Sjögren’s Syndrome and Gut Bacteria – What’s the Connection?

Over 2000 years ago, Hippocrates wrote that “All Disease Begins in The Gut.” And it turns out he may have been right.

More than 100 trillion bacteria live in and on our bodies. In fact, the number of bacteria that live in our body outnumber our human cells by a ratio of up to 10:1. Most of these organisms reside in the gut, specifically the colon. Other organisms like fungi and viruses are also present, but less is known about their composition. While initially thought of as casual bystanders, it is now understood that these bacteria are metabolically active and are important in both keeping us healthy and in causing disease. The most common gut bacteria belong on the phyla Firmicutes and Bacteroidetes, followed by Actinobacteria and Proteobacteria. Bacteria can be characterized by whether they are beneficial to our bodies (i.e. commensal bacteria), harmful to our bodies (i.e. pathogens...
Commensal bacteria have many beneficial effects on our bodies. 

- Gut bacteria help us extract nutrients from food. For example, many plant polysaccharides cannot be digested by our bodies. Gut bacteria digest the polysaccharides into short-chain fatty acids (SCFAs), like acetic acid and butyric acid, that are then absorbed into our blood stream. Along with being an important source of energy for cells, butyric acid suppresses inflammation by enhancing the death of T cells, thus decreasing levels of T-cell derived inflammatory cytokines such as interferon (IFN)-γ. Butyrate also promotes proliferation of regulatory T cells in the intestine whose job it is to control inflammation and prevent the development of autoimmune disease. 

- In fact, gut bacteria constantly interact with our immune system and improve the ability of our bodies to fight infection. Animals raised in a germ-free environment (and that therefore have no gut bacteria) are very susceptible to infection. Gut bacteria also provide a barrier that protects us from the attachment and proliferation of pathogens (like Salmonella). 

- Gut bacteria are involved in vitamin synthesis (like vitamin B and K) and help the body metabolize bile acids and sterols (like cholesterol), thus playing an active role in the hepato-enteric recirculation of bile acids. 

- Gut bacteria stimulate proliferation and differentiation of intestinal epithelial cells, which are the primary site of nutrient absorption and are typically renewed every four to six days in an average human gut. 

However, gut bacteria can also be harmful to our bodies. 

- Gram negative bacteria contain a substance called lipopolysaccharide (LPS) (also known as endotoxin) in their cell walls. A healthy gut has a good barrier and minimizes LPS translocation into the blood stream. However, a “leaky” gut has a compromised barrier, which allows LPS (and bacteria) to migrate from the gut into the blood stream and cause inflammation. 

- LPS induces a strong inflammatory response because our body uses LPS as a way to identify bacteria. In large amounts, LPS causes us to have symptoms of infection (i.e. fever and malaise). In small amounts, however, as occurs with slow leaking from the gut, LPS can cause no symptoms but instead lead to a chronic inflammatory response. 

- Our body has developed ways to sense LPS. Our liver and lungs make a protein that binds to LPS (LPS-binding protein) and this complex in turn binds to a protein called CD14 on white blood cells (macrophages). This complex then binds to another protein named Toll-like receptor 4 (TLR-4) on white blood cells that activates the innate immune system. Gram positive bacteria also contain a substance (Lipoteichoic Acid or LTA) that stimulates our immune system in a similar way (through Toll-like receptor 2). 

- Fortunately, our body has multiple ways to try to keep gut bacteria in check. One way the body maintains control is via a protein called intestinal alkaline phosphatase (ALPI). ALPI slows the growth of pathogens (like Salmonella) and neutralizes LPS by dephosphorylating a part of the molecule (lipid A). This modified LPS can no longer induce the TLR-4 dependent inflammatory response. ALPI can also prevent the translocation of live bacteria into lymph nodes around the gut following an injury (this was demonstrated in animal models). 

Diet is one factor that can modulate our gut bacteria and inflammatory response. 

- The facts: An increase in inflammatory cells and proteins can be detected in blood after a meal, including increased while blood cells, reactive oxygen species (ROS), interleukin (IL)-6, CD14, and TLR4. In a study comparing cream, glucose, and orange juice, ingestion of cream led to increased plasma LPS, while ingestion of glucose and cream led to elevations in other inflammatory markers, such as mononuclear cell NF-kB binding activity, tumor necrosis factor (TNF)-α, and IL-1β. This indicates that post-meal inflammation can occur through LPS dependent and independent mechanisms. 

- The bad: A diet high in fat and carbohydrates can lead to a transient increase in blood LPS after a meal. An increase in “gut leakiness” is thought to allow the translocation of LPS into blood after a high fat meal, either
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INDICATIONS
NeutraSal® is indicated for dryness of the mouth (hyposalivation, xerostomia) and dryness of the oral mucosa due to drugs that suppress salivary secretion. NeutraSal® may be used for relief of dryness of the oral mucosa when hyposalivation results from Sjögren’s syndrome.

IMPORTANT SAFETY INFORMATION
- Not intended to prevent xerostomia or oral mucositis
- Patients should avoid eating or drinking for at least 15 minutes after use
- Solution should not be swallowed but be spit out
- Not intended for systemic use to treat any diseases of the throat or upper gastrointestinal tract
- Not intended for use as an antacid
- No adverse events anticipated if swallowed accidentally
- Contains sodium; consult with patients on a low sodium diet
- No known interactions with medicinal or other products

REFERENCES:

Learn more at Neutrasal.com/Sjogrens
by damage to epithelial cells which lets LPS pass between the cells or by increased uptake of LPS through epithelial cells. In one study, 12 healthy men ate a 900 kcal meal (three slices of toast with 50 grams of butter) which increased the median blood LPS levels by 50%. Eating egg and sausage muffin sandwiches and hash browns similarly caused an elevation in blood LPS levels. Dietary fat may be more of a culprit than carbohydrates as cream (100% fat) but not glucose (100% carbohydrate) or orange juice (92% carbohydrate), caused an elevation of LPS after a meal. In fact, orange juice consumed at the time of high-fat, high-carbohydrate meal dampened the rise in LPS.

The good: Omega-3 (found in salmon and flax seeds) is converted into resolin E1 in our bodies. This lipid product has been found to increase ALPI levels. Furthermore, foods such as wheat bran, olive oil, and walnuts have been shown to decrease inflammation in blood after a meal.

Genetic predisposition may also influence our gut bacteria.

- A case controlled study looked at healthy individuals who were HLA-B27 positive and compared their gut bacteria to their HLA-B27 negative siblings. HLA-positivity is a risk factor for a number of autoimmune diseases including Sjögren’s, spondyloarthritis, inflammatory bowel disease, and uveitis. Interestingly, significant differences in the gut bacteria were noted between healthy HLA-B27 positive and HLA-B27 negative siblings, suggesting a genetic influence on gut bacterial composition. Specifically, HLA-B27 positive individuals had increased Rothia mucilaginosa and lower levels of Bifidobacterium and Odoribacter compared to their HLA-B27 negative siblings.

