ANNALISA NA, DPT, PhD[1-3] • LAURA M. OPPERMANN, PT, DPT[4] • DANIEL C. JUPITER, PhD[2,5]
RONALD W. LINDSEY, MD[2] • ROGELIO A. CORONADO, PT, PhD[6-8]

Diabetes Mellitus Blunts the Symptoms, Physical Function, and Health-Related Quality of Life Benefits of Total Knee Arthroplasty: A Systematic Review With Meta-analysis of Data From More Than 17 000 Patients

OBJECTIVE: To compare physical function, pain, impairments (stiffness, range of motion, and strength), and health-related quality of life (HRQoL) outcomes between patients with and without diabetes mellitus, before and after a total knee arthroplasty (TKA).

DESIGN: Prognosis systematic review.

LITERATURE SEARCH: We searched MEDLINE/PubMed, CINAHL, SPORTDiscus, and Web of Science to August 2019.

STUDY SELECTION CRITERIA: We included longitudinal studies that examined physical function, pain, impairments, and HRQoL outcomes among patients receiving a TKA and with or without diabetes.

DATA SYNTHESIS: For quantitative synthesis, we stratified outcomes based on time relative to TKA: preoperative, less than 1 year after a TKA (early postoperative), and 1 year or more after a TKA (late postoperative). We used random-effects meta-analysis to calculate standardized mean differences (SMDs) and 95% confidence intervals (CIs). We used the Grading of Recommendations Assessment, Development and Evaluation system for qualitative synthesis.

RESULTS: We included 21 studies (n = 17 472 patients). Patients with diabetes mellitus had worse preoperative physical function (SMD, −0.16; 95% CI: −0.24, −0.08) and HRQoL (SMD, −0.16; 95% CI: −0.26, −0.05), worse early postoperative pain (SMD, −0.22; 95% CI: −0.39, −0.05) and strength (SMD, −0.45; 95% CI: −0.77, −0.14), and worse late postoperative physical function (SMD, −0.23; 95% CI: −0.40, −0.06), range of motion (SMD, −0.23; 95% CI: −0.46, 0.00), and HRQoL (SMD, −0.19; 95% CI: −0.29, −0.08) than patients without diabetes mellitus. The overall risk of bias across studies was high, and the certainty of evidence ranged from low to very low.

CONCLUSION: Patients with diabetes mellitus had worse patient-reported and clinician-assessed outcomes before and after a TKA. Given the limitations of included studies, these results may change with future research. *J Orthop Sports Phys Ther 2021;51(6):269-280. Epub 19 Apr 2021. doi:10.2519/jospt.2021.9515*

KEY WORDS: *comorbidity, lower extremity, outcomes, replacement*

The coexistence of diabetes mellitus and arthritis is a leading cause of functional deficits in older adults.[19,24,51] In the United States, the prevalence of arthritis among adults with diabetes mellitus is approximately 50%.[10] Diabetes mellitus can accelerate joint degeneration,[39] leading to rapid disease progression that limits range of motion (ROM), inhibits strength, worsens arthritis symptoms (eg, pain and stiffness), and perpetuates loss of physical function. Total knee arthroplasty (TKA) is often indicated to improve physical function and mobility.[17,28] However, the physiological stress response of surgery, compounded with diabetes mellitus pathogenesis, can elevate glucose levels, increase the risk of complications, impair healing, and attenuate postoperative gains.[2,38] Patients with

[1]Division of Rehabilitation Sciences, The University of Texas Medical Branch, Galveston, TX. [2]Department of Orthopaedic Surgery and Rehabilitation, The University of Texas Medical Branch, Galveston, TX. [3]Department of Physical Therapy and Rehabilitation Sciences, Drexel University, Philadelphia, PA. [4]Department of Physical Therapy, The University of Texas Medical Branch, Galveston, TX. [5]Department of Preventive Medicine and Population Health, The University of Texas Medical Branch, Galveston, TX. [6]Department of Orthopaedic Surgery, Vanderbilt University Medical Center, Nashville, TN. [7]Center for Musculoskeletal Research, Vanderbilt University Medical Center, Nashville, TN. [8]Department of Physical Medicine and Rehabilitation, Vanderbilt University Medical Center, Nashville, TN. At the time of this work, Dr Na received funding from the Foundation for Physical Therapy Research and postdoctoral fellowship funding from the Interdisciplinary Rehabilitation Research Training Program of the National Institute on Disability, Independent Living, and Rehabilitation Research (US Department of Health and Human Services' Administration for Community Living; number 90AR5009). Dr Coronado received funding from a US National Institutes of Health Rehabilitation Research Career Development Program grant (number K12 HD055929). The authors certify that they have no affiliations with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the article. Address correspondence to Dr Annalisa Na, Department of Physical Therapy and Rehabilitation Sciences, Drexel University, 1601 Cherry Street, Philadelphia, PA 19102. E-mail: An838@drexel.edu

diabetes mellitus may be realizing fewer TKA benefits while being subjected to greater risks than those without diabetes mellitus.

A previous systematic review[55] identified an increased risk for complications and worse function (measured with the Knee Society Score [KSS]) among patients with diabetes mellitus compared to patients without diabetes mellitus. However, it is unclear whether diabetes mellitus also has negative effects on other key patient-reported outcome measures, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[27] or clinical measures of knee symptoms and impairments. We consider improvements in knee symptoms (eg, pain, stiffness), strength, ROM, and health-related quality of life (HRQoL) as hallmarks of successful TKA, given their strong associations with function.

Summary evidence to guide discussion about prognosis and patients' expectations would facilitate shared decision making between clinicians and patients with diabetes mellitus. The purpose of our systematic review with meta-analysis was to compare physical function, pain, impairments (stiffness, ROM, and strength), and HRQoL outcomes between patients with and without diabetes mellitus, before and after a TKA.

METHODS

The reporting of this systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[35]

Data Sources

We searched MEDLINE/PubMed, CINAHL, SPORTDiscus, and Web of Science from database inception to April 2018. We repeated the search in December 2018 and August 2019 to identify any new articles. Reference lists were hand searched to identify articles that were missed in the database search.

Eligibility Criteria

Peer-reviewed manuscripts that met the criteria for study design, population, exposure, and outcomes were included. Included studies had cohort or case-control designs and examined the influence of diabetes mellitus on function, pain, impairments (stiffness, ROM, and strength), and HRQoL outcomes before and after TKA. The exposure variable, diabetes mellitus, was confirmed with medical records (eg, International Classification of Diseases [ICD] codes) or laboratory tests (eg, blood glucose).

Search Strategy

Population, exposure, and outcomes defined the systematic search. When applicable, medical subject headings or key terms were used and adapted to each database (the PubMed search is displayed in **APPENDIX A**, available at www.jospt.org). Search results were imported into and managed in Mendeley Version 1.19.2 (Elsevier, Amsterdam, the Netherlands).

Study Selection

Two reviewers independently screened titles, abstracts, and full-text articles for eligibility. Disagreements were resolved by consensus or by a third reviewer if consensus could not be reached. Reasons for full-text exclusions were recorded.

Quality Assessment

Two reviewers independently assessed study quality using the Newcastle-Ottawa scale (NOS). Disagreements were resolved by consensus or by a third reviewer if consensus could not be reached.

The NOS comprises 8 items to assess selection (4 items), comparability (1 item), and exposure/outcome (3 items). Fulfilled criteria received a star, with a maximum of 4 for selection, 2 for comparability, and 3 for exposure/outcome. For comparability, we selected body mass index (BMI), a leading risk factor for poor outcomes for both diabetes mellitus and arthroplasty,[13,30] as a primary covariate, so that studies controlling for BMI were given a star. Other study covariates warranted a second comparability star. Studies with 3 or more stars for selection, 1 or more for comparability, and 2 or more for outcome were considered to be of good quality. Studies with 2 stars for selection, 1 or 2 stars for comparability, and 2 or 3 stars for outcome were considered to be of fair quality. Those studies with fewer stars were considered to be of poor quality.[41] Interexaminer reliability was assessed with Cohen's kappa (less than 0.60, weak; 0.60-0.79, moderate; and 0.80 or greater, strong).[31]

Data Extraction

Two reviewers independently extracted the following data items from each included study: country, objectives, design, surgery, diabetes mellitus indicator, sample size, criteria, age, BMI, sex, follow-up period, and statistical analyses. Summary data (eg, means, SDs) for physical function, pain, stiffness, ROM, strength, and HRQoL were extracted. We stratified outcome data as preoperative, early postoperative (less than 1 year post TKA), or late postoperative (1 year or more post TKA) to account for potential plateaued functional recovery within the first postoperative year.[33]

Data Analysis

We established a hierarchy for outcome analysis and data synthesis to account for studies that reported more than 1 measure per outcome and shared the same time relative to surgery (preoperative, early postoperative, and late postoperative). When appropriate, we prioritized patient-reported measures over clinician-based measures, psychometric properties reported in the literature,[45] the number of studies sharing the same measure, and measures of cumulative versus single measurement (eg, total ROM versus flexion only). The hierarchy for each outcome is reported in **APPENDIX B** (available at www.jospt.org).

The quantitative synthesis was a random-effects meta-analysis for each outcome reported by more than 1 study within each time-point subgroup (preoperative, early postoperative, and late

postoperative). When necessary, SDs were computed from the standard error of the mean.[20] All outcome measures were scaled so that larger values suggested better outcomes. We calculated standardized mean differences (SMDs) and 95% confidence intervals (CIs) to compare outcomes between patients with and without diabetes mellitus. A positive SMD indicated superior outcomes for the diabetes mellitus group compared to the non–diabetes mellitus group. We assessed statistical heterogeneity using the I^2 statistic,[20] in which a score of less than 40% indicates low heterogeneity and a score of 40% or greater suggests high heterogeneity.

For individual studies with data that were not pooled, we calculated effect sizes and interpreted them, per Cohen's *d*, as negligible (less than 0.20), small (0.20-0.49), medium (0.50-0.79), or large (0.80 or greater).[43]

For qualitative synthesis, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria to determine whether the certainty of evidence was high, moderate, low, or very low. The rating was specific to the body of studies reviewed for each outcome (physical function, pain, impairments, and HRQoL) and at each time point (preoperative, early postoperative, and late postoperative). The certainty of evidence was first rated based on study design. A high rating was given when most studies (greater than 50%) had randomized designs. A low rating was given when most studies were observational trials. Ratings were upgraded when effect sizes were very large or downgraded based on study limitations, inconsistencies, indirectness, imprecision, and publication biases.[4,18]

Study limitations were assessed and downgraded based on NOS scores. For outcomes with only good-quality studies, limitations were rated as not serious and were not downgraded. For outcomes with any number of fair- or poor-quality studies, limitations were rated as serious and downgraded 1 level. Outcomes with mostly poor-quality studies (ie, 50% or greater) were rated as very serious and downgraded 2 levels.

The remaining factors of inconsistencies, indirectness, imprecision, and publication biases were rated at 2 levels. A minor or no violation across most studies received a "not serious" designation and was not downgraded, whereas a violation of the criteria by most studies was rated as "serious" and downgraded 1 level. For outcomes with half the studies suggesting that we downgrade a factor and half of the studies suggesting that we not downgrade, we prioritized the studies that were meta-analyzed.

Inconsistencies were considered serious and downgraded when the 95% CIs between most studies did not overlap. Indirectness was considered serious and downgraded when most studies differed in population, intervention, and outcome. Population differences were evaluated by diabetes mellitus diagnosis and definition (type 2 diabetes mellitus versus type 1 diabetes mellitus and diagnostic confirmation via chart review or medical history versus laboratory testing). Intervention differences were evaluated by type of surgery (primary versus secondary) and by how bilateral TKAs and postoperative complications were managed. Outcome differences were based on how measures were managed. For example, HRQoL can be scored and measured as physical only, emotional only, or a combination of the two, depending on the measurement. Inconsistencies and indirectness required 2 or more studies; therefore, an outcome with 1 study was marked as not applicable. Imprecision was considered serious and downgraded when, in most studies, 95% CIs were not reported, unable to be calculated, or deemed significant but crossed zero. Publication biases were considered serious and downgraded for retrospective designs.

RESULTS

Of 2132 studies identified and screened, 21 met eligibility criteria (**FIGURE 1**) and yielded 17472 pa-

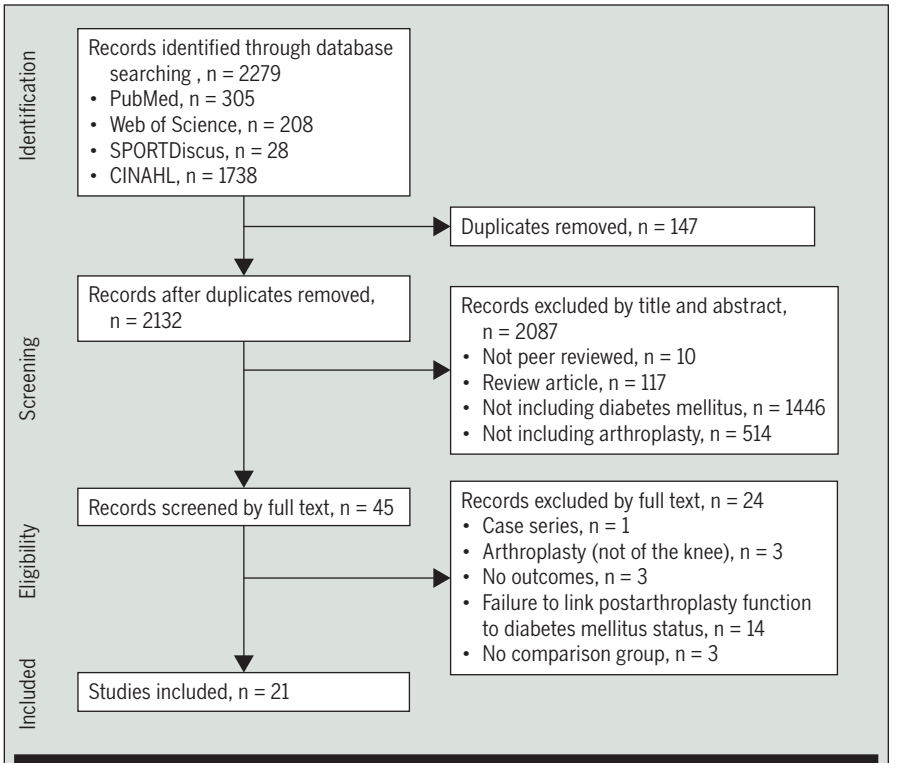


FIGURE 1. Flow chart of the study-selection process.

tients. Mean ages ranged from 64 to 73 years and mean BMIs ranged from 22.0 to 38.5 kg/m^2. Eighteen studies reported the sex of patients, of whom 6046 (62%) were female. Ten studies were conducted in the United States (67% of the total patient sample), 3 in Canada (5%), 4 in the United Kingdom (21%), and 1 each in Singapore (5%), Korea (2%), Finland (less than 1%), and Japan (less than 1%) (**APPENDIX C**, available at www.jospt.org).

