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RESEARCH

Comparative efficacy and safety of antidiabetic drugs for obese patients with knee osteoarthritis: a network meta-analysis of randomized controlled trials

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Abstract

Background Obesity-related knee osteoarthritis (KOA) is a significant public health concern, affecting quality of life. Recent evidence suggests some antidiabetic drugs may help manage KOA in obese patients due to their anti-inflammatory and weight-reducing effects.

Objective This study aimed to compare the efficacy and safety of antidiabetic drugs for managing pain and adverse events in obese KOA patients through a network meta-analysis of randomized controlled trials (RCTs).

Methods A systematic search of multiple databases identified relevant RCTs on antidiabetic drugs for KOA. Treatment efficacy was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score improvement, and safety was evaluated based on the incidence of serious adverse events. The Surface Under the Cumulative Ranking Curve (SUCRA) scores were used to rank the treatments, and effect sizes were reported as mean differences (MD) with 95% confidence intervals (CI).

Results A total of nine RCTs were included in the analysis. For pain relief, metformin demonstrated the largest effect size with a mean difference of − 1.13 (95% CI − 1.48, − 0.78) compared to usual care, followed by Metformin-Phosphatidylcholine (MFPH) (− 0.92, 95% CI − 1.70, − 0.13) and semaglutide (− 0.90, 95% CI − 1.48, − 0.32). In terms of safety, usual care exhibited the lowest risk of adverse events, with liraglutide (0.09, 95% CI − 0.74, 0.92) and semaglutide (0.21, 95% CI − 0.46, 0.88) also showing favorable safety profiles. The SUCRA rankings further supported these findings, with metformin ranking highest for efficacy (SUCRA: 86.8%) and usual care ranking highest for safety (SUCRA: 75.7%). However, these rankings should be interpreted alongside the effect sizes and clinical context to fully assess the trade-offs between efficacy and safety across interventions.

Conclusions Metformin and MFPH are promising for managing KOA pain in obese patients. Semaglutide offers a balanced efficacy and safety profile, while liraglutide may be a safe option for selected patients. Further research is needed to confirm these findings and assess long-term outcomes.

Keywords Obesity · Knee osteoarthritis · Antidiabetic drugs · Network meta-analysis · Metformin · Safety · Efficacy

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Introduction

Knee osteoarthritis (KOA) is a chronic, degenerative joint disease characterized by progressive cartilage degeneration, inflammation, and joint pain, which severely impacts mobility and quality of life [1]. The prevalence of KOA is rising globally, largely due to aging populations and increasing rates of obesity [2]. Obesity is a well-established risk factor for KOA, with studies showing that individuals who are overweight have a significantly higher risk of developing the condition compared to those with a healthy weight [3]. The relationship between obesity and KOA is complex. Mechanically, excess body weight increases stress on the knee joints, accelerating cartilage wear and joint degeneration [4]. Metabolically, obesity promotes systemic inflammation through the release of adipokines, which exacerbate synovial inflammation and cartilage breakdown [5]. These combined factors make KOA particularly difficult to manage in obese patients, as weight loss is often required but challenging to achieve and maintain through conventional interventions alone. Recent research suggests that certain antidiabetic medications may offer a novel approach to managing KOA in obese individuals.

Current treatments for KOA primarily focus on symptom management, aiming to relieve pain and improve joint function. Common approaches include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, and physical therapy. However, these treatments have limitations. NSAIDs and corticosteroids, while effective for short-term relief, are associated with significant side effects, including gastrointestinal, cardiovascular, and metabolic risks, especially with long-term use [6, 7]. Moreover, these therapies do not address the underlying inflammatory and metabolic processes contributing to KOA progression, particularly in obese patients. As a result, there remains a significant gap in effective, targeted treatments.

