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Research Article

Prevalence of Comorbidities in Patients with Osteoarthritis of Knee

Dr. Priya Singh (PT), Dr. Bhavana Mhatre (PT) *, Dr. Sarawati Iyer (PT)

Department of PT School and Center, KEM hospital, Parel, Maharashtra University of Health Sciences (MUHS), India

***Corresponding Author:** Dr. Bhavana Mhatre (PT), Department of PT School and Center, KEM hospital, Parel, Maharashtra University of Health Sciences (MUHS), India.

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Abstract

Introduction: Osteoarthritis (OA) is the most common musculoskeletal disorder affecting weight bearing joints like the knee, which leads to reduced functional capacity and disability in adults. Due to pain and movement limitations OA knee patients, generally spend most of their waking hours sedentary, and such behaviour could ultimately lead to harmful comorbidities like diabetes, obesity, high blood pressure, and lipid disorders. Hence, there is a need to identify any of these comorbidities that may be present in the Indian population who are diagnosed with Osteoarthritis and referred for Physiotherapy management.

Methods: An interview-based questionnaire was prepared and validated by 6 expert physiotherapists, including the patient's demographic data, lifestyle information, and comorbidities.

Results: The mean age of the study was 52.49 (SD: 6.62) years; with a mean BMI of 27.8 kg/m2 (SD: 4.61). 61% of subjects with OA knee had one or more than one comorbidities, the maximum being obesity followed by hypertension and diabetes mellitus.

Conclusions: Early recognition of the comorbid conditions associated with OA knee is essential for designing integrated care approach for a faster and efficient recovery, ultimately, improving the patient's Quality of Life.

Keywords: Osteoarthritis; OA Knee; Comorbidities

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder affecting weight bearing joints like the knee, hip, and spine, which leads to reduced functional capacity and disability in adults [1,2]. OA is a progressive, irreversible disease, heterogeneous in nature, which can be unilateral or bilateral, and is the major health problem in an aging population that impacts socioeconomic status [3-5].

It is estimated that 3.8% of the world's population suffers from symptomatic OA knee, which equates to approximately 277 million people living with OA knee worldwide, and it is expected to increase with the aging of the population, especially in middle and low-income nations [4]. In India, it is the leading cause of disability in older adults and the second-most common rheumatologic prevalent disease. The most commonly affected joint is the knee and the prevalence of knee OA in rural and urban India is estimated to be 3.9% and 5.5% respectively [4,6]. A multi-center based study from India estimated OA prevalence in 40 or more age groups as 28.7% consistent with findings where the prevalence varied from 12 to 30% [7].

OA is a particularly important public health problem in an aging population due to sedentary lifestyles, lack of proper nutrition, unhealthy food habits, and lack of exercise [8]. Clinically, patients with knee OA present with complaints of pain, swelling, stiffness, decreased ability to move the joint and instability which results in difficulty while performing activities of daily living and participation in society. Treatment includes pharmaceutical interventions like analgesics and anti-inflammatories, natural supplements, and intra-articular injections of corticosteroids or hyaluronic acid. In addition, a systematic review states that active treatment like physical therapy and orthotics is also indicated. Physical therapy intervention includes exercises, and manual therapy to improve the strength, and mobility of the knee joint. When conservative management fails, joint surgeries like arthroplasty become necessary [2,4]. OA has a high impact on healthcare use and costs in hospitals; for example, joint replacements [3]. Even with primary care of OA for example, consultations, and pharmacological management increases healthcare use and cost [3].

Literature now reports that OA is seen earlier in the age group of 30-40 years and is in need of joint replacements [8]. One of the factors for this early development of osteoarthritis in younger adults reported is a sedentary lifestyle [9]. Sedentary behaviour is defined as any waking behaviour characterized by an energy expenditure of ≤1.5 metabolic equivalents (METs), while in a sitting, reclining, or lying posture, and this is calculated as per the physical activity of the individual [10]. Physical activity is defined as any bodily movement produced by skeletal muscle that requires energy expenditure [11]. The metabolic equivalent of task (MET) is the measure of the ratio of the rate at which a person expends energy, relative to the mass of that person, while some specific physical activity [12]. It is a physiological measure expressing the intensity of physical activities. [11] Sedentary lifestyles also increase the risk of cardiovascular diseases, diabetes, obesity, high blood pressure, and lipid disorders, and these are the major comorbidities reported in OA knee patients [5,13]. According to the WHO, 60 to 85% of the world population, including both developed and developing countries, are leading sedentary lifestyles, making it one of the most serious public health problems. [13] Knee OA patients, due to pain and movement limitations, generally spend most of their waking hours sedentary, and such behaviour could ultimately lead to harmful comorbidities [14].