Quality Assessment

Per the NOS, 12 studies (57%) were of good quality and 9 studies were of poor quality[41] (**TABLE 1**). Three studies were prospective,[3,22,44] 10 studies involved retrospective data,[11,26,29,32,36,41,47,48,53,54] and 8 studies recruited participants from databases but completed prospective follow-ups.[9,12,14,15,25,49,50,52] Nine studies controlled for BMI.[9,14,15,22,25,41,44,47,50] Diabetes mellitus was defined via documented diagnosis in 11 studies,[3,11,12,14,15,22,32,41,47,48,54] ICD-9 codes in 3 studies,[29,49,50] hemoglobin A1c in 6 studies,[9,25,26,36,44,53] and random blood glucose in 1 study.[52] Postoperative follow-up was early in 6 studies and late in 18 studies. Late postoperative follow-up occurred at 1 year in 8 studies,[9,12,14,15,26,29,32,53] at 2 years in 3 studies,[43,50,52] at 3 years in 1 study,[22] and between 1 and 14 years in 9 studies.[9,25,32,36,41,47-50] Interexaminer reliability for NOS scoring was strong for selection (κ = 0.87) and comparability (κ = 0.87) and moderate for exposure/outcome (κ = 0.75).

Study designs were observational; therefore, GRADE ratings of outcomes with 2 or more studies started at low quality for each outcome. Additional limitations, inconsistencies, indirectness, imprecision, and/or publication biases resulted in downgraded GRADE ratings (**TABLE 2**).

TABLE 1 Quality Index per the Newcastle-Ottawa Scale for Observational Studies[a]

Study	Selection	Comparability	Exposure/ Outcome	Score	Quality
Amusat et al[3]	3	1	1	5	Poor
Brock et al[9]	4	2	2	8	Good
Cheuy et al[11]	3	2	3	8	Good
Clement et al[12]	4	1	2	7	Good
Fisher et al[14]	3	2	3	8	Good
Gandhi et al[15]	4	2	3	9	Good
Jones et al[22]	4	2	1	7	Poor
Lavernia et al[25]	4	2	2	8	Good
Lenguerrand et al[26]	4	2	2	8	Good
Magone et al[29]	4	1	2	7	Good
Meding et al[32]	4	0	3	7	Poor
Moon et al[36]	4	2	3	9	Good
Papagelopoulos et al[41]	4	2	2	8	Good
Rajamäki et al[44]	3	2	1	6	Poor
Robertson et al[47]	3	2	2	7	Good
Serna et al[48]	4	1	1	6	Poor
Singh[49]	1	1	1	3	Poor
Singh and Lewallen[50]	4	2	1	7	Poor
Teo et al[52]	4	0	3	7	Poor
Wada et al[53]	4	2	3	9	Good
Wang et al[54]	1	0	2	3	Poor

[a]*Values are number of stars (selection, 0-4; comparability, 0-2; exposure/outcome, 0-3; overall score, 0-9).*

Preoperative Physical Function

Preoperative physical function differences between patients with and without diabetes mellitus were reported by 11 studies using 6 questionnaires[3,11,12,26,32,36,41,47,50,52,53] (**APPENDIX D**, available at www.jospt.org). Nine of the 11 studies had adequate data for pooling and included 2 good-quality studies[11,26] and 1 poor-quality study[3] that reported WOMAC function scores, 1 good-quality study[12] and 1 poor-quality study[52] that reported Oxford Knee Score (OKS) scores, 3 good-quality studies[36,41,47] that reported KSS function scores, and 1 good-quality study that reported scores from the new KSS function scale.[53] There was low-certainty evidence that patients with diabetes mellitus had significantly worse preoperative function than those without diabetes mellitus (SMD, −0.16; 95% CI: −0.24, −0.08; I^2 = 13.9%) (**FIGURE 2**). Two poor-quality studies had inadequate data and were not pooled.[32,50] We downgraded the evidence because of the number of low-quality studies and retrospective designs (**TABLE 2**).

Preoperative Pain, Impairments, and HRQoL

Preoperative pain was reported in 6 studies using 5 measures,[3,11,26,32,36,44] stiffness in 2 studies using 1 measure,[11,26] ROM in 5 studies with 4 techniques,[11,15,47,52,53] strength in 2 studies with 2 techniques,[11,53] and HRQoL in 3 studies using 3 measures[3,12,52] (**APPENDIX E**, available at www.jospt.org).

Preoperative HRQoL meta-analysis included 1 good-quality study using the Medical Outcomes Study 12-Item Short-Form Health Survey (SF-12),[12] 1 poor-quality study using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36),[52] and 1 poor-quality study using the Health Utilities Index Mark 3.[3] There was very low–certainty evidence that patients with diabetes mellitus had significantly worse preoperative HRQoL than those without diabetes mellitus (SMD, −0.16; 95% CI: −0.26, −0.05; I^2 = 0%) (**FIGURE 3**). We downgraded the evidence given poor study qualities, population differences, and retrospective designs (**TABLE 2**).

There was low-certainty evidence (**TABLE 2**) for no difference in preoperative pain (SMD, −0.07; 95% CI: −0.20, 0.06), stiffness (SMD, −0.03; 95% CI: −0.25, 0.18), ROM (SMD, −0.06; 95% CI: −0.20, 0.08), or strength (SMD, 0.10; 95% CI: −0.21, 0.42) between patients with and without diabetes mellitus. Meta-analysis of preoperative pain included 2 good-quality studies[11,26] and 1 poor-quality study[3] that used the WOMAC pain subscale and 1 good-quality study[36] that used the KSS pain subscale (**FIGURE 4**). Heterogeneity was low (I^2 = 0%). Pain data not pooled included the WOMAC pain subscale from 1 good-quality study[9] and 1 poor-quality study[22] due to inadequate data.

Meta-analysis of preoperative WOMAC stiffness scores included 2 good-quality studies.[11,26] Heterogeneity among the pooled studies was low (I^2 = 0%). Meta-analysis of preoperative knee extension strength included 2 good-quality studies.[11,53] Heterogeneity among the pooled studies was low (I^2 = 0%). Meta-analysis of preoperative ROM (**FIGURE 5**) included 2 good-quality studies reporting total ROM[11,47] and 1 good-quality study[53] and 1 poor-quality study[52] reporting flexion ROM. Heterogeneity among the pooled studies was low (I^2 = 27%). One poor-quality study reporting flexion ROM was not pooled due to the lack of appropriate data[15] (**APPENDIX G**, available at www.jospt.org). We downgraded the evidence given the variability in diabetes mellitus definitions (eg, diabetes mellitus with[3,26] versus without laboratory value confirmations[11]), mechanisms of TKAs (ie, primary[32] versus nonprimary[36] TKAs), and limited number of studies that were mostly of poor quality for each outcome (**TABLE 2**).

Early Postoperative Physical Function

Early postoperative physical function differences between patients with and

TABLE 2 GRADE Evidence Profile

Time Point/Outcome	Studies, n	Limitation[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication Bias[e]	GRADE Score[f]
Pre TKA							
Physical function	11	Serious	Not serious	Not serious	Not serious	Serious	Low
Pain	6	Serious	Not serious	Not serious	Not serious	Serious	Low
Stiffness	2	Not serious	Not serious	Not serious	Serious	Serious	Low
Range of motion	5	Serious	Not serious	Not serious	Not serious	Serious	Low
Strength	2	Not serious	Not serious	Not serious	Serious	Serious	Low
HRQoL	3	Very serious	Not serious	Serious	Serious	Serious	Very low
Early post TKA							
Physical function	6	Serious	Serious	Not serious	Serious	Serious	Very low
Pain	5	Very serious	Not serious	Not serious	Serious	Serious	Very low
Stiffness	2	Not serious	Serious	Not serious	Serious	Serious	Very low
Range of motion	3	Not serious	Serious	Not serious	Not serious	Serious	Low
Strength	2	Not serious	Not serious	Not serious	Not serious	Serious	Low
HRQoL	1	Very serious	NA	NA	NA	Not serious	Low
Late post TKA							
Physical function	12	Serious	Serious	Not serious	Serious	Serious	Very low
Pain	6	Serious	Serious	Serious	Serious	Serious	Very low
Stiffness	2	Not serious	Serious	Not serious	Serious	Serious	Very low
Range of motion	5	Serious	Serious	Not serious	Not serious	Serious	Very low
Strength	1	Not serious	NA	NA	NA	Serious	Low
HRQoL	5	Serious	Not serious	Serious	Serious	Serious	Very low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; NA, not applicable; TKA, total knee arthroplasty.

[a] *Methodological quality of studies was assessed by the Newcastle-Ottawa scale, with a 1-level downgrade for any number of fair- or poor-quality studies and a 2-level downgrade for 50% or greater poor-quality studies.*

[b] *Point estimates varied widely across studies; downgrade for confidence intervals showing minimal or no overlap or, when appropriate, if $I^2 \geq 40\%$.*[21]

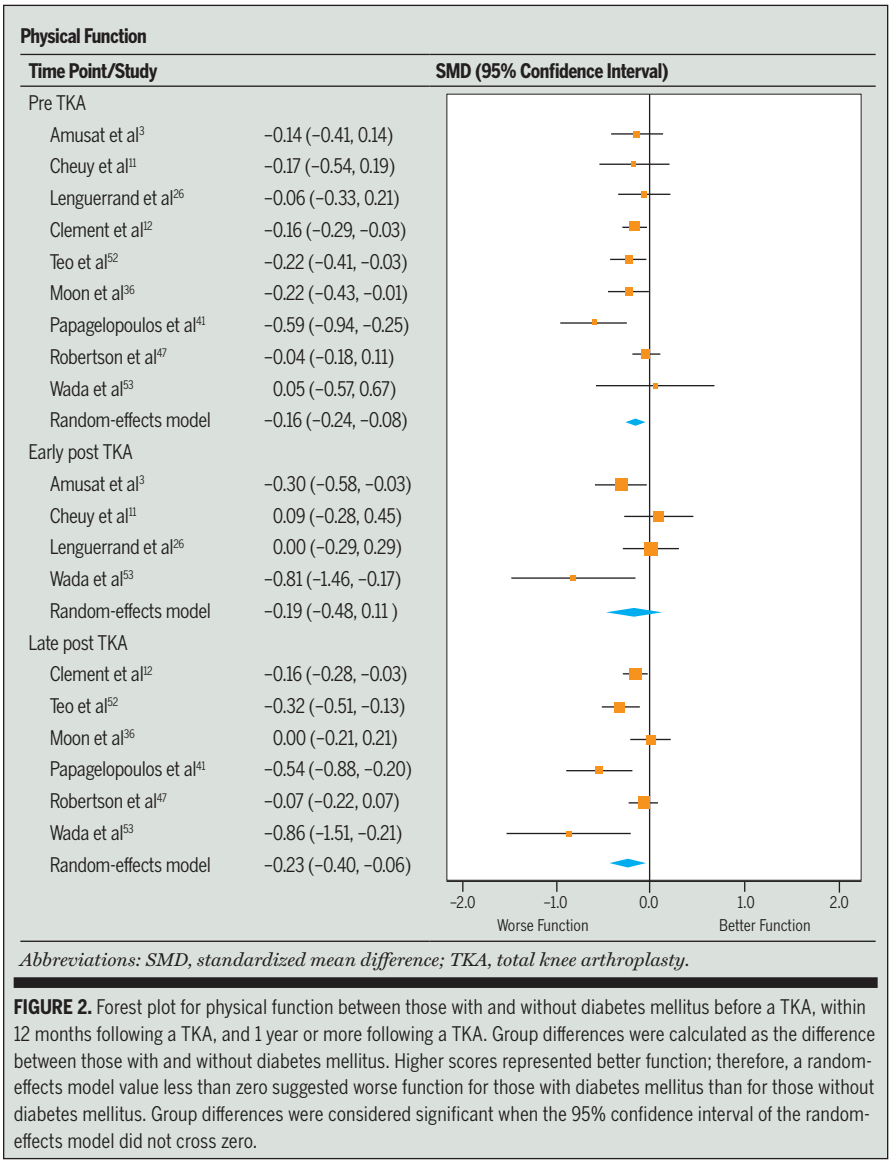
[c] *Assess population, intervention, and outcome measure; downgrade for differences between studies.*

[d] *The 95% confidence interval is unable to be calculated, or a wide interval represents different conclusions.*

[e] *Potential selection or recruitment bias from a previous study or retrospective database.*

[f] *The outcome of the GRADE rating is defined in 4 categories, based on the confidence in estimated effects and the need for future research to change the estimated effects: high, very confident; moderate, moderately confident but the estimated effect is likely to change; low, limited confidence and the estimated effect is very likely to change; very low, little confidence and the estimated effect is very likely to change.*[16]

without diabetes mellitus were examined by 6 studies using 4 questionnaires, from 5 days to 6 months following surgery[3,11,22,26,53,54] (**APPENDIX D**). Four of the 6 studies had adequate data for pooling. The 4 studies included 2 good-quality studies[11,26] and 1 poor-quality study[3] using the WOMAC function subscale and 1 good-quality study using the physical function subscale of the new KSS.[53] There was very low–certainty evidence (**TABLE 2**) for no difference in early postoperative physical function (SMD, −0.19; 95% CI: −0.48, 0.11; I^2 = 63.8%) (**FIGURE 2**). One poor-quality study[22] was not pooled because follow-up time for postoperative WOMAC function ranged between 6 months and 3 years, precluding differentiation between early and late postoperative periods. Other early postoperative studies that were not pooled included 1 poor-quality study[54] examining Functional Independence Measure motor scores, due to the lack of data reported, and a good-quality study[11] that examined physical performance (ie, timed up and go and 30-second sit-to-stand), because its WOMAC function scores were already pooled. We downgraded the evidence given the heterogeneity, high number of low-quality studies, retrospective designs, and mixed findings (**TABLE 2**).



Abbreviations: SMD, standardized mean difference; TKA, total knee arthroplasty.

FIGURE 2. Forest plot for physical function between those with and without diabetes mellitus before a TKA, within 12 months following a TKA, and 1 year or more following a TKA. Group differences were calculated as the difference between those with and without diabetes mellitus. Higher scores represented better function; therefore, a random-effects model value less than zero suggested worse function for those with diabetes mellitus than for those without diabetes mellitus. Group differences were considered significant when the 95% confidence interval of the random-effects model did not cross zero.

