ASSOCIATION OF DEPRESSION, ANXIETY AND STRESS WITH KNEE JOINT OSTEOARTHRITIS IN PERIMENOPAUSAL AND POST MENOPAUSAL WOMEN AS COMPARED TO MEN OF THE SAME AGE GROUP: A CROSS-SECTIONAL COMPARATIVE STUDY

M. Koch[1] and P.C. Sarma[2*]

[1]Gauhati Medical College and Hospital, Guwahati, Assam, India
& Assam down town University, Guwahati, Assam, India
[2*]Faculty of Sciences & Paramedical Sciences, Assam down town University, Panikhaiti, Guwahati, Assam
drpratapchsarma@gmail.com

ABSTRACT

Substantial research has proven that psychological co-morbidities (stress, anxiety and depression) are highly prevalent among patients with OA and are frequently associated with higher pain and physical limitation. Moreover, association of these psychological co-morbidities with menopause is also well documented in literature. This study seeks to investigate whether menopause is an added factor and the association of these co-morbidities in perimenopausal and post menopausal women is higher when compared to male patients of the same age group with knee joint osteoarthritis.The study consisted of 150 perimenopausal and postmenopausal women (40-65 years of age) with knee joint osteoarthritis (group 1). The comparison group consisted of 150 male subjects of the same age group with knee joint osteoarthritis (group 2). Outcome measures for pain: Numeric Pain Rating Scale (NPRS); psychometric evaluation: Depression Anxiety Stress Scale (DASS)-42 questionnaire .SPSS 21.0 software was used for statistical analysis and Student's t-test was used to determine statistical difference between both the groups. Results reveal that perimenopausal and post menopausal women showed higher frequency of psychiatric co-morbidities like depression, anxiety and stress compared to control group and the differences between the scores were statistically significant in all the three variables.

Keywords: *Knee osteoarthritis, Anxiety*, *Depression*, *Stress, DASS-42*.

Introduction

Osteoarthritis (OA) is among one of the frequently encountered musculoskeletal disease in the clinical practice globally (Johnson VL, Hunter DJ, 2014). The distinguishable features of OA are degeneration of the articular cartilage, osteophyte formation, and asymmetric joint space narrowing (Lories RJ, Luyten FP, 2011). These changes frequently lead to significant pain and disability and create a considerable individual, societal, and economic burden (Hunter DJ et al, 2014; Litwic A et al, 2013).

The mean prevalence rates for concurrent major depression in patients identified as having pain is 56% (21%-89%) in orthopedic clinics or rheumatology clinics (Magni G et al, 1993). A persistent association is found between osteoarthritis and stress, anxiety and depression. Moreover, numerous published studies have supported that women are particularly vulnerable to depression during menopause due to changes in reproductive hormone levels.

In a medical or biological context stress is a physical, mental, or emotional factor that causes bodily or mental tension (Medterms medical dictionary). According to the American Psychological Association: Anxiety is characterized by feelings of tension, worry and irritability along with physical changes like increased blood pressure; Depression is characterized by sadness, a lack of interest in daily activities, weight loss or gain, sleeplessness or excessive sleeping, lack of energy, inability to concentrate, feelings of worthlessness or excessive guilt, and recurrent thoughts of death or suicide.

Out of several elements which are being scrutinized to delineate the differences between the patient reported symptoms and outcomes, stress, anxiety and depression have transpired as strong contenders (Axford J et al, 2010; van Baar ME et al, 1998). An individual's capability to function can be affected markedly by the somatic and cognitive changes which usually concord with stress, anxiety and depression (American Psychiatric Association, 2013).

Apart from OA, research studies have persistently reported that anxiety and depression have a robust association with various other conditions related to the cardiovascular system, respiratory system, and gastrointestinal tract (Maurer J et al, 2008; Januzzi JL et al, 2000; Mikocka-Walus AA et al, 2007). Anxiety and depression are often reported as co- morbidities by patients who are agonized by chronic painful disabling conditions (He Y, Zhang M, Lin EH, et al, 2008). Furthermore, these co-morbidities can enhance the pain sensitivity in such patients (Neogi T et al, 2010). Since chronic pain in itself can cause or enhance anxiety and depression (Hansen GR, Streltzer J, 2005), a vicious cycle begins, which can remarkably impact the duration and treatment of these chronic diseases and OA is no exception.