A large number of studies have demonstrated that patients with OA are at a higher risk of developing comorbidities than people without OA [15]. The presence of various comorbidities along with OA leads to functional impairments, activity limitations, and participation restrictions in society, ultimately giving rise to disability and affecting the quality of life (QOL) of the individual [7,15].

Comorbidities are known to affect the healing of tissues and can be a contributing factor to development and maintenance of OA, hence adding more problems to already existing disabilities, thus increasing the complexity of rehabilitation in terms of cost and time. Therefore, OA assessment and management should not be restricted to articular disorder alone, but rather should be comprehensive. An integrated approach involving the assessment of comorbidities should be routinely incorporated and if diagnosed should be included in the management program by the physiotherapist for early recovery of function in OA patients. Hence, there is a need to identify any of these comorbidities that may be present in the Indian population who are diagnosed with Osteoarthritis and referred for Physiotherapy management.

A sedentary lifestyle is a risk factor for the development of comorbidities and OA knee. Therefore, the level of physical activity in patients with OA also needs consideration for the management of OA patients. Physical activity was measured by the physical activity rating measure scale and was classified as per WHO criteria into light (<3.0 METs), moderate (3.0-6.0 METs), and vigorous (>6.0 METs) [11,16].

Considering the current burden of OA and its association with lifestyle-related comorbidities, a study was undertaken to find the prevalence of comorbidities in OA knee patients using an interview- based questionnaire [17]. Interviewer-administered questionnaires do not require respondent literacy, questions and responses can be clarified; it allows probing for additional information; complex and open-ended questions are framed. Also, answering the questionnaire by the intended person is assured, fewer "blanks" and participation is potentially increased by personal contact [18]. It has been used as a data collection method in similar descriptive studies [19]. Thus, an interviewer- administered questionnaire was prepared and validated. The questionnaire included demographic data, lifestyle information, and the presence of comorbidities.

Methods

Study design

A descriptive cross-sectional study was conducted in a tertiary health care center.

Study population

Patients diagnosed with OA by Orthopaedic surgeons and referred to the physiotherapy department were enrolled in the study.

Inclusion criteria

About 100 patients diagnosed with unilateral or bilateral osteoarthritis of the knee in an age group of 40 to 60 years, both males and females that visited the department, were enrolled in the study using a convenient purposive sampling method. The diagnostic criteria for osteoarthritis were based on the clinical criteria of the American College of Rheumatology. Table 1 lists the background characteristics of all the participants.

Exclusion criteria

Neurological conditions having cognitive disorders and any musculoskeletal conditions like inflammatory, infective, and neoplastic of the lower extremity were excluded from the study.

Study instrument/tools

A questionnaire was prepared, including the patient's demographic data, lifestyle information, and comorbidities. Each section included 6-7 questions and it took 10 minutes to complete the questionnaire. This questionnaire was validated by 6 expert physiotherapists. Each was given a copy of the questionnaire

and face validation was done. The interviewer completed the questionnaire by asking all the questions to the participants and missing data was completed from the medical records of the patients.

Interviewer completed an interviewer-administered questionnaire (Appendix) that included part I ofthe patient's demographic data like age, gender, height, weight, and lifestyle information such as occupation, smoking habit, and physical activity. Part II included the patient's comorbidities like hypertension, cardiovascular diseases, dyslipidemia, diabetes, and obesity, and part III included theuse of health care resources and treatment taken for it, like medications and follow-up with the physician; and any other interventions-diet, yoga, etc.

Patients were screened for their medical records regarding their comorbidities and medications and follow up for the same.

Ethical consideration

The study obtained approval from the *Institutional Research Ethics Committee*. Before the interview, written consent was obtained from the patients.