Early Postoperative Pain, Impairments, and HRQoL

Early postoperative pain was reported in 5 studies with 3 measures,[3,11,22,26,32] strength in 2 studies using 2 techniques,[11,53] ROM in 3 studies using 4 techniques,[11,15,53] stiffness in 2 studies with 1 measure,[11,26] and HRQoL in 1 study with 1 measure[3] (**APPENDIX E**).

Meta-analysis was performed for 3-month WOMAC pain scores from 2 good-quality studies[11,26] and 1 poor-quality study.[3] There was very low–certainty evidence (**TABLE 2**) that patients with diabetes mellitus had significantly worse early postoperative pain than those without diabetes mellitus (SMD, −0.22; 95% CI: −0.39, −0.05; I^2 = 0%) (**FIGURE 4**). Three pain measures from 3 studies were not pooled. In 1 poor-quality study,[22] WOMAC pain scores between 6 months and 3 years were combined and were unable to be differentiated between early and late postoperative periods. In 1 poor-quality study,[32] KSS pain data were inadequate and not pooled (**APPENDIX E**). Data from 1 good-quality study[26] included both WOMAC pain and visual analog scale (VAS) scores; therefore, VAS results were excluded. Effect sizes for the nonpooled studies ranged between small and negligible (d = 0.31-0.15). We downgraded the evidence for early postoperative pain given the poor study qualities, retrospective designs, and small to negligible effect sizes (**TABLE 2**).

Early postoperative knee extension strength was pooled from 2 good-quality studies.[11,53] There was low-certainty evidence (**TABLE 2**) that patients with diabetes mellitus had significantly worse early postoperative strength than those without diabetes mellitus (SMD, −0.45; 95% CI: −0.77, −0.14; I^2 = 0%) (**FIGURE 6**). We downgraded the evidence given the retrospective study designs, risk of publication biases, and different measurement and normalization methods (**TABLE 2**).

Early postoperative ROM was pooled from 2 good-quality studies.[11,53] There

was low-certainty evidence (**TABLE 2**) for no significant group differences for early postoperative ROM (SMD, −0.26; 95% CI: −0.73, 0.22; I^2 = 45.3%). Nonpooled studies included 1 good-quality study[15] with insufficient data that reported a higher proportion of patients with diabetes mellitus than those without diabetes mellitus who did not achieve a 90° flexion cutoff at 6 weeks. We downgraded the evidence given the high heterogeneity and retrospective designs among the studies.

Early postoperative WOMAC stiffness scores were pooled from 2 good-quality studies.[11,26] There was very low–certainty evidence (**TABLE 2**) for no significant group differences (SMD, −0.94; 95% CI: −2.89, 1.01; I^2 = 98.3%). We downgraded the evidence given the high heterogeneity, mixed findings, and retrospective design of the studies.

Early postoperative HRQoL from 1 poor-quality study[3] was worse for diabetes mellitus at 3 months, no different at 1 and 6 months, and had small to negligible effect sizes (d = 0.23-0.07) (**TABLE 2, APPENDIX E**).

Late Postoperative Physical Function

Late postoperative physical function differences between patients with and without diabetes mellitus were assessed by 12 studies using 6 measures, ranging from 1 to 14 years[9,12,22,26,32,36,41,47,48,50,52,53] post TKA (**APPENDIX D**), and physical function was worse overall for those with diabetes mellitus (**APPENDIX F**). Six of the 12 studies had adequate data for pooling. The 6 studies included 5 good-quality studies using the OKS[12] or KSS function scale[36,41,47,53] and 1 poor-quality study using the OKS.[52] There was very low–certainty evidence that patients with diabetes mellitus had significantly worse late postoperative function than those without diabetes mellitus (SMD, −0.23; 95% CI: −0.40, −0.06; I^2 = 74.6%) (**FIGURE 2**). The 6 studies with inadequate data for pooling included 2 good-quality studies using the WOMAC function subscale[9,26] and 4 poor-quality studies using the WOMAC function subscale,[22] KSS function scale,[32] Hospital for Special Surgery Knee Score function scale,[48] or the Mayo knee questionnaire[50] (**APPENDIX D**). All 6 studies not pooled reported worse postoperative physical function between 1 and 14 years after TKA in patients with diabetes mellitus than in those without diabetes mellitus (**APPENDIX F**). We downgraded the evidence given the large variability in follow-up time, retrospective study designs, variable diabetes mellitus definitions, and high heterogeneity (**TABLE 2**).

Late Postoperative Pain, Impairments, and HRQoL

Late postoperative ROM in 5 studies using 4 techniques,[14,15,47,52,53] stiffness in 2 studies with 1 measure,[9,26] pain in 6 studies

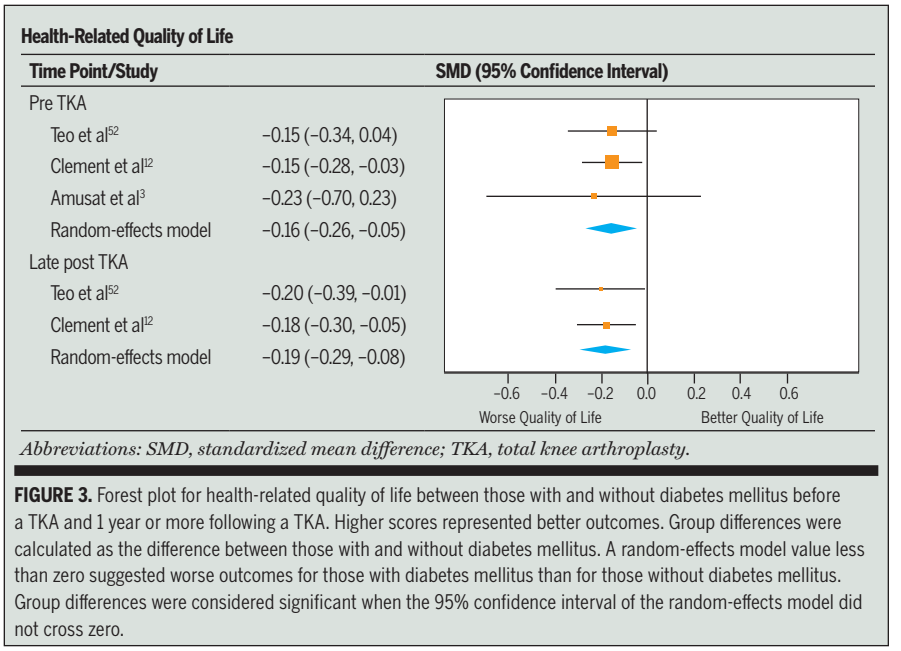


FIGURE 3. Forest plot for health-related quality of life between those with and without diabetes mellitus before a TKA and 1 year or more following a TKA. Higher scores represented better outcomes. Group differences were calculated as the difference between those with and without diabetes mellitus. A random-effects model value less than zero suggested worse outcomes for those with diabetes mellitus than for those without diabetes mellitus. Group differences were considered significant when the 95% confidence interval of the random-effects model did not cross zero.

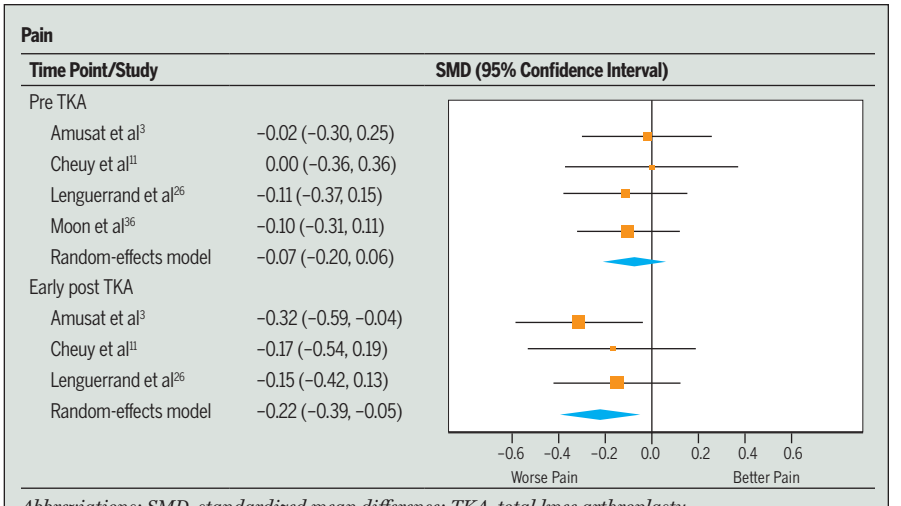


FIGURE 4. Forest plot for pain between those with and without diabetes mellitus before a TKA and within 12 months following a TKA. Higher scores represented better outcomes. Group differences were calculated as the difference between those with and without diabetes mellitus. A random-effects model value less than zero suggested worse outcomes for those with diabetes mellitus than for those without diabetes mellitus. Group differences were considered significant when the 95% confidence interval of the random-effects model did not cross zero.

with 5 measures,[9,22,26,32,36,44] strength in 1 study with 1 technique,[53] and HRQoL in 5 studies with 3 measures[9,12,29,49,52] were assessed between 1 and 10 years post TKA (**APPENDIX E**).

For late postoperative ROM, 1 good-quality study for total ROM,[47] 1 good-quality study for peak knee flexion,[53] and 1 poor-quality study for peak knee flexion[52] were pooled. There was very low–certainty evidence (**TABLE 2**) that patients with diabetes mellitus had significantly worse late postoperative ROM than those without diabetes mellitus (SMD, −0.23; 95% CI: −0.46, 0.00; I^2 = 62.4%). Two good-quality studies[14,15] were not pooled due to inadequate data; however, both reported less peak knee flexion at 1 year post TKA in patients with diabetes mellitus than in those without diabetes mellitus. Extension ranges were included in studies that reported flexion or total ROM; therefore, the data were not pooled. Nevertheless, extension data from 2 good-quality studies[47,53] were conflicting at 1 year, indicated worse ROM in those with diabetes mellitus at 5 and 10 years (**APPENDIX G**), and included wide 95% CIs and small effect sizes. We downgraded the evidence given the small effect sizes, wide 95% CIs, variability in methodology, and high heterogeneity (**TABLE 2**).

For late postoperative HRQoL, 1 good-quality study using the SF-12[12] and 1 poor-quality study using the SF-36[52] were pooled. There was very low–certainty evidence (**TABLE 2**) that patients with diabetes mellitus had worse late postoperative HRQoL than those without diabetes mellitus (SMD, −0.19; 95% CI: −0.29, −0.08; I^2 = 0%). For studies reporting physical component summary (PCS) and mental component summary scores, only PCS scores were extracted and compared. Health-related quality of life was worse for those with diabetes mellitus as measured by the PCS subscale of the SF-36 in 2 good-quality studies,[9,29] and there was no difference in 1 poor-quality study.[49] We downgraded the evidence given the variability in data, the number of poor-quality studies, and medium to small effect sizes of the non-pooled studies (**TABLE 2**).

Late postoperative pain and stiffness differences between those with and without diabetes mellitus were inconclusive because study data were insufficient for pooling and yielded mixed results.

For postoperative pain, 1 good-quality study[26] and 1 poor-quality study[22] using the WOMAC pain subscale, 1 poor-quality study using the KSS pain scale,[32] and 1 poor-quality study using painful joint status, persistent pain status, and the VAS for pain with movement[44] reported that patients with diabetes mellitus had worse late postoperative pain between 1 and 7 years post TKA than those without diabetes mellitus. Meanwhile, 1 good-quality study using the WOMAC pain subscale,[9] 1 good-quality study using the KSS pain scale,[36] and 1 poor-quality study using the VAS for pain at rest[44] reported no differ-

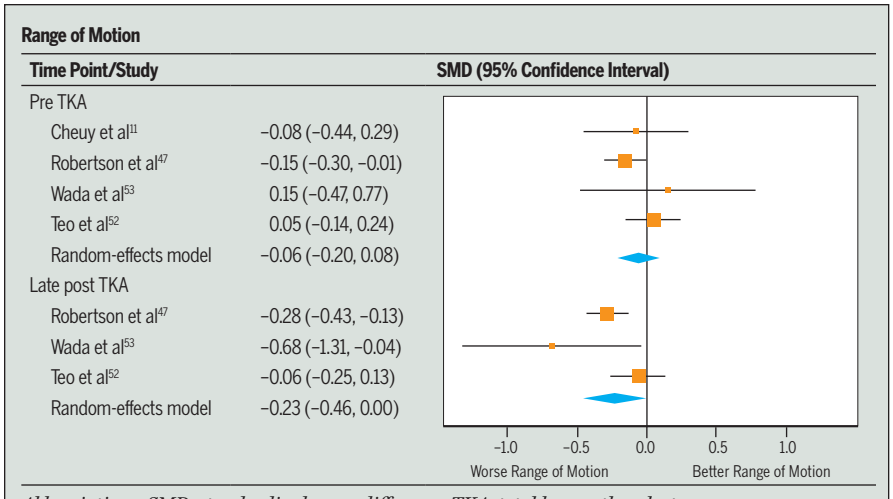


FIGURE 5. Forest plot for range of motion between those with and without diabetes mellitus before a TKA and 1 year or more following a TKA. Higher scores represented better outcomes. Group differences were calculated as the difference between those with and without diabetes mellitus. A random-effects model value less than zero suggested worse outcomes for those with diabetes mellitus than for those without diabetes mellitus. Group differences were considered significant when the 95% confidence interval of the random-effects model did not cross zero.

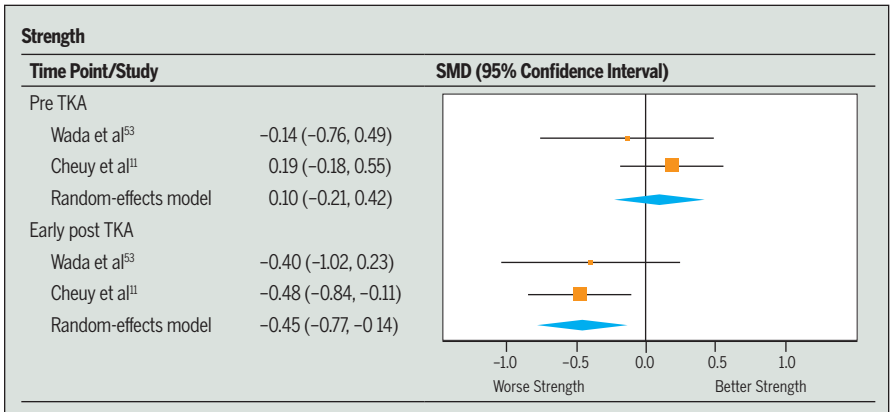


FIGURE 6. Forest plot for strength between those with and without diabetes mellitus before a TKA and within 12 months following a TKA. Higher scores represented better outcomes. Group differences were calculated as the difference between those with and without diabetes mellitus. A random-effects model value less than zero suggested worse outcomes for those with diabetes mellitus than for those without diabetes mellitus. Group differences were considered significant when the 95% confidence interval of the random-effects model did not cross zero.

ence. Postoperative stiffness at 1 year was reported by 2 good-quality studies that yielded conflicting results and were insufficient for pooling.[9,26] There was low- to very low–certainty evidence for each late postoperative pain and stiffness study. We downgraded the evidence given the number of poor-quality studies, insufficient data, and mixed findings.

