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Depression development in patients with OA, and its impact on treatment outcome- a literature review

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Abstract

Introduction and aim of the study:
Osteoarthritis (OA) and depression are leading causes of disease burden worldwide and important public health problems. A number of recent studies reported depression as a comorbidity of OA and its impact on reduced quality of life and worse treatment outcome of OA patients. The clinical management strategies of those patients still haven't been developed, which is a challenge of future research on this topic. The aim of this review is to shed a light on important aspects of depression relationship with OA including its prevalence among OA patients and its influence on course and treatment of OA with a purpose of increasing awareness of this problem among physicians which may subsequently lead to a better overall medical care of patients with OA and depression.

Methods and materials:
This literature review is based on articles published in the PubMed database, GoogleScholar, ScienceDirect, and available medical textbooks.

Conclusions:
Recent literature reports a higher prevalence of depression among OA patients when compared to general population and its impact on osteoarthritis course, both on psychological and biomolecular level. Future research may lead to a better understanding of molecular background of depression and OA interrelation and to more complex and individualized

management strategies which may result in a better outcome of treatment and improved life quality of osteoarthritis patients. Therefore, in order to optimize management of OA patients, physicians should pay more attention to depression and use multidisciplinary approach including assessment of mental health status to develop a more effective strategies of medical care in osteoarthritis.

Key worlds: osteoarthritis, depression, impact, epidemiology, management

1. Introduction

Osteoarthritis (OA) is a multifactorial joint disease that affects quality of life of millions of people around the world, with a higher prevalence among older individuals, women, some racial and ethnic groups, and individuals with lower socioeconomic status[1]. It is estimated that there are 240 million individuals with OA, including 10% and 18% of men and women among age 60 respectively, making it the most common musculoskeletal disease [2]. Furthermore, OA is placed among top 10 disabilities worldwide. It is predicted that its prevalence will increase due to rising problem of OA risk factors such as aging of population and emerging problem of obesity[3]. Literature characterized OA as structural changes at the level of a joints which result in broad spectrum of symptoms including joint pain, stiffness, swelling, reduced joint range of motion, that subsequently lead to many functional limitations that impair ability to participate in physical activities and finally make walking impossible[4]. Not only does it increase risk of progression of OA and cardiometabolic diseases but also influences quality of life on many other levels[4]. OA is associated with serious physical limitations[5] and also with many psychological problems including poor quality of sleep, fatigue[6, 7], anxiety and depression[8].

Similarly to osteoarthritis, depression is a major global issue and its prevalence is growing rapidly[9]. More and more studies are focusing on depression association with OA[10, 11], its influence on course of this disorder[12], and impact on symptoms such as pain, stiffness and limitation of activities[13, 14]. As recent systematic review reports 19.9% (95% CI: 15.9–24.5%) of people with OA had depressive symptoms, with a higher relative risk of depression occurrence in those with OA compared to those without[8]. Literature has already shown that OA is not the only musculoskeletal disease with depression possible contribution to its course as rheumatoid arthritis (RA) and established comorbid depression were associated with poorer outcome of RA management[15]. Even though depression association with OA has been

reported by many studies, according to Gleicher et al only half of OA patients with probable depression received mental health support[12]. It is not satisfactory number as recent studies show possible role of cognitive behavioral therapy, exercise and integrated depression management in improving outcome of patients with comorbid depression in OA[16].

The aim of this study is to review articles on depression prevalence among patients with OA and address the issue of its impact on OA symptoms severity, its course and treatment options.

