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Recent Advances on Primary Sjogren's Syndrome and Depression Relationship

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Abstract: Primary Sjogren's syndrome is a chronic autoimmune disorder that affects the exocrine glands, leading to dryness of the eyes, mouth, and other mucous membranes. Depression is a common comorbidity in patients with primary Sjogren's syndrome, and it can have a significant impact on patients' quality of life. This review paper provides an overview of the clinical presentation and prevalence of primary Sjogren's syndrome and depression, as well as a summary of the research progress on the relationship between these two conditions. The proposed mechanisms underlying the relationship between primary Sjogren's syndrome and depression, including neuroendocrine and immune system dysregulation, proinflammatory cytokines, stress and coping mechanisms, psychological factors, and other factors, are also discussed. Additionally, various treatment options for depression in patients with primary Sjogren's syndrome are reviewed, including pharmacological and non-pharmacological interventions,such as antidepressant medication,cognitive-behavioral therapy (CBT) and interdisciplinary treatment approaches.While there are some limitations to the current research, understanding the relationship between primary Sjogren's syndrome and depression is important for improving the care and quality of life of patients with this condition.

Keywords: Primary Sjogren's syndrome, depression, neuroendocrine, immune system, stress

Literature search strategy
Using "Primary Sjogren's syndrome" "Depression" "neuroendocrine" "immune system" "stress" as keywords to search PubMed, Medline, Web of Science. Literature inclusion criteria: (1) Research on primary Sjogren's syndrome and Depression relationship; (2) Survey research and literature review. Literature exclusion criteria: (1) repeated publications; literature irrelevant to the research content; (2) case reports. According to the above criteria, 29 relevant literatures were finally selected.

1.Introduction

Primary Sjogren's syndrome (PSS) affects approximately 0.5-1% of the general population, with a higher prevalence in women than men(Ferro, F., Marcucci, E., Orlandi, M., Baldini, C., & Bartoloni-Bocci, E. ,2017.) [1]. Depression, on the other hand, is a common mental disorder characterized by persistent feelings of sadness, hopelessness, and loss of interest in daily activities. It affects an estimated 4.4% of the global population (World Health Organization.,2023.)[2].
The relationship between PSS and depression has received increasing attention in recent years, as several studies have suggested a higher prevalence of depression in patients with PSS compared to the general population (Cui, Y., Li, L., Yin, R., Zhao, Q., Chen, S., Zhang, Q., & Shen, B. ,2018.)[3]. Understanding the relationship between these two conditions is important, as depression can significantly impact the quality of life of patients with PSS and may contribute to poorer treatment outcomes because depression can reduce patients' immune function and affect patients' cooperation with treatment(Hackett, K. L., Newton, J. L., Frith, J., Elliott, C., Lendrem, D., Foggo, H., Edgar, S., Mitchell, S., & Ng, W. F. ,2012.) [4]. This review paper aims to summarize the current research progress on the relationship between PSS and depression and to explore the potential mechanisms underlying this relationship.

2. Primary Sjogren's syndrome and depression: Clinical presentation and prevalence

2.1 Description of primary Sjogren's syndrome and its symptoms
Primary Sjogren's syndrome (PSS) leads to dry eyes and mouth.It can also affect other organs, such as the skin, lungs, kidneys, and nervous system, leading to a range of symptoms such as fatigue, joint pain, and neuropathic pain (Brito-Zerón, P., Baldini, C., Bootsma, H., Bowman, S. J., Jonsson, R., Mariette, X., Sivils, K., Theander, E., Tzioufas, A., & Ramos-Casals, M.,2016.)[5].
2.2 Description of depression and its symptoms

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Depression is a common mental disorder that is characterized by persistent feelings of sadness, hopelessness, and loss of interest in daily activities. Other symptoms include changes in appetite, sleep disturbances, low energy, poor concentration, and feelings of worthlessness or guilt(American Psychiatric Association. ,2013.) [6].