Late postoperative strength at 1 year was assessed by 1 good-quality study[53] (**APPENDIX G**). There was low-certainty evidence for no group differences. We downgraded the evidence given the retrospective study design and associated biases (**TABLE 2**).

DISCUSSION

We found that when receiving a TKA, patients with diabetes mellitus had worse (1) preoperative physical function and HRQoL, (2) early postoperative pain and strength, and (3) late postoperative function, ROM, and HRQoL than patients without diabetes mellitus. Examining such outcomes for patients with diabetes mellitus is essential for developing and establishing effective TKA clinical recommendations. Patients with diabetes mellitus receiving a TKA are at higher risk for attenuated healing and complications that delay rehabilitation and impact outcomes.[55] However, the low to very low certainty of evidence, due to studies rated as poor quality by the NOS, retrospective designs, and heterogeneity, suggests high risk for bias and warrants robust future prospective studies. Regardless, these findings lay the groundwork for considering comorbid burdens in TKA clinical management and research in patients with diabetes mellitus.

Preoperative Physical Function and HRQoL

Worse preoperative function and HRQoL in patients with diabetes mellitus could suggest accelerated functional decline or delayed TKAs, potentially due to inadequate glycemic levels,[16] which can yield greater functional disability and lower quality of life. Recent studies reported that among the various preoperative presentations and subgroups, those with metabolic issues, which included diabetes mellitus, were often older and had worse outcomes than other patient types.[6,7,37] These findings should be considered in future studies to help guide arthritis management and preoperative clinical decisions.

Postoperative Physical Function

Our review provided additional data and updated findings that were consistent with a previous meta-analysis examining postoperative physical function differences between patients with and without diabetes mellitus.[55] Building on previous work, we found worse late postoperative physical function in patients with diabetes mellitus.[55]

Postoperative Pain, Strength, and ROM

Worse early postoperative pain and strength and late postoperative ROM were also associated with diabetes mellitus and may contribute to long-term functional limitations and worse HRQoL. We speculate that the physiological impacts of both surgery and diabetes mellitus may influence postoperative pain, strength, ROM, and function. Total knee arthroplasties in patients with diabetes mellitus can disrupt neurovascular processes, challenge the healing process, and attenuate postoperative gains.[2] Surgery can induce intraoperative physiological stress responses that tax glucose levels and homeostasis and increase complication risks.[2] Elevated blood glucose exposure can produce advanced glycation end products that increase collagen crosslinks.[1] These factors can attenuate tissue healing and increase scar tissue development that limits ROM gains and pain reduction. Long-term negative impacts can also attenuate strength gains and symptom reduction, making future research in this area warranted.

Fortunately, pain and ROM limitations that challenge functional gains are also responsive to rehabilitation. Postoperative rehabilitation may especially benefit these vulnerable patients by including targeted interventions for pain and ROM. Patients with diabetes mellitus may benefit from alternative strategies like the booster rehabilitation sessions provided for those with knee arthritis.[5,8] Among patients with diabetes mellitus, postoperative booster sessions may promote symptom reduction, improve function, and raise activity levels, which is also beneficial for managing glucose control. We did not study the impact of rehabilitation on TKA outcomes, as most studies did not report postoperative rehabilitation beyond a "standardized hospital protocol." Future studies must examine postoperative functional recovery to identify modifiable mechanisms, to classify a subgroup of patients at risk for long-term functional limitations, and to establish long-term strategies that positively impact function in patients with diabetes mellitus.

Limitations

Our systematic review was intentionally broad to ensure that we captured the breadth of the literature. We recognize that broad eligibility criteria increased study variability and decreased the certainty of the evidence for the examined outcomes. We have highlighted areas in our results where variability influenced the certainty of evidence. In addition, we only included studies that were published in English, did not register our protocol, and limited our data search to 4 databases. Excluding non-English studies and limiting searches to the reported databases and sources may introduce language bias and publication bias. A scoping search was completed in other databases but yielded a minimal number of studies that were already identified. Given that the reviewed papers were published between 1994 and 2018, surgical and rehabilitation changes can influence results and need to be considered. We also chose to define the early postoperative period as less than 12 months, which grouped studies with follow-ups ranging from 5 days to

less than 12 months.[3,11,26,54] This may contribute to inconclusive early postoperative findings, as functional recovery often starts with decreased function during the first month and is followed by improvements in subsequent months.[34] Early assessments with questionnaires like the WOMAC, which queries patients about kneeling, squatting, and running,[40] may subject outcomes to floor effects and limit group differences. Amusat et al[3] found no differences at 1 month, but worse function in the diabetes mellitus group at 3 and 6 months. The study by Cheuy et al[11] found no differences at 3 months using the WOMAC function subscale, but reported differences in physical performance at 3 months and was the only study that used both self-reported and performance assessments. Future studies should follow suit to determine whether findings are reproducible. Despite the limitations, our review highlights the complex pathophysiological relationships among diabetes mellitus, aging, joint degeneration, and TKA recovery. While these relationships warrant further research, our review and previous studies[6,7,37] suggest that TKA management is complicated by comorbidities.

CONCLUSION

Patients with diabetes mellitus had worse patient-reported and clinician-assessed outcomes before and after TKA compared to patients without diabetes mellitus. Given the methodological limitations of the reviewed studies, these results are likely to change with future research. ◉

KEY POINTS

FINDINGS: When receiving a total knee arthroplasty, patients with diabetes mellitus had worse (1) preoperative physical function and health-related quality of life, (2) early postoperative pain and strength, and (3) late postoperative function, range of motion, and health-related quality of life than patients without diabetes mellitus.

IMPLICATIONS: Postoperative rehabilitation for patients with diabetes mellitus receiving a total knee arthroplasty needs to account for comorbid burdens and long-term functional outcomes.

CAUTION: While the meta-analyses identified statistically significant group differences, the certainty of evidence based on these findings ranged between low and very low. Weak study designs, large variabilities in determinants of diabetes mellitus, and underlying pathology for a total knee arthroplasty must be considered when interpreting study results.

STUDY DETAILS

AUTHOR CONTRIBUTIONS: All coauthors made substantial scientific contributions to the study and manuscript. Drs Na and Coronado conceived and designed the study. Drs Na and Oppermann assessed study eligibility and performed data extraction and grading. Dr Na undertook data synthesis, with contributions from Drs Coronado and Jupiter. Dr Na wrote the first draft of the manuscript, and Drs Coronado, Oppermann, Jupiter, and Lindsey all made valuable scientific additions to the manuscript. All authors approved the final manuscript.

DATA SHARING: All data relevant to the study are included in the article or are available as online appendices.

PATIENT AND PUBLIC INVOLVEMENT: No patients were involved in the study.

REFERENCES

1. Abate M, Schiavone C, Salini V, Andia I. Management of limited joint mobility in diabetic patients. *Diabetes Metab Syndr Obes*. 2013;6:197-207. https://doi.org/10.2147/DMSO.S33943
2. Akiboye F, Rayman G. Management of hyperglycemia and diabetes in orthopedic surgery. *Curr Diab Rep*. 2017;17:13. https://doi.org/10.1007/s11892-017-0839-6
3. Amusat N, Beaupre L, Jhangri GS, et al. Diabetes that impacts on routine activities predicts slower recovery after total knee arthroplasty: an observational study. *J Physiother*. 2014;60:217-223. https://doi.org/10.1016/j.jphys.2014.09.006
4. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328:1490. https://doi.org/10.1136/bmj.328.7454.1490
5. Bennell KL, Kyriakides M, Hodges PW, Hinman RS. Effects of two physiotherapy booster sessions on outcomes with home exercise in people with knee osteoarthritis: a randomized controlled trial. *Arthritis Care Res (Hoboken)*. 2014;66:1680-1687. https://doi.org/10.1002/acr.22350
6. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. *Lancet*. 2011;377:2115-2126. https://doi.org/10.1016/S0140-6736(11)60243-2
7. Blanco FJ, Ruiz-Romero C. Osteoarthritis: metabolomic characterization of metabolic phenotypes in OA. *Nat Rev Rheumatol*. 2012;8:130-132. https://doi.org/10.1038/nrrheum.2012.11
8. Bove AM, Smith KJ, Bise CG, et al. Exercise, manual therapy, and booster sessions in knee osteoarthritis: cost-effectiveness analysis from a multicenter randomized controlled trial. *Phys Ther*. 2018;98:16-27. https://doi.org/10.1093/ptj/pzx104
9. Brock TM, Shirley M, Bardgett M, Walker M, Deehan DJ. Inadequate pre-operative glycaemic control in patients with diabetes mellitus adversely influences functional recovery after total knee arthroplasty: patients with impaired glycaemic control exhibit poorer functional outcomes at 1-year post-arthroplasty. *Knee Surg Sports Traumatol Arthrosc*. 2017;25:1801-1806. https://doi.org/10.1007/s00167-016-4249-0
10. Centers for Disease Control and Prevention. Arthritis as a potential barrier to physical activity among adults with diabetes—United States, 2005 and 2007. *MMWR Morb Mortal Wkly Rep*. 2008;57:486-489.
11. Cheuy VA, Loyd BJ, Hafner W, Kittelson AJ, Waugh D, Stevens-Lapsley JE. Influence of diabetes mellitus on the recovery trajectories of function, strength, and self-report measures after total knee arthroplasty. *Arthritis Care Res (Hoboken)*. 2019;71:1059-1067. https://doi.org/10.1002/acr.23741
12. Clement ND, MacDonald D, Burnett R, Breusch SJ. Diabetes does not influence the early outcome of total knee replacement: a prospective study assessing the Oxford knee score, short form 12, and patient satisfaction. *Knee*. 2013;20:437-441. https://doi.org/10.1016/j.knee.2013.07.009
13. Davis AM, Wood AM, Keenan AC, Brenkel IJ, Ballantyne JA. Does body mass index affect clinical outcome post-operatively and at five years after primary unilateral total hip replacement performed for osteoarthritis? A multivariate analysis of prospective data. *J Bone Joint Surg Br*. 2011;93:1178-1182. https://doi.org/10.1302/0301-620X.93B9.26873
14. Fisher DA, Dierckman B, Watts MR, Davis K. Looks good but feels bad: factors that contribute to poor results after total knee arthroplasty. *J Arthroplasty*. 2007;22:39-42. https://doi.org/10.1016/j.arth.2007.04.011
15. Gandhi R, de Beer J, Leone J, Petruccelli D,

Winemaker M, Adili A. Predictive risk factors for stiff knees in total knee arthroplasty. *J Arthroplasty*. 2006;21:46-52. https://doi.org/10.1016/j.arth.2005.06.004