The composition of bacteria that live in our gut is known as the gut microbiome. Individuals with autoimmune disease have been found to have differences in their gut microbiome compared to healthy controls. This association is likely a two way street. On one hand, gut microbiome abnormalities can lead to systemic inflammation in our bodies and, conversely, systemic inflammation can preferentially deplete beneficial gut bacteria and promotes the growth of commensal bacteria with potential pathogenic properties.

Arthritis

Stool from three groups of adults were compared using 16S ribosomal RNA technology: individuals with spondyloarthritis (SpA), rheumatoid arthritis (RA), and healthy controls. Various alterations in gut bacteria were found in both arthritis groups when compared to healthy controls. The gut microbiome from the SpA group was specifically noted to be enriched with Ruminococcus gnavus compared to the RA and control group. The presence of this bacteria correlated with SpA activity in patients having a history of inflammatory bowel disease (IBD). Patients with RA on the other hand were found to have a lower abundance of common commensals such as Bifidobacteria and Bacteroides as compared to controls.

Behçet disease

Stool from individuals with Behçet disease was found to have a decreased abundance of Roseburia and Subdoligranulum as compared to co-habitating controls. Furthermore, bacteria from individuals with Behçet disease also produced less butyric acid as compared to controls.

Juvenile idiopathic arthritis (JIA)

Stool from children with JIA was found to have reduced levels of bacteria from the phylum Firmicutes (21%) compared to controls (33%) and increased abundance of bacteria from the phylum Bacteroidetes (78% vs. 65%). Furthermore, children with JIA (both the polyarticular and oligoarticular forms) had higher levels of LPS and LBP in blood compared to controls. Clinical disease activity scores positively correlated with LBP. This suggests that children with JIA have increased systemic exposure to endotoxin made by gut bacteria and supports the concept that the gut is a source of immune stimulation in JIA.

Sjögren’s Syndrome

Stool from individuals with Sjögren’s was found to have greater relative abundances of Pseudobutyryrivibrio, Escherichia/Shigella, and Streptococcus and reduced relative abundance of Bacteroides, Parabacteroides, Faecalibacterium, and Prevotella compared to controls. Furthermore, reduced gut microbiome diversity correlated with more severe ocular and systemic disease. As approximately half of individuals with Sjögren’s have another autoimmune disease (most commonly RA), overlaps likely occur in the microbiome data between RA and Sjögren’s patients.

In animal models, changing the microbiome can prevent or cause disease.

Raising HLA-B27/human β2-microglobulin transgenic rats (a rat model of SpA) in a germ free environment in which the animals do not have gut bacteria prevents the development of disease. On the other hand, transplanting gut bacteria from IBD patients with diarrhea or healthy controls into germ-free mice led to signs of IBD (faster gastrointestinal transit, intestinal barrier dysfunction, innate immune activation, and anxiety-like behavior) in the IBD but not in the control group.
composition of the gut microbiome may have a beneficial effect on disease severity. Several strategies have been explored that may change the microbiome.

**Dietary changes**

Changing the intake of carbohydrates, proteins and fats may alter the composition of the gut microbiome and inflammatory markers. A caveat to this is that the gut microbiome is relatively stable within an individual and may not change much with small or short-term changes in diet. Furthermore, a meta-analysis of 15 studies involving 837 individuals with RA did not find conclusive evidence for a favorable disease response by various changes in diet (vegetarian, Mediterranean, elemental).

**Probiotic supplementation**

Probiotics are defined as living organisms that if ingested in adequate amounts can create a health benefit. Probiotics are most often sold as dietary supplements or added to food. Probiotics are hypothesized to work by changing the composition and function of the gut microbiome, enhancing gut barrier function (decreasing “leakiness”), and modulating intestinal immunity. It is not known, however, which probiotics are best for which disease and whether their use can lead to long term changes in the gut microbiome. Furthermore, their track record for the treatment of autoimmune diseases is not strong. In a meta-analysis of nine rheumatoid arthritis studies involving 361 patients, the pro-inflammatory cytokine IL-6 was significantly lower in the probiotics compared to the placebo group, but there was no difference in clinical disease activity between groups.

Similarly, probiotics were not found to improve clinical manifestations in JIA.

**Fecal microbial transplant (FMT)**

In FMT, a fecal preparation of bacteria from carefully screened, healthy donors is transplanted into the colon of a patient, most often via enema or colonoscopy. FMT is an approved treatment for recalcitrant C. difficile infections and has also been used to remove multidrug resistant organisms from the gut.

More recently, FMT has been studied as a treatment for immune mediated diseases. In graft versus host disease (GVHD), a condition that also results in severe dry eye, four patients underwent FMT derived from a spouse or relative and delivered once or twice via nasoduodenal tube. Although it was a small study, some of the patients had improvements in gastrointestinal symptoms and peripheral regulatory T cells.

In ulcerative colitis (UC), FMT or placebo was given by colonoscopic infusion, followed by self-administered enemas five days per week for eight weeks. FMT enemas were each derived from between three and seven unrelated donors. At eight weeks, 11 (27%) of 41 patients in the FMT group and three (8%) of 40 patients in the placebo group (p=0.021) achieved steroid-free clinical and endoscopic remission. Furthermore, microbial diversity increased with and persisted after FMT. In another trial, patients with UC were given FMT (50 mL, delivered via enema from healthy anonymous donors, n=38) or placebo (50 mL water enema; n=37) once weekly for six weeks. Of the 70 patients who completed the trial, nine in the FMT group (24%) and two in the placebo group (5%) were in remission at seven weeks. In both UC trials, there were no significant differences in adverse events between the groups.

**Conclusions and relevance to Sjögren’s**

Despite the enormous personal and public health burden produced by Sjögren’s, there are no satisfactory long-term therapies for the disease. This is not for a lack of investigation. Many agents have been evaluated in Sjögren’s including corticosteroids, piroxicam, hydroxychloroquine, antimetabolites, androgens, doxycycline, and anti-TNF agents. While some provided symptomatic relief, none improved histological abnormalities or exocrine gland function. Rituximab has been the best-studied therapy with mixed results. Abatacept has also been shown to decrease disease activity and fatigue in Sjögren’s patients with disease duration of less than five years. However, no effect on salivary or lacrimal gland function was noted. Currently, there is a Phase III interventional double-blind placebo-controlled trial in progress studying the use of abatacept in Sjögren’s patients with an estimated completion date in late 2019.

