V. Voulgari, Niki Tsifetaki, Alexandros A. Drosos, André F. Carvalho, Thomas Hyphantis. Illness perceptions and psychological distress associated with physical health-related quality of life in primary Sjögren's syndrome compared to systemic lupus erythematosus and rheumatoid arthritis. *Rheumatology International* 2014; Volume 34, Issue 12 , pp 1671-1681.
13. Epstein LC, et al. Characterization of cognitive dysfunction in Sjögren's syndrome patients. *Clinical Rheumatology* 2014; 33:4 pg 511-21.
14. Hyphantis T, et al. *Clin Exp Rheumatol*. The psychological defensive profile of primary Sjögren's syndrome patients and its relationship to health-related quality of life. *Clinical & Experimental Rheumatology* 2011; 29(3):485-93.
15. <http://www.cdc.gov/hrqol/>
16. Garrat A M, Ruta D A, Abdalla M I, et al. The SF-36 Health Survey Questionnaire: an outcome measure suitable for routine use within the NHS. *British Medical Journal* 1993; 306: 1440-1444.
17. <http://www.sf-36.org/tools/sf36.shtml>
18. <http://www.cdc.gov/hrqol/methods.htm>
19. B. Bruce, J.F. Fries. The Health Assessment Questionnaire (HAQ). *Clinical & Experimental Rheumatology* 2005; 23 (Suppl. 39):S14-S18.

20. Inal V, et al. Evaluation of quality of life in relation to anxiety and depression in primary Sjögren's syndrome. *Modern Rheumatology* 2010; 20:588–597.
21. López-Jornet P, et al. Quality of life in patients with Sjögren's syndrome and sicca complex. *Journal of Oral Rehabilitation*. 2008; 35; 875–881.
22. Skopouli F, Dafni U, Ioannidis J, Moutsopoulos H. Clinical evolution, and morbidity and mortality of primary Sjögren's syndrome. *Seminars in Arthritis and Rheumatism* 2000; 29:296–304.
23. Anaya JM, Talal N. Sjögren's syndrome. In: Kassirer JP, Greene HL, eds. *Current Therapy in Adult Medicine*. 4th ed. Baltimore, Md: Mosby 1997; 1291-1298.
24. Radfar L, Shea Y, Fisher S, et al. Fungal load and candidiasis in Sjögren's syndrome. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, Endodontology* 2003; 96:283–287.
25. Enger TB, Palm Ø, Garen T, Sandvik L, Jensen JL. Oral distress in primary Sjögren's syndrome: implications for health-related quality of life. *European Journal of Oral Sciences* 2011; 119(6):474-80.
26. Jolien F. van Nimwegen, Suzanne Arends, Greetje S. van Zuiden, Arjan Vissink, Frans G. M. Kroese and Hendrika Bootsma. The impact of primary Sjögren's syndrome on female sexual function. *Arthritis & rheumatology* 2014; Vol. 66, p. S1113-S1113.
27. Fabre LF, Smith LC. The effect of major depression on sexual function in women. *The Journal of Sexual Medicine* 2012; 9:231_9.
28. Ng WF, Bowman SJ. Primary Sjögren's syndrome: too dry and too tired. *Rheumatology (Oxford)* 2010; 49:844–53.
29. Katie L. Hackett, Julia L. Newton, James Frith, Chris Elliott, Dennis Lendrem, Heather Foggo, Suzanne Edgar, Sheryl Mitchell, and Wan-Fai NG. Impaired Functional Status in Primary Sjögren's Syndrome. *Arthritis Care & Research* 2012; Volume 64, Issue 11, pages 1760–1764.

30. Tensing EK, Solovieva SA, Tervahartiala T, Nordström DC, Laine M, Niissalo S, Konttinen YT. Fatigue and health profile in sicca syndrome of Sjögren's and non-Sjögren's syndrome origin. *Clinical & Experimental Rheumatology* 2001; 19(3):313-6.
31. Lawrence Leung. Pain Catastrophizing: An Updated Review. *Indian Journal of Psychological Medicine* 2012; 34(3): 204–217.
32. BM Segal, B Pogatchnik, N Rhodus, K Moser Sivils, G McElvain, CA Solid. Pain in primary Sjögren's syndrome: the role of catastrophizing and negative illness perceptions. *Scandinavian Journal of Rheumatology* 2014; 43:234–241.
33. Robert I Fox. Sjögren's syndrome. *Lancet* 2005; 366(9482):321-31.
34. Gemignani F, Marbini A, Pavesi G, et al. Peripheral neuropathy associated with primary Sjögren's syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry* 1994; 57:983-986.
35. Akpek EK, Lindsley KB, Adyanthaya RS, Swamy R, Baer AN, McDonnell PJ. Treatment of Sjögren's syndrome-associated dry eye an evidence-based review. *Ophthalmology* 2011; 118:1242–1252.
36. Clio P Mavragani, Niki M Moutsopoulos and Haralampos M Moutsopoulos. The management of Sjögren's syndrome. *Nature Reviews Rheumatology* 2 2006; 252-261.
37. Akpek EK, Lindsley KB, Adyanthaya RS, Swamy R, Baer AN, McDonnell PJ. Treatment of Sjögren's syndrome-associated dry eye an evidence-based review. *Ophthalmology* 2011; 118:1242–1252.
38. Rihl M, Ulbricht K, Schmidt RE, Witte T. Treatment of sicca symptoms with hydroxychloroquine in patients with Sjögren's syndrome. *Rheumatology (Oxford)* 2009; 48:796–799.
39. <http://www.biomedcentral.com/1741-7015/11/93>

40. Devauchelle-Pensec V, et al. Effects of rituximab therapy on quality of life in patients with primary Sjögren's syndrome. *Clinical & Experimental Rheumatology* 2011; 29(1):6-12.
41. Hyphantis T, et al. The psychological defensive profile of primary Sjögren's syndrome patients and its relationship to health-related quality of life. *Clinical & Experimental Rheumatology* 2011; 29:3 pg 485-93.
42. Vissink A, et al. Current and future challenges in primary Sjögren's syndrome. *Current Pharmaceutical Biotechnology* 2012; Volume 13, Number 10, pp. 2026-2045(20).
45. Usmani ZA, et al. Sleep disordered breathing in patients with primary Sjögren's syndrome: a group controlled study. *SleepMed* 2012; 13:8 pg 1066-70.
46. Turner MD. Salivary gland disease in Sjögren's syndrome: sialoadenitis to lymphoma, review article. *Oral & Maxillofacial Surgery Clinics of North America* 2014; 26(1):75-81.
47. Eur J. Oral distress in primary Sjögren's syndrome: implications for health-related quality of life. *International Journal of Oral Science* 2011; 119: 474–480. 2011.