Menopause is defined as the irreversible discontinuance of menstrual period which is associated with decreasing ovarian functions (Menopause Overview, 2013; WHO, 1996). Perimenopause is defined as the time period from the onset of menopause-related symptoms, e.g. irregular bleeding, until 1 year after complete amenorrhea. Post menopause includes women who have experienced a complete stoppage of menstruation exceeding 12 months (WHO, 1996). Roughly 12 million women will enter the menopausal transition by the year 2030 globally as per the World Health Organization (WHO, 1996). Hence, menopause-related health concerns, especially depression is booming up as a major health issue deserving utmost priority. Various authors of relevant research studies have concluded that women are particularly vulnerable to depression in the years leading to menopause and after it too because of alterations in reproductive hormone levels (Deecher D et al, 2008; Liukkonen T et al, 2008). Depression was estimated to be prevalent in 45% of women receiving outpatient menopausal services as per a previous research study (Hay, A. G et al, 1994).

Substantial research has proven that psychological co-morbidities (stress, anxiety and depression) are highly prevalent among patients with OA and are frequently associated with higher pain and physical limitation (Sale JE et al 2008; Rosemann T et al, 2007; Kirkness CS et al, 2012). Moreover, association of these psychological co-morbidities with menopause is also well documented in literature (Deecher D et al, 2008; Liukkonen T et al, 2008; Hay, A. G, 1994). Hence, this study seeks to provide a comprehensive understanding regarding whether menopause is an added factor and the association of these co-morbidities in perimenopausal and post menopausal women is higher when compared to male patients of the same age group with osteoarthritis.

Hypothesis

Null hypothesis: There will be no statistically significant difference between the association of stress, anxiety and depression with knee joint osteoarthritis in perimenopausal women and post menopausal women when compared to men of the same group.

Alternate hypothesis: There will be statistically significant difference between the association of stress, anxiety and depression with knee joint osteoarthritis in perimenopausal women and post menopausal women as compared to men of the same group.

Objectives of Study

1. To find out whether there is an association of stress, anxiety and depression with knee joint osteoarthritis in perimenopausal and post menopausal women (40-65 years).
2. To find out whether there is an association of stress, anxiety and depression with knee joint osteoarthritis in men aged 40-65 years.
3. To compare the association of stress, anxiety and depression with knee joint osteoarthritis in perimenopausal and post menopausal women to the men of the same age group.

Materials and Methods

This is a cross-sectional comparative study. The study was approved by the Institutional Ethics Committee.

Sample

The study group comprised of 150 perimenopausal and postmenopausal women (40-65 years of age) with knee joint osteoarthritis (group 1). The comparison group

comprised of 150 male subjects with knee joint osteoarthritis (group 2). All these cases were referred to the physiotherapy department by a physician or orthopedic doctor. Both groups were matched for age, marital status and severity of osteoarthritis. Patients who were willing to participate were included in the study after obtaining written informed consent.

Criteria of sample selection

The inclusion criteria were as follows: (1) Female patients in the age group of 40-65 years with menopause or menopause related symptoms, diagnosis of knee OA according to the American College of Rheumatology (ACR) criteria and severity grade2-3 as per Kellegren Lawrence, knee pain for more than 6 weeks. (2) Control subjects: Males in the age group of 40-65 years, diagnosis of knee OA according to the American College of Rheumatology criteria and severity grade2-3 as per Kellegren Lawrence, knee pain for more than 6 weeks.

The exclusion criteria were as follows: Patients younger than 40 years of age and older than 65 years of age, not fulfilling ACR criteria for diagnosis of OA knee, knee pain for less than 6 weeks, low back ache ,history of any lower extremity injury or underlying pathology or surgery, any spinal surgery, any physical / medical problems for which exercises would be contraindicated ,any deformity of knee, hip and back, history of any inflammatory joint disease ,patients using an assistive device for ambulation ,patients who received physical therapy or an intra-articular injection in the knee within the past 3 months, any established mental illness.