2. OA and depression: Epidemiology

Osteoarthritis is a highly prevalent disease, and it is the most common form of arthritis. It is estimated that nearly 240 million people around the world are diagnosed with OA. In addition, literature proved relationship between age, low socioeconomic status, sex and higher possibility of OA onset[17-19]. Furthermore, OA is placed as one of the world's leading causes of disability, it accounts for 2,4% of all years lived with disability (YLD)[20, 21]. It is also third most rapidly rising condition associated with disability after diabetes and dementia with 75% increase of OA, related in years 1990-2013[20]. Comparably to OA, depression is one of a leading public health problems and it is one of the main causes of disease burden in recent years[22, 23]. It's prevalence is rising as depressive symptoms among adolescents increased from 24% (95% CI: 0.19-0.28) between 2001 and 2010 to 37% (95% CI: 0.32-0.42) between 2011 and 2020[24]. Depression association with OA is getting more and more highlighted. In recent systematic review by Stubbs et al authors estimated that prevalence of depression in patients with OA is 19,9% (95% CI: 15.9–24.5%)[8]. Mixed lower limb osteoarthritis was more associated with depression when compared to isolated knee osteoarthritis, where pooled prevalence of depressive symptoms was 23% (95% CI: 16.4% to 30.2%; I2:95.8%) and 18.5% (95% CI: 13.8% to 23.7%; I2:85.4%) respectively[8]. In cross-sectional survey of 1,021 patients with OA Roseman et al reported that prevalence of depression among OA patients was 19.76% of male and 19.16% of female participants, those patients reported a PHQ-9 score of ≥15[25]. Similar results were presented by Sale et al in cross-sectional study as among 1227 individuals with OA 21,3% scored >or= 16 in CES-D scale, which supports depressed mood[14]. Total joint replacement (TJR) is a treatment for end-stage OA. In study by Gad B.V. et al 21% of patients awaiting TJR had concomitant physician-reported depression[26]. Kirkness et al confirmed those results as among patients scheduled for total knee arthroplasty comorbid depression was highly prevalent[27]. Scott et al in their meta-analysis reported that 23% of TJR patients had diagnosed depression before

surgery and one year later depression prevalence among those patients decreased to 13%[28]. In recent years number of studies have touched on topic of depression development and prevalence in patients with OA. Zheng S et al in his study estimated that in patients with knee OA the presence and incidence of depression was 25.4 and 11.2%, respectively[11]. As literature reports the disease burden of OA is similar when compared to rheumatoid arthritis (RA)[29, 30]. In addition, review by Matcham el al showed that depression is highly prevalent among RA patients and it is associated with poorer outcomes of this disease treatment[15].

3. Comorbid depression in osteoarthritis: Risk factors

Numerous studies have explored factors that may affect depression prevalence among OA patients. Lower education level, obesity, female sex and age were proven to be risk factors for both OA and depression[31]. One of the most researched factors contributing to development of OA and depression is having higher BMI[32, 33]. Literature explains this phenomenon as OA, depression and obesity might share common pathophysiology which involve increase in several proinflammatory cytokines that subsequently lead to various complications including inflammation-induced cartilage catabolism in the knee[34-39]. Moreover, Jacobs et al used novel approach to identify structural changes in knee osteoarthritis (KOA) as they compared non-obese patients, obese patients without depression and obese patients with depressed mood, in two years follow up. Results showed that among those 3 groups obese patients with depression had significantly worse symptoms. Authors explained their results using inflammatory theory to combine those three disorders. Increased excretion of collagen terminal peptide markers was observed in the urine of obese patients with depression, which suggests more severe progression of cartilage damage. These results show that depression might increase inflammatory burden in patients with OA and obesity and lead to increased possibility of more severe cartilage degeneration[40].

Second risk factor of depression in OA patients that literature reports is female sex. Recent longitudinal study by Li M et al among others highlighted female sex as a potential risk factor of depression in OA[41]. Furthermore, Sale et al reported that higher probability of concomitant depression in OA was independently and significantly associated with the female sex[14]. In addition, Zheng et al in his recent study confirmed those results as being a woman was associated with higher incidence of depression among patients with knee OA[11]. However, results are inconsistent as Parmelle et al reported that women experienced greater

pain and marginally greater disability than men, but there was lack of proven relationship between sex and higher prevalence of depression in studied group[42]. One theory that might explain differences of depression prevalence between men and women with OA is associated with estrogen and its receptors. Recent scientific evidence indicate estrogen involvement in depression pathophysiology[43]. First of all, estrogen might influence serotonin receptors number and function[44] and fluctuating concentration of estrogen was associated with depressed mood[45]. What's more estrogen receptor α (ESR1) has been reported to have a relationship with major depressive disorder(MDD)[46]. Estrogen and its receptors not only play a role in sexual and reproductive functions but also in other tissues such as bones. ESR1 is expressed in chondrocytes, stromal cells, and osteoblasts[47] and its genetic variants have been reported to impact OA[48, 49].