Looking at the list above, immune modulation has been the goal of therapy as a chronic immune mediated attack on exocrine glands occurs in Sjögren’s. However, medications are not the only means by which to modulate the immune system. Changing the gut microbiome is an unexplored yet promising approach to the treatment of Sjögren’s.

While still in preliminary stages of investigation, gut microbiome alterations have been found in individuals with Sjögren’s and correlate with disease activity. This review highlights that more research is needed to study the connection between gut bacteria and manifestations of Sjögren’s (inflammation, dry eye, dry mouth) and in the future, modulation of gut bacteria (through diet, probiotics, or FMT) may be explored as a potential therapy in conjunction with current topical and systemic treatments.

Based on this preliminary data, we are in the process of setting up a clinical trial, funded by the Sjögren’s Syndrome Foundation, to study the effect of FMT
on peripheral manifestations of Sjögren’s (inflammation, dry eye, dry mouth) in those with disease and gut microbiome abnormalities (dysbiosis). We are currently collecting stool from individuals with Sjögren’s to profile their gut microbiome as a step to this clinical trial. We hope that this and future work will provide another avenue of treatment that will improve symptoms, histological and functional abnormalities, and most important, quality of life in individuals with Sjögren’s.

References
New for 2018, the SSF is pleased to introduce the feature, “Recommended Reading: Expert Book Reviews” into the Sjögren’s Quarterly. Here, guest authors will have the opportunity to review new and important texts on Sjögren’s and related fields. If you have recommendations for books that you’d like to see reviewed, please contact Matt Makara at mmakara@sjogrens.org.

In 126 pages Sjögren’s Syndrome (Oxford Rheumatology Library; Oxford University Press 2016) presents current understanding of Sjögren’s from a general overview of the disease (history, genetics, epidemiology, socioeconomic impact) in Chapter 1 to specific diagnosis and treatment concerns in each area of clinical importance in seven subsequent chapters. Six case studies in the final chapter reinforce key points made throughout the book.

Sjögren’s Syndrome consists of contributions by 16 European experts in rheumatology, ophthalmology, immunology, and oral and maxillofacial surgery. The book is edited by Wan-Fai Ng, Musculoskeletal Research Group, Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, U.K.

The organization of the book is reader friendly. Three pages of symbols and abbreviations precede the text — a great user benefit other publications should adopt. Pertinent “key points” introduce each section and references are provided at the end of each chapter. The index is complete, and with the lateral margin of each page containing chapter title and page number it is easy to look up specific topics.

Three appendices are included. ESSDAI (EULAR Sjögren’s Syndrome Disease Activity Index) and ESSPRI (EULAR Sjögren’s Syndrome Patient Reported Index) are mentioned in several chapters as indicators of health related quality of life. With the EULAR sicca score the patient reports on a scale measuring ocular and oral dryness.

Boxes, tables, and figures throughout the book are pertinent and useful. In Box 2.6 it would be helpful to have examples of medications that exacerbate sicca symptoms: For instance – alpha blockers (e.g. prazosin, terazosin); antidepressants (e.g. amitriptyline, nortriptyline), etc.

As part of the diagnostic work-up in Chapter 2, I would add 25-OH vitamin D level. In this same chapter there is a nice presentation of classification criteria with efforts noted to “harmonize” ACR criteria (2012) with AECG (American European Consensus Group) criteria (2002). Oral features in Chapter 3 might include halitosis as a symptom. The algorithm for MALT lymphoma is excellent. The concern about Sjögren’s-associated lymphoma is addressed throughout the book (Chapters 2, 3, 8, 9). Chapter 4 (Ocular features) includes an excellent table (4.3) on dry eye severity level and hierarchy of treatment. This chapter might be an appropriate place to present more information on hydroxychloroquine monitoring with use of formal visual field testing and SD-OCT (spectral density optical coherence tomography) in addition to the Amsler Test Grid (Box 6.1). The chapter on evidence-based evaluation and therapies provides a summary of treatments investigated and extensive studies done previously or underway.

Overall Sjögren’s Syndrome is a concise, comprehensive review of current knowledge regarding Sjögren’s. I would recommend it for anyone with interest in Sjögren’s at any level. On the back cover it is written that the book will be “an ideal cross discipline tool for the practicing physician… and of interest to trainees in rheumatology, ophthalmology, oral medicine and surgery, specialist practitioners and therapists involved in the care of patients with Sjögren’s syndrome, as well as primary care physicians.” I believe that the editor and his contributors have accomplished this.

Sjögren’s Syndrome
Edited by Fai Ng

Reviewed by Jeffrey W. Wilson, MD, FACR
Member, SSF Medical & Scientific Advisory Board At-Large Medical and Scientific Editor and Reviewer, Sjögren’s Quarterly, Retired, Rheumatology practice, Lynchburg, VA
the evaluation of Sjögren’s and examine and clarify the discordance between the different measures.

For the literature review, the research team primarily used Embase, a comprehensive biomedical literature database. A selection of agreed upon terms aimed at identifying original clinical and observational research papers and review articles that included patient-reported outcome (PRO) measures of the patient burden of Sjögren’s were used. Only English-language studies, consisting of original articles, articles in press, and reviews published between January 2005 and September 2015 were considered for inclusion. In addition to the search conducted through Embase, members of the research team searched their own collections of literature.

In all, a combined 374 articles were identified through both search methods, with 157 of them meeting the necessary inclusion criteria to be analyzed as a part of this study. Study types included: 128 research articles; 21 clinical review articles; four validation studies; two diagnostic reviews; and two articles of an unspecified type. Data from the included articles could be broken down into three categories: glandular symptoms (sicca, general dryness, oral dryness, and ocular dryness); extraglandular symptoms (fatigue, pain, depression, anxiety, sleep, sexual function, emotional function, cognitive performance, discomfort, impact of symptoms, learned helplessness, physical activity, personality, relationship status, autonomic function, headache, gastrointestinal disease, and lung involvement), and patient functional status (quality of life [QoL], physical functioning, employment, and utility).

After reviewing the studies, 143 different PRO measures were found to measure the previously mentioned categories and symptoms. These included 46 measures for glandular symptoms, 78 measures for extraglandular symptoms, and 19 measures for functional status. The greatest number of measures were for oral symptoms (24), fatigue (14), pain (14), QoL (11), and ocular symptoms (11). It is important to note that the majority of measures identified have not been validated.

A key finding from this review is that a comparison between studies was made difficult by the existence of many different non-validated Visual Analogue Scales (VAS), with a wide range of anchor words. VAS are seemingly the most commonly used PRO measure in drug therapy trials, however, there is no documented validation of such scales in patients with Sjögren’s to date.