Instruments

All the study subjects underwent a detailed clinical examination. Each subject completed a general information form in which they reported information regarding their demographic details including name, age, gender, occupation. *Numeric Pain Rating Scale (NPRS):* Assessment of pain was done using Numeric Pain Rating Scale (NPRS). It is a one-dimensional measure of pain intensity in adults (Childs JD et al, 2015; Jensen MP, McFarland CA., 1993; Rodriguez CS., 2001), including those with chronic pain due to rheumatic diseases (Rodriguez CS., 2001; Ferraz MB et al, 1990). The 11-point segmented numeric scale ranges from '0' representing one pain extreme (e.g. “no pain”) to '10' representing the other pain extreme (e.g. “pain as bad as you can imagine” or “worst pain imaginable”) (Jensen MP, McFarland CA., 1993; Rodriguez CS., 2001). Respondents were asked to report pain intensity “in the last 24 hours” or an average pain intensity (Dworkin RH et al, 2005).

Depression, Anxiety and Stress Scale (DASS-42): The psychometric evaluation using DASS-42 was carried out, by the same investigator on all members of group 1and group 2 before treatment of osteoarthritis was initiated. The DASS is a 42-item questionnaire designed by Lovibond, S.H. & Lovibond, P.f., 1995). It includes three inter-related subscales to self report the negative emotional states of depression, anxiety and stress (Crawford JR, Henry JD, 2003; Lovibond, S.H. & Lovibond, P.f., 1995).It requires no special skills to administer. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The Stress scale (items) is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Participants rated the extent to which they had experienced each symptom over the previous week on a four-point scale ranging from 0 [did not apply to me at all] to 3 [applied to me very much, or most of the time] (Crawford JR, Henry JD, 2003; Lovibond, S.H. & Lovibond, P.f. ,1995; Nieuwenhuijsen K et al, 2003).

The DASS shows good convergent and discriminant validity, and high internal consistency and reliability, with Cronbach’s alpha reported at 0.94 for Depression, 0.87 for Anxiety and 0.91 for Stress (Antony M, 1998; Kalkur C, 2015).

Statistical analysis

A descriptive analysis was performed in order to study the behavior of both the groups for

each variable of interest: NPRS and DASS-42. Student's *t*-test for unrelated samples was used to compare the two groups regarding these variables. Differences were considered significant when $p \leq 0.05$. All statistical analyses were carried out using the version 21.0 of the SPSS software.

Results

This study consisted of 150 perimenopausal and postmenopausal women (40-65 years of age) with knee joint osteoarthritis and 150 male subjects with knee joint osteoarthritis as the comparison group. Both groups were matched for age, marital status and severity of osteoarthritis. Using DASS-42 scales for psychometric evaluation, the perimenopausal and postmenopausal women with osteoarthritis were found to exhibit higher frequency of psychiatric co-morbidities like depression, anxiety and stress than comparison group and the results were statistically significant.

Table no. 1: Descriptive statistics on the mean age of the study participants and testing the significant difference in the mean age among males and females

Independent Samples Test

AGE(Group Statistics)				t-test for Equality of Means						
	MEAN	SD	SE	T	df	Sig. (2-tailed)	Mean difference	SE difference	95% CI of the difference	
Males	51.50	8.798	.718	-.021	298	.984	-.020	.967	Lower	Upper
Females	51.52	7.931	.648						-1.923	1.883

SD: Standard Deviation, SE: Standard Error, df: degrees of freedom, Sig: statistical significance, CI: Confidence interval; p= 0.984; statistically no significant difference is observed in the mean age of males and females (p>0.05)

Table no.2: Descriptive statistics on the mean pain scores of the study participants and testing the significant difference in the mean pain scores [NPRS] among males and females

Independent Samples Test

NPRS(Group Statistics)				t-test for Equality of Means						
	MEAN	SD	SE	t	df	Sig. (2-tailed)	Mean difference	SE difference	95% CI of the difference	
Males	6.81	1.485	.121	-4.779	298	.000*	-.800	.167	Lower	Upper
Females	7.61	1.413	.115						-1.129	-.471

SD: Standard Deviation, SE: Standard Error, df: degrees of freedom, Sig: statistical significance, CI: Confidence interval; *Statistically significant; p= 0. 000; statistically very high significant difference is observed in pain scores [NPRS] among males and females (p<0.001)

Table no. 3: Descriptive statistics on the mean depression, anxiety and stress score of the study participants