When it comes to aging, it is proven risk factor of OA. On the other hand, in depression, overall prevalence is lower in elderly than younger people[50]. Nevertheless, coexisting comorbidities among elderly people elevate risk of depression[51]. Rosemann T et al in their study reported that increasing age in OA was a lower predictor of PHQ-9 scores[25]. To conclude, it is important to remember about higher prevalence of depression among younger patients with OA.

Pain and correlating physical limitation are also proven risk factors of depression prevalence among patients with OA. Hawker et al reported that pain in OA induced future fatigue, disability, and depressed mood[13]. Pain itself was reported by literature to have a relationship with depression[52, 53]. Fonseca-Rodrigues D et al in their systematic review demonstrated a significant correlation between pain and depression/anxiety severity in OA patients[54]. Many more studies touched on pain, depression and OA interrelations[11, 25, 55]. Walking difficulty occur as result of a severe pain in OA patients [56], and it itself may contribute to worsening of depressive symptoms among them[57]. Mobility impairment is a proven risk factor for physical limitation[58]. Physical activity, on the other hand, is a proven factor which influences depression course[59]. Above-mentioned studies show that management of pain and joint dysfunctions might contribute to improvement of depressive symptoms[60].

4. Mechanisms of depression development in patients with OA

Development of depression symptoms in patients with OA might be mediated by various multifactorial mechanisms which are not yet fully understood. As there are many reasons why OA patients could develop depression, it is believed that comorbidity of OA and depression may be mediated by biological, sociological, psychological and behavioral mechanisms which lead to various etiologies and risk factors[22, 61]. Negative impact on depression course, prevalence and treatment outcome of chronic diseases has been reported by studies in the past[52, 62].

There are several theories on biological link between those two disorders. First, the involvement of inflammatory mediators and inflammatory theory as potential compound in pathophysiology of OA have been reported by literature in the past[63, 64]. Recent research by Chow Y.Y. and Chin K.Y. identified inflammatory mediators found in OA patients which include tumor necrosis factor-α, interleukin-6, and interleukin-1β[65]. Furthermore, Shimura et al reported that patients with knee osteoarthritis with comorbid depression, had a higher serum interleukin-6 levels than patients with OA alone. Lastly, D'Mello and Swain et al proposed mechanism in which inflammation contributes to development of depression[66]. That may explain inflammatory response as a possible cause of correlation between OA and depression. Another proposed mechanism of comorbidity of OA and depression relates to elevated serum concentration of cortisol. Villafañe JH et al in their review explored cortisol contribution to pathophysiology of osteoarthritis. Even though, there wasn't enough evidence to support relationship between cortisol and OA, they reported significantly increased cortisol level in patients with pain, which is one of the main OA symptoms. Furthermore, there are some studies that prove elevated cortisol serum levels in patients with depression[67, 68]. Therefore, variations in serum cortisol contraction might contribute to concomitant depression in OA patients. Gerrits MM et al suggested that not chronic disorder itself but pain as a result of chronic disease contributes to depressive symptoms development[52]. There is multifactorial explanation on why pain could impact depression prevalence among OA patients. Biological point of view suggests that pain may cause changes such as dysregulation of the HPA axis (by increasing cortisol) and dysregulation of the HPA axis is one of the proposed mechanisms of depression development[69]. To back this up K. Wingenfeld et al in their research showed a relationship between self-reported depression and reactivity of the HPA axis in patients with chronic pelvic pain[70]. Furthermore, studies have shown that pain has impact on neuronal pathways and brain function in areas of cognition and emotion.