16. Giori NJ, Ellerbe LS, Bowe T, Gupta S, Harris AH. Many diabetic total joint arthroplasty candidates are unable to achieve a preoperative hemoglobin A1c goal of 7% or less. *J Bone Joint Surg Am*. 2014;96:500-504. https://doi.org/10.2106/JBJS.L.01631
17. Gossec L, Paternotte S, Maillefert JF, et al. The role of pain and functional impairment in the decision to recommend total joint replacement in hip and knee osteoarthritis: an international cross-sectional study of 1909 patients. Report of the OARSI-OMERACT Task Force on total joint replacement. *Osteoarthritis Cartilage*. 2011;19:147-154. https://doi.org/10.1016/j.joca.2010.10.025
18. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926. https://doi.org/10.1136/bmj.39489.470347.AD
19. Hawker GA, Croxford R, Bierman AS, et al. Osteoarthritis-related difficulty walking and risk for diabetes complications. *Osteoarthritis Cartilage*. 2017;25:67-75. https://doi.org/10.1016/j.joca.2016.08.003
20. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions*. Oxford, UK: The Cochrane Collaboration; 2011.
21. Hiyama Y, Wada O, Nakakita S, Mizuno K. Factors affecting mobility after knee arthroplasty. *J Knee Surg*. 2017;30:304-308. https://doi.org/10.1055/s-0036-1584562
22. Jones CA, Cox V, Jhangri GS, Suarez-Almazor ME. Delineating the impact of obesity and its relationship on recovery after total joint arthroplasties. *Osteoarthritis Cartilage*. 2012;20:511-518. https://doi.org/10.1016/j.joca.2012.02.637
23. Kim HJ, Lee HM, Kim HS, et al. Bone metabolism in postmenopausal women with lumbar spinal stenosis: analysis of bone mineral density and bone turnover markers. *Spine (Phila Pa 1976)*. 2008;33:2435-2439. https://doi.org/10.1097/BRS.0b013e3181829fca
24. King LK, Kendzerska T, Waugh EJ, Hawker GA. Impact of osteoarthritis on difficulty walking: a population-based study. *Arthritis Care Res (Hoboken)*. 2018;70:71-79. https://doi.org/10.1002/acr.23250
25. Lavernia CJ, Heiner AD, Villa JM, Alcerro JC, Rossi MD. Preoperative glycemic control on total joint arthroplasty patient-perceived outcomes and hospital costs. *J Arthroplasty*. 2017;32:6-10. https://doi.org/10.1016/j.arth.2016.07.002
26. Lenguerrand E, Beswick AD, Whitehouse MR, Wylde V, Blom AW. Outcomes following hip and knee replacement in diabetic versus nondiabetic patients and well versus poorly controlled diabetic patients: a prospective cohort study. *Acta Orthop*. 2018;89:399-405. https://doi.org/10.1080/17453674.2018.1473327
27. Lingard EA, Katz JN, Wright RJ, Wright EA, Sledge CB, Kinemax Outcomes Group. Validity and responsiveness of the Knee Society Clinical Rating System in comparison with the SF-36 and WOMAC. *J Bone Joint Surg Am*. 2001;83:1856-1864. https://doi.org/10.2106/00004623-200112000-00014
28. Löfvendahl S, Bizjajeva S, Ranstam J, Lidgren L. Indications for hip and knee replacement in Sweden. *J Eval Clin Pract*. 2011;17:251-260. https://doi.org/10.1111/j.1365-2753.2010.01430.x
29. Magone K, Kemker BP, 3rd, Pilipenko N, O'Connor E, Walter N, Atkinson T. The new surgical technique for improving total knee and hip arthroplasty outcomes: patient selection. *J Arthroplasty*. 2017;32:2070-2076. https://doi.org/10.1016/j.arth.2017.02.034
30. Martínez-Huedo MA, Jiménez-García R, Jiménez-Trujillo I, Hernández-Barrera V, del Rio Lopez B, López-de-Andrés A. Effect of type 2 diabetes on in-hospital postoperative complications and mortality after primary total hip and knee arthroplasty. *J Arthroplasty*. 2017;32:3729-3734.e2. https://doi.org/10.1016/j.arth.2017.06.038
31. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*. 2012;22:276-282. https://doi.org/10.11613/BM.2012.031
32. Meding JB, Reddleman K, Keating ME, et al. Total knee replacement in patients with diabetes mellitus. *Clin Orthop Relat Res*. 2003:208-216. https://doi.org/10.1097/01.blo.0000093002.90435.56
33. Mizner RL, Petterson SC, Clements KE, Zeni JA, Jr., Irrgang JJ, Snyder-Mackler L. Measuring functional improvement after total knee arthroplasty requires both performance-based and patient-report assessments: a longitudinal analysis of outcomes. *J Arthroplasty*. 2011;26:728-737. https://doi.org/10.1016/j.arth.2010.06.004
34. Mizner RL, Stevens JE, Snyder-Mackler L. Voluntary activation and decreased force production of the quadriceps femoris muscle after total knee arthroplasty. *Phys Ther*. 2003;83:359-365. https://doi.org/10.1093/ptj/83.4.359
35. Moher D, Shamseer L, Clarke M, et al. Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. https://doi.org/10.1186/2046-4053-4-1
36. Moon HK, Han CD, Yang IH, Cha BS. Factors affecting outcome after total knee arthroplasty in patients with diabetes mellitus. *Yonsei Med J*. 2008;49:129-137. https://doi.org/10.3349/ymj.2008.49.1.129
37. Na A, Jansky L, Gugala Z. Clinical characteristics of patients with type 2 diabetes mellitus receiving a primary total knee or hip arthroplasty. *J Diabetes Res*. 2019;2019:9459206. https://doi.org/10.1155/2019/9459206
38. Na A, Middleton A, Haas A, Graham JE, Ottenbacher KJ. Impact of diabetes on 90-day episodes of care after elective total joint arthroplasty among Medicare beneficiaries. *J Bone Joint Surg Am*. 2020;102:2157-2165. https://doi.org/10.2106/JBJS.20.00203
39. Neumann J, Guimaraes JB, Heilmeier U, et al. Diabetics show accelerated progression of knee cartilage and meniscal lesions: data from the Osteoarthritis Initiative. *Skeletal Radiol*. 2019;48:919-930. https://doi.org/10.1007/s00256-018-3088-0
40. Nilsdotter AK, Lohmander LS, Klässbo M, Roos EM. Hip disability and osteoarthritis outcome score (HOOS) – validity and responsiveness in total hip replacement. *BMC Musculoskelet Disord*. 2003;4:10. https://doi.org/10.1186/1471-2474-4-10
41. Papagelopoulos PJ, Idusuyi OB, Wallrichs SL, Morrey BF. Long term outcome and survivorship analysis of primary total knee arthroplasty in patients with diabetes mellitus. *Clin Orthop Relat Res*. 1996:124-132. https://doi.org/10.1097/00003086-199609000-00015
42. Penson DF, Krishnaswami S, Jules A, Seroogy JC, McPheeters ML. Evaluation and Treatment of Cryptorchidism. Rockville, MD: Agency for Healthcare Research and Quality; 2012.
43. Portney LG, Watkins MP. *Foundations of Clinical Research: Applications to Practice*. 2nd ed. Upper Saddle River, NJ: Prentice Hall Health; 2000.
44. Rajamäki TJ, Jämsen E, Puolakka PA, Nevalainen PI, Moilanen T. Diabetes is associated with persistent pain after hip and knee replacement. *Acta Orthop*. 2015;86:586-593. https://doi.org/10.3109/17453674.2015.1044389
45. Reynaud V, Verdilos A, Pereira B, Boisgard S, Costes F, Coudeyre E. Core outcome measurement instruments for clinical trials of total knee arthroplasty: a systematic review. *J Clin Med*. 2020;9:2439. https://doi.org/10.3390/jcm9082439
46. Robertson C, Archibald D, Avenell A, et al. Systematic reviews of and integrated report on the quantitative, qualitative and economic evidence base for the management of obesity in men. *Health Technol Assess*. 2014;18:1-424. https://doi.org/10.3310/hta18350
47. Robertson F, Geddes J, Ridley D, McLeod G, Cheng K. Patients with type 2 diabetes mellitus have a worse functional outcome post knee arthroplasty: a matched cohort study. *Knee*. 2012;19:286-289. https://doi.org/10.1016/j.knee.2011.06.001
48. Serna F, Mont MA, Krackow KA, Hungerford DS. Total knee arthroplasty in diabetic patients. Comparison to a matched control group. *J Arthroplasty*. 1994;9:375-379. https://doi.org/10.1016/0883-5403(94)90047-7
49. Singh JA. Effect of comorbidity on quality of life of male veterans with prevalent primary total knee arthroplasty. *Clin Rheumatol*. 2009;28:1083-1089. https://doi.org/10.1007/s10067-009-1195-y
50. Singh JA, Lewallen DG. Diabetes: a risk factor for poor functional outcome after total knee arthroplasty. *PLoS One*. 2013;8:e78991. https://doi.org/10.1371/journal.pone.0078991
51. Stenholm S, Sainio P, Rantanen T, Alanen E, Koskinen S. Effect of co-morbidity on the

association of high body mass index with walking limitation among men and women aged 55 years and older. *Aging Clin Exp Res*. 2007;19:277-283. https://doi.org/10.1007/BF03324702

52. Teo BJX, Chong HC, Yeo W, Tan AHC. The impact of diabetes on patient outcomes after total knee arthroplasty in an Asian population. *J Arthroplasty*. 2018;33:3186-3189. https://doi.org/10.1016/j.arth.2018.06.021

53. Wada O, Nagai K, Hiyama Y, Nitta S, Maruno H, Mizuno K. Diabetes is a risk factor for restricted range of motion and poor clinical outcome after total knee arthroplasty. *J Arthroplasty*. 2016;31:1933-1937. https://doi.org/10.1016/j.arth.2016.02.039

54. Wang X, Rintala DH, Garber SL, Henson HK. Association of hemoglobin levels, acute hemoglobin decrease, age, and co-morbidities with rehabilitation outcomes after total knee replacement. *Am J Phys Med Rehabil*. 2005;84:451-456; quiz 457-459. https://doi.org/10.1097/01.phm.0000163719.93855.b7

55. Yang Z, Liu H, Xie X, Tan Z, Qin T, Kang P. The influence of diabetes mellitus on the post-operative outcome of elective primary total knee replacement: a systematic review and meta-analysis. *Bone Joint J*. 2014;96-B:1637-1643. https://doi.org/10.1302/0301-620X.96B12.34378

APPENDIX A

DETAILED SEARCH TERMS AND RESULTS PER STEP IN PUBMED

Category/Step Number	Search	Results, n[a]
Population		
1	Osteoarthritis (MeSH)	54535
2	Arthritis (MeSH)	235526
3	Osteoarthritis	76010
4	Arthritis	302472
5	OA	28853
6	Degenerative Joint Disease	79244
7	1 OR 2 OR 3 OR 4 OR 5 OR 6	331023
8	Arthroplasty (MeSH)	56421
9	Hemiarthroplasty (MeSH)	589
10	Reconstructive Surgical Procedures (MeSH)	179723
11	Joint Prosthesis (MeSH)	40124
12	Arthroplasty	76934
13	Hemiarthroplasty	2860
14	Reconstructive Surgical Procedures	188051
15	Joint Prosthesis	78282
16	Prosthesis Implantation	138447
17	Replacement	285251
18	Revision Arthroplasty	15133
19	Knee Prosthesis	31425
20	8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19	523733
21	7 AND 20	29581
Exposure		
22	Diabetes mellitus (MeSH)	378552
23	Glucose Metabolism Disorders (MeSH)	383952
24	Glycemic Index (MeSH)	2648
25	Glycated Hemoglobin A (MeSH)	29871
26	Glucose (MeSH)	278379
27	Diabetic Retinopathy (MeSH)	22040
28	Hyperglycemia (MeSH)	32289
29	Glucose Tolerance Test (MeSH)	32711
30	Blood Glucose Self-Monitoring (MeSH)	5442
31	Diabetes mellitus	438710
32	Glucose Metabolism Disorders	393723
33	Glycemic Index	10296
34	Glycated Hemoglobin A	29909
35	Glucose	518485
36	Diabetic Retinopathy	31489
37	Hyperglycemia	62911
38	Glucose Tolerance Test	44185
39	Blood Glucose Self-Monitoring	7242
40	Diabetic	249678
41	Diabetes	621086
42	HbA1C	44283

Table continues on page A2.

APPENDIX A

Category/Step Number	Search	Results, n[a]
43	Insulin Resistance	89956
44	Noninsulin Dependence	68
45	Prediabetes	9750
46	Noninsulin Responsive	77
47	22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46	1039736
Outcomes		
48	Pain (MeSH)	355293
49	Health (MeSH)	318751
50	Quality of life (MeSH)	159262
51	Range of Motion, articular (MeSH)	43778
52	Motion (MeSH)	57384
53	Patient Satisfaction (MeSH)	77919
54	Outcome Assessment (Health Care) (MeSH)	922467
55	Patient Reported Outcomes Measures (MeSH)	1345
56	Physical Examination (MeSH)	1248262
57	Muscle Strength (MeSH)	26693
58	Muscle Contraction (MeSH)	191697
59	Community Participation (MeSH)	37526
60	Patient Participation (MeSH)	22187
61	Mobility Limitation (MeSH)	3704
62	Human Activities (MeSH)	413739
63	Activities of Daily Living (MeSH)	62138
64	Locomotion (MeSH)	217044
65	Musculoskeletal Physiological Phenomena (MeSH)	930002
66	Orthopedic Equipment (MeSH)	90545
67	Frail Elderly (MeSH)	9309
68	Accidental Falls (MeSH)	20344
69	Disability Evaluation (MeSH)	47282
70	Recovery of Function (MeSH)	43145
71	Pain	728490
72	Health	3990820
73	Quality of life	324843
74	Range of Motion, articular	45492
75	Motion	257169
76	Patient Satisfaction	125990
77	Outcome Assessment (Health Care)	211309
78	Patient Reported Outcomes Measures	37321
79	Physical Examination	1312533
80	Muscle Strength	58612
81	Muscle Contraction	222212
82	Community Participation	55337
83	Patient Participation	58434
84	Mobility Limitation	7206
85	Human Activities	936438
86	Activities of Daily Living	76722

Table continues on page A3.

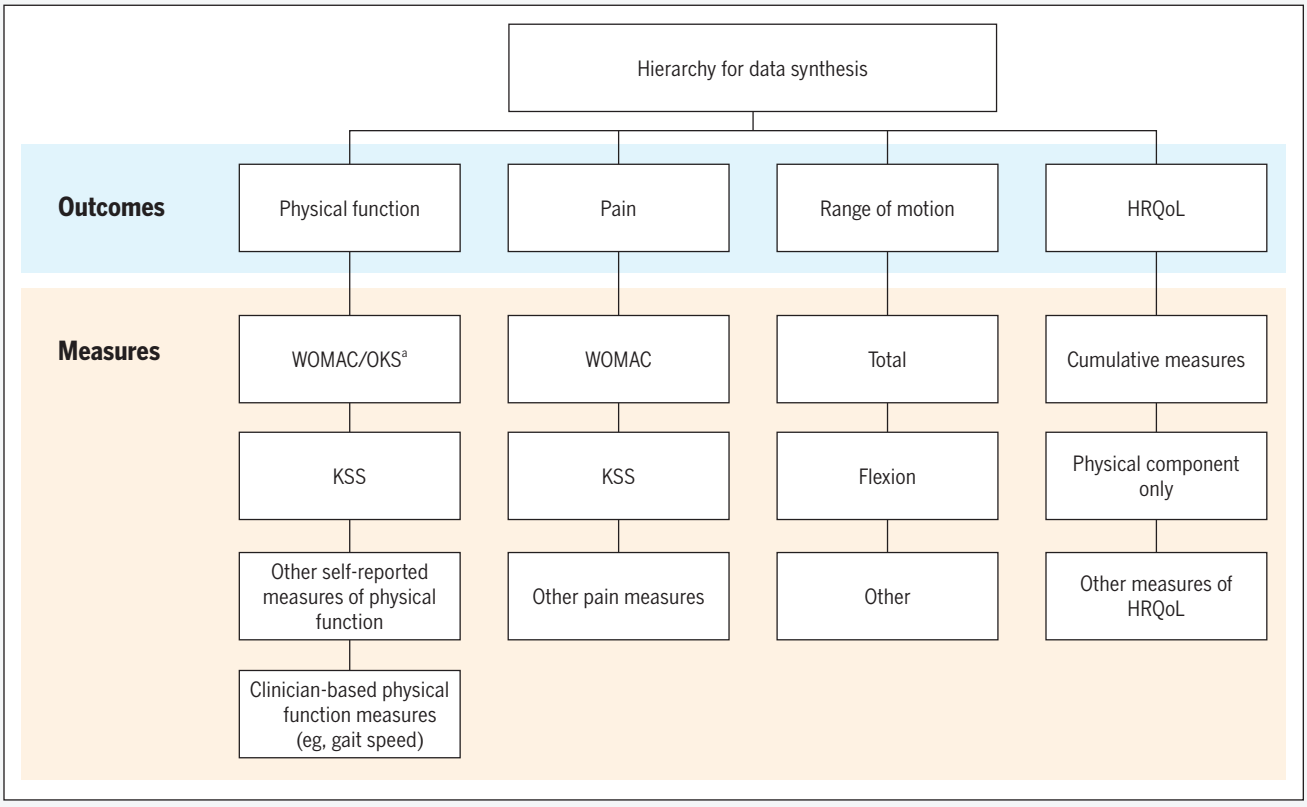
APPENDIX A

Category/Step Number	Search	Results, n[a]
87	Locomotion	231935
88	Musculoskeletal Physiological Phenomena	930237
89	Orthopedic Equipment	92947
90	Frail Elderly	12131
91	Accidental Falls	20880
92	Disability Evaluation	63944
93	Recovery of Function	105502
94	Function	12127446
95	Disability	224065
96	Satisfaction	174221
97	Outcome	2030841
98	Strength	306323
99	Participation	157779
100	Mobility	150316
101	Activities	2770902
102	Activity	2981726
103	Locomotion	231935
104	Walking	102949
105	Stiffness	55331
106	Stiff	9674
107	Timed Up and Go	3463
108	Speed	188955
109	Stair	5717
110	Step	501872
111	Stand	83264
112	Performance	861668
113	Falls	56458
114	48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112 OR 113	16613729
115	21 AND 47 AND 114	375