Group Statistics

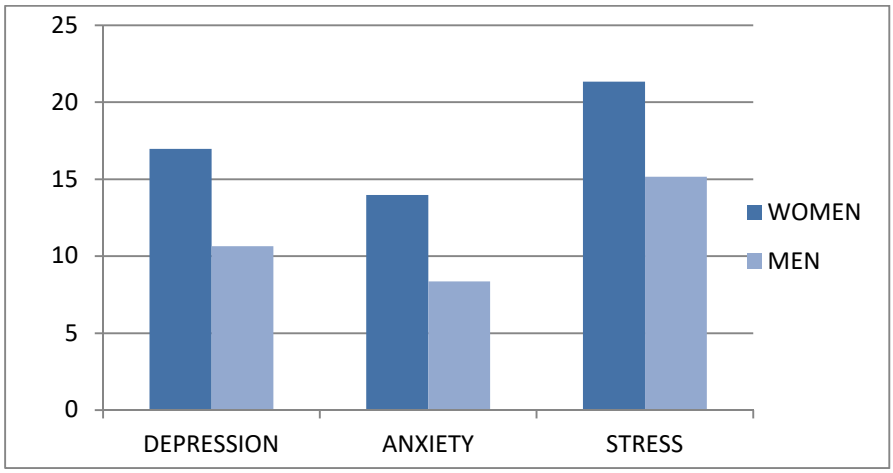
Variables	Gender	N	Mean	Standard Deviation	Standard. Error Mean
Depression	Males	150	10.65	2.908	.237
	Females	150	16.97	2.986	.244
Anxiety	Males	150	8.36	2.358	.193
	Females	150	13.98	2.254	.184
Stress	Males	150	15.15	5.170	.422
	Females	149	21.34	4.440	.364

Table no.4: Testing the significant difference in the mean depression, anxiety and stress score among males and females

	t-test for Equality of Means						
	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Depression	-18.569	298	.000*	-6.320	.340	-6.990	-5.650
Anxiety	-21.100	298	.000*	-5.620	.266	-6.144	-5.096
Stress	-11.101	297	.000*	-6.189	.557	-7.286	-5.092

df: degrees of freedom, Sig: statistical significance, CI: Confidence interval; *Statistically significant; p= 0. 000; statistically very high significant difference is observed in depression, anxiety, stress among males and females (p<0.001).

Fig 1: Multiple bar diagram representing the comparison of differences in mean depression, anxiety, stress levels in perimenopausal and postmenopausal women and men of the same age group



Discussion

The current study was carried out to assess depression, anxiety and stress levels in perimenopausal and post menopausal women and compare it with the men of the same age group.

In the current study, according to the DASS-42 scale: Mean Depression score in perimenopausal and post menopausal women was 16.97 as compared to the 10.65 in the comparison group, Mean Anxiety scores in perimenopausal and post menopausal women was 13.98 as compared to 8.36 in the comparison group and Mean Stress score in perimenopausal and post menopausal women was 21.34 as compared to 15.15 in the comparison group consisting of men of the same age. Hence, psychological assessment using DASS-42 reveals that perimenopausal and post menopausal women with knee joint osteoarthritis showed higher frequency of psychiatric co-morbidities like depression, anxiety and stress compared to the comparison group. It was also found that the differences between the scores of the both the groups were statistically significant in all the three variables.

Though statistically no significant difference is observed in the mean age of males and females [p= 0.984] and even the included subjects in both the groups were matched for the severity of osteoarthritis as grade II or III in the Kellegren Lawrence Scale but statistically very high significant difference is observed in pain

scores [NPRS] among males and females [p= 0. 000]. Therefore, it can be concluded from the present study that average pain perception in females is significantly higher when compared to males with similar severity of knee joint OA. Our study demonstrates that the added morbidity of depression, anxiety and stress with knee osteoarthritis pain is strongly associated with increased pain perception.

Descriptive statistical analysis reveals that males suffering from knee OA exhibit mild depression, anxiety and stress whereas females have moderate depression, anxiety and stress. Thus, the present study reveals that depression, anxiety and stress is an associated with knee joint osteoarthritis in all subjects of both the groups i.e. in both perimenopausal and post menopausal women and men of the same age group. Statistically very high significant difference is observed in depression, anxiety, stress among males and females (p= 0. 000). Thus, it can be concluded that menopause is an added factor in enhancing the severity of depression associated with knee joint osteoarthritis.

The statistical analysis results depict that higher levels of depression, anxiety, stress in perimenopausal and post menopausal women with knee OA is associated with increased pain perception i.e decreased pain threshold. This finding is supported by the literature which reports that depression makes pain worse. Depression weakens a person's ability to deal and cope with pain. A person's perception about their condition might become more negative when compared with individuals who are not depressed (Arthritis Foundation) and these co-morbidities can enhance the pain sensitivity in such patients (Neogi T et al, 2010).

