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The Combination of Depression and Obesity Is Associated With Increased Incidence of Subsequent Total Knee Arthroplasty

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ABSTRACT. ***Objective.*** To compare the incidence of total knee arthroplasty (TKA) within the first 5 years after knee osteoarthritis (OA) diagnoses between matched groups of individuals with or without comorbid diagnoses of obesity and/or depression. We hypothesized that the greatest incidence of TKA within 5 years of OA diagnosis would be in the cohort of individuals with combined obesity and depression.

Methods. The PearlDiver Mariner Ortho157 database was used to identify 4 cohorts of individuals with knee OA based on diagnosis codes that were matched by age, sex, and the Charlson Comorbidity Index: those without diagnoses associated with depression or obesity (Control), those with obesity but not depression (Obesity), those with depression but not obesity (Depression), and those with diagnoses of both obesity and depression (Depression + Obesity). The incidence of subsequent TKA within the first 5 years after the index OA diagnosis were compared between the 4 matched cohorts.

Results. Each cohort comprised 274,403 unique individuals (180,563 females, 93,840 males; mean age = 55 [SD 7] years). The incidence of TKA was greatest for the Depression + Obesity group (11.9%) when compared to the Control group (8.3%, $P < 0.001$; risk ratios [RR] 1.43, 95% CI 1.41-1.45, $P < 0.001$), Obesity group (10.2%, $P < 0.001$; RR 1.13, 95% CI 1.11-1.14, $P < 0.001$), or Depression group (7.8%, $P < 0.001$; RR 1.53, 95% CI 1.50-1.55, $P < 0.001$).

Conclusion. The incidence of subsequent TKA was greatest for those with the combination of obesity and depression when compared to the control group and those with an individual diagnosis of obesity or depression.

Key Indexing Terms: knee, knee replacement, mood disorder, obese, osteoarthritis

More than 72 million Americans are projected to have physician-diagnosed arthritis by the year 2030, with symptomatic knee osteoarthritis (OA) being the most common joint disorder.[1] For many patients with knee OA, the disease progresses slowly over the course of multiple years; however, approximately 15% to 30% of patients with knee OA experience a more rapid progression of cartilage degradation, knee pain, and disability over a 2-year period.[2,3] Progression of knee OA is associated with increased pain, reduced mobility, reduced quality of life, and increased healthcare utilization.[4,5] Clinically, there is a need to identify subsets of patients that may be at greatest risk of more rapid OA progression in order to prevent or slow its occurrence.

Depression and obesity are common comorbidities among those with knee OA, and both have been individually associated with worse OA pain and pain progression.[6,7] Additionally, both depression and obesity have been identified as independent risk factors for poor outcomes following total knee arthroplasty (TKA).[8] As such, the potential interplay between obesity and depression must be explored to potentially improve OA treatment while also optimizing patients that may undergo future TKA. The purpose of this claims database study was to compare the incidence of TKA within the first 5 years after knee OA diagnoses between matched groups of individuals with or without comorbid diagnoses of obesity and/or depression. We hypothesized that the greatest incidence of TKA within 5 years of OA diagnosis would be in the cohort of individuals with combined obesity and depression.

METHODS

In this study, we used the PearlDiver Mariner Ortho157 database, which contains insurance claims information on > 157 million orthopedic