Procedure

Subjects from the physiotherapy department were recruited for this study as per the inclusion and exclusion criteria. Written informed consent was taken from the participants and the study was conducted further. Participants completed an interviewer-administered questionnaire by one interviewer who was same throughout the study. Physical activity for each patient was calculated as per the physical activity rating measure for the Asian Indian population in MET values and was categorized into light (<3.0 METs), moderate (3.0-6.0 METs), and vigorous (>6.0 METS) as per WHO classification [11,16]. Anthropometric measurements; height, weight and body mass index [BMI: weight/height (kg/m2)] were taken. WHO grading criteriafor BMI were used to categorize obesity [20]. The data obtained were statistically analysed.

Statistical analysis

Descriptive statistics were used to document the data.

Results

The mean age of the subjects who participated in the study was 52.49 (SD: 6.62) years; 53.4 (6.13) years for males (n = 34) and 52.05 (6.77) years for females (n = 66). (Table 1).

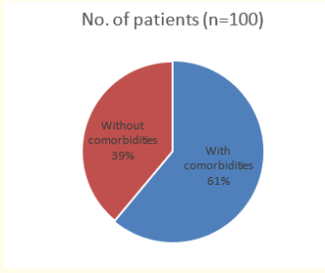
Mean height was 158.02 m (SD: 10.87) with; 167 m (9.76) in male and 153.43 m (8.14) in female. (Table 1) Mean weight was 68.96 kg (SD: 11.19) with; 72.85 kg (12.86) in male and 67 kg (9.53) in female. (Table 1).

Mean BMI was 27.8 kg/m2 (SD: 4.61) with; 26.17 (4.10) kg/m2 in male and 28.6 (4.60) kg/m2 in female. (Table 1) Among 100 subjects 11 were smokers all were male. (Table 1).

Mean (SD) selected characteristics	Total (n = 100)	Men (n = 34)	Women (n = 66)
Age (Years)	52.49 (6.62)	53.35 (6.13)	52.05 (6.77)
Height (cm)	158.02 (10.87)	167 (9.76)	153.43 (8.14)
Weight (kg)	68.96 (11.19)	72.85 (12.86)	67 (9.53)
BMI (kg/m^2)	27.8 (4.61)	26.17 (4.10)	28.6 (4.60)
Prevalence of selected characteristics (%)	Total	Men	Women
Smoking	11	11	0

Table 1: Background characteristics of the participants.

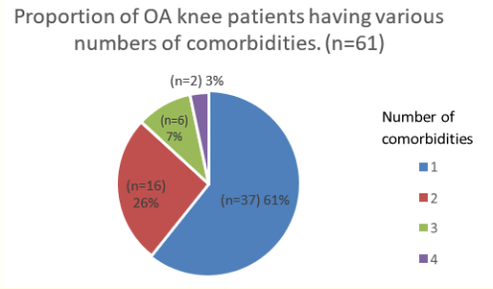
Out of 100 subjects with OA knee, 61 (61%) were found to have comorbidities and 39 patients (39%) did not have any comorbidities. (Graph 1).



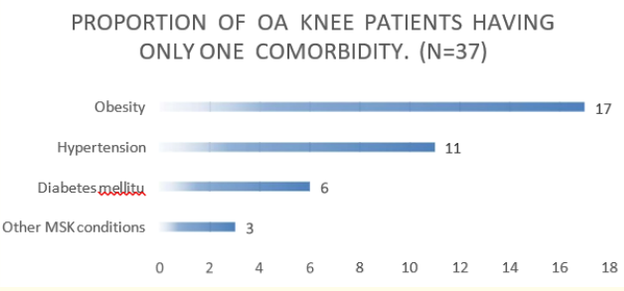
Graph 1: Number of OA knee patients (n = 100) with and without comorbidities.

Among 61 patients, 37 patients (60.66%) had only 1 comorbidity; 16 patients (26.23%) had 2 comorbidities; 6 patients (6.56%) had 3 comorbidities, and 2 patients (3.28%) had 4 comorbidities. (Graph 2).

Subjects with only 1 comorbidity presented with either hypertension (n = 11), diabetes mellitus (n = 6), obesity (n = 17) or other MSK conditions (n = 3). (Graph 3).