Anxiety and depression differentially impact lives of male and female patients with OA. Sale et al reported that higher level of depressed mood was independently and significantly associated with the female sex (Sale JE et al, 2008). Similarly, sex differences are prevalent independently in OA, anxiety, and depression (McLean CP, 2011; O'Connor MI, 2007). Studies have reported that female patients with OA report greater anxiety and depression (Sale JE et al, 2008; Theis KA et al, 2007) than males. The present study extends our understanding of the same fact.

Contrary to it, available literature also suggests that pain incites depression. Living with daily pain is physically and emotionally stressful. Chronic stress is known to change the levels of the stress hormones and neurochemicals – like cortisol, serotonin and norepinephrine – thus affecting the mood, thinking and behavior. Disruption of body's balance of these chemicals can bring on depression in some people (Arthritis Foundation).

A potential link exists between chronic pain and anxiety or depression, which might complicate physical and mental health management for persons with arthritis (DiMatteo MR, 2000).

Having arthritis has been associated with reduced adherence to treatment for depression (Fuller-Thomson E, Shaked Y, 2009).In clinic-based rheumatic disease studies, both anxiety and depression were associated with reduced response to treatment (Matcham F et al, 2016) and poorer quality of life (Sambamoorthi U et al, 2017). Published literature report that individuals with osteoarthritis and depression tend to have more functional limitations, are less likely to adhere to their treatment regimens, and have increased odds of developing other health problems. The vicious cycle of pain, poor health and negative mood can significantly change the course and management of arthritis (Arthritis Foundation).The occurrence of widespread anxiety and depression symptoms among adults with arthritis points to an unmet need that health care providers can address.

Anxiety, depression and OA-related joint pain frequently co-exist (de Heer E et al, 2014). The current study results provide the same understanding. Despite all these evidence, in the context of co-morbidity, anxiety, depression and chronic pain are seldom prioritized by either patient or clinician, both engaging in attributional styles that normalize symptoms as an understandable reaction to chronic disease and to be expected (Coventry P et al, 2011). Furthermore, general practitioners were frequently found to have a lack of knowledge related to anxiety and depression in their patients suffering from osteoarthritis as reported in a study by Memel D S et al (Memel

D S et al, 2000). Primary care physicians or GPs infrequently considered or found it difficult to diagnose anxiety and/or depression in patients with OA (Rosemann T et al, 2007; Kingsbury SR & Conaghan PG, 2012).

Literature review unveils that that the prevalence of knee joint osteoarthritis shows an upward trend in females during peri-menopausal period and continues to soar up throughout menopause. Studies suggest that declining levels of estrogen during menopause increases a women's risk of acquiring osteoarthritis (Spector TD, Campion GD, 1989). In contrast to 51 years in western countries, the average menopausal age in Indian women is 46.3 years predisposing Indian women to the risk of developing osteoarthritis at an earlier age in comparison to their western counterparts (Kapur P et al, 2009). One report suggested that women 45 to 55 years old experience the highest incidence of depression (Kessler RC et al, 1993). Depressive symptoms are common in all populations but appear to increase among women in the transition to menopause. The results of the current study also shows that depression, anxiety and stress are more prevalent in and around menopause in comparison to male patients of knee OA in the same age group. These results are comparable to the National Co-morbidity Survey which reported that major depression is more common in women than in men in all age groups until late life, with a lifetime prevalence of 21 % compared to 12 % for men (Bener A et al, 2016).

Thus, the present study contributes to the literature that stress, anxiety and depression are co-morbidities accompanying knee joint osteoarthritis in both men and women though in case of women, menopause acts an additional factor enhancing the levels of these psychological co-morbidities. These findings suggest an increased prevalence of depression among patients with OA and emphasize the need for recognition and appropriate treatment.

Literature review of recently published studies have testified that as a part of central pain modulation system, neurotransmitters namely serotonin and nor epinephrine dampens peripheral nociceptive signals. Correspondingly, depression is also connected with dysregulation of the same neuro transmitters and both share a common pathway. Hence, whenever there is a decline in the levels of these two neurotransmitters, there is a concomitant enhancement of peripheral pain messages. It explain the fact how antidepressants that increase these neurotransmitters decreases the perception of pain (Fields HL, 2000; Nekovarova T et al, 2014).