Emerging evidence suggests that antidiabetic drugs, such as metformin, semaglutide, and other GLP-1 receptor agonists, may help fill this gap. Preclinical and clinical studies indicate that metformin may reduce inflammation in the joint environment by inhibiting key inflammatory pathways [8]. Likewise, GLP-1 receptor agonists, like semaglutide and liraglutide, have demonstrated anti-inflammatory effects and have been shown to induce significant weight loss, addressing both mechanical and metabolic contributors to KOA [9]. These drugs present a promising dual-action therapeutic approach, targeting both symptom relief and the underlying mechanisms of the disease.

Despite these promising findings, there is a lack of comprehensive comparative analyses that assess the efficacy and safety of these antidiabetic drugs specifically in obese patients with KOA. Most existing studies are small-scale or focused on individual drugs, rather than offering a comparative analysis. Furthermore, the safety profiles and potential risks of adverse events in this patient population remain insufficiently explored. The primary aim of this study is to systematically evaluate and compare the efficacy and safety of antidiabetic drugs in managing KOA in obese patients. Using network meta-analysis, we assess the impact of these drugs on pain reduction (measured by the WOMAC pain score) and the incidence of adverse events. By synthesizing data from randomized controlled trials, this analysis provides a clearer understanding of the relative performance of treatments such as metformin, semaglutide, liraglutide, and others.

Methods

Study design and data sources

This study was conducted as a systematic review and network meta-analysis, adhering to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Although a formal study protocol was not registered or published, the review was conducted based on a clearly predefined methodology, which included objectives, eligibility criteria, data extraction procedures, and statistical methods. The PRISMA 2020 checklist has been uploaded (Supplementary file 1).

A comprehensive search strategy was implemented across multiple electronic databases, including PubMed, Embase, the Cochrane Library, and Web of Science, covering the period from the inception of each database up to December 2024. The search strategy utilized a combination of keywords and Medical Subject Headings (MeSH) terms related to “knee osteoarthritis,” “obesity,” “antidiabetic drugs,” “randomized controlled trials,” and “network meta-analysis.” Specific keywords and MeSH terms related to ‘antidiabetic drugs’ were also employed, including ‘metformin,’ ‘liraglutide,’ ‘semaglutide,’ ‘pioglitazone,’ ‘biguanides,’ ‘thiazolidinediones,’ and ‘GLP-1 receptor agonists,’ among others. In addition to database searches, manual searches of reference lists from included studies and relevant reviews were conducted to identify any additional eligible studies. Grey literature, such as conference abstracts and unpublished data, was also reviewed where available to minimize the potential for publication bias. The search strategy can be found in Supplementary file 2.

Inclusion and exclusion criteria

Eligibility criteria

The process of determining irrelevance was based on several factors: Population Characteristics: Studies were excluded if the population did not meet the specific inclusion criteria of being obese [defined as a body mass index (BMI) ≥ 30 kg/m^2] [10]. This was a key criterion for determining relevance, as the focus of this meta-analysis was on obese patients with KOA. Specifically, studies that focused on overweight individuals (BMI < 30 kg/m^2), individuals with other types of arthritis, or those without a diagnosis of KOA were excluded. Intervention: Only studies evaluating antidiabetic drugs were included. Studies that did not involve medications with antidiabetic properties, or those that evaluated non-pharmacologic interventions (e.g., physical therapy, surgery), were excluded. Outcomes: Studies were excluded if they did not report outcomes related to the efficacy or safety of antidiabetic drugs in managing KOA symptoms, such as pain reduction (e.g., WOMAC pain score) or adverse events. Study Design: Only RCTs were considered. Any observational studies, case reports, or other non-RCT designs were excluded. Language: Studies published in languages other than English were excluded, as resources for translating studies were unavailable. Relevance of Data: Studies that did not provide sufficient or relevant data on the primary outcomes of interest (i.e., efficacy and safety of antidiabetic drugs for KOA) were also excluded.