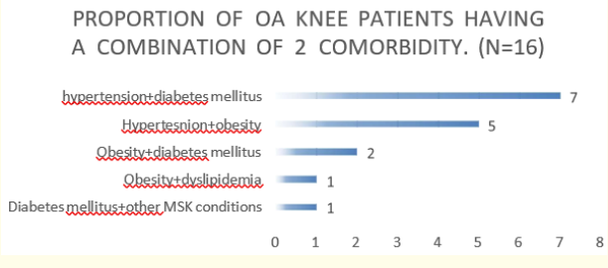


Graph 2: Proportion of OA knee patients having various numbers of comorbidities. (n = 61).



Graph 3: Proportion of OA knee patients having only one comorbidity. (n = 37).

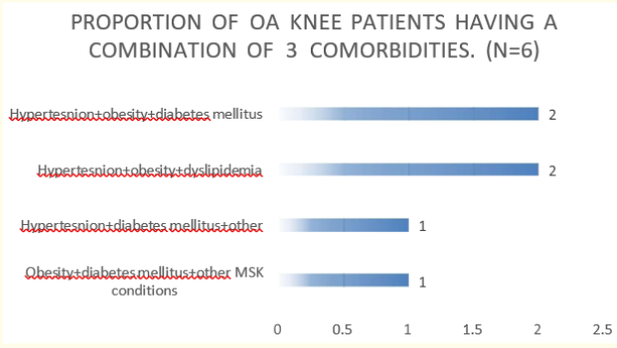
The observed combination of 2 comorbidities was either both hypertension and diabetes mellitus (n = 7), hypertension and obesity (n = 5), diabetes mellitus and obesity (n = 2), diabetes mellitus and other MSK conditions (n = 1), or dyslipidemia and obesity (n = 1). (Graph 4).



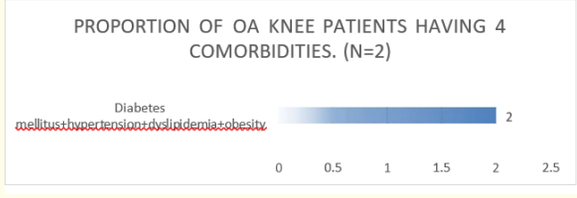
Graph 4: Proportion of OA knee patients having a combination of 2 comorbidities. (n = 16).

The observed combination of 3 comorbidities was either hypertension, diabetes mellitus and obesity (n = 2) or hypertension, obesity and dyslipidemia (n = 2) or hypertension, diabetes mellitus and other MSK conditions (n = 1) or diabetes mellitus, obesity, and other MSK conditions (n = 1). (Graph 5).

The observed combination of 4 comorbidities was hypertension, diabetes mellitus, obesity, and dyslipidemia (n = 2). (Graph 6).

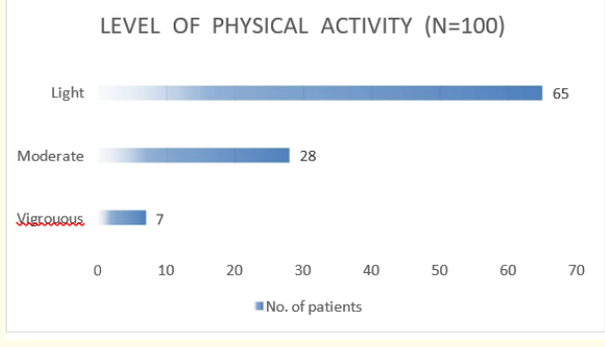


Graph 5: Proportion of OA knee patients having a combination of 3 comorbidities. (n = 6).



Graph 6: Proportion of OA knee patients having 4 comorbidities. (n = 2).

As per physical activity classification for Asian Indians, out of 100 patients, 65 patients performed light physical activity (<3.0 METs), 28 patients performed moderate level of physical activity (3.0-6.0METs) and 7 patients performed vigorous level of physical activity (>6.0 METS). (Graph 7).