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patients between January 2010 and October 2021. Using International Classification of Diseases, 9th revision (ICD-9) and 10th revision (ICD-10) codes (Table; Supplementary Table, available from the authors upon request), we identified 4 cohorts of individuals with knee OA based on the presence of diagnosis codes associated with knee OA: those without diagnoses associated with depression or obesity (Control), those with obesity but not depression (Obesity), those with depression but not obesity (Depression), and those with diagnoses of both obesity and depression (Depression + Obesity). To be included in the analyses, individuals must have had continuous insurance coverage for 2 years before and 5 years following the index OA diagnosis and must not have had diagnoses related to rheumatoid arthritis. Index OA diagnosis was the first instance of a knee OA diagnostic code (Table). The cohorts were then matched 1:1:1:1 by age, sex, and Charlson Comorbidity Index (CCI; Figure 1). CCI is provided in the PearlDiver database and is based on diagnosis codes within the database at the time of index OA diagnosis. Categories of comorbidities in the CCI include diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, liver disease, hemiplegia or paraplegia, renal disease, malignancy, leukemia, lymphoma, and AIDS. Sex and CCI were matched exactly with the same number in each of the 4 groups. Age was matched with the same number of patients in each group in the following age ranges: 30-34 years (n = 113), 35-39 years (n = 4747), 40-44 years (n = 18,710), 45-49 years (n = 35,753), 50-54 years (n = 56,977), 55-59 years (n = 72,622), 60-64 years (n = 63,717), 65-69 years (n = 20,159), and 70-74 years (n = 1605).

Statistical analyses. Using Current Procedural Terminology (CPT) code 27447, we determined the incidence of subsequent TKA within the first 5 years after the index OA diagnosis. Kaplan-Meier survivorship curves were generated for each cohort, and relative risk (RR) ratios were calculated to compare the incidence of subsequent TKA between the Control, Obesity, Depression, and Depression + Obesity groups. Analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing) within the PearlDiver platform. *P* values are exceedingly small due to the large sample size but have been included for completeness.

Statement of ethics and consent. This study uses deidentified insurance claims data and as such was not considered human research and did not require institutional review board approval.

RESULTS

Each cohort comprised 274,403 unique individuals (180,563 females, 93,840 males; mean age = 55 [SD 7] years). The incidence of TKA was greater for the Obesity group when compared to the Control group (Obesity = 29,071 [10.6%], Control = 22,888 [8.3%]; RR 1.23, 95% CI 1.21-1.25, $P < 0.001$); however, the incidence of TKA was greatest for the Depression + Obesity group (32,736 [11.9%]) when compared to the Control group (RR 1.43, 95% CI 1.41-1.45, $P < 0.001$; Figure 2). Surprisingly, the incidence of TKA in the Depression group (21,411 [7.8%]) was significantly lower than the Control group (RR 0.94, 95% CI 0.92-0.95, $P < 0.001$). The incidence of TKA was significantly greater for those with the combination of obesity and depression compared to those with either isolated obesity (11.9% vs 10.2%, $P < 0.001$; RR 1.13, 95% CI 1.11-1.14, $P < 0.001$) or isolated depression (11.9% vs 7.8%, $P < 0.001$; RR 1.53, 95% CI 1.50-1.55, $P < 0.001$).

Table. Diagnosis codes (ICD-9 and ICD-10) used to identify patients included in the study.

Description	Diagnosis Codes
Knee OA	ICD-9-D-715.16, ICD-9-D-715.26, ICD-9-D-715.36, ICD-9-D-715.96, or ICD-10-D-M17
Obesity	ICD-9-D-278.0, ICD-9-D-278.00, ICD-9-D-278.01, ICD-9-D-278.02, ICD-9-D-278.03, or ICD10-D-E66.0:ICD-10-D-E66.9
Depression	ICD-9-D-296.2:ICD-9-D-296.36, ICD-9-D-296.51:ICD-9-D-296.59, ICD-9-D-300.4, ICD9-D-309.0:ICD-9-D-309.2, ICD-9-D-311, ICD-10-D-F31.3:ICD-10-D-F31.5, ICD-10-D-F32:ICD-10-D-F33, ICD-10-D-F34.1, or ICD-10-D-F43.2:ICD-10-D-F43.29

ICD-9: International Classification of Diseases, 9th revision; ICD-10: ICD, 10th revision; OA: osteoarthritis.