[a]*After limiting step 76 to English and humans, n = 305.*

APPENDIX B

HIERARCHY OF DATA SELECTED FOR ANALYSIS AND SYNTHESIS WHEN MORE THAN 1 MEASURE WAS USED TO ASSESS AN OUTCOME AT THE SAME TIME POINT



The hierarchy was selected based on psychometric properties reported in previous literature.[44] [a]For physical function, WOMAC and OKS scores were not reported by the same studies, and both measures have superior psychometric properties to those of the KSS. Abbreviations: HRQoL, health-related quality of life; KSS, Knee Society Score; OKS, Oxford Knee Score; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

APPENDIX C

CHARACTERISTICS OF INCLUDED STUDIES

Study/Country	Design	Eligibility	Group Characteristics[a]	DM Indicator	Outcome	Rehabilitation	Time Point
Amusat et al[3] Canada	Prospective cohort	1. Primary TKA 2. No hemicompartmental or unicompartmental revisions, emergency, or bilateral TKAs	DM impacted activity, n = 19 (female: n = 14, 74%); age, 65 ± 12 y; BMI, 35.8 ± 7.1 kg/m^2 DM did not impact activity, n = 41 (female: n = 19, 46%); age, 68 ± 9 y; BMI, 35.8 ± 7.1 kg/m^2 Non-DM, n = 345 (female: n = 216, 63%); age, 68 ± 10 y; BMI, 31.7 ± 6.3 kg/m^2	Patient report and record review for glucose level and antidiabetic medication	WOMAC	Standardized physical therapy during hospital stay	1, 3, and 6 mo
Brock et al[9] United Kingdom	Retrospective cohort with prospective follow-up	1. With DM, including DM information, or without DM who matched those with DM based on age, sex, and BMI 2. Freeman joint registry	DM with HbA1c level ≥8%, n = 17 (female: n = 10, 59%); age, 64 y (45-82 y); BMI, 33.9 kg/m^{2b} DM with HbA1c level <8%, n = 83 (female: n = 49, 59%); age, 71 y (44-91 y); BMI, 31.6 kg/m^{2b} Non-DM, n = 100 (female: n = 58, 58%); age, 70 y (48-94 y); BMI, 31.2 kg/m^{2b}	Record linkage for HbA1c, glycemic control intervention (diet, tablet, insulin); DM complication status	WOMAC	NR	1 y
Cheuy et al[11] United States	Retrospective database	1. ≥3 post-TKA physical therapy visits and record of visits 2. Nonrevision TKA 3. Record of DM status	DM, n = 37 (female: n = 23, 62%); age, 65 ± 8 y; BMI, 36 ± 8 kg/m^2 Non-DM, n = 132 (female: n = 74, 56%); age, 65 ± 8 y; BMI, 32 ± 7 kg/m^2	Record review	WOMAC, timed up and go, 30-s sit-to-stand, and 4-m walk test	Average total number of physical therapy visits: DM, n = 16; without DM, n = 17	90 d
Clement et al[12] United Kingdom	Retrospective cohort with prospective follow-up	Indication in chart, with or without DM	DM, n = 275 (female: n = 153, 56%); age, 70.1 ± 8.5 y; BMI NR Non-DM, n = 2114 (female: n = 1222, 58%); age, 70.4 ± 9.5 y; BMI NR	Patient report and record review	OKS and specific activity questions	Standardized physical therapy protocol, with mobilization on postoperative day 1	6 wk, 6 and 12 mo
Fisher et al[14] United States	Retrospective cohort with prospective follow-up	1. 12 mo post TKA 2. No preoperative stiffness 3. No postoperative infection 4. Stiff: <90° of flexion or KSS score ≤30	Stiff, n = 71 (female, 79%); age, 64.4 y (range, 32-86 y); BMI, 33.6 kg/m^2 (range, 19-42 kg/m^2) Control, n = 148 (female, 60%); age, 67.6 y (range, 39-92 y); BMI, 30.5 kg/m^2 (range, 18-43 kg/m^2)	Patient report and record review	ROM	3-d clinical pathway before discharge: 90° of knee flexion, independence in straight leg raise, transfers, and ambulation. At 6 wk, those with flexion <90° had a manipulation under anesthesia	12 mo
Gandhi et al[15] Canada	Retrospective cohort with prospective follow-up	1. Primary TKA 2. Stiff: 1-y postoperative flexion <90° 3. Control: 1-y postoperative flexion >90°	Stiff, n = 45 (female: n = 33, 73%); age, 67.7 ± 8.8 y; BMI, 35 ± 8.5 kg/m^2; with DM, 17.8% Control, n = 45 (female: n = 33, 73%); age, 67 ± 9.6 y; BMI, 33.1 ± 6.2 kg/m^2; with DM, 6.7%	Record review	ROM	NR	6 wk, 6 and 12 mo

Table continues on page A6.

APPENDIX C

Study/Country	Design	Eligibility	Group Characteristics[a]	DM Indicator	Outcome	Rehabilitation	Time Point
Jones et al[22] Canada	Prospective cohort	1. Waiting for primary TKA 2. ≥40 y of age 3. Residing in health region of interest 4. ≥7 d before surgery 5. No hemicompartmental revisions, no emergency arthroplasties, or not residing in long-term care institution	All: age, 69.4 ± 9.2 y; female, n = 170 (59%) DM, n = 37; BMI of <30 kg/m^2, n = 13; BMI of 30-39 kg/m^2, n = 19; BMI of ≥40 kg/m^2, n = 5 Non-DM, n = 252; BMI of <30 kg/m^2, n = 118; BMI of 30-39 kg/m^2, n = 11; BMI of ≥40 kg/m^2, n = 17	Patient report, record review, and CCI	WOMAC	WBAT ambulation on postoperative day 1. Bone grafts or complications: weight-bearing restrictions for 6 wk. Discharged to home with HEP and referred to community physical therapy as required	1 and 6 mo, 3 y
Lavernia et al[25] United States	Retrospective cohort with prospective follow-up	1. Primary TKA 2. No bilateral or staged arthroplasty 3. DM	Optimal glycemic control, n = 61 (female: n = 43, 70%); age, 71.6 y (range, 49.3-84.4 y); BMI, 32.9 kg/m^2 (range, 22.2-49.4 kg/m^2) Suboptimal glycemic control, n = 59 (female: n = 38, 64%); age, 73 y (range, 32.4-85.5 y); BMI, 32.1 kg/m^2 (range, 22.0-45.8 kg/m^2)	HbA1c	WOMAC	Full WBAT ambulation on postoperative day 1	6 wk, 3 mo, 6 mo, 1 y, and yearly thereafter (range, 2.1-10.7 y; mean, 5.9 y)
Lenguerrand et al[26] United Kingdom	Retrospective review of patients participating in an RCT	1. Primary unilateral TKA 2. Ability to provide consent and complete questionnaires 3. No comorbidities that precluded the use of spinal anesthesia, regional blocks, and strong analgesics postoperatively	DM, n = 64 (female: n = 30, 47%); age, 70 ± 8 y; BMI, 34 ± 6 kg/m^2 Non-DM, n = 523 (female: n = 295, 56%); age, 68 ± 10 y; BMI, 31 ± 6 kg/m^2	Self-report and HbA1c	WOMAC	NR	3 mo, 6 mo, 12 mo
Magone et al[29] United States	Retrospective database	1. Data at 3 and 12 mo post TKA 2. No missing data 3. No multiple revisions	All: age <70 y, n = 57; age ≥70 y, n = 44; female: n = 73, 72%; BMI <30 kg/m^2, n = 53; BMI ≥30 kg/m^2, n = 48 DM with TKA, n = 29; non-DM with TKA, n = 72	Record review for ICD-9 code for DM	SF-36	NR	12 mo
Meding et al[32] United States	Retrospective database	Continuous series of TKAs from database	DM, n = 329 knees in 291 patients (female: n = 151, 52%); age, 70 y (range, 43-84 y); BMI NR Non-DM, n = 4891 knees in 3228 patients (female: n = 1937, 60%); age, 70 y (range, 49-88 y); BMI NR	Record review	KSS	WBAT ambulation on postoperative day 1 and ROM on postoperative day 2	8 wk, 6 mo, 1 y, 2-3 y (average: DM, 52 mo; non-DM, 58 mo)

Table continues on page A7.

APPENDIX C

Study/Country	Design	Eligibility	Group Characteristics[a]	DM Indicator	Outcome	Rehabilitation	Time Point
Moon et al[36] Korea	Retrospective database	1. Minimum follow-up of 2 y 2. Primary TKA	DM, n = 222 knees in 171 patients (female: n = 155, 91%); age, 67.6 y (range, 50-86 y); BMI, 26.5 kg/m^2; weight distribution: normal, 33.3%; overweight, 53.6%; obese, 13.1% Non-DM, n = 171 patients (female: n = 155, 91%); age, 67.4 y; BMI, 25.9 kg/m^2; weight distribution: normal, 33.3%; overweight, 53.6%; obese, 13.1%	Record review, HbA1c, DM treatment	KSS and HSS Knee Score	WBAT ambulation and ROM exercises on postoperative day 1	6 wk, 6 mo, 1 y, yearly (range, 24-132 mo; average: DM, 53.2 mo; non-DM, 54.4 mo)
Papagelopoulos et al[41] United States	Retrospective database	1. Type 2 DM 2. Adequate follow-up 3. No mortality in first year	DM, n = 68 knees in 51 patients (female: n = 26, 51%); age NR; BMI NR; 34 (67%) patients were 20% over their ideal body weight and obese Non-DM, n = 68 knees in 51 patients (female: n = 26, 51%); age NR; BMI NR	Record review	KSS and HSS Knee Score	NR	2-14 y (mean, 8 y)
Rajamäki et al[44] Finland	Prospective	1. Primary TKA 2. No oral corticosteroid, canceled operation, inadequate postoperative glucose monitoring, revision, or >1 joint replacement 3. Responded to postal questionnaires	TKA: all, n = 80 All patients: age, 67 y (42-89 y); female: n = 89, 66%; BMI, 29 kg/m^2 (21-49 kg/m^2)[b]	Fasting plasma glucose, HbA1c, 2-h oral glucose tolerance test	1. painDETECT questionnaire 2. Persistent pain 3. Visual analog scale	Patients requiring revision were excluded from the study	1-2 y after surgery (median follow-up, 18 mo; range, 11-28 mo)
Robertson et al[47] United Kingdom	Retrospective database	1. Primary TKA 2. No complications	DM, n = 367; age, 70 ± 6.8 y; BMI, 31.6 ± 4.9 kg/m^2 Non-DM, n = 367; age, 68.6 ± 7.6 y; BMI, 30.9 ± 4.7 kg/m^2 Sex was not reported, but there were no differences between groups (P = .54)	Record review	KSS	Passive motion machine was used for 24 h, followed by intensive physical therapy	1 y, 5 y, 10 y
Serna et al[48] United States	Retrospective database	1. TKA due to RA or OA 2. Minimum of 2-y follow-up	DM, n = 44 knees in 40 patients (all female); age, 67 y (range, 39-82 y); weight, 184 kg (range, 105-262 kg); height, 66 cm (range, 59-77 cm) Non-DM, n = 53 patients (female: n = 40, 75%); age, 70 y; BMI NR	Record review	HSS Knee Score	NR	24-126 mo. Mean: DM, 54 mo; non-DM, 56 mo
Singh[49] United States	Retrospective cohort with prospective follow-up	1. Primary TKA; male 2. No total hip arthroplasty, contralateral TKA, or revisions 3. Complete data 4. Responded to survey	Total (DM and non-DM), n = 293 (all male); age, 70.3 ± 8.8 y; BMI NR	Record review for ICD-9 codes for DM and DM with complications	SF-36	NR	Mean ± SD, 2.1 ± 0.7 y

Table continues on page A8.

APPENDIX C

Study/Country	Design	Eligibility	Group Characteristics[a]	DM Indicator	Outcome	Rehabilitation	Time Point
Singh and Lewallen[50] United States	Retrospective cohort with prospective follow-up	1. TKA 2. Completed preoperative questionnaires 3. Completed responses at 2-y follow-up	DM with DM complication, n = 187 pre TKA. At 2 y, n = 159 (female, 47%); age, 69.5 ± 8.6 y; BMI, 34.7 ± 7.7 kg/m^2. At 5 y, n = 62 (female, 51.5%); age, 68.2 ± 9.7 y; BMI, 34.8 ± 8.5 kg/m^2 DM with no complication, n = 538. At 2 y, n = 479 (female, 52.1%); age, 69.3 ± 8.1 y; BMI, 34.4 ± 6.6 kg/m^2. At 5 y, n = 159 (female, 50.5%); age, 69.1 ± 7.7 y; BMI, 34.1 ± 6.5 kg/m^2 Non-DM, n = 6250. At 2 y, n = 6100 (female, 56.2%); age, 68.3 ± 10.1 y; BMI, 30.6 ± 5.8 kg/m^2. At 5 y, n = 3707 (female, 55.4%); age, 69.1 ± 7.7 y; BMI, 30.5 ± 5.6 kg/m^2	Record review for ICD-9 codes for DM and DM with complications	Mayo knee questionnaire	NR	2 and 5 y
Teo et al[52] Singapore	Retrospective database with prospective follow-up	1. Primary TKA 2. Preoperative KL grade ≥3 3. Arthritis not from inflammation or infection 4. Complete follow-up	DM, n = 123 (female: n = 96, 78%); age, 67.7 ± 7.2 y; BMI pre TKA, 29.2 ± 5.3 kg/m^2; post TKA, 28.1 ± 4.6 kg/m^2 Non-DM, n = 782 (female: n = 614, 79%); age, 65.7 ± 7.8 y; BMI, 28.1 ± 4.6 kg/m^2	Record review for random blood glucose	KSS and OKS	Continuous passive motion on postoperative day 1 and daily inpatient physical therapy assessment. Ambulation on postoperative day 1 or 2. Discharge to outpatient physical therapy or to community hospital	2 wk, 2 mo, 6 mo, 1 y, 2 y
Wada et al[53] Japan	Retrospective database	1. Primary TKA; KL grade ≥3 2. Age <80 y 3. No history of musculoskeletal surgery or neurologic impairment 4. No second arthroplasty	DM, n = 20 (female: n = 10, 50%); age, 71.8 ± 7.3 y; BMI, 26.7 ± 3.9 kg/m^2 Non-DM, n = 20 (female: n = 10, 50%); age, 70.8 ± 7.2 y; BMI, 27.6 ± 2.2 kg/m^2	Record review, HbA1c	KSS (new)	5-d inpatient physical therapy, twice per day; 12-wk outpatient physical therapy. WBAT with assistive device on postoperative day 1. Passive ROM, patellofemoral and incision mobilization as needed, flexibility, icing, gait training, and transfers. Discharge to outpatient physical therapy, once per week, and HEP	6 and 12 m

Table continues on page A9.