Given these findings, the authors of this study suggest considerations be given to further qualitative research that captures patient preferences, patient satisfaction, and the degree of risk that patients are willing to accept related to their treatment. Additionally, and in hopes that it could provide a more realistic picture of the patient burden in Sjögren’s, it’s important to recognize that PRO endpoints are needed that are specific to Sjögren’s and can demonstrate improvement, with a focus on aspects of QoL that are important to Sjögren’s patients and that can measure change in function rather than the severity of a given symptom.

Citation
Hammitt KM, Naegeli AN, van den Broek RWM, Birt JA. Patient burden of Sjögren’s: a comprehensive literature review revealing the range and heterogeneity of measures used in assessments of severity. RMD Open. 2017. 3:e000443. doi: 10.1136/rmdopen-2017-000443

Commentary by Theresa Lawrence Ford, MD, FACR
This article by Hammitt et al. is a comprehensive literature review. First described in the 1930s, there have yet to be any FDA approved therapies for Sjögren’s. Validated indices for clinical outcome measures that are meaningful to patients are still needed. Current classification criteria ensure a uniform group for clinical trials but do not address chronicity or damage. Sjögren’s patients also have heterogeneous manifestations that wax and wane overtime, often making their management challenging. The burden of disease is high but underappreciated. As eloquently stated by the authors, these challenges have led to misdiagnosis or delays in diagnosis.

As a clinician and researcher, it is imperative that we develop outcome measures that are, in fact, meaningful to our patients. This review underscores the importance of utilizing patient-reported outcomes as well as understanding the existing disconnect between these and clinician-reported outcomes. Hammitt et al. both challenge and encourage us to embrace an approach to patients that not only focuses on signs and symptoms but also function, quality-of-life, and ultimately, prevention of organ damage.

Our progression makes me somewhat reminiscent of the Tower of Babel as an explanation for our obstructions. Our attempts to build towards our goal have been limited by a confounding of our speech.

With increased awareness and education, cultivated by SSF leadership, the Sjögren’s community can achieve a clearer understanding of the disease that will allow providers to optimize care and support and assist in development of novel therapeutics for our patients.
The Sjögren’s Syndrome Foundation (SSF) was delighted to select two winners for this year’s Outstanding Abstract Award at the 2017 American College of Rheumatology (ACR) Scientific Meeting in San Diego, CA. The recipients, Drs. Jessica Tarn and Katrine Brække Norheim, were recognized for their exceptional work during the Sjögren’s Study Group on Sunday, November 5, 2017.

Dr. Jessica Tarn, Institute of Cellular Medicine, New Castle University Medical School, Newcastle upon Tyne, United Kingdom, received the award for her abstract entitled, “The Effect of Non-Invasive Vagus Nerve Stimulation on Fatigue and Immune Responses in Patients with Primary Sjögren’s Syndrome.” This study used the gammcore device to dissect the relationship between the vagus nerve, fatigue and immune response in Sjögren’s and found that non-invasive vagus nerve stimulation may reduce clinical symptoms of fatigue, which could be underpinned by biological changes detectable in the whole blood.

Dr. Katrine Brække Norheim, Clinical Immunology Department, Stavanger University Hospital, Stavanger, Norway, received the award for her abstract entitled, “Genetic Determinants of Fatigue in Primary Sjögren’s Syndrome – a Genome Wide Association Study.” This study, the largest of its kind, examined fatigue in autoimmune disease and identified genetic variants in RTP4 that exceeded the study’s level for association with fatigue. These findings provide additional evidence to a genetic regulation of fatigue.

The SSF Outstanding Abstract Award is designed to recognize exceptional research efforts in the field of Sjögren’s and encourage new or early stage investigators to continue their focus on Sjögren’s throughout their career. The winning abstracts were selected by a distinguished panel of scientists from 84 eligible applicants and are available online on the SSF website at http://www.sjogrens.org/home/research-programs/outstanding-abstract.
Clinical News: Rheumatology

Extraglandular Manifestations in Sjögren’s and HCQ

A recent study sought to compare the incidence rate of extraglandular manifestations (EGM) in Sjögren’s patients who were treated with hydrochloroquine (HCQ) therapy versus those who were not. Through a multicenter, retrospective study design, 221 patients were identified using the European classification criteria for Sjögren’s diagnosis. Inclusion criteria also required that patients have at least one year of follow-up, and for those being treated with HCQ, to have at least three months of continuous use. Of the 221 patients, 215 (97.3%) were women and 170 (77%) were treated with HCQ. Nearly half of the patients experienced at least one EGM, however, the occurrence of an EGM was found to be less frequent in those being treated with HCQ (36.5% vs. 63.5%, p<0.001). The most frequent EGM’s in patients not treated with HCQ were arthritis (p<0.001), fatigue (p<0.001), and purpura (p=0.01). Additional studies are needed to confirm these findings, though the lower incidence of EGM observed in patients on HCQ therapy supports its efficacy in Sjögren’s.

Citation

Sex Bias in Autoimmune Disease: Examining the Association of VGLL3

The results of a recent study have identified VGLL3, a protein-coding gene, as having a strong association with a variety of autoimmune diseases, including lupus and Sjögren’s. Researchers used high-resolution global transcriptome analyses to analyze 31 female and 51 male biopsy samples and identified 661 genes differentially sequenced between the sexes – 268 upregulated genes in males and 393 upregulated genes in females. The results found transcriptomic differences between sexes that are associated with extensive genome-wide co-expression gene networks, which influence a variety of immunological processes. Additionally, these results identify VGLL3-regulated gene networks as novel inflammatory pathways promoting female-biased autoimmunity and help to reinforce the need for studying immunological processes in females and males separately. Additionally, these findings may have far reaching implications for the development of novel therapies.

Citation

Pneumococcal Vaccine Efficacy in Patients with RA and Sjögren’s

The purpose of this study was to examine whether antibody response and functionality of antibodies after being immunized with a 13-valent pneumococcal conjugate vaccine (PCV13) is impaired in rheumatoid arthritis (RA) and Sjögren’s patients being treated with methotrexate (MTX), hydrochloroquine (HCQ), or patients without treatment, compared to healthy controls. The study included 61 RA patients, 10 of which were being treated with MTX, 23 Sjögren’s patients, five of which were being treated with HCQ, and 49 controls, all of whom were vaccinated with a single 0.5ml dose of PCV13 intramuscularly. Serotype-specific antibody concentrations for pneumococcal serotypes 6B and 23F were taken immediately prior to vaccination as well as four to six weeks after. Both serotypes saw a significant increase in antibody concentrations between pre- and post-vaccination in the patient and control groups (p<0.001). The antibody response to serotypes 6B and 23F decreased in patients with RA on MTX treatment, but not in any of the other patient groups compared to the controls and there were not significant differences between groups in the proportion of antibody responders when analyzing either serotype. Post-vaccination, opsonophagocytic activity (OPA) increased in RA patients without DMARD treatment (p<0.001), Sjögren’s patients without DMARD (p=0.01), and the control group (p<0.001). There were no significant changes in OPA in RA patients on MTX and Sjögren’s patients on HCQ.