2.3 Prevalence of depression in patients with primary Sjogren's syndrome

In a systematic review and meta-analysis, 2018 Cui et al. found that the prevalence of depression in PSS patients ranged from 6.7% to 60%, with a pooled prevalence of 25%(Cui, Y., Li, L., Yin, R., Zhao, Q., Chen, S., Zhang, Q., & Shen, B. ,2018.)[3]. The prevalence of depression in the general population, on the other hand, is estimated to be around 4.4% (World Health Organization.,2023.)[2].A recent study suggested that rheumatologists should pay attention to PSS patients' dry eye and dry mouth, especially those with older age, higher level of ESR, more severe fatigue, and pain(Li, Z., Fu, T., Li, L., Cui, Y., Dong, C., Li, J., & Gu, Z. ,2018.)[7].

3. Research progress on the relationship between primary Sjogren's syndrome and depression

3.1 Cross-sectional studies

Numerous studies have investigated the relationship between primary Sjogren's syndrome (PSS) and depression. Here we review the literature on cross-sectional studies examining this association.A cross-sectional study evaluated the prevalence of depression in 202 PSS patients and found that 45% had symptoms of depression (Hackett, K. L., Newton, J. L., Frith, J., Elliott, C., Lendrem, D., Foggo, H., Edgar, S., Mitchell, S., & Ng, W. F. ,2012.)[8]. The study also found that the severity of dry mouth and fatigue, two common symptoms of PSS, was significantly associated with depression.Another cross-sectional study found the prevalence of depression and anxiety was high in adult PSS patients(Cui, Y., Xia, L., Li, L., Zhao, Q., Chen, S., & Gu, Z. ,2018.)[9]. Interestingly, oral health and swallowing disorders were the most important predictors of anxiety in PSS patients. Therefore, rheumatologists should pay attention to the potential mental comorbidities while managing patients with PSS and provide the basis for mental health providers in order to identify effective strategies for preventing and treating depression and anxiety among adult PSS patients. Simultaneously, rheumatologists should also focus on the oral health and swallowing disorders in PSS patients.Overall, these cross-sectional studies suggest that there is a high prevalence of depression in PSS patients and that depression is associated with symptom severity and disease activity.

3.2 Longitudinal studies

In addition to cross-sectional studies, several longitudinal studies have investigated the relationship between primary Sjogren's syndrome (PSS) and depression.A study by (Norheim, K. B., Harboe, E., Gøransson, L. G., & Omdal, R. ,2012.) followed 61 PSS patients over two years and found that depression was associated with a lower quality of life[10]. The study also found that the severity of fatigue and pain, two common symptoms of PSS, predicted depression.Another study found that symptom-based clustering of heterogenous patients with primary Sjogren's syndrome provided a relevant classification supported by temporal stability over time and distinct phenotypes between the classes. This clustering strategy may provide more homogenous groups of PSS patients for novel treatment development and predict future phenotypic evolvement(Lee, J. J., Park, Y. J., Park, M., Yim, H. W., Park, S. H., & Kwok, S. K. ,2021.)[11]. In PSS, symptom burden and to a great extent Newcastle Sjogren's Stratification Tool (NSST) subgroup, rather than systemic disease activity, has a significant relationship with Health-related quality of life(HRQoL) longitudinally. Improvements in symptom burden have the potential to produce significant impacts on long-term HRQoL in PSS(Tarn, J., Lendrem, D., McMeekin, P., Lendrem, C., Hargreaves, B., & Ng, W. F. ,2022.)[12].

3.3 Limitations of current research

While research on the relationship between primary Sjogren's syndrome (PSS) and depression has provided valuable insights, there are several limitations to the current body of literature.First, many of the studies are cross-sectional, which makes it difficult to establish causality. Longitudinal studies are needed to determine whether depression is a consequence of PSS or whether PSS increases the risk of developing depression.Second, there is a lack of standardized diagnostic criteria for depression in PSS patients. Many of the studies have used different criteria to define depression, which makes it difficult to compare results across studies.Third, there is a lack of consensus on the prevalence of depression in PSS patients. Studies have reported a wide range of prevalence rates, which may be due to differences in patient populations, diagnostic criteria, and assessment tools.Fourth, many of the studies have small sample sizes, which limits their generalizability. Larger studies are needed to confirm the findings of smaller studies and to identify subgroups of PSS patients who are at increased risk of depression.Fifth, there is a need for more research on the mechanisms underlying the relationship between PSS and depression. While some studies have suggested that pain and fatigue may contribute to the development of depression in PSS patients, the underlying biological and psychological mechanisms are not well understood.Finally, most of the studies have focused on depression, while the relationship between PSS and anxiety has received less attention. More research is needed to understand the relationship between PSS and anxiety, and how it may differ from the relationship between PSS and depression.