Neuroimaging studies have shown significant change in prefrontal cortex and hippocampus as a result of experienced pain[71, 72]. In MRI scan study, hippocampal volume decreased faster in patients with OA when compared to patients without OA and with normal cognition[73]. As above-mentioned studies show there are brain structure and function changes in patients with OA and co-existing pain which might contribute to comorbidity of OA and depression. Hawker A. et al in their original article assessed relationship between pain, fatigue and depression on large sample size of community based older adults with OA, using wide range of scales (WOMAC, MFSI-SF and CES-D). They reported a direct link between pain and subsequent depressed mood through pain-fatigue-disability-depression cycle and emphasized need for a multidimensional approach to OA treatment[13]. Furthermore, literature suggests several novel mechanisms that indicate genetic relationship between depression and OA[74], which brings potential for future studies to investigate this topic.

There's no doubt that biological factors play a role in osteoarthritis. On the other hand, literature show much evidence on psychological and social aspects of developing depression in OA. There are many features of psychological background in patients with OA. First of all, it is commonly known that OA has tremendous effect on quality of population existence and everyday activities as it accounts for 2,4% of all years lived with disability[20]. Its impact on poor psychological state may arise on behalf of exclusion from everyday activities. King L. K. et al conducted the study using multivariable logistic regression modeling and concluded that the number of hips and knees affected by symptomatic OA was the strongest determinant of walking difficulty. From 18,490 cohort participants 10% and 15,4% met the criteria of hip OA and knee OA diagnosis respectively[56]. They also stated that the predicted probability of difficulty in walking for a 60-year-old middle-income with OA in 2 hips/knees might occur in 40% of patients[56]. As a result of OA, disability, functional limitations and loss of independence occur[5]. Limitations generated by OA lead to gradual withdrawal from social life and mental health benefiting activities[75]. Sugai et al studied impact of knee dysfunction and pain on depression onset in a community-based 2-year cohort and the authors concluded that if normal activities, which involve going outside start to become a burden for an older adults with OA, they are more likely to develop depressive symptoms[76]. Impaired physical and social functioning may subsequently lead to a vicious cycle of negative coping strategies caused by both pain and affective symptoms[77-79]. Poor physical functioning itself was correlated with higher depression prevalence, across most of the depression definitions[80]. Occurrence of those problems result in impaired functioning in society and subsequently

social isolation, which is a psychosocial factor that may negatively influence concomitant depression in OA. Siviero et al in his prospective study proved a higher risk of social isolation of people with knee or hip osteoarthritis when compared to healthy individuals[81]. As above-mentioned studies prove it is possible that OA may directly or indirectly have impact on functioning in society and interactions with other people by increasing risk of a social isolation which subsequently induces depressive symptoms occurrence. Lack of social support, impaired physical functioning in society and everyday interactions are a factors of worsening of depression, literature reports that lack of a life partner is associated with higher depression prevalence[80].

Fear and stress that might be a result of OA course subsequently lead to sleep problems[7]. Lack of sleep is a proposed mechanism of contribution not only to depression[82], but also worsening of a OA course[83]. Furthermore, Parmelee et al proposed cross-sectional relationship between sleep disturbance, pain and depression. They highlighted sleep management as a medical care intervention that may prevent OA-related functional decline[84]. This might also be a mechanism in which these two diseases influence each other's course. Literature shows that psychological and social aspects of depression development in patients with OA are as important as biological and more longitudinal studies are required on this topic.

5. Depression impact on OA symptoms severity and treatment outcome

As possible interrelation between OA and depression has been shown by many studies, the problem of its impact on symptoms and treatment outcome has become a topic of discussion, over the past decade. Hawker et al suggested that pain influenced prevalence of depressed mood which exacerbated fatigue and disability and subsequently led to worsening of OA pain[13]. Furthermore, Rathbun A.M. et al estimated the dynamic causal effects of depressive symptoms on osteoarthritis knee pain and concluded that pain severity significantly increased with the persistence of depressed mood, yet the causal effect of depressive symptoms on OA knee pain did not change over time[79]. Zheng et al presented similar results as multisite pain significantly increased prevalence and development of depression, yet baseline depression was not correlated with knee joint symptomatic progression over 2 years[11]. Which supports the notion that managing of pain in OA patients may help to prevent and alleviate depressive symptoms[13, 60].