Citation
**The Associated Risk for Parkinson’s Disease with Sjögren’s**

A team of Chinese researchers have found a significant association between Sjögren’s and an increased risk of Parkinson’s disease. This population-based case-control study included 7,716 newly diagnosed Parkinson’s disease patients and 75,129 matched controls from the Longitudinal Health Insurance Database between 2000 and 2010. In total, 143 (1.9%) Parkinson’s patients and 893 (1.2%) controls were identified as having Sjögren’s (p<0.001). The crude odds ratio for Parkinson’s disease in patients with Sjögren’s was 1.56 (95% CI 1.30-1.86; p<0.01). After adjustment for potential confounding variables, the odds ratio was 1.37 (95% CI 1.15-1.65; p<0.01), suggesting Sjögren’s is strongly associated with the risk of Parkinson’s disease, though further investigation is needed.

*Citation*


**Sex Differences in the Clinical Presentation of Sjögren’s**

Investigators have found that despite being less prone to develop Sjögren’s, as with other autoimmune diseases, male Sjögren’s patients had an enhanced serological response and higher frequencies of lymphoma-related extraglandular manifestations, including lymphoma, compared to women. In total, 967 patients, including 899 (93%) and 68 males (7%) were included after being identified from Scandinavian clinical centers. The research team compared clinical data, including serological and hematological parameters and glandular and extraglandular manifestations between male and female Sjögren’s patients. The serology for male patients was characterized by more frequently being positive for anti-RO/SSA and anti-La/SSB (p=0.02) and ANA (p=0.02). Additionally, males were diagnosed with interstitial lung disease (p=0.008), lymphadenopathy (p=0.04) and lymphoma (p=0.07) more frequently when compared to females. In female patients, concomitant hypothyroidism was more common (p=0.009) compared to their male counterparts.

*Citation*


**Rheumatoid Arthritis Drugs Associated With Higher Rates of Herpes Zoster**

A recent study by a team of Japanese researchers sought to investigate the association between the use of disease-modifying antirheumatic drugs (DMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs) and the incidence of herpes zoster in patients with rheumatoid arthritis. Using the Registry of Japanese Rheumatoid Arthritis Patients on Biologics for Long-Term Safety database, a prospective cohort of patients from 1987 was selected, including 43 patients who developed herpes zoster and 214 that did not. The IR of herpes zoster was found to be 6.66. The OR of tumor necrosis factor inhibitors (TNFi) and oral corticosteroids were 2.28 and 1.13, respectively, both of which were significantly elevated compared to non-TNFi’s and methotrexate. The authors of this study suggest that physicians should monitor patients with rheumatoid arthritis closely for the development of herpes zoster when placed on TNFi’s and oral corticosteroids.

*Citation*


**Consensus Recommendations: Addressing Unmet Needs to Advance Rheumatologic Care**

Recently, an international panel of experts was tasked with identifying, discussing and formulating a list of unmet needs in the field of rheumatology, which could then serve as a roadmap for research and support for clinicians in terms of how best to manage patients. In conjunction with systemic literature reviews, the panel was split into a variety of working groups based on their expertise. Through review and discussion, several unmet needs and a variety of questions were recognized, answers for which will help to bring scientific clarity on managing clinical conditions.

*Editors Note: Specifics on the unmet needs and recommendations for Sjögren’s will be discussed in a future issue of the Sjögren’s Quarterly.*

*Citation*

A Comparison of Tear Film Proteins in Nonautoimmune DES and Sjögren’s Patients

This study, presented at the American Association of Ophthalmology’s 2017 Annual Meeting, investigated complementary biomarkers that potentially separate Sjögren’s from nonautoimmune dry eye syndrome (DES). Each of the 31 female Sjögren’s patients, 19 DES patients, and 24 controls involved in the study contributed two tear samples for analysis of cathepsin S (CTSS), secretory IgA (Slga), lactoferrin (LF), and cystatin C (CysC) in proportion to total protein. CTSS was significantly elevated in Sjögren’s patients (P<0.001) but not in DES patients (P<0.76) compared to the control group. Comparing Sjögren’s patients to DES patients, median CTSS activity was 6.88 times higher and Slga, LF, and CysC levels showed decreases of 8.50, 9.69, and 3.33, respectively. The results of this study could assist in the diagnostic workup of Sjögren’s

Citation

The Efficacy of Desktop Humidifiers to Treat DES Symptoms in Computer Users

The purpose of this study was to evaluate the potential for a desktop humidifier as a means to improve tear-film parameters, ocular surface characteristics, and subjective comfort in computer users, a group that frequently reports dry eye as a problem. In all, 44 participants were chosen for this prospective, masked, randomized crossover study, which included one hour of continuous computer use both with and without exposure to the desktop humidifier. Both before and after use, researchers measured lipid-layer grade, noninvasive tear-film breakup time, tear meniscus height, and qualitative feedback from participants on ocular comfort. No significant differences in lipid-layer grade and tear meniscus height were found between the humidified and non-humidified environments, which had a relative difference in humidity of +5.4 ± 5.0% (P<0.001). An increase in the median noninvasive tear-film breakup time of +4.0 seconds was found in the humidified environment (P<0.001), which was associated with participants reporting an increase in comfort compared to baseline measures (36% vs. 5%, p<0.001). These results support the use of desktop humidifiers as a way to potentially improve tear-film stability and subjective comfort in computer users.

Citation

Novel Artificial Tear Formula Improves Ocular Discomfort and Visual Tasking Activities

A team of U.S. researchers have published their findings analyzing a new artificial tear product, Rohto® Dry-Aid™, on its ability to relieve the signs and symptoms of dry eye disease (DED). Researchers designed a prospective, single-center, open-label, parallel group study that compared the effects of Rohto® Dry-Aid™ to another product, Systane® patients, again found significantly greater Schirmer scores (P<0.0001) when using ITN stimulation (17.3±12.0 mm) versus no stimulation (7.9±6.4mm). No serious events related to the devices were reported and both studies support ITN as an effective way to increase tear production in dry eye patients.

Citation
Ultra, as a positive comparator. A total of 80 participants were split into two groups, each receiving one of the two treatments, with assessments at two and four weeks. Participants in both groups reported statistically significant improvements in their ocular discomfort scores, though qualitative trends found more favorable reports in the morning compared to night for the Systane® Ultra group, but not the Rohto® Dry-Aid™ group, indicating that Rohto® Dry-Aid™ may provide longer lasting relief to DED symptoms. Participants in the Rohto® Dry-Aid™ group also reported significant improvements in visual tasking activities, such as watching T.V. and driving at night.