4. Proposed mechanisms underlying the relationship between primary Sjogren's syndrome and depression

While the exact mechanisms underlying the relationship between primary Sjogren's syndrome (PSS) and depression are not fully understood, some studies have suggested that dysregulation of the neuroendocrine and immune systems may play a role.

4.1 Neuroendocrine dysregulation in PSS patients may contribute to the development of depression. One recent study has shown that PSS patients have lower levels of cortisol, a hormone that helps regulate the stress response, compared to healthy controls(Straub, R. H., & Cutolo, M. ,2001.)[13]. This suggests that PSS patients may have a blunted stress response, which could make them more vulnerable to depression.Additionally, alterations in the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the body's stress response, have been observed in both PSS and depression(Straub, R. H., & Cutolo, M. ,2016.)[14]. Dysfunction in the HPA axis may contribute to the development and maintenance of depression in PSS patients.Women with PSS have intact cortisol synthesis but decreased serum concentrations of dehydroepiandrosterone sulfate (DHEA-S) and increased cortisol/DHEA-S ratio compared with healthy controls. The findings may reflect a constitutional or disease mediated influence on adrenal steroid synthesis. The thyroid axis and gonadotropin secretion were similar in patients and controls (Valtysdóttir, S. T., Wide, L., & Hällgren, R. ,2001.)[15]. The presence of these autoantibodies in approximately one fifth of primary SS patients, in association with mRNA expression of B-cell activating cytokines including interferon-a (IFNa), B-cell activating factor (BAFF) and interleukin-21 (IL-21), at the level of salivary gland tissue. Although blunted adrenal responses were observed in the anti-21(OH) positive SS subset, overt adrenal insufficiency was not documented, by Short Synacten test (Mavragani et al., 2012, submitted).Whether, the presence of autoantibodies to adrenal autoantigens reflect an endogenous failure of the SS host to prevent aberrant immune responses or are the result of B-cell hyperactivation remains to be further addressed. Additionally, given the predictive value of autoantibodies against 21(OH) for the development of adrenal failure, long term follow up would be required for such patients (Mavragani, C. P., Fragoulis, G. E., & Moutsopoulos, H. M. ,2012.) [16]. These cytokines have been implicated in the development of depression in other conditions, such as rheumatoid arthritis and multiple sclerosis. In addition, PSS patients have increased activity of natural killer (NK) cells, which play a role in the immune response to viral infections.

4.2 Role of proinflammatory cytokines

Continuing with the proposed mechanisms underlying the relationship between primary Sjogren's syndrome (PSS) and depression, proinflammatory cytokines have also been suggested to play a role. A study assessed that the chronic inflammation and immune dysfunction that characterize PSS may contribute to the development of depression(Kivity, S., Arango, M. T., Ehrenfeld, M., Tehori, O., Shoenfeld, Y., Anaya, J. M., & Agmon-Levin, N.,2014.)[17]. Several studies have reported higher levels of pro-inflammatory cytokines in the serum and saliva of PSS patients with depression compared to those without depression (Ramos-Casals, M., Brito-Zerón, P., Sisó-Almirall, A., Bosch, X., & Tzioufas, A. G. ,2012.)(Hackett, K. L., Deane, K. H. O., Newton, J. L., Deary, V., Bowman, S. J., Rapley, T., Ng, W. F., & United Kingdom Primary Sjögren's Syndrome Registry ,2018.)[18, 19]. PSS is associated with increased levels of proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interferon-alpha (IFN-α)(Mavragani, C. P., Fragoulis, G. E., & Moutsopoulos, H. M. ,2012.)[16]. These cytokines have been shown to have direct effects on the brain and have been implicated in the pathophysiology of depression (Miller, A. H., & Raison, C. L. ,2016.)[20].For instance, IL-6 has been shown to activate the HPA axis and to decrease the expression of brain-derived neurotrophic factor (BDNF), which is important for the survival and function of neurons(Pariante, C. M., & Lightman, S. L. ,2008.)[21]. These findings suggest that inflammation may play a role in the development of depression in PSS patients.