The topic of impact of depression on outcomes in OA treatment has been presented by many studies. Firstly, depression adversely impacts results of surgical interventions in few ways. Lopez-Olivo et al reported that patients with depression 6 months after total knee replacement had worse WOMAC scores and poorer total KSRS scores[85]. Furthermore, Hanusch et al in their research presented that patients experiencing depression had worse recovery rates from total knee replacement[86]. Concomitant depression in patients undergoing this procedure was also reported to have a relationship with worse postoperative pain[87]. In general, depression led to lower satisfaction rate of operation outcome[88]. Furthermore, an interaction between clinical depression symptoms and pain catastrophizing was associated with poor pain outcome expectation, which subsequently affected future total knee arthroplasty utilization[89]. Non-operative treatment of OA such as physical therapy was also reported to be influenced by comorbid depression[90]. Recent systematic review by Vajapey et al which included 30 studies showed that depression increases the risk of persistent pain, dissatisfaction, and complications after total joint arthroplasty (TJA)[91]. On the other hand, in systematic review by Bletterman et al they stated that healthcare providers who take care of patients awaiting for total joint arthroplasty should not overestimate the role of preoperative psychosocial factors as there's no proof of longitudinal relationship with psychosocial factors and outcomes of TJA. Reason behind this statement is due to risk of bias, poor quality of research and the failure to calculate trial sample sizes or the high rates of loss to follow-up in prospective longitudinal studies on this topic[92].

Overall, it seems that depression may have impact on treatment outcome and clinical management of patients with OA. Clinicians should include psychological and psychiatric approach to depression in OA to improve physical activity, OA treatment recovery and well-being of patients in general. However, we need more longitudinal studies on this issue with better quality research in the future.

6. Conclusion

In summary, this review presents several studies on prevalence of depression among patients with OA, its epidemiology, risk factors, possible mechanisms of development and finally depression impact on treatment outcome of osteoarthritis. There was some variability when it comes to incidence of depression between studies. Nevertheless, it seems to be certain that patients with OA are in a higher risk of concomitant depression when compared to a general population. Furthermore, most studies that touch on this subject suggest that depression in OA is associated with reduced quality of life and worse clinical outcomes of treatment.

Understanding of comorbid depression in OA patients has made significant progress, yet there are some issues that still need to be addressed in further research. Knowledge about the mechanisms of depression development, especially on neurobiological level remains limited. Changes in neurobiology, hormones and molecular biology have been partially presented in above-mentioned studies, yet we are far from understating biological background of depression development in OA patients. Future research that will manage to explain this phenomenon, might bring a whole new perspective on individualized and targeted depression treatment in OA.

Next problem that needs to be addressed is complexity of interrelating depression and OA as there are many psychosocial, clinical and demographic factors involved. Future studies should focus on separating potential coexisting causes of depression in OA patients to provide more relevant data in the future. Psychological aspects of osteoarthritis need further research too. Deeper understating of psychological and social factors such as social isolation, sleep deprivation and pain catastrophizing which lead to impaired functioning in society, might contribute to development of more complex OA treatment strategies which not only involve pharmacological and surgical options but also targeted psychotherapy. Further research based on high-quality randomized control trials should focus on developing definitive management strategies which ought to include screening, diagnosis and complex treatment of depression in OA patients.

Author's contribution:

Conceptualization: I.T.; Data curation, I.T., K.W., P.H., A.T., K.S.; Writing - rough preparation: I.T., K.D., A.Ś., U.Ż.; Writing - review and editing: I.T., Z.K., D.M, H.C.K., K.A., J.P.; Supervision: I.T.; Project administration: I.T., K.D. All authors have read and agreed with the published version of the manuscript.

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