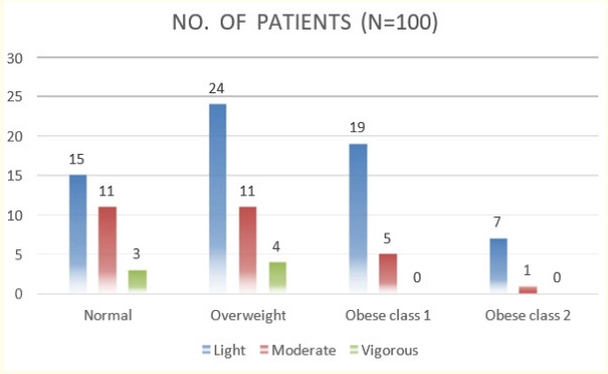
Graph 7: Graph shows the proportion of OA knee patients concerning their level of physical activity as light (<3.0 METs), moderate (3.0–6.0 METs), and vigorous (>6.0 METS).

The distribution of BMI as per WHO guidelines were 29 patients was normal; 39 patients were overweight; 24 patients were class 1 obese and 8 patients were class 2 obese. (Table 2).

Classification	BMI (kg/m2)	No. of patients (Total n = 100)	Men	Women
Normal weight	18.5-24.9	29	16	13
Overweight	25-29.9	39	10	29
Obesity Class 1	30-34.9	24	7	17
Obesity Class 2	35-39.9	8	1	7

Table 2: The table shows the distribution of BMI in patients having OA knee.

The level of physical activity in OA knee patients according to BMI (n = 100) was 15 light, 11 moderate, and 3 vigorous physical activity in normal BMI patients, 24 light, 11 moderate, 4 vigorousphysical activity in overweight patients, 19 light and 5 moderate physical activity in obese class 1 patients, and 7 light and 1 moderate physical activity in obese class 2 patients. (Graph 8).

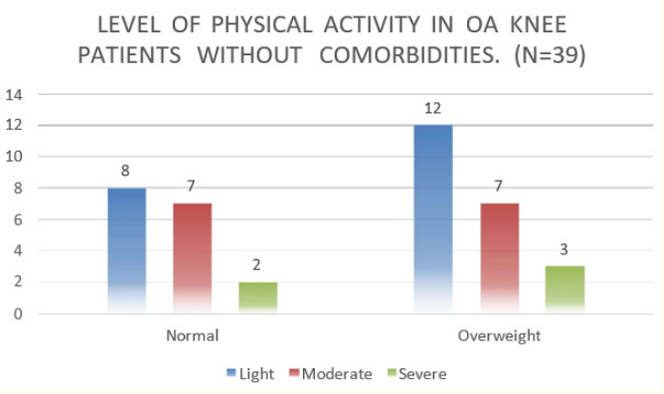


Graph 8: The graph shows the proportion of OA knee patients based on their BMI and level of physical activity.

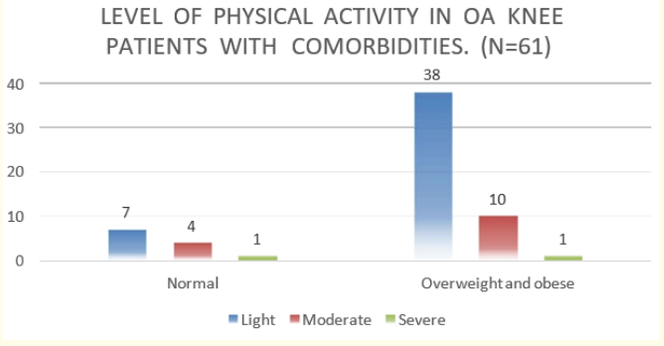
The level of physical activity in OA knee patients without comorbidities (n = 39) was 8 patients performed light, 7 moderate, and 2 vigorous physical activity in normal BMI patients, and 12 light, 7 moderate, and 3 vigorous physical activity in overweight patients. (Graph 9).

The level of physical activity in OA knee patients with comorbidities (n = 61) was 7 light, 4 moderate,and 1 vigorous physical activity in normal BMI patients, and 38 light, 10 moderate, and 1 vigorous physical activity in overweight and obese patients. (Graph 10).

In order to find associations between levels of physical activity in subjects with and without comorbidities, we performed Chi-square test. Since these are categorical data Chi-square test was employed. Chi-square test was performed in subjects with normal BMI and in overweight and obese categories. In subjects with normal BMI, there was no significant difference between



Graph 9: Level of physical activity in OA knee patients without comorbidities. (n = 39).