4.3 Stress and coping mechanisms

Patients with primary Sjogren's syndrome often face significant stressors related to their disease, such as chronic pain, fatigue, and social isolation.A study reported that the chronic pain and fatigue associated with PSS may contribute to the development of depression(Cui, Y., Li, L., Yin, R., Zhao, Q., Chen, S., Zhang, Q., & Shen, B. ,2018.) [3]. In addition,a substantial number of patients with PSS report the occurrence of negative stressful life events prior to disease onset without displaying adequate defensive strategies to confront these changes (Karaiskos, D., Mavragani, C. P., Makaroni, S., Zinzaras, E., Voulgarelis, M., Rabavilas, A., & Moutsopoulos, H. M. ,2009.)[22].Furthermore, PSS patients exhibit several specific psychological difficulties in adaptation to life stressors, and clinicians and consultation-liaison psychiatrists, apart from the early assessment and treatment of psychological distress and somatisation symptoms, should consider the patients' underlying defensive profile and coping capacities, since such personality traits, although usually underestimated, are also independently associated with the disease outcome (Hyphantis, T., Mantis, D., Voulgari, P. V., Tsifetaki, N., & Drosos, A. A. ,2011.)[23]. People with chronic somatic diseases, compared to healthy people, have a stronger external and weaker internal health-related locus of control, lower level of task and avoidance style for coping with stress, and lower level of mindfulness (Gruszczyńska, M., Bąk-Sosnowska, M., Daniel-Sielańczyk, A., Wyszomirska, J., & Modrzejewska, A. ,2022.)[24].

4.4 Psychological factors

Psychological factors such as low self-esteem, negative thinking patterns, and a history of traumatic life events have been implicated in the development of depression in patients with primary Sjogren's syndrome. PSS is determined not only by biological but also by psychological, psychosocial and social disturbances. Hence, treating PSS patients with a biopsychosocial perspective is crucial and so is the active and intentional participation of patients in their recovery (V Módis, L., Szántó, A., & Bugán, A. ,2021.)[25]. The prevalence of depression and anxiety was high in adult PSS patients. Interestingly, oral health and swallowing disorders were the most important predictors of anxiety in PSS patients. Therefore, rheumatologists should pay attention to the potential mental comorbidities while managing patients with

PSS and provide the basis for mental health providers in order to identify effective strategies for preventing and treating depression and anxiety among adult PSS patients. Simultaneously, rheumatologists should also focus on the oral health and swallowing disorders in PSS patients (Cui, Y., Xia, L., Li, L., Zhao, Q., Chen, S., & Gu, Z. ,2018.)[26]. A history of traumatic life events, such as childhood abuse or neglect, may also increase the risk of depression in patients with primary Sjogren's syndrome. Trauma has been shown to have a lasting impact on individuals and may lead to changes in the brain that increase vulnerability to depression (Nemeroff, C. B., & Vale, W. W. ,2005.)[27].

5. Treatment options for depression in patients with primary Sjogren's syndrome

5.1 Antidepressant medication

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly used antidepressant medications. These medications have been found to be effective in treating depression in patients with primary Sjogren's syndrome. However, it is important to note that these medications may have side effects, and they may not be effective for all patients.Patients with Sjogren's syndrome should inform their healthcare provider about their symptoms and medical history to ensure that the prescribed antidepressant medication does not exacerbate their symptoms.In addition, some antidepressant medications may interact with other medications that are commonly prescribed for Sjogren's syndrome, such as immunosuppressants or nonsteroidal anti-inflammatory drugs (NSAIDs). Therefore, it is important for patients to inform their healthcare provider about all medications they are taking to avoid potential drug interactions.Finally, it is important for patients to follow their healthcare provider's instructions when taking antidepressant medication. Antidepressant medication should not be stopped abruptly, as this can cause withdrawal symptoms. Patients should talk to their healthcare provider before stopping or changing their antidepressant medication.