Literature suggests that one's personal attitude toward pain, rather than pain severity itself, is related to physical activity. There for a physiotherapy protocol to be effective, psychological co-morbidities, if present, should be taken into consideration for better prognosis (Uritani D et al, 2020). Moreover, exercise has a significant antidepressant effect on people with depression (Schuch FB et al, 2016). This therefore provides a further rationale for prescribing exercise for people with OA in addition to its well-documented benefits on pain, strength and function (National Clinical Guideline Centre UK, 2014).

Conclusion

Since depression, anxiety and stress has been found to have significant association with both the groups of osteoarthritis patients, significantly more in perimenopausal and post menopausal women, hence the alternate hypothesis of the study is accepted. The high prevalence rates of pain and co-morbid depression point to the clinical importance of assessing depression in chronic pain samples.

Although in general it is acknowledged by almost all medical professionals that anxiety or depression and chronic pain usually co-occur and that their concordance is more disabling than either condition alone, yet these co-morbidities are usually overlooked by general physicians, orthopedicians or physiotherapists who solely focus on physical assessment and treatment ignoring the psychological co-morbidities.

Depression complicates the management of patients with osteoarthritis because they don't remain motivated to perform therapeutic exercises and carry on other physical activities and is associated with poorer treatment outcomes. It is imperative to recognize these co-morbidities, as these can influence disease

course and management, ultimately affecting functional outcomes.

Thus, orthopedic doctors and musculoskeletal physiotherapists should make it a mandate to implement appropriate screening scales or questionnaires on all osteoarthritis patients so that the psychological co morbidities are detected at an earlier stage and, if needed, referral to the concerned psychiatry department should be done. This would ensure that the patient doesn't have to go through the vicious cycle of chronic pain leading to depression which in turn leads higher pain sensitivity. Such a protocol would surely improve the outcomes of physiotherapy or medical or surgical management of the osteoarthritis patients and would lessen the future health care cost and burden on the community.

Physiotherapeutic challenges exist in managing patients with OA with co-morbid anxiety and depression. These challenges juxtaposed with the demographics of this patient cohort (advanced age and presence of other medical co-morbidities) make physiotherapy difficult.

Acknowledgements

The authors would like to thank all the subjects of the study for their participation and duly acknowledge the statistical help obtained from Dr. Manjula Anil.

References

1. Johnson VL, Hunter DJ. (2014). The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol, 28(1):5–15.
2. Lories RJ, Luyten FP. (2011). The bone-cartilage unit in osteoarthritis. Nat Rev Rheumatol, 7(1):43–49.
3. Hunter DJ, Schofield D, Callander E. (2014). The individual and socioeconomic impact of osteoarthritis. Nat Rev Rheumatol, 10(7):437–441.
4. Litwic A, Edwards MH, Dennison EM, Cooper C. (2013). Epidemiology and burden of osteoarthritis. Br Med Bull, 105:185–199.
5. Magni GMarchetti MMoreschi CMerskey HLuchini SR. (1993). Chronic musculoskeletal pain and depressive symptoms in the National Health and Nutrition Examination, I: epidemiologic follow-up study. Pain, 53163-168.
6. Axford J, Butt A, Heron C, et al. (2010). Prevalence of anxiety and depression in osteoarthritis: use of the Hospital Anxiety and Depression Scale as a screening tool. Clin Rheumatol, 29(11):1277–1283.
7. van Baar ME, Dekker J, Lemmens JA, Oostendorp RA, Bijlsma JW. (1998) .Pain and disability in patients with osteoarthritis of hip or knee: the relationship with articular, kinesiological, and psychological characteristics. J Rheumatol, 25(1):125–133.
8. American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: APA.
9. Maurer J, Rebbapragada V, Borson S, et al. (2008). ACCP Workshop Panel on Anxiety and Depression in COPD Anxiety and depression in COPD: current understanding, unanswered questions, and research needs. Chest, 134(4 suppl):43S–56S.
10. Januzzi JL, Jr, Stern TA, Pasternak RC, DeSanctis RW. (2000). The influence of anxiety and depression on outcomes of patients with coronary artery disease. Arch Intern Med, 160(13):1913–1921.
11. Mikocka-Walus AA, Turnbull DA, Moulding NT, Wilson IG, Andrews JM, Holtmann GJ. (2007). Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: a literature review. Inflamm Bowel Dis, 13(2):225–234.
12. He Y, Zhang M, Lin EH, et al.(2008). Mental disorders among persons with arthritis: results from the World Mental Health Surveys. Psychol Med, 38(11):1639–1650.
13. Neogi T, Nevitt MC, Yang M, Curtis JR, Torner J, Felson DT. (2010). Consistency of knee pain: correlates and association with function. Osteoarthritis Cartilage, 18(10):1250–1255.