**Citation**


**Promising Results for Novel 0.3% Hyaluronic Acid Treatment for Dry Eye Disease**

Researchers have reported positive results for a novel 0.3% hyaluronic acid artificial tear for the treatment of moderate-to-severe dry eye. Patients (n=16) were randomly assigned to use Visaid, the 0.3% hyaluronic acid solution, or a 0.9% NaCl solution, which served as the control for this experiment. Patients in each group applied between three and eight drops per day during a one month period, followed by an additional month at the same dosage where the patient groups switched treatments. Patients using Visaid showed significant improvements in a number of endpoints, including Ocular Surface Disease Index questionnaire scores (ΔY: −9.66%±10.90), tarsal hyperemia (ΔY: −16.67%±27.89), corneal staining extension (ΔY: −34.90%±42.41), tear break-up time (TBUT (ΔY: 13.98%±26.19), and subjective satisfaction (ΔY: 38.06%±47.06). Significant differences between Visaid and the 0.9% NaCl solution were found when comparing TBUT (ΔY: 13.98%±26.19 vs. 10.15%±42.34, respectively; P=0.0214).

**Citation**


**Discovery of New Communications Mechanism Post Nerve Trauma**

Researchers from Kings College London, London, England, have discovered a new mechanism of cellular communication involving neurons and immune cells related to neuropathic pain. By studying a cluster of neurons in the dorsal root ganglion (DRG) in cellular and mouse models post nerve injury, it was found that pain neurons in the affected area released small particles containing microRNA-21 (miR-21), which were subsequently taken up by the surrounding immune cells. This process resulted in local inflammation and neuropathic pain. However, an anti-inflammatory affect was observed as a result of blocking the DRG pain neurons from releasing miR-21 particles, which prevented neuropathic pain from occurring. Currently, the only drugs available for neuropathic pain are opioids or antiepileptic drugs. Of note, the process described in this study does not lead to any side effects. Researchers will next look at whether the same mechanism described in this study applies to other chronic pain conditions.

**Citation**

Chemosensory Function and ORHQoL

A team of Norwegian researchers from the University of Oslo and Oslo University Hospital, Rikshospitalet, Oslo, Norway, sought to evaluate the olfactory and gustatory functions of 31 Sjögren’s patients compared to a group of 33 controls. The authors looked at chemosensory function, burning sensations in the tongue (BST), halitosis, saliva secretion and oral health-related quality of life (OHRQoL). Self-reported occurrences of dysguesia, BST, and halitosis proved higher in Sjögren’s patients and were also associated with poorer scores on the Oral Health Impact Profile, which evaluates a patient’s OHRQoL. Furthermore, Sjögren’s patients were more likely to display impaired chemosensory and salivary functions when compared to the controls.

Citation

Analysis Finds TENS Not Supported for Use in Patients with Xerostomia

A meta-analysis of studies examining the use of transcutaneous electrical nerve stimulation (TENS) found that the current pool of evidence does not support the use of TENS in patients with xerostomia. Six studies were included with data from a total of 369 participants, which showed that TENS did not have a statistically significant effect on salivary flow (SMD 95% CI, 0.63, [-0.03-1.29]). Additional randomized controlled trials are needed to provide evidence either for or against the use of TENS in xerostemia.

Citation

A Systematic Review of the Relationship Between Sjögren’s and Periodontal Status

A review of the literature, conducted based on the PRISMA methodology, did not provide strong evidence that periodontal status is affected by Sjögren’s. Studies were independently selected by three researchers from various databases, including: PubMed/MEDLINE; LILACS, Web of Science, and Science Direct. Hand searches and gray literature were also taken into consideration. Seventeen studies were identified, nine of which were included in the meta-analysis. Included studies were those that correlated Sjögren’s with plaque index, gingival index, probing depth and bleeding on probing. In total, 518 patients with Sjögren’s and 544 controls were included. The analysis found that all but the gingival index was greater in Sjögren’s patients compared to the controls. Of note, researchers felt the majority of the included studies should be judged as having a high risk of bias.

Citation

Retrospective Study Provides Additional Support for MSGB for Diagnosing Sjögren’s

A team out of the Department of Oral and Maxillofacial Surgery, Massachusetts General Hospital, Boston, MA conducted a retrospective cohort study to better define the role of minor salivary gland biopsy (MSGB) in establishing the diagnosis of Sjögren’s. In total, 87 patients met the inclusion criteria for the study, including 75 women and 19 men. Based on the focus score histologic criteria, 15 of the MSGB results were positive, 12 of which allowed for a definitive diagnosis of Sjögren’s. The remaining three cases found a diagnosis without the contribution of MSGB. These findings support MSGB as an important contributor to the diagnosis of Sjögren’s as well as being the most frequently positive of the major criteria used to diagnose the disease.

Citation
New Formulation of GSK’s Benlysta Approved

A new formulation of Benlysta (belimumab), a prescription B cell activating factor inhibitor, has been approved for certain adults with lupus. This new subcutaneous formula enables the drug to be administered at a patient’s home by either a single-dose pre-filled syringe or single-dose auto-injector pen once per week. This approval allows greater flexibility for patients being treated with Benlysta, who previously could only receive the drug intravenously in a medical setting.

Additionally, clinical trials on the safety and efficacy of belimumab and rituximab in patients with Sjögren’s are underway with an anticipated completion date of January 2020. Previously, studies on the safety and efficacy of belimumab in Sjögren’s patients have been conducted in both Italy and France with encouraging results, which justified future trials with Sjögren’s patients who would be most likely to benefit from the treatments.

New Low-Cost Alternative to Restasis May Soon be Available

Imprimis Pharmaceuticals will soon offer a compound-ed cyclosporine-based formula to compete with Allergan’s Restasis. Imprimis announced that the patent-pending product will be priced to initially be filled for $0.99 and refilled for $79 per month. Mark Baum, Imprimis CEO, stated that “We [Imprimis] believe that affordability can affect access to needed medications, and it is our hope that our formulations will allow more patients to gain access to a high quality customized cyclosporine.”

FDA Launches New Biosimilar Education Campaign

Biosimilars are relatively new in the U.S. and the U.S. Food and Drug Administration (FDA) has launched a new campaign to educate both patients and medical professionals about these new and upcoming treatment options. Biosimilars are “highly similar” versions of originator biologics, which are used to treat a wide range of conditions, including rheumatoid arthritis and other autoimmune diseases. A variety of campaign resources will provide definitions, facilitate understanding of the various processes for development, describe the rigorous standards that must be met for a biosimilar to be approved, and more. The introduction of biosimilars to the U.S. market will increase the number of treatment options for patients, and through market competition, may greatly reduce healthcare costs.