Graph 10: Level of physical activity in OA knee patients with comorbidities. (n = 61).

levels of physical activity in subjects with and without comorbidities (p-value = 0.832). Similarly, subjects in overweight and obese category showed no significant difference between levels of physical activity and comorbidities. (p-value = 0.061). (Table 3).

Discussion

The results showed that 61% of patients diagnosed with OA had one or more comorbidities. The mean age of the subjects who participated in the study was 52.49 years. Sixty-six % of females were diagnosed with OA knee.

Normal BMI	With comorbidities	Without comorbidities
Light	7	8
Moderate	4	7
Vigorous	1	2
P-value	0.832342	
Overweight and obese	With comorbidities	Without comorbidities
Light	38	12
Moderate	10	7
Vigorous	1	3
P-value	0.061108	

Table 3: The table shows the Chi-square test performed in individuals with and without comorbidities, to find association between BMI and levels of physical activity.

The predominance of female populations was also observed in studies done previously [4,14,21,22]. Srikanth., *et al*. also reported that males have a significantly lower risk for the prevalence of OA knee than females [23]. This could be because of the lack of estrogen in women of this age. [23] Estrogen influences the size and shape of the skeleton and also contributes to skeletal homeostasis. [24] Hence, in menopause, estrogen deficiency induces cancellous as well as cortical bone loss, disturbed architecture, and reduced bone strength [25].

The most common comorbidity seen was obesity (32%) followed by hypertension (30%) and diabetes mellitus (22%) which were similar to studies reported by Cunha-Miranda Luís., *et al*, Rosemann., *et al*, and others [2,21].

Obesity is a well-known powerful risk factor for OA knee due to its biomechanical implications on the joint, and it is also a risk factor for diabetes, heart disease, and hypertension [26]. This was also reflected in our study where the overall mean BMI was 27.8kg/m^2, with the mean BMI in females (28kg/m^2) more than the mean BMI of males (26 kg/m^2). In this study, 71% of the population had an increased BMI; 39% population were overweight (mean = 27.11), and 32% were obese (mean = 33.21).

The study also reported that 22% of subjects with OA were diabetics. Carnevale., *et al*. hypothesized that the reason could be that DM patients (both Type 1 and Type 2) have deranged bone mineral density due to metabolic alterations such as increased calcium excretion, lower intestinal absorption of calcium, and inappropriate homeostatic response in terms of parathyroid hormone and vitamin D regulation [27]. Also, it is reported that certain complications associated with DM predispose these patients to OA for example, insulin release, growth factor resistance, accumulation of advanced glycosylated end products in Extracellular fluid (ECF), and microangiopathic and neuropathic complications [27]. A similar study conducted in general practice in the Netherlands found that chronic conditions like diabetes mellitus and heart diseases were associated with OA [28].

Thirty percent of subjects in this study had hypertension. This could be due to shared risk factors between hypertension and OA knees, such as aging, obesity, chronic inflammation, proinflammatory cytokine interleukin 6, and polymorphisms in the vitamin D receptors [29]. Subjects in this study also showed more than 1 comorbidities, 2 patients had hypertension, obesity, dyslipidemia, and diabetes mellitus, 2 patients had hypertension, obesity, and diabetes mellitus, and 2 patients had hypertension, dyslipidemia, and obesity.

The study reported that out of 66 female subjects, 43 females had one or more than one comorbidities Kadam, U T., *et al*. also reported similar findings. [3] Also, increased BMI was seen in 80% (n = 66) females as against 53% (n = 34) males.

In the study, 15% of OA knee patients were smokers. Literature reports that cigarette smoking is a risk for cartilage loss, and so people who smoke cigarettes sustain more cartilage loss, have more severe pain than those who do not smoke and have a higher risk of developing OA [30].

Literature has reported that OA knee patients are at risk for the development of comorbidities and have low levels of physical activities [9,15]. Similar findings was seen in our study as 32% of patients were obese and 71% were overweight with, a maximum number of subjects performing light physical activities. As the overweight class includes a greater number of subjects, hence just by improving the levels of physical activities, it is expected that various comorbidities can be prevented in them. Hence, assessing these parameters in OA knee population is essential. Also in our study, individuals in overweight and obese category mainly performed light activities.