14. Hansen GR, Streltzer J.(2005). The psychology of pain. Emerg Med Clin North Am, 23(2):339–348.
15. Eunice Kennedy Shriver National Institute of Child Health and Human Development. (28 June 2013). "Menopause: Overview". Archived from the original on 2 April 2015. Retrieved 8 March 2015;8:2.
16. PubMedHealth. (29 August 2013). "Menopause: Overview". Archived from the original on 10 September 2017. Retrieved 8 March 2015.
17. WHO Scientific Group on Research on the Menopause in the 1990s (1994: Geneva, Switzerland) & World Health Organization.) 1996). Research on the menopause in the 1990s : report of a WHO scientific group. World Health Organization. (World Health Organization Technical Report Series No. 866). https://apps.who.int/iris/handle/10665/41841. ISBN 924120866X
18. Deecher D, Andree T. H., Sloan D., & Schechter L. E. (2008). From menarche to menopause: Exploring the underlying biology of depression in women experiencing hormonal changes. Psychoneuroendocrinology, 33(1), 3-17.
19. Liukkonen T., Vanhala M., Jokelainen J., Keinänen-Kiukaanniemi S., Koponen H., & Timonen M. (2008). Effect of menopause and use of contraceptives/hormone therapy on association of C-reactive protein and depression: A population-based study. European Psychiatry, 23(2), S257.
20. Hay A. G., Bancroft J., & Johnstone E. C. (1994). Affective symptoms in women attending a menopause clinic. British Journal of Psychiatry, 164(4), 513-516.
21. Sale JE, Gignac M, Hawker G. (2008) . The relationship between disease symptoms, life events, coping and treatment, and depression among older adults with osteoarthritis. J Rheumatol, 35(2):335–342.
22. Rosemann T, Backenstrass M, Joest K, Rosemann A, Szecsenyi J, Laux G. (2007) . Predictors of depression in a sample of 1,021 primary care patients with osteoarthritis. Arthritis Rheum, 57(3):415–422.
23. Kirkness CS, McAdam-Marx C, Unni S, et al. (2012). Characterization of patients undergoing total knee arthroplasty in a real-world setting and pain-related medication prescriptions for management of postoperative pain. J Pain Palliat Care Pharmacother, 26(4):326–333.
24. Dailiana ZH, Papakostidou I, Varitimidis S, et al. (2015) .Patient-reported quality of life after primary major joint arthroplasty: a prospective comparison of hip and knee arthroplasty. BMC Musculoskelet Disord, 16:366.
25. Childs JD, Piva SR, Fritz JM. (2015) Responsiveness of the numeric pain rating scale in patients with low back pain. Spine,30:1331–4.
26. Jensen MP, McFarland CA. (1993). Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain, 55: 195–203.
27. Rodriguez CS. (2001). Pain measurement in the elderly: a review. Pain Manag Nurs, 2:38–46
28. Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith CH. (1990). Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol, 17:1022–4
29. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain, 113:9–19.
30. Crawford JR, Henry JD. (2003). The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non-clinical sample. Br J Clin Psychol, 42:111–31.
31. Lovibond, S.H. & Lovibond, P.f. (1995). Manual for the Depression anxiety Stress Scales. (2nd Ed) Psychology Foundation: Sydney.
32. Nieuwenhuijsen K, de Boer AG, Verbeek JH, Blonk RW, van Dijk FJ. (2003). The Depression Anxiety Stress Scales (DASS): Detecting anxiety disorder and depression in employees absent from work because of