Allergan’s Patents for Restasis® Ruled Invalid

A recent court ruling found that Allergan’s patents for Restasis®, a dry eye drug that accounts for nearly $1.5 billion annually, were invalid. The patents in question involve those that were given to the Saint Regis Mohawk Tribe in 2017, which gave the tribe patents and a payment of $13.75 million, with the potential for additional annual payments. This ruling opens the door for generic competition.

Allergan has stated that it will appeal the decision, though the company has announced they will be eliminating upwards of 1,400 jobs that had focused on products and categories that are subject to a loss of exclusivity and generic competition, which includes Restasis®.

Lipiscan™ and LipiFlow™ Widely Available in U.S. and Canada

As previously reported in the Fall 2017 issue of the Sjögren’s Quarterly, Johnson & Johnson Vision acquired TearScience as part of the strategy to expand the company’s portfolio. At the recent American Academy of Ophthalmology Annual Meeting in New Orleans, LA, TearScience representatives announced that LipiScan™, a Meibomian gland imaging solution, and LipiFlow™, the only FDA-approved device for Meibomian Gland Dysfunction, are now available in more than 800 optometrist and ophthalmologist offices in the U.S. and Canada.
Aurinia Launches Development Program for Treatment of Dry Eye Syndrome

Aurinia Pharmaceuticals announced plans to evaluate its proprietary nanomicellar voclosporin ophthalmic solution (VOS) for the treatment of dry eye syndrome (DES). The company is planning to begin a Phase IIa tolerability study of VOS versus the standard of care for the treatment of DES during the Spring of 2018. To this point, VOS, a topical solution, has shown evidence of efficacy in partnered canine studies and human Phase I studies.

NovaTears®+Omega-3 for Evaporative Dry Eye Approved in Europe

Novaliq GmbH has announced the European registration of their product, NovaTears®+Omega-3, for the treatment of evaporative dry eye disease. In addition to using EyeSol®, a water-free drug delivery technology, this new treatment is the first drop to contain a high-concentration of Omega-3 ethyl ester (0.2%) of plant origin. In the tear film, this treatment works by stabilizing the lipid layer and the addition of Omega-3s helps reduce the evaporation of the underlying water. NovaTears®+Omega-3 is available in a multi-dose bottle.

TearSolutions Receives Investment to Continue Phase I/II Trials of Lacriprep™

Investors, led by Middletown Capital’s Virginia Tech Carilion Innovation Fund and Pharmastandard International, have raised $8.5 million in Series B financing for TearSolutions, Inc., a clinical state ocular-health-focused pharmaceutical company. The funding will be used to advance Lacriprep™, a novel replacement therapy for dry eye disease comprised of naturally occurring peptide fragments of lacritin. Lacriprep™ will act to restore tearing and homeostasis to the ocular surface. Currently, a Phase I/II clinical trial examining varying doses of Lacriprep™ in more than 200 Sjögren’s patients is underway at sites found throughout the U.S. Clinical trial sites were selected with the help of the Sjögren’s Syndrome Foundation.

New Collaboration Between MeiraGTx and Oxford Genetics

MeiraGTx, a London, U.K., and New York-based gene therapy company, has partnered with Oxford-based Oxford Genetics. This collaboration will enable the companies to develop new adeno-associated virus vectors (AAV), packaging, and producer cell lines to support the needs of MeiraGTx’s growing pipeline of gene therapy products. This partnership will work to create a fully scalable AAV production system that can meet the requirements for increased viral vector yields, process robustness, and product effectiveness. The agreement grants MeiraGTx exclusive global research and manufacturing rights for new serotype-specific AAV vectors and any associated packaging and producer cell lines. Leadership from both companies expressed their enthusiasm for the partnership and its potential.

Nanocomposite eye drops move on to Phase III trials

Huons, a subsidiary of South Korean Huons Global, has announced positive results from their Phase II clinical trial of HU007, a nanocomposite solution comprised of 0.02% cyclosporine and 3% trehalose. Consisting of 105 adult patients with dry eye, the multicenter, placebo-controlled, randomized, double-blind trial produced clinically meaningful benefits to tear film protection as well as anti-inflammatory effects according to the principal investigator. The solutions nanoparticles, measuring less than 20nm in diameter, are thought to ensure that more of the active ingredient reaches the user’s eyes while also eliminating the need to shake the bottle before use. The next step for HU007 will be a Phase III clinical trial, with hopes for receiving marketing approval in Korea by 2019.

FDA Accepts Sun Pharmaceuticals NDA for novel DED Treatment

India-based Sun Pharmaceutical Industries has announced that the U.S. FDA has accepted their new drug application for OTX-101, a nanomicellar formula of 0.09% cyclosporine A for the treatment of dry eye disease (DED). This preservative-free aqueous solution, now under FDA review, produced positive results in a 12 week, multicenter, randomized, double-masked, vehicle controlled Phase III confirmatory study involving 744 DED patients. Patients receiving the novel treatment showed statistically significant improvement in their Shirmer’s test scores (p<0.0001) compared to those being treated with the vehicle. Of note, OTX-101 was found to demonstrate efficacy more quickly compared to similar drugs. If approved, OTX-101 will be commercialized in the U.S. by Sun Ophthalmics, a division of Sun Pharmaceuticals, based in Princeton, NJ.

Shire’s Xiidra Approved in Canada

U.K.-based Shire Pharmaceuticals has received regulatory approval for Xiidra, a lifigestрат ophthalmic solution used to treat dry eye disease in adults. Xiidra is already approved for use in the U.S., and should be available for patients in Canada sometime in early 2018. The company is currently seeking marketing authorization for the treatment in Europe.

Uncertainty Surrounds Kala Pharmaceutical’s DE Drug

Massachusetts-based Kala Pharmaceuticals’ drug, KPI-121, has produced mixed results in recent trials. The drug, which treats acute, episodic dry eye flares rather than continuous symptoms, achieved three of their four main
SSF In Action

SSF Participates at 2017 NIAMS Coalition Meeting

The SSF once again participated in the biennial National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Outreach & Education Meeting. This year’s event, held October 17, 2017 at the National Institutes of Health Natcher Conference Center, Bethesda, MD, brought together more than 70 representatives from various member organizations of the coalition.

As part of the day’s itinerary, two poster sessions were scheduled, in which Matt Makara, SSF Director of Research and Scientific Affairs, presented on the summary of major findings from the SSF national patient survey, conducted in 2016. Additionally, this meeting featured sessions with a variety of NIH directors, including Stephen I. Katz, MD, PhD, Director, NIAMS, Eric Dishman, Director, All of Us Research Program, and Eliseo Pérez-Stable, MD, Director, National Institute on Minority Health and Health Disparities.