The level of physical activity was found to be light (<3 METs) in 65% of the subjects with OA knee, suggesting a sedentary lifestyle. Due to various impairments in OA knee patients, have reported in literature performing light activities which lead to sedentary lifestyles, hence predisposing patients to other comorbidities [9,14]. Since this is an important risk factor not only for OA but for various associated comorbidities like obesity, hypertension, and diabetes mellitus, assessment of physical activity is also essential.

In the study, among individuals with and without comorbidities, there was no significant correlation between levels of physical activities with BMI. However, following inferences can be made. One, in normal BMI individuals, moderate level of PA was performed more in individuals without comorbidities than with comorbidities. Two, in individuals with increased BMI having comorbidities, light level of PA was performed more than moderate and vigorous PA. Both of these findings are suggestive of sedentary lifestyle leading to the development of comorbidities. Three, in individuals with increased BMI not having comorbidities, light level of PA was performed more than moderate and vigorous PA. Indicating sedentary lifestyle leading to obesity.

These findings were different from other studies how showed inverse correlation between PA and obesity. In the study most of the individuals were from low socioeconomic strata, they continued their jobs, must have stress, improper diet are other factors which must have led to development of OA knee and comorbidities. Although most of individuals performed light PA in overweight and obese category having comorbidities. Suggesting increased levels of PA can help OA knee patients having comorbidities.

OA knee patients due to pain and other functional impairments will lead to activity limitation and participation restriction in society, ultimately affecting their QOL. Also, the presence of obesity will further lead to a sedentary lifestyle. This vicious cycle will continue if a diagnosis of comorbidities in OA knee patients is missed or delayed. Physiotherapists with their knowledge of exercise science can address impairments due to OA and associated comorbidities in these patients by enhancing the healing of tissues and bone mineral density with a tailored, graded exercise program. By keeping comorbidities and OA into consideration, physiotherapists can formulate an adequate cardiorespiratory endurance program for prevention of cardiovascular diseases as, due to limited physical activity and comorbidities, they are at higher risk. By studying patients' activity levels and sedentary behaviour, advice on increasing physical activity and reducing sedentary behaviour can be given by physiotherapists.

Limitations

There are limitations to the study. One is that severity of each comorbidities and their duration of presence was not noted, as that could have impacted the severity of OA knee and levels of physical activities. Second, the sample size was too small to comment on the prevalence of comorbidities in OA patients. Third, occupational status of patients was not considered as that could have affected the results.

Future scope

Larger sample size can be used for further exploring the trend. Retrospective analysis can be formed in order to find whether comorbidities have led to OA knee or, due to OA knee, subjects having developed comorbidities. Severity of comorbidities can be compared with physical activity levels in patients with OA knee.

Conclusions

Early recognition of the comorbid conditions associated with OA knee is essential for designing integrated care approach for a faster and efficient recovery, ultimately, improving the patient's Quality of Life.

Questionnaire

(Tick  Yes, Cros  No)

Bibliography

1. Nasonov EL and Alekseeva LI. "Osteoarthritis and comorbidities". *Medicographia* 35 (2013): 152-157.

2. Buechele G., *et al*. "Osteoarthritis-patterns, cardio-metabolic risk factors and risk of all-cause mortality: 20 years follow-up in patients after hip or knee replacement". *Scientific Reports* 8.1 (2018): 1-8.

3. Kadam UT., *et al*. "Clinical comorbidity in patients with osteoarthritis: a case- control study of general practice consulters in England and Wales". *Annals of the Rheumatic Diseases* 63.4 (2004): 408-414.

4. Sancheti P., *et al*. "India-based knee osteoarthritis evaluation (iKare): A multi-centre cross-sectional study on the management of knee pain andearly osteoarthritis in India". *Clinics in Orthopedic Surgery* 9.3 (2017): 286-294.

5. Cunha-Miranda L., *et al*. "Assessing the magnitude of osteoarthritis disadvantage on people's lives: the MOVES study". *Revista Brasileira de Reumatologia* 55 (2015): 22-30.