APPENDIX C

Study/Country	Design	Eligibility	Group Characteristics[a]	DM Indicator	Outcome	Rehabilitation	Time Point
Wang et al[54] United States	Retrospective database	1. Primary TKA 2. No psychosis, peripheral vascular disease, RA, or stroke 3. Admitted to inpatient rehabilitation 4. No complications	DM, n = 20; non-DM, n = 29 All patients: age, 64.4 ± 11.1 y; female, n = 2 (4%); BMI NR	Record review	FIM motor score	Inpatient physical therapy	Mean: DM, 5.9 d; non-DM, 5.1 d

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; DM, diabetes mellitus; FIM, Functional Independence Measure; HbA1c, glycated hemoglobin; HEP, home exercise program; HSS, Hospital for Special Surgery; ICD, International Classification of Diseases; KL, Kellgren-Lawrence; KSS, Knee Society Score; NR, not reported; OA, osteoarthritis; OKS, Oxford Knee Score; RA, rheumatoid arthritis; RCT, randomized controlled trial; ROM, range of motion; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; TKA, total knee arthroplasty; WBAT, weight bearing as tolerated; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a]*Age values are mean ± SD or median (range). BMI values are mean ± SD.*

[b]*Calculation of value was not specified.*

APPENDIX D

SUMMARY RESULTS OF FUNCTIONAL DIFFERENCES BETWEEN PATIENTS WITH AND WITHOUT DIABETES

	Is DM Status Related to Function?[ab]	
Measurement/Study	**Presurgery**	**Postsurgery**
WOMAC function subscale		
Amusat et al[3]	No (P = .10)	No at 1 mo (P = .11) Yes at 3 mo: those with DM had worse function than those without DM (ES, 0.30; P<.001)[c] Yes at 6 mo: those with DM had worse function than those without DM (ES, 0.31; P = .02)[c]
Brock et al[9]	NR. Preoperative scores were a predictor of post-operative outcomes (regression estimate, −0.41; P<.01 for postoperative score)	Yes at 1 y: those without DM had the largest improvements of all groups (values NR, P<.05)
Cheuy et al[11]	No (group mean difference, −5.0; 95% CI: −14.0, 5.0; P = .343)	No at 90 d (P = .61; group mean difference, 2.00; 95% CI: −6.00, 10.0)
Jones et al[22]	NR	Yes at 6 mo to 3 y. Random-effects model of DM fitted for function scores: coefficient, 0.96 (95% CI: −4.31, 6.22; P = .72). The DM status-by-time interaction found that function improved for individuals without DM and worsened for individuals with DM (coefficient, 0.21; 95% CI: 0.07, 0.36; P = .005)
Lenguerrand et al[26]	No (ES, 0.06; group mean difference, 1.0; 95% CI: −3.81, 5.81)	No at 3 mo (ES, 0.0; P = .90; group mean difference, 0.0; 95% CI: −5.45, 5.45) No at 6 mo (group median difference, 6.00; P = .10) Mixed at 1 y (group median difference, 11.0; unadjusted P = .02). Group differences resolved after adjusting for age, sex, site of surgery, trial intervention, body mass index, and number of comorbidities
KSS function scale		
Meding et al[32]	Yes (group mean difference, 8.0; P = .0001)	Yes at 1, 3, 5, and 7 y. Function was worse for those with DM than for those without DM (P = .0001). Group mean differences: at 1 y, 12.0; at 3 y, 13.0; at 5 y, 11.0; at 7 y, 10.0
Moon et al[36]	No (ES, 0.22; P>.05; group mean difference, 3.0; 95% CI: 0.13, 5.87)	No at 24 to 132 mo (average, 53 mo) (ES, 0.00; P>.05; group mean difference, 0.00; 95% CI: −4.25, 4.25)
Papagelopoulos et al[41]	Yes (group mean difference, 12.0; 95% CI: 5.24, 18.76; P<.05)	Yes at 2 to 14 y (average, 8 y). Function was worse for those with DM than for those without DM (P<.05; group mean difference, 12.0)
Robertson et al[47]	No (ES, 0.04; P = .85; group mean difference, 0.60; 95% CI: −1.61, 2.81)	Yes at 1 y. Function was worse for those with DM than for those without DM (ES, 0.16; P = .03; group mean difference, 2.30; 95% CI: 0.27, 4.33) No at 5 y (ES, 0.07; P = .35; group mean difference, 1.20; 95% CI: −1.16, 3.56) Yes at 10 y. Function was worse for those with DM than for those without DM (ES, 0.32; P = .03; group mean difference, 4.50; 95% CI: 2.46, 6.54)
Teo et al[52]	No (ES, 0.19; P>.05; group mean difference, 3.50; 95% CI: −0.15, 7.15)	Yes at 2 y. Function was worse for those with DM than for those without DM (ES, 0.35; P = .001; group mean difference, 7.10; 95% CI: 3.25, 10.9)
Wada et al[53] (new version)	No (ES, 0.05; P = .54; group mean difference, 3.40; 95% CI: −8.03, 14.8)	Yes at 6 mo (ES, 0.82; P<.05; group mean difference, 10.3; 95% CI: 2.36, 18.2) Yes at 12 mo (ES, 0.88; P<.05; group mean difference, 11.70; 95% CI: 3.16, 20.2). Function and its improvement were worse for those with DM at both 6 and 12 mo than for those without DM (P = .02)
OKS		
Clement et al[12]	Yes. Function was worse for those with DM than for those without DM (ES, 0.16; P = .01; group mean difference, 1.20; 95% CI: 0.28, 2.17)	Yes at 1 y. Function was worse for those with DM than for those without DM (ES, 0.15; P = .01; group mean difference, 1.60; 95% CI: 0.33, 2.91) No at 1 y. Pre-to-post change: ES, 0.04; P = .54; group mean difference, 0.5 (95% CI: −0.83, 1.60)
Teo et al[52]	Yes. Function was worse for those with DM than for those without DM (ES, 0.22; P = .02; group mean difference, −1.80; 95% CI: −3.33, −0.27)	Yes at 2 y. Function was worse for those with DM than for those without DM (ES, 0.29; P = .002; group mean difference, −2.10; 95% CI: −3.35, −0.85)

Table continues on page A11.

APPENDIX D

	Is DM Status Related to Function?[a,b]	
Measurement/Study	**Presurgery**	**Postsurgery**
HSS Knee Score		
Moon et al[36]	No (ES, 0; *P*>.05). Average was 66 and defined as "poor"	No at 24 to 132 mo (average, 53 mo) (ES, 0; *P*>.05)
Papagelopoulos et al[41]	NR. Mean DM, 53 (range, 18-82); non-DM NR	Yes at 2 to 14 y (average, 8 y) (ES, 0.81; *P*<.05)
Serna et al[48]	NR. Mean DM, 50 (range, 21-55); non-DM NR	Yes at 24 to 126 mo (average, 54 mo) (group mean difference, 7)
Mayo knee questionnaire		
Singh and Lewallen[50]	Yes: 78.3% of those with DM but with no complication reported moderate to severe ADL limitation, and 68.7% of those without DM reported moderate to severe ADL limitation	Yes at 2 y. The DM diagnosis increased the odds of moderate to severe ADL limitation following a TKA when compared to non-DM patients (OR = 1.45; 95% CI: 1.04, 2.01; *P* = .03) Yes at 5 y. The DM diagnosis increased the odds of moderate to severe ADL limitation following a TKA when compared to non-DM patients (OR = 1.59; 95% CI: 1.04, 2.41; *P* = .03) DM was independently associated with poor functional outcome after a primary TKA. The association was present after adjustments, including preoperative functional limitations
TUG, 4-m walk, 30-s STS		
Cheuy et al[11]	No. Group differences: 4-m walk ES, 0.43 (*P* = .17); 30-s STS ES, 0.28 (*P* = .65); TUG ES, 0.33 (*P* = .07)	Yes at 90 d. Mixed-effect model between-group differences: 4-m walk, 0.22 (95% CI: 0.09, 0.35; *P* = .001); 30-s STS, 2.22 (95% CI: 0.10, 4.34; *P* = .040); TUG, −1.92 (95% CI: −3.55, −0.29; *P* = .021)
FIM motor scores		
Wang et al[54]	NR	No at admission (ie, immediately following TKA): group mean difference, 1.0; *P*>.05 No at discharge from rehabilitation facility (ie, 5-6 d; DM: mean, 5.9 d; non-DM: mean, 5.1 d): group mean difference, 0.3; *P*>.05

Abbreviations: ADL, activities of daily living; CI, confidence interval; DM, diabetes mellitus; ES, effect size; FIM, Functional Independence Measure; HbA1c, glycated hemoglobin; HSS, Hospital for Special Surgery; KSS, Knee Society Score; NR, not reported; OKS, Oxford Knee Score; OR, odds ratio; STS, sit-to-stand; TKA, total knee arthroplasty; TUG, timed up and go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a]*Values in parentheses are 95% confidence interval. Mean difference was calculated by subtracting the mean score of the DM group from that of the non-DM group in studies reporting group means without reporting variance.*

[b]*Effect size was calculated, using Cohen's* d*, via the means and SDs of the DM and non-DM groups in studies that used the* t *test.*

[c]*Study reported subgroup analyses and required means and SDs of 2 or more DM groups to be combined.*

APPENDIX E

SUMMARY RESULTS FOR OTHER OUTCOME DIFFERENCES, BASED ON DIABETES STATUS

		Is Diabetes Status Related to Outcome Differences?[ab]	
Measurement/Study	**Groups**	**Presurgery**	**Postsurgery**
ROM			
Total			
Cheuy et al[11]	DM and non-DM	No (ES, 0.07; *P* = .78; group mean difference, 1.0; 95% CI: −6.0, 7.0)	No at 3 mo (ES, 0.00[c]; *P* = .99; group mean difference, 0.10; 95% CI: −6.00, 6.00)
Robertson et al[47]	DM and non-DM	No (ES, 0.15; *P* = .08; group mean difference, 2.80; 95% CI: 0.14, 5.46)	Yes at 1 y (ES, 0.28; *P*<.001; group mean difference, 4.60; 95% CI: 2.22, 6.98) Yes at 5 y (ES, 0.24; *P* = .001; group mean difference, 4.2; 95% CI: 1.72, 6.68) Yes at 10 y (ES, 0.32; *P* = .01; group mean difference, 5.0; 95% CI: 2.77, 7.23)
Flexion			
Fisher et al[14]	With and without stiffness	NR	Yes at 1 y. DM patients were 2.8 times (OR = 2.8) more likely to have knee flexion ROM limitations (ie, <90° or KSS ≤30; *P* = .04)
Robertson et al[47]	DM and non-DM	No (ES, 0.08; *P* = .12; group mean difference, 1.30; 95% CI: −1.08, 3.68)	Yes at 1 y (ES, 0.27; *P*<.001; group mean difference, 4.00; 95% CI: 1.85, 6.15) Yes at 5 y (ES, 0.22; *P* = .004; group mean difference, 3.50; 95% CI: 1.20, 5.80) Yes at 10 y (ES, 0.35; *P* = .01; group mean difference, 4.70; 95% CI: 2.75, 6.65)
Teo et al[52]	DM and non-DM	No (ES, 0.05; *P*>.05; group mean difference, −1.0; 95% CI: −5.16, 3.16)	No at 2 y (ES, 0.06; *P*>.05; group mean difference, 1.00; 95% CI: −2.19, 4.19)
Wada et al[53]	DM and non-DM	No (ES, 0.15; *P* = .73; group mean difference, −2.0; 95% CI: −10.4, 6.39)	Yes at 6 mo (ES, 0.59; *P*<.05; group mean difference, 8.80; 95% CI: −0.74, 18.3) Yes at 1 y (ES, 0.69; *P*<.05; group mean difference, 9.80; 95% CI: 0.72, 18.88)
Flexion <90°			
Gandhi et al[15]	With and without stiffness	Yes. In the stiff group (less flexion), 17.8% with DM; in the nonstiff group, 6.7% with DM	Yes at intraoperative, 6 wk, and 1 y. The stiff group had significantly less ROM than the nonstiff group (*P*<.001)
Fixed flexion (lack of extension)			
Robertson et al[46]	DM and non-DM	No (ES, 0.08; *P* = .79; group mean difference, −0.20; 95% CI: −1.23, 0.83)	No at 1 y (ES, 0.27; *P* = .10; group mean difference, −0.40; 95% CI: −1.07, 0.27) Yes at 5 y (ES, 0.22; *P* = .02; group mean difference, −0.70; 95% CI: −1.38, −0.02) Yes at 10 y (ES, 0.35; *P* = .04; group mean difference, −0.60; 95% CI: −1.16, −0.04)
Extension			
Wada et al[53]	DM and non-DM	No (ES, 0.20; *P* = .42; group mean difference, 1.3; 95% CI: −2.89, 5.49)	Yes at 6 mo (ES, 0.43; group mean difference, 1.8; 95% CI: −0.85, 4.45) Yes at 1 y (ES, 0.39; group mean difference, 1.20; 95% CI: −0.79, 3.19)
Strength			
Extension			
Wada et al[53]	DM and non-DM	No (ES, 0.14; group mean difference, 0.06; 95% CI; −0.34, 0.22)	No at 6 mo (ES, 0.40; group mean difference, 0.15; 95% CI: −0.39, 0.90) No at 1 y (ES, 0.44; group mean difference, 0.06; 95% CI: −0.39, 0.07)
Cheuy et al[11]	DM and non-DM	No (ES, 0.18; *P* = .33; group mean difference, 0.54; 95% CI: −1.61, 0.54)	Yes for daily recovery trajectory up to 90 d (ES, 0.48; *P* = .046; group mean difference, 0.02; 95% CI: 0.00, 0.04) Yes at 90 d (*P* = .007; group mean difference, 1.29; 95% CI: 0.35, 2.23)
Health-related quality of life			
SF-36 PCS			
Brock et al[9]	DM and non-DM	NR[c]	Yes at 1 y (estimate, −6.54; SE, 2.18 with the SF-36 PCS as the predictor variable; *P* = .003)
Magone et al[29]	DM and non-DM	NR[c]	Yes at 1 y for preoperative-to-postoperative change score (ES, 0.63; *P* = .006; group mean difference for change, 6.02; 95% CI: 1.73. 10.3)
Teo et al[52]	DM and non-DM	No (ES, 0.16; *P* NS; group mean difference, 1.6; 95% CI: −0.39, 3.59)	No at 2 y (ES, 0.20; *P* NS; group mean difference, 2.1; 95% CI: 0.13, 4.07)
Singh[49]	DM and non-DM	NR	No at average ± SD of 2.1 ± 0.7 y (group mean difference, 0.40; *P* NS)

Table continues on page A13.