SSF’s Ford Presents on the Role of the JAK-STAT Pathway in Rheumatoid Arthritis

In this highly anticipated presentation at the 2017 American College of Rheumatology’s Annual Meeting in San Diego, CA, SSF Medical and Scientific Advisory Board Chair Theresa Lawrence Ford, MD, FACR spoke about the importance of the Janus kinase / signal transducers and activators of transcription (JAK-STAT) pathway in rheumatoid arthritis. Sponsored by Eli Lilly, this Innovation Theater session provided attendees with an introductory course on the four JAKs and seven STATs that make up the pathway, how they pair and associate with different cytokines, and the impact of this process on inflammation and joint destruction. This standing room only event featured a six-piece orchestra to help emphasize Dr. Lawrence Ford’s key points, playing in harmony to demonstrate how our bodies should function and out of sync to demonstrate a dysfunctional system.

SSF Exhibits at National Optometry Meeting

The SSF was excited to participate in the 2017 Annual Meeting of the American Academy of Optometry (AAO), held in Chicago, IL. This four-day meeting provided a platform for students and professionals to learn about groundbreaking research and participate in educational opportunities. This was the SSF’s first time exhibiting at AAO and was among 200 other companies and organizations at this year’s meeting. While there, nearly 100 attendees visited the SSF booth, where they could learn more about Sjögren’s, receive materials, and interact with SSF staff to learn how to get involved with the foundation.

SSF Participates in NHC Meetings and Conferences

On September 18-19, 2017, SSF CEO Steven Taylor and Vice President of Medical and Scientific Affairs Kathy Hammitt attended the National Health Council’s (NHC) 2017 Chief Medical/Scientific Officers Conference. Themed, “Lessons Learned and Pathways Forward: Practical Experiences in Patient Engagement,” this year’s event featured presentations and talks that profiled examples of the science of patient engagement in research and care delivery, highlighting good practices, successful methods, shortcomings, and gaps to be addressed. As a result of this meeting, a white paper will be developed on emerging good practices in the science of patient input with a focus on both what is working as well as areas with limitations. When completed, this paper will recommend future directions for enhancing emerging good practices and a portfolio of practices will be developed and made available online.
goals, but failed to show a statistically significant reduction in eye discomfort in one of their trials. Next steps for the drug have yet to be determined.

**The Future of Alcon and Bion® Tears Availability**

Due to recent struggles, Alcon, which was fully acquired by Novartis in 2011, has been given until 2019 before a determination is made on whether to spin them off into a stand-alone company with a separate listing. Alcon is the producer of Bion® Tears, a formulation of 0.1% Dextron 70 and 0.3% hypomellose 2910, used for the treatment of dry eye and a product that many have found difficult to find in recent years. After reaching out, a representative from Novartis has suggested that patients looking to obtain Bion® Tears check Amazon.com. While Bion® Tears is not a widely distributed product, it can usually be found in the online marketplace.

**Partnership Brings I-PEN® Osmolarity System to United States**

Canadian-based I-MED Pharma Inc. has entered into an exclusive agreement with OcuSOFT for the rights to distribute this system in the U.S. This system is a handheld platform that serves as a quick and reliable tool for eye care professionals when screening dry eye patients. As of December 2017, the FDA has issued an Acceptance Review Notification for the product, with final approval expected sometime in the first quarter of 2018. ■

**Efficacy of Computer-Guided Versus Conventional Implant Placement Treatments**

A recent study has found that no statistically significant differences exist between computer-guided versus conventional implant placement treatments. Using a PICO-based search strategy, researchers identified 16 randomized controlled trials focused on treatments that used a digital workflow for oral implant placement compared to conventional procedures. This method resulted in 16 studies, with an additional 21 studies being identified through a manual search. Of the 37 studies identified, only two met the criteria for data extraction. Of note, and though no significant differences were found between treatments, one of the included studies did reveal a higher rate of self-reported pain and swelling from patients in the conventional treatment group. Investigators encourage additional research to help identify in which clinical situations computer guided implant surgery would be most beneficial. ■

**Citation**

Stress has been linked as one potential factor in contributing to the development of disease, including Sjögren's, and, once someone has Sjögren's, stress can exacerbate symptoms. Some tips to becoming more mindful and reducing and coping with stress follows.

- Identify and learn to recognize stressors in your life.
- Know your limits and pace yourself.
- Set realistic expectations and plan ahead.
- Listen to your body and take time out as needed to get through your day.
- Don’t be afraid to ask for help.
- Build a support system. To the greatest extent possible, avoid those who are not supportive.
- Educate your friends and family about your disease and what you are going through.
- Join an SSF Support Group and attend an SSF National Patient Conference to meet others with Sjögren's and learn from Sjögren's experts. Engage with others online by joining Smart Patients, the online SSF support group, and join the SSF Facebook group.
- Practice relaxation techniques such as meditation and consider mindful exercises such as yoga and tai chi.
- Get sufficient rest and sleep every night.
- Eat well! Avoid junk food and too much caffeine and alcohol. Eat nutritiously.
- Get moving every day! If you have not been exercising, start slowly and build up. If you have any major health problems such as cardiovascular or lung issues, consult with your doctor before starting an exercise routine.
- If you are employed, request accommodations as needed because of your medical condition. If you can work from home, you can gain more flexibility with your time and work routine.
- Develop a close working relationship with your doctor(s). Report major changes in your psychological well-being such as depression and anxiety.
- Seek help in lowering your stress level. Consider consulting with a mental health professional to talk about your stress, the effect on your quality of life and your disease, and methods for coping.
- Avoid triggers for your stress as often as you can. When you can’t avoid stress, practice techniques that reduce stress and lean on your support system.
- Add laughter to your life! Make time for friends or to make new friends, and engage in stimulating social and mental activities.
Register for the 14th ISSS!

Registration is open for the 14th International Symposium on Sjögren’s Syndrome. This symposium, taking place in Washington D.C. from April 18-21, 2018, is designed to facilitate precision medicine practices in all aspects of clinical care, including patient diagnosis, prognosis, therapeutic responses, and prevention. This two-and-a-half day conference will bring together representatives from science, technology, evidence-based medicine and leaders in the Sjögren’s /autoimmune research community and will provide important updates that will help to narrow the gaps in knowledge related to Sjögren’s.

Additionally, late-breaking abstracts are being accepted January 15 – February 15, 2018. Eligible abstracts will describe cutting-edge scientific research for which no preliminary data were available for the previous general abstract submission deadline.

Dates & Location
Wednesday, April 18, 2018 4:00 PM – Saturday, April 21, 2018 12:00 PM
Capital Hilton Hotel, Washington, DC

Visit http://tinyurl.com/ISSS2018 for the most up-to-date program and registration information.