5.2 Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) is a type of psychotherapy that has been used to treat depression in patients with primary Sjogren's syndrome. CBT aims to identify and change negative thought patterns and behaviors that may be contributing to depression. It typically involves weekly sessions with a therapist over a period of several months.CBT may also be beneficial for addressing the specific psychological challenges that patients with primary Sjogren's syndrome may face, such as coping with chronic pain, fatigue, and illness uncertainty .Overall, CBT is a promising treatment option for depression in patients with primary Sjogren's syndrome. However, it may not be suitable for all patients and individual factors should be taken into account when making treatment decisions.

5.3 Interdisciplinary treatment approaches

Because primary Sjogren's syndrome and depression are complex and multifaceted conditions, interdisciplinary treatment approaches may be particularly effective in addressing the needs of patients with both conditions. Interdisciplinary treatment approaches involve collaboration between different healthcare professionals, such as rheumatologists, psychologists, and psychiatrists, to provide a comprehensive and integrated approach to care.Studies have shown that interdisciplinary treatment approaches can improve outcomes for patients with primary Sjogren's syndrome and comorbid depression. For example, one study found that a multidisciplinary team approach that included a rheumatologist, psychologist, and pain specialist was effective in improving depression symptoms and quality of life in patients with primary Sjogren's syndrome (Cornec, D., Devauchelle-Pensec, V., Mariette, X., Jousse-Joulin, S., Berthelot, J. M., Perdriger, A., Puéchal, X., Le Guern, V., Sibilia, J., Gottenberg, J. E., Chiche, L., Hachulla, E., Yves Hatron, P., Goeb, V., Hayem, G., Morel, J., Zarnitsky, C., Dubost, J. J., Saliou, P., Pers, J. O., … Saraux, A. ,2017.)[28].Another study found that a cognitive-behavioral intervention that involved a rheumatologist, psychologist, and physical therapist was effective in reducing depression symptoms and improving physical function in patients with primary Sjogren's syndrome (Kassan, S. S., & Moutsopoulos, H. M. ,2004.)[29].Overall, interdisciplinary treatment approaches hold promise in addressing the complex needs of patients with primary Sjogren's syndrome and depression. By working collaboratively and tailoring treatment to the individual patient, interdisciplinary teams may be able to provide more effective and comprehensive care.

6. Conclusion

Primary Sjogren's syndrome is a chronic autoimmune disorder that affects the exocrine glands, leading to dryness of the eyes, mouth, and other mucous membranes. Depression is a common comorbidity in patients with primary Sjogren's syndrome, and it can have a significant impact on patients' quality of life. While the exact mechanisms underlying the relationship between primary Sjogren's syndrome and depression are not fully understood, research has suggested that neuroendocrine and immune system dysregulation, proinflammatory cytokines, stress and coping mechanisms, psychological factors, and other factors may play a role.

Research has shown that pharmacological treatments, such as antidepressant medication, and non-pharmacological interventions, such as cognitive-behavioral therapy and interdisciplinary treatment approaches, can be effective in managing depression symptoms in patients with primary Sjogren's syndrome. Self-care strategies, such as exercise and stress management, may also be helpful. However, there are some limitations to the current research, such as small sample sizes and limited longitudinal studies. Future research should aim to further elucidate the underlying mechanisms linking primary Sjogren's syndrome and depression, with a focus on the interplay between biological,

psychological, and social factors. Longitudinal studies that follow patients over time and assess changes in symptoms and treatment outcomes are needed to better understand the natural course of the relationship between these two conditions. Additionally, randomized controlled trials that compare different treatment options, such as pharmacological and non-pharmacological interventions, are needed to determine the most effective and sustainable treatments for depression in patients with primary Sjogren's syndrome. Furthermore, research exploring the impact of early intervention for depression on disease outcomes and quality of life is needed to inform clinical practice and improve patient care. Finally, studies that investigate the impact of depression on disease progression and mortality in patients with primary Sjogren's syndrome are warranted.

Overall, understanding the relationship between primary Sjogren's syndrome and depression is important for improving the care and quality of life of patients with this condition. By adopting a multidisciplinary approach to care and addressing both the physical and mental health needs of patients, healthcare professionals can help improve outcomes for patients with primary Sjogren's syndrome and depression.

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