mental health problems. Occup Environ Med, 60:77–82.
33. Antony M, Bieling P, Cox B, Enns M, Swinson R. (1998). Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. Psychol Assess, 10:176.
34. Kalkur C., Sattur A. P., & Guttal K. S. (2015). Role of Depression, Anxiety and Stress in Patients with Oral Lichen Planus: A Pilot Study. Indian journal of dermatology, 60(5), 445–449.
35. Sale JE, Gignac M, Hawker G. (2008). The relationship between disease symptoms, life events, coping and treatment, and depression among older adults with osteoarthritis. J Rheumatol, 35(2):335–342.
36. McLean CP, Asnaani A, Litz BT, Hofmann SG. (2011). Gender differences in anxiety disorders: prevalence, course of illness, comorbidity and burden of illness. J Psychiatr Res, 45(8):1027–1035.
37. O'Connor MI. (2007). Sex differences in osteoarthritis of the hip and knee. J Am Acad Orthop Surg, 15(suppl 1):S22–S25.
38. Theis KA, Helmick CG, Hootman JM. (2007). Arthritis burden and impact are greater among U.S. women than men: intervention opportunities. J Womens Health (Larchmt) ,16(4):441–453.
39. DiMatteo MR, Lepper HS, Croghan TW. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med, 160:2101–7.
40. Fuller-Thomson E, Shaked Y. (2009). Factors associated with depression and suicidal ideation among individuals with arthritis or rheumatism: findings from a representative community survey. Arthritis Rheum, 61:944–50.
41. Matcham F, Norton S, Scott DL, Steer S, Hotopf M. (2016). Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. Rheumatology (Oxford), 55:268–78.
42. Sambamoorthi U, Shah D, Zhao X. (2017). Healthcare burden of depression in adults with arthritis. Expert Rev Pharmacoecon Outcomes Res, 17:53–65.
43. de Heer E, Gerrits M, Beekman A, Dekker J, van Marwijk H, de Waal M, et al. (2014). The association of depression and anxiety with pain: a study from NESDA. PLos One,15(9):e106907.
44. Coventry P, Hays R, Dickens C, Bundy C, Garrett C, Cherrington A, et al. (2011). Talking about depression: barriers to managing depression in people with long term conditions in primary care. BMC Fam Pract, 12:10.
45. Memel D S, Kirwan J R , Sharp D J and Hehir M. (2000). General practitioners miss disability and anxiety as well as depression in their patients with osteoarthritis. British Journal of General Practice , 50 (457): 645-648.
46. Rosemann T, Gensichen J, Sauer N, Laux G, Szecsenyi J. (2007). The impact of concomitant depression on quality of life and health service utilisation in patients with osteoarthritis. Rheumatol Int, 27(9):859–863.
47. Kingsbury SR, Conaghan PG. (2012). Current osteoarthritis treatment, prescribing influences and barriers to implementation in primary care. Prim Health Care Res Dev, 13(4):373–381.
48. Spector TD, Campion GD. (1989). Generalised osteoarthritis: a hormonally mediated disease. Ann Rheum Dis, 48(6):523-7.
49. Kapur P, Sinha B, Pereira BM. (2009). Measuring climacteric symptoms and age at natural menopause in an Indian population using the Greene Climacteric Scale. Menopause, 16(2):378-84.
50. Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. (1993). Sex and depression in the National Comorbidity Survey. I: Lifetime prevalence, chronicity and recurrence. J Affect Disord, 29(2-3):85-96.
51. Bener, A., Saleh, N. M., Bakir, A., & Bhugra, D. (2016). Depression, Anxiety, and Stress Symptoms in Menopausal Arab Women: Shedding More Light on a Complex Relationship. Annals of medical

and health sciences research, 6(4), 224–231.

52. Fields HL. (2000). Pain modulation: expectation, opioid analgesia and virtual pain. Prog Brain Res,122:245-53.
53. Nekovarova T., Yamamotova A., Vales K., Stuchlik A., Fricova J., & Rokyta R. (2014). Common mechanisms of pain and depression: are antidepressants also analgesics?. Frontiers in behavioral neuroscience, 8, 99.
54. Uritani D., Kasza J., Campbell P.K. , Metcalf B , Egerton T . (2020). The association between psychological characteristics and physical activity levels in people with knee osteoarthritis: a cross-sectional analysis. BMC Musculoskelet Disord 21, 269 .
55. Schuch FB, Vancampfort D, Richards J et al. (2016). Exercise as a treatment for depression: a meta-analysis adjusting for publication bias. J Psychiatr Res, 77: 42–51.
56. National Clinical Guideline Centre (UK) (2014 February). Osteoarthritis: care and management in adults. NICE Clinical Guidelines No. 177. https://www.nice.org.uk/guidance/cg177/resources/osteoarthritis-care-and-management-pdf-35109757272517