Exclusion criteria

Study Design: Non-randomized studies, observational studies, case reports, reviews, or meta-analyses. Population: Trials not specifically involving obese patients with KOA or those combining other forms of arthritis without separate analysis for KOA. Intervention: Studies that evaluated interventions unrelated to antidiabetic drugs or those where the specific drug regimen was not clearly defined. Outcomes: Studies were eligible for inclusion if they used either WOMAC pain scores or other validated pain scales such as the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS) to assess pain. In cases where different scales were used, we harmonized the pain subscales to ensure comparability across studies. Insufficient Data: Studies with incomplete or insufficient data for inclusion in the network meta-analysis, such as missing comparator groups or lack of statistical reporting.

Screening and selection procedure

The screening process was conducted by a primary reviewer who assessed the titles and abstracts of identified studies. A second reviewer independently verified the list of included and excluded studies at the full-text stage. Discrepancies between the reviewers were resolved through discussion and consensus, and in cases where disagreements persisted, a third reviewer was consulted.

Outcome measures

The primary outcome of this study was the improvement in knee pain as measured by the WOMAC pain score. The improvement in WOMAC pain scores was used as the key indicator of treatment efficacy.

The secondary outcome focused on the safety profiles of the included interventions. Safety was evaluated to balance the benefits of pain relief with potential risks associated with the treatments.

Data extraction and quality assessment

Data were extracted systematically from the included studies using a predefined data extraction form. Key variables included study characteristics (author, year, location, and design), participant demographics (sample size, age, gender, body mass index), intervention details (type of antidiabetic drug, dosage, duration), and the diagnosis of osteoarthritis.

The quality of the included studies was evaluated using the Cochrane Risk of Bias 2.0 tool. This tool assesses bias across several domains, including randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting.

Assessment of publication bias

Publication bias was assessed using funnel plots for both the primary outcome (WOMAC pain score improvement) and safety outcomes (serious adverse events). Funnel plots were visually inspected for asymmetry, which may indicate potential bias in the included studies.

Statistical analysis

The network meta-analysis was conducted within a Bayesian framework using Stata to estimate the comparative efficacy and safety of the included antidiabetic drugs. The efficacy was measured by the improvement in the WOMAC pain score, while safety was assessed based on adverse events. To rank the treatments, we calculated the Surface Under the Cumulative Ranking Curve (SUCRA) probabilities, which range from 0 to 100%, with higher values indicating better performance for the respective outcome. To ensure comparability across studies, we categorized them based on follow-up duration into short-term (less than 6 months), and long-term (over 6 months) groups. Heterogeneity across

the network was assessed using the I^2 statistic, which was categorized as low (< 25%), moderate (25–50%), or high (> 50%) heterogeneity. Consistency between direct and indirect comparisons was evaluated through node-splitting models within the Bayesian framework or by calculating inconsistency factors using a frequentist approach. Contribution graphs were generated to evaluate the impact of individual studies on the overall network estimates. These graphs display the proportion of direct and indirect evidence provided by each study for every treatment comparison within the network meta-analysis. Additionally, rankograms were constructed to visualize the probability distributions of treatment rankings for both efficacy (WOMAC pain score improvement) and safety (adverse events). Each rankogram shows the likelihood of a treatment achieving each possible rank (e.g., 1st, 2nd, 3rd) across the network. These probabilities were derived from the network meta-analysis model and represented as a series of bars for each rank.

Results

Study selection and characteristics

A total of 1056 records were identified through database searches, with no additional records identified from other sources. After removing 621 duplicates, the remaining 435 records were screened based on titles and abstracts. Of these, 608 records were excluded for irrelevance, leaving 13 full-text articles assessed for eligibility. Out of the 13 full-text articles, four studies were excluded due to being a review article (n = 1) or lacking sufficient or relevant data (n = 3). Ultimately, nine RCTs [11–19] were included in the qualitative and quantitative syntheses (Fig. 1). These studies, conducted across diverse geographic regions including Denmark, Egypt, China, and Iraq, involved a total sample size ranging from 50 to 407 participants per trial. The trials examined various antidiabetic drugs, including