6. Arden N and Nevitt MC. "Osteoarthritis: epidemiology". *Best Practice and Research Clinical Rheumatology* 20.1 (2006): 3-25.

7. Swain S and Choudhury P. "Comorbidity and healthcare utilization in osteoarthritis; a primary care survey from Odisha, India". *Clinical Epidemiology and Global Health* 7.4 (2019): 661-667.

8. ET Bureau. "Painful knees not an old-age problem anymore: Bad lifestyle, wrong food choicesto be blamed". Economic Times (2018).

9. Murtagh EM., *et al*. "Interventions outside the workplace for reducing sedentary behaviour in adults under 60". *The Cochrane Database of Systematic Reviews* 2 (2017).

10. Tremblay MS., *et al*. "Sedentary behavior research network (SBRN)-terminology consensus project process and outcome". *International Journal of Behavioral Nutrition and Physical Activity* 14.1 (2017): 1-17.

11. WHO guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO (2020).

12. Wikipedia contributors. "Metabolic equivalent of task." Wikipedia, The Free Encyclopedia. Wikipedia, The Free Encyclopedia (2022).

13. Prakash R. "Physical inactivity a leading cause of disease and disability, warns WHO. WHO. World Health Organization (2002).

14. Sliepen M., *et al*. "Objective assessment of physical activity and sedentary behaviour in knee osteoarthritis patients–beyond daily steps and totalsedentary time". *BMC Musculoskeletal Disorders* 19.1 (2018): 1-10.

15. Van Dijk GM., *et al*. "Comorbidity, limitations in activities and pain in patients with osteoarthritis ofthe hip or knee". *BMC Musculoskeletal Disorders* 9.1 (2008): 1-0.

16. Misra A., *et al*. "Consensus physical activity guidelines for Asian Indians". *Diabetes Technology and Therapeutics* 14.1 (2012): 83-98.

17. Pal CP., *et al*. "Epidemiology of knee osteoarthritis in India and related factors". *Indian Journal of Orthopaedics* 50.5 (2016): 518-522.

18. World Health Organization. Foodborne disease outbreaks: guidelines for investigation and control. World Health Organization (2008): 107-108.

19. Bieleman HJ., *et al*. "Functional capacity of people with early osteoarthritis: a comparison between subjects from the cohort hip and cohort knee (CHECK) and healthy ageing workers". *International Archives of Occupational and Environmental Health* 83.8 (2010): 913-921.

20. World Health Organization (WHO). WHO/Europe| "Nutrition-Body mass index". WHO (2014).

21. Rosemann T., *et al*. "Osteoarthritis: quality of life, comorbidities, medication and health service utilization assessed in a large sample of primary care patients". *Journal ofOrthopaedic Surgery and Research* 2.1 (2007): 1-9.

22. Felson DT. "The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study". In *Seminars in Arthritis and Rheumatism* 20.3 (1996): 42-50.

23. Srikanth VK., *et al*. "A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis". *Osteoarthritis and Cartilage* 13.9 (2005): 769-781.

24. Manolagas SC., *et al*. "The role of estrogen and androgen receptors in bonehealth and disease". *Nature Reviews Endocrinology* 9.12 (2013): 699.

25. Väänänen HK and Härkönen PL. "Estrogen and bone metabolism". *Maturitas* 23 (1996): S65- S69.

26. Powell A., *et al*. "Obesity: a preventable risk factor for large joint osteoarthritis which may act through biomechanical factors". *British Journal of Sports Medicine* 39.1 (2005): 4-5.

27. Carnevale V., *et al*. "Skeletal involvement in patients with diabetes mellitus". *Diabetes/Metabolism Research and Reviews* 20 (2004): 196-204.

28. Schellevis FG., *et al*. "Comorbidity of chronic diseases in general practice". *Journal of Clinical Epidemiology* 46.5 (1993): 469-473.

29. Zhang YM., *et al*. "Association between hypertension and risk of knee osteoarthritis: A meta-analysis of observational studies". *Medicine* 96.32 (2017).

30. Amin S., *et al*. "Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis". *Annals of the Rheumatic Diseases* 66.1 (2007): 18-22.