DISCUSSION

Obesity and depression are individually associated with worse OA pain and pain progression,[6,7] and the current results support our hypothesis that these factors exacerbate one another, leading to an increased incidence of TKA within 5 years of OA diagnosis. In a recent study of well-characterized cohorts, depression was not found to be prognostic of subsequent TKA[9]; however, the combination of obesity and depression were not assessed. Obesity is a known risk factor for both pain and structural OA progression,[10,11] and the current results agree with others that have reported an additive effect when obesity is combined with comorbid depression.[12,13] In the current study, the combination of depression and obesity was associated with a significantly greater incidence of subsequent TKA when compared to those with either obesity or depression alone. Surprisingly, depression in the absence of obesity resulted in a statistically significant reduction in the incidence of subsequent TKA. Statistical significance may have been related to the large sample size of the current study, and clinical relevance of the magnitude of the risk reduction must be interpreted with caution. The relative RR was 0.94, so this may not represent a clinically meaningful finding, as the relative RRs of obesity (RR 1.23) and obesity plus depression (RR 1.43) were much larger in comparison to the small effect of depression alone.

Knee OA pain, structural progression, and the eventual need for TKA are complex phenomena and are influenced by biological, mechanical, and psychosocial factors.[14] From a biological perspective, knee OA, obesity, and depression may share, at least in part, similar inflammatory mechanisms. Knee OA has been described as a chronic inflammatory condition with macrophages, monoctyes, and proinflammatory cytokines contributing to the cycle of cartilage degradation.[15] The intraarticular inflammatory process may also be mediated by systematic inflammation.[16] This creates a potential "outside-in" mechanism of inflammatory cartilage degradation, as those with increased peripheral expression of proinflammatory cytokines demonstrate more rapid knee OA progression.[2] Comorbid obesity and/or depression may further compound this process as both conditions are also associated with increased systemic inflammation and expression of proinflammatory cytokines.[15,17]

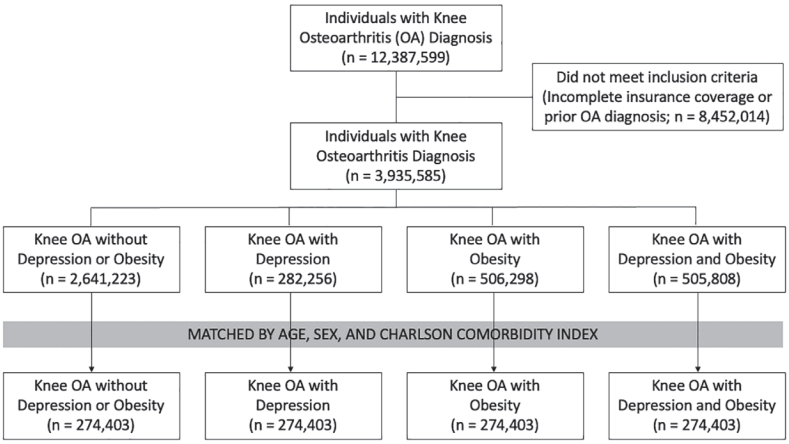

Figure 1. Flow diagram of how individuals were identified for analysis and assigned to groups. OA: osteoarthritis.

From a mechanical perspective, routine physical activity has been shown to reduce knee OA pain and functional limitations.[18] However, knee OA, obesity, and depression are associated with sedentary behaviors and reduced physical activity.[19] As such, the combination of knee OA, obesity, and depression may create barriers to initiating and maintaining routine exercise, thus creating a cycle of pain, inactivity, and cartilage degradation. Increasing physical activity is particularly important because breaking the cycle of depression, obesity, and inactivity associated with OA pain and cartilage degradation may result in less pain and more optimal loading of the articular cartilage, thereby preventing further cartilage loss.[19] Messier et al reported that a combined intervention involving both diet and exercise resulted in small but statistically significant improvements in knee pain for those with knee OA and overweight or obesity.[20] However, low mood, lack of motivation, misconceptions about joint pain and stiffness, and inadequate problem solving and coping resources pose significant barriers to sustained adherence to healthier lifestyle choices (eg, diet and exercise).[21] Additional research is needed to determine whether sustained changes in diet and exercise result in meaningful improvements in knee OA pain and potentially reduce the 5-year incidence of TKA for this high-risk subset of those with obesity, depression, and symptomatic knee OA.

Additionally, the incidence of TKA in the current study was greater than in previously published cohorts. In the current study, 8.3% of those in the Control group underwent TKA within 5 years of their index knee OA diagnosis. This represents a 2- to 3-fold increase when compared to the Cohort Hip and Cohort Knee (CHECK) study (2.5% TKA incidence over 6 years) and the UK Clinical Practice Research Datalink (4.4% over 6 years).[22,23] Collins et al[24] reported slightly greater TKA incidence with the Osteoarthritis Initiative dataset (11% over 7 years), although their analyses included an established OA cohort with half of the sample having Kellgren-Lawrence grade 3 or 4 changes at baseline. We suggest that perhaps the matching process used in the current study resulted in a greater density of higher-risk participants used in our analyses. For example, if the Depression + Obesity group had a greater comorbidity burden

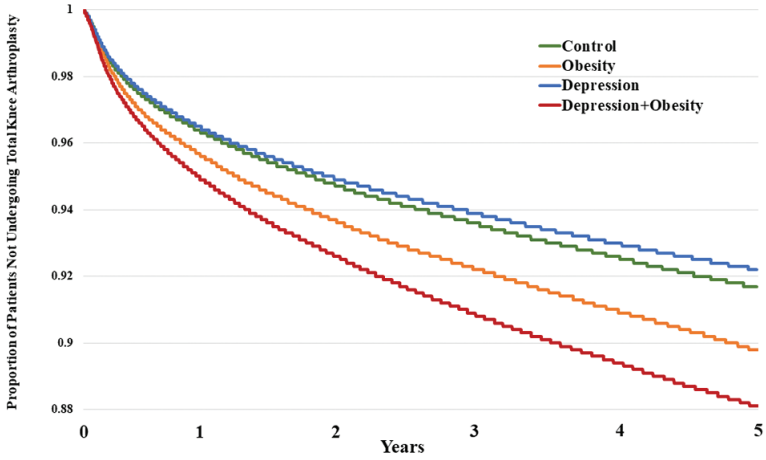

Figure 2. Kaplan-Meier survival curves comparing the incidence of subsequent total knee arthroplasty in the first 5 years after knee osteoarthritis diagnosis between groups of patients with or without comorbid obesity and/or depression.

than the Control group prior to matching, the matching process would have created a Control group in the current study that may be more medically complicated than a true control. Future work is necessary to determine not only the generalizability of these results but also to externally validate these findings in other cohorts and/or populations.

Common to all insurance claims database studies, the results can be affected by coding variability. CPT and ICD-9 codes do not indicate laterality, so we cannot definitively determine if the same knee that had the index OA diagnosis underwent subsequent TKA. We are also limited by only being able to use diagnosis codes to identify the prevalence of OA, obesity, and depression. We could not identify the presence of depressive symptoms in the absence of depression diagnosis, nor did we have exact BMI data. Radiographic data, BMI, and depression screening questionnaires are not available as part of the claims database. Further, with countless providers involved with the more than 1 million individuals in this study, there is undoubtedly variability in the clinical criteria used for diagnosing OA and depression between providers. Because we relied on a diagnostic code for depression, it is likely that the prevalence of depression is underrepresented in the current study, as depression is underdiagnosed and undertreated in older adults and those with OA.[25] Thus, it is possible that some participants in the nondepression control groups were misclassified, which could bias results toward the null. Also, although patients were categorized into groups based on the presence of depression diagnoses that preceded the initial knee OA diagnosis, we did not evaluate whether increased time between depression and OA diagnosis influenced the incidence of subsequent TKA. Finally, we were unable to perform interaction analyses to further assess the interplay between depression and obesity due to the limited statistical analytical methods that are available within the PearlDiver platform.

In conclusion, the 5-year incidence of TKA in our study was significantly greater for those with knee OA plus the combination of comorbid depression and obesity than those without either comorbidity or those with each comorbidity individually. Future studies are necessary to further elucidate whether pain behaviors, biological factors, and/or lifestyle differences, such as diet and exercise, may contribute to the increased incidence of TKA for those with comorbid depression and obesity, and to develop targeted interventions for this subset at greatest risk of undergoing TKA.

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