APPENDIX E

		Is Diabetes Status Related to Outcome Differences?[ab]	
Measurement/Study	**Groups**	**Presurgery**	**Postsurgery**
SF-12 PCS			
Clement et al[12]	DM and non-DM	Yes (P = .02; group mean difference, 1.00; 95% CI: 0.14, 1.96)	Yes at 1 y for group difference (P = .007; group mean difference, 1.9; 95% CI: 0.52, 3.21) No at 1 y for change score group differences (P = .22; group mean difference for preoperative-to-postoperative change, 0.80; 95% CI: −0.50, 2.16)
SF-36 MCS			
Brock et al[9]	DM and non-DM	NR[c]	No at 1 y with the SF-36 MCS as the predictor variable (estimate, −0.01; SE, 2.48; P NS)
Magone et al[29]	DM and non-DM	NR[c]	No at 1 y for preoperative-to-postoperative change (ES, 0.20; P = .37)
Teo et al[52]	DM and non-DM	Yes (ES, 0.31; P = .001; group mean difference, 3.40; 95% CI: 1.35, 5.45)	No at 2 y (ES, 0.14; P NS; group mean difference, 1.40; 95% CI: −0.56, 3.36)
Singh[49]	DM and non-DM	NR	No at average ± SD of 2.1 ± 0.7 y (P>.05; group mean difference, 0.30)
SF-12 MCS			
Clement et al[12]	DM and non-DM	Yes (P = .008; group mean difference, 2.10; 95% CI: 0.54, 3.58)	No at 1 y (P = .59; group mean difference, 0.40; 95% CI: −0.97, 1.71) Yes at 1 y (P = .03; group mean difference for preoperative-to-postoperative change, 1.70; 95% CI: 0.14, 3.22)
HUI Mark 3			
Amusat et al[3]	DM and non-DM	No (ES, 0.23[d]; P = .07)	No at 1 mo (ES, 0.07[c]; P = .18) Yes at 3 mo (ES, 0.23[c]; P<.001) No at 6 mo (ES, 0.08[c]; P = .16)
Pain			
WOMAC pain subscale			
Amusat et al[3]	DM and non-DM	No (ES, 0.02[c])	No at 1 mo (ES, 0.15[c]) No at 3 mo (ES, 0.31[c]) No at 6 mo (ES, 0.28[c])
Brock et al[9]	DM and non-DM	NR	No at 1 y with pain as the predictor variable (estimate, −4.58; SE, 4.04; P NS)
Cheuy et al[11]	DM and non-DM	No (ES, 0.00[c]; P = 1.00; group mean difference, 0.00; 95% CI: −2.13, 2.12)	No at 3 mo (P = .37; ES, 0.17[c]; group mean difference, −1.00; 95% CI: −3.00, 1.00)
Jones et al[22]	DM and non-DM	NR	Yes at 6 mo to 3 y: significant DM-by-time interaction effect (coefficient, 0.25; 95% CI: 0.04, 0.46; P = .02)
Lenguerrand et al[26]	DM and non-DM	No (ES, 0.12; group mean difference, 2.0; 95% CI: −2.60, 6.60)	No at 3 mo (ES, 0.15; P = .30; group mean difference, 3.0; 95% CI: −2.51, 8.51) No at 6 mo (ES, 0.15; P = .20; group mean difference, 3.0; 95% CI: −2.22, 8.21) Yes at 1 y (median group difference, 10; P = .01)
KSS pain scale			
Meding et al[32]	DM and non-DM	No (group mean difference, 1.00)	Yes (P = .005). Group mean differences: at 6 mo, 5; at 1 y, 5; at 3 y, 5; at 5 y, 8; at 7 y, 5
Moon et al[36]	DM and non-DM	No (ES, 0.10; group mean difference, 1.0; 95% CI: −1.13, 3.13)	No at 24 to 132 mo (average, 53 mo) (ES, 0.00; group mean difference, 0.00; 95% CI: −1.81, 1.81)
Painful joint and persistent pain			
Rajamäki et al[44]	DM and non-DM	NR	Yes at 1-2 y Painful joint, OR = 2.2 (95% CI: 0.70, 6.30) Persistent pain, OR = 8.5 (95% CI: 1.90, 38.0)
VAS			
Rajamäki et al[44]	DM and non-DM	Yes for pain at rest (median group difference, 22 points; P = .01) No for pain in motion (median group difference, 2 points; P = .09)	No at 1-2 y for improvements in VAS score for pain at rest (P = .10) Yes at 1-2 y for improvement in VAS score for pain in motion (P = .02)

Table continues on page A14.

APPENDIX E

		Is Diabetes Status Related to Outcome Differences?[ab]	
Measurement/Study	**Groups**	**Presurgery**	**Postsurgery**
Lenguerrand et al[26]	DM and non-DM	NR	Yes at 3 d for pain at rest (ES, 0.40; *P* = .004) and pain with movement (ES, 0.31; *P* = .03)
Stiffness			
WOMAC stiffness subscale			
Brock et al[9]	DM and non-DM	NR	No at 1 y with stiffness as the predictor variable (estimate, −6.04; SE, 3.72; *P* NS)
Cheuy et al[11]	DM and non-DM	No (*P* = .90; group mean difference, 0.06; 95% CI: −0.84, 0.96)	No at 3 mo (*P* = .27; group mean difference, 0.5; 95% CI: −0.4, 1.4)
Lenguerrand et al[26]	DM and non-DM	No (ES, 0.0; group mean difference, −1.0; 95% CI: −6.76, 4.76)	No at 3 mo (ES, 0.05; *P* = .70; group mean difference, 1.0; 95% CI: −4.84, 6.84) No at 6 mo (ES, 0.15; *P* = .50; group mean difference, 3.0; 95% CI: −3.09, 9.09) Yes at 1 y (median group difference, 34 points; *P* = .02)

Abbreviations: CI, confidence interval; DM, diabetes mellitus; ES, effect size; HbA1c, glycated hemoglobin; HUI, Health Utilities Index; KSS, Knee Society Score; MCS, mental component summary; NR, not reported; NS, not significant (P value NR); OR, odds ratio; PCS, physical component summary; ROM, range of motion; SF-12, Medical Outcomes Study 12-Item Short-Form Health Survey; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; TKA, total knee arthroplasty; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a]*Values in parentheses are 95% confidence interval. Mean difference was calculated by subtracting the mean score of the DM group from that of the non-DM group in studies reporting group means without reporting variance.*

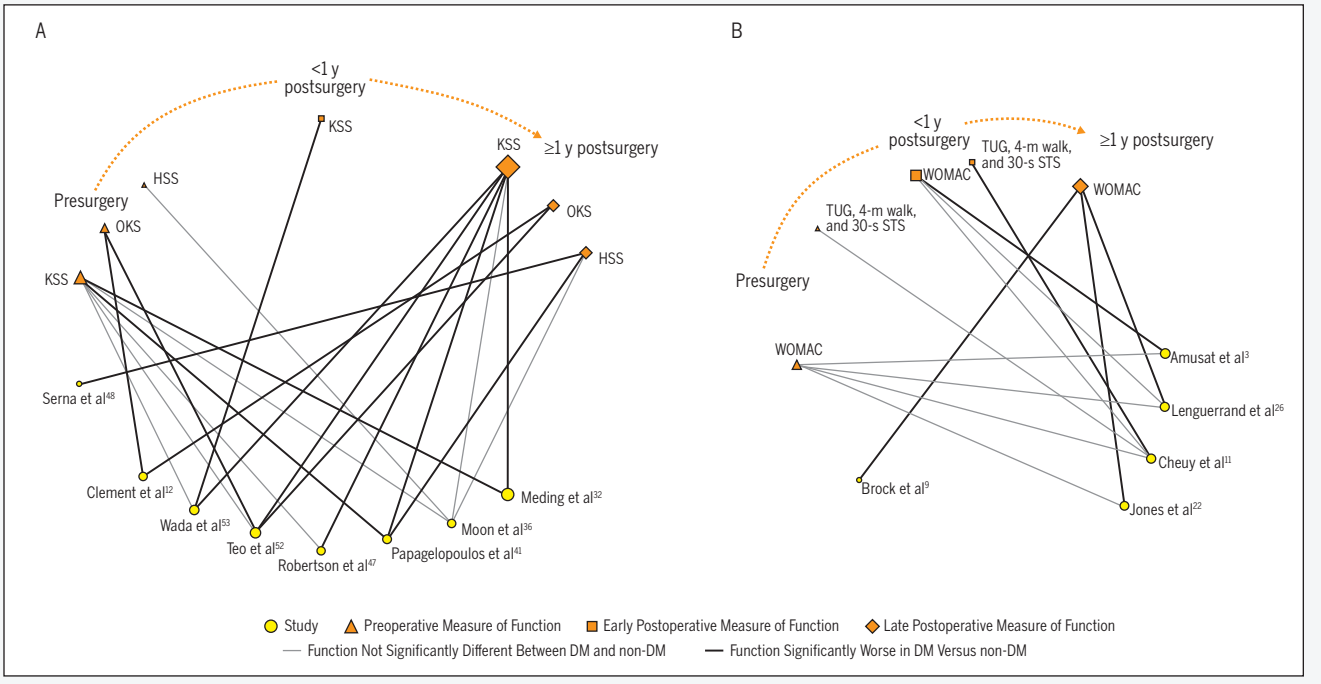
[b]*Effect size was calculated, using Cohen's d, via the means and SDs of the DM and non-DM groups in studies that used the t test.*

[c]*Reported change score (ie, the difference between preoperative and postoperative scores) only, and not individual preoperative or postoperative scores.*

[d]*Scores for the DM group were reported separately, so combined means and SDs were calculated to determine the ES.*

APPENDIX F

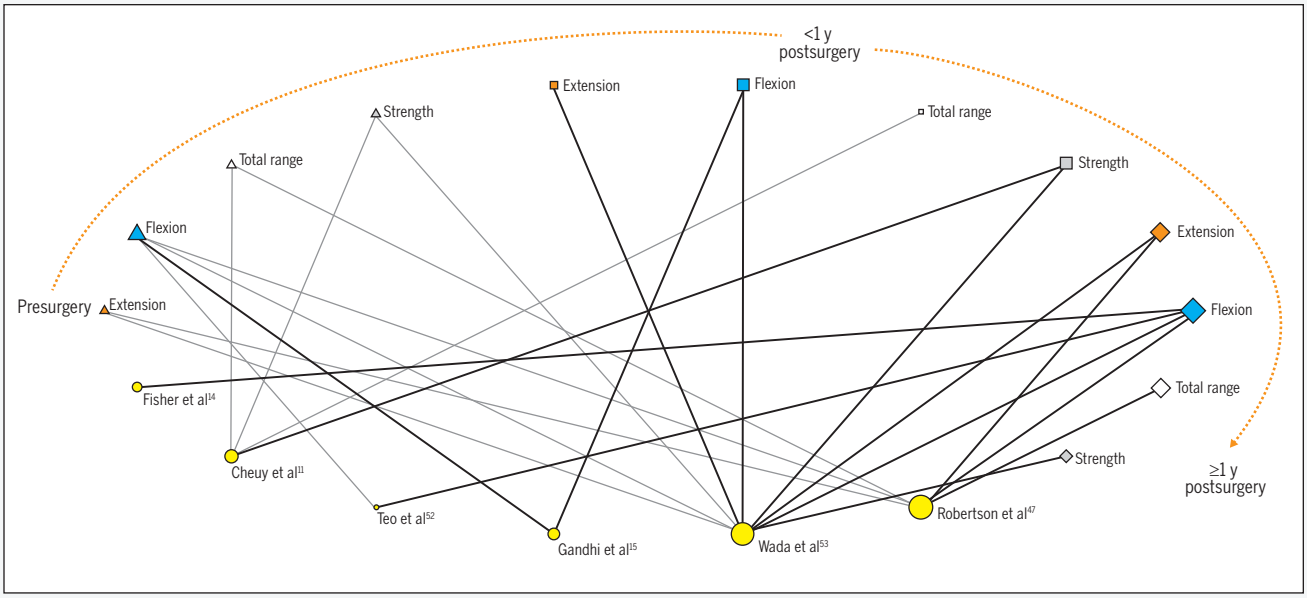
SUMMARY OF FUNCTIONAL DIFFERENCES BETWEEN PATIENTS WITH AND WITHOUT DIABETES PER STUDY, MEASURE, AND TIME POINT



Functional differences between those with and without DM at 3 time points: preoperative, early postoperative (within 1 year after surgery), and late postoperative (1 year or more after surgery). (A) The KSS, OKS, and HSS. (B) The WOMAC, TUG, 4-m walk, and 30-second STS. Node sizes are related to the number of studies reporting on the measure, with larger shapes associated with a greater number of studies. Not included in this figure are the Functional Independence Measure motor score, reported by Wang et al,[53] and the Mayo knee questionnaire, reported by Singh and Lewallen,[49] due to having fewer than 2 studies per measure. Abbreviations: DM, diabetes mellitus; HSS, Hospital for Special Surgery Knee Score; KSS, Knee Society Score; OKS, Oxford Knee Score; STS, sit-to-stand; TUG, timed up and go; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

APPENDIX G

SUMMARY OF RANGE-OF-MOTION AND STRENGTH DIFFERENCES BETWEEN PATIENTS WITH AND WITHOUT DIABETES PER STUDY, MEASURE, AND TIME POINT



Outcome differences between those with and without diabetes mellitus at 3 time points: preoperative, early postoperative (within 1 year after surgery), and late postoperative (1 year or more after surgery) for extension range of motion, flexion range of motion, total range of motion, and extension strength. Colors represent measurement categories, shapes represent measurement time points, and sizes are related to the number of studies reporting on the outcome measure, with larger nodes associated with a greater number of studies and a greater number of measures. The lines represent the relationships between study and outcome (lighter lines suggest lesser or no relationship).