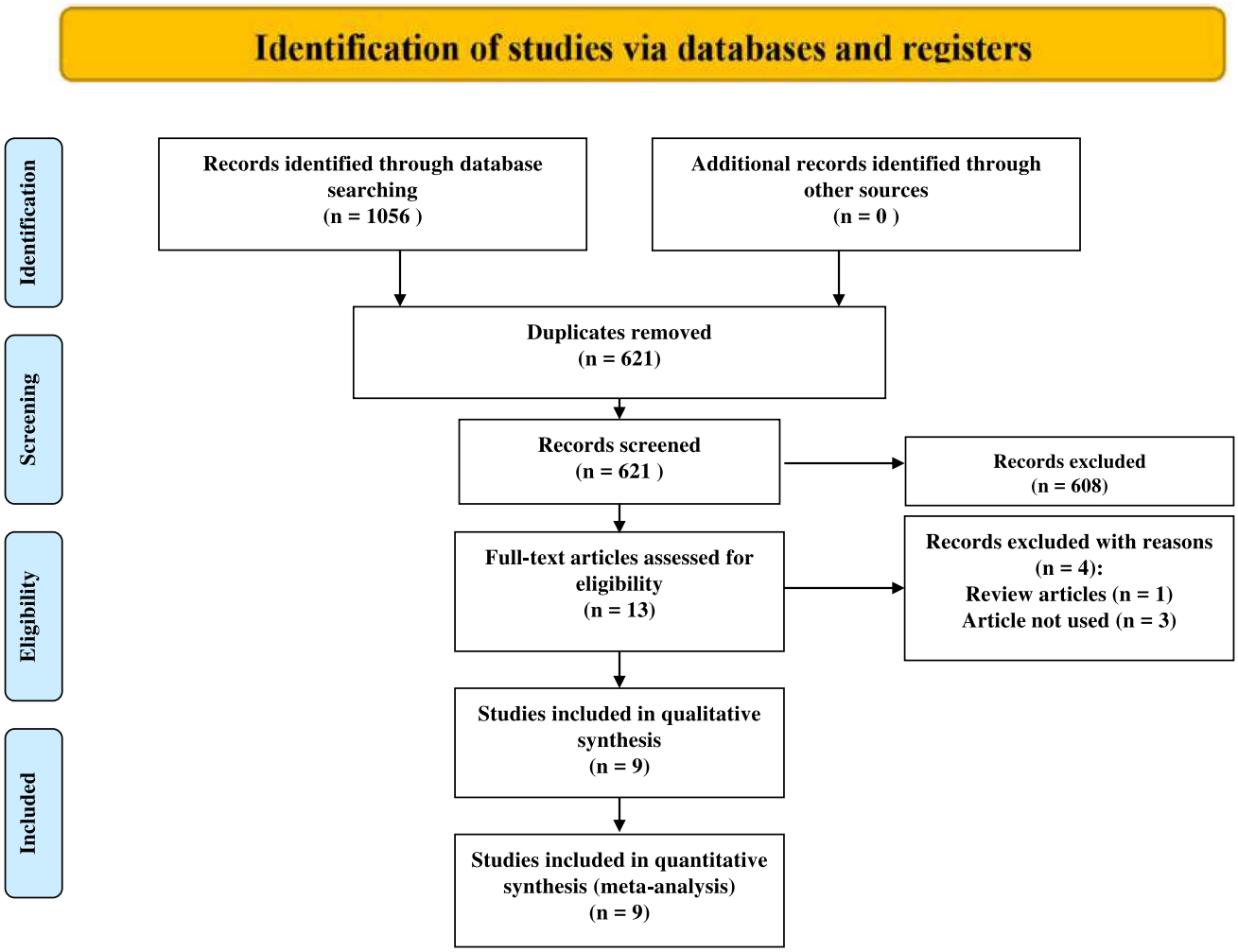

Fig. 1 Study identification and selection

GLP-1 receptor agonists (e.g., semaglutide and liraglutide), biguanides (e.g., metformin), and thiazolidinediones (e.g., pioglitazone), for their efficacy and safety in obese patients with KOA. Study durations varied from 4 to 68 weeks, with participants' mean ages ranging from 41.93 to 65.2 years and BMI values from 24.1 to 40.5 kg/m^2. The diagnostic criteria for KOA were based on established guidelines, including the American College of Rheumatology criteria, European League Against Rheumatism (EULAR) guidelines, Kellgren-Lawrence classification, and radiographic changes. The proportion of female participants ranged from 13 to 88% across treatment groups (Table 1). Notably, only one study on semaglutide and one on liraglutide met the inclusion criteria. As a result, the findings related to these GLP-1 receptor agonists are derived from these two trials, each involving populations with unique characteristics. For instance, the semaglutide trial included participants with a mean baseline BMI of 40.5 kg/m^2 and a mean WOMAC pain score above 70, indicating higher disease severity compared to other KOA studies. Similarly, the liraglutide trial involved a distinct patient population with specific baseline characteristics. These differences highlight the potential limitations in generalizing the results to other subsets of obese patients with KOA, particularly those with less severe disease or differing comorbidities.

Risk of bias assessment

The risk of bias assessment for the included studies is summarized in Fig. 2. Figure 2A illustrates the overall distribution of bias categories across all studies. Most studies demonstrated a low risk of bias in domains such as random sequence generation (selection bias) and allocation concealment (selection bias). However, some uncertainty was noted in the domains of blinding of participants and personnel (performance bias) and blinding of outcome assessment (detection bias), where a moderate proportion of studies were classified as having an unclear risk of bias. Attrition bias, associated with incomplete outcome data, and selective reporting (reporting bias) also exhibited varying levels of unclear risk, with one study presenting a high risk of selective reporting. Other biases were generally well-controlled, with the majority of studies classified as low risk. Figure 2B provides a study-specific breakdown of risk of bias assessments. Each included trial was evaluated across seven domains. The majority of studies scored consistently low risk across most domains, but specific concerns were noted for individual studies.

Methodological quality assessment

All included studies were evaluated across 16 AMSTAR 2 items, with particular emphasis on critical domains such as protocol registration, comprehensive literature search, and risk of bias assessment in individual studies. Most studies demonstrated a high methodological quality, with no non-critical weaknesses, ensuring a comprehensive and accurate summary of the available evidence. However, some studies were classified as moderate or low quality due to non-critical weaknesses or the presence of a critical flaw. A summary of the AMSTAR 2 classification for each study is presented in Supplementary File 3, which provides a detailed breakdown of individual item assessments.

Pain relief outcomes

For WOMAC pain score improvement, metformin demonstrated the largest effect size with a MD of − 1.13 (95% CI − 1.48, − 0.78) compared to usual care, followed by MFPH (MD: − 0.92, 95% CI − 1.70, − 0.13) and semaglutide (MD: − 0.90, 95% CI − 1.48, − 0.32). Pioglitazone (MD: − 0.78, 95% CI − 1.27, − 0.19) and liraglutide (MD: − 0.37, 95% CI − 0.86, 0.12) showed smaller reductions in pain scores (Fig. 3A). Despite these differences in effect sizes, most treatment comparisons were derived from only one study each, limiting the robustness of indirect estimates.

The SUCRA rankings for WOMAC pain score improvement (Fig. 4A) identified metformin as the most effective treatment, with a SUCRA value of 86.8% and the highest probability of being ranked first (50.2%). Metformin-Phosphatidylcholine (MFPH) (66.8%) and semaglutide (66.1%) followed, demonstrating substantial efficacy. Usual care consistently ranked the lowest, with a SUCRA value of 1.5%, indicating minimal impact on pain relief.

Safety outcomes

For safety outcomes (Fig. 3B), usual care ranked as the safest intervention with a SUCRA value of 75.7% and a high probability of being ranked first (24.9%). Liraglutide (62.8%) and semaglutide (52.5%) also demonstrated favorable safety profiles. Pioglitazone, with a SUCRA value of 24.1%, exhibited the lowest safety ranking due to its higher likelihood of adverse events. The cluster analysis (Fig. 4B) revealed a trade-off between efficacy and safety among the interventions. Metformin and MFPH were positioned as highly effective for pain relief but exhibited moderate safety concerns. In contrast, usual care demonstrated superior tolerability but limited efficacy (Supplemental Content). The cluster analysis (Fig. 4C) highlighted a trade-off between efficacy and safety: Metformin and MFPH were highly effective for pain relief but had moderate safety concerns. Usual care had the highest safety ranking but minimal impact on pain relief. These findings suggest that treatment selection should balance efficacy and tolerability for optimal patient outcomes.

Table 1 Characteristics of all studies and included arms

Author (Years)	Study design, location	Sample of study (n)	Drug classification	Medication (group size)		Duration (Weeks)	Female (%)		Age (years)		BMI (kg/m^2)		Diagnosis of osteoarthritis
				A	B		A	B	A	B	A	B	
Henning Bliddal (2024)	RCT, Denmark	407	GLP-1 receptor agonists	Semaglutide initiated at a dose of 0.24 mg, with dose escalation intended to reach the 2.4-mg target at week 16	Usual care Placebo (n = 136)	68	228 (84.1%)	104 (76.5%)	56 ± 10	56 ± 10	40.5 ± 7.3	40.0 ± 7.1	American College of Rheumatology criteria
Amany Abd Elaal Aiad (2024)	RCT, Egypt	50	Biguanide	Metformin 500 mg tablet orally twice daily plus celecoxib 200 mg capsule orally once daily for 12 weeks	Usual care Placebo (n = 25)	12	22 (88%)	22 (88%)	51.00 ± 5.75	52.28 ± 6.1	36.40 ± 5.55	38.49 ± 5.93	European League Against Rheumatism (EULAR) guidelines
Henrik Gudbergsen (2021)	RCT, Denmark	168	GLP-1 receptor agonists	Liraglutide 3 mg/d	Usual care Placebo (n = 76)	52	52 (65%)	49 (64%)	59.2 ± 10.8	59.3 ± 9.7	32.8 ± 5.5	31.3 ± 4.0	KOA changes in knee radiography
Nahid Alimoradi (2023)	RCT, Iran	88	Biguanide	Metformin 0.5 g/day for the first week, increase to 1 g/day for the second week, and further increase to 1.5 g/day for the remaining period	Usual care Placebo (n = 44)	12	34 (77.3%)	30 (68.2%)	49.3 ± 9.3	47.2 ± 9.0	29.1 ± 3.1	29.0 ± 3.8	Kellgren-Lawrence (K-L) classification
Marwah Salih Abed (2024)	RCT, Egypt	78	Biguanide; Ultrasound therapy	Phonophoresis of metformin gel (MFPH)	Usual care Ultrasound therapy (n = 26)	4	16 (60%)	15 (57%)	54 ± 6.4	54.2 ± 7.6	27.8 ± 1.2	27 ± 1.5	American College of Rheumatology criteria
Mohammed M. Mohammed (2014)	RCT, Iraq	57	Biguanide; TZDs	Meloxicam(15 mg/day) + Metformin(1000 mg/day); Meloxicam (15 mg/day) + Pioglitazone(15 mg/day)	Usual care Meloxicam (15 mg/day) (n = 20)	12	–	–	–	–	–	–	KOA changes in knee radiography
Shi Songqing (2018)	RCT, China	80	Biguanide	Metformin 500 mg tablet orally twice daily	Usual care Placebo (n = 40)	24	30 (75%)	32 (80%)	65.2 ± 7.3	64.7 ± 6.9	24.3 ± 3.2	24.1 ± 2.8	KOA changes in knee radiography
Zhang Congbin (2022)	RCT, China	83	GLP-1 receptor agonists	Liraglutide 0.6 mg	Metformin 500 mg (n = 40)	12	16 (38%)	19 (46.3%)	54.23 ± 4.61	54.14 ± 4.57	–	–	Expert Consensus on Knee Osteoarthritis Ladder Treatment

Table 1 (continued)

Author (Years)	Study design, location	Sample of study (n)	Drug classification	Medication (group size)		Duration (Weeks)	Female (%)		Age (years)		BMI (kg/m^2)		Diagnosis of osteoarthritis
				A	B		A	B	A	B	A	B	
Yu Yanfei (2019)	RCT, China	58	TZDs	Pioglitazone (4mgmg/day)	Usual care Placebo (n = 29)	12	4 (13%)	5 (17%)	41.93 ± 10.54	40.34 ± 11.95	27.13 ± 2.91	26.59 ± 3.16	Expert Consensus on Knee Osteoarthritis Ladder Treatment

Publication bias and robustness of findings

To evaluate the robustness of our meta-analysis results, a leave-one-out sensitivity analysis was conducted (Fig. 5). The results demonstrated that the overall effect estimates remained stable, with no single study exerting a disproportionate influence on the pooled estimate.

The funnel plots for WOMAC pain score improvement (Fig. 6A) and serious adverse events (Fig. 6B) assessed publication bias and heterogeneity. Both plots showed an approximately symmetrical distribution, suggesting no strong evidence of significant bias.

However, while SUCRA offers a useful ranking method, it does not establish clinical significance. The limited number of studies and heterogeneous treatment regimens suggest that rankings should be interpreted alongside effect sizes, confidence intervals, and consistency measures.

Regarding the exploration of heterogeneity, we assessed loop inconsistency, which is crucial for evaluating the consistency between direct and indirect evidence in the network. Specifically, we tested for loop inconsistency by analyzing closed loops between treatments. The results showed that the confidence intervals included zero, indicating no significant loop inconsistency. This data is included in the attached figure (Supplementary content).

Discussion

The network meta-analysis identified metformin and as the most effective treatments for WOMAC pain reduction, followed by semaglutide. In contrast, usual care ranked lowest, offering minimal pain relief. For safety, usual care was the safest, followed by liraglutide and semaglutide, while pioglitazone ranked lowest due to increased adverse events. Direct comparisons showed similar safety profiles between liraglutide, semaglutide, and usual care, whereas metformin, MFPH, and pioglitazone had slightly higher risks. The cluster analysis highlighted a trade-off between efficacy and safety, with metformin and MFPH being highly effective but moderately safe, while usual care was safest but least effective.

Comparison with existing literature

The findings of this study align with prior research suggesting that antidiabetic drugs, particularly metformin and GLP-1 receptor agonists, have potential benefits in managing KO in obese patients. Previous studies and meta-analyses have reported that metformin can alleviate pain and reduce inflammation in KOA, likely through its anti-inflammatory and weight-modulating effects. Similarly, GLP-1 receptor agonists such as liraglutide and semaglutide

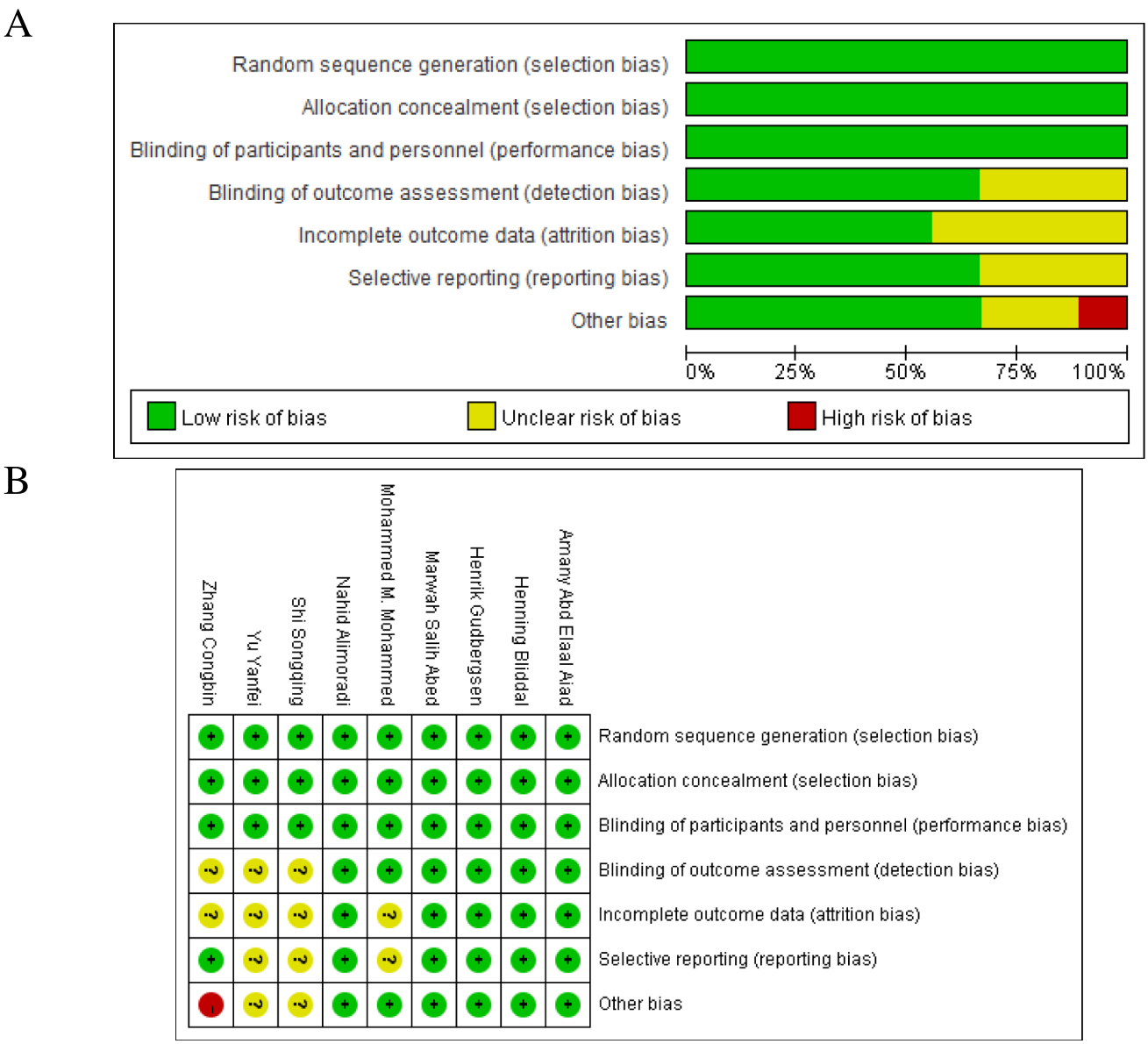

Fig. 2 The risk of bias summary for studies included in the meta-analysis

have been highlighted in earlier trials for their ability to promote weight loss and modulate metabolic inflammation, both of which are critical factors in the progression of KOA [9, 18]. However, this study provides a more nuanced understanding of these effects by ranking treatments based on efficacy and safety using a network meta-analysis framework.

Some consistencies with prior research include the confirmation of metformin's efficacy and the favorable safety profiles of GLP-1 receptor agonists. However, discrepancies were also observed, particularly regarding the lower efficacy of pioglitazone and the variability in safety profiles across studies. These differences may be attributed to heterogeneity in study populations, including differences in obesity severity, KOA diagnostic criteria, and comorbid conditions. Variations in drug dosages, treatment durations, and study designs across the included trials could also explain some of the observed inconsistencies. Additionally, the lack of long-term follow-up data in previous studies may have limited the evaluation of sustained efficacy and safety, which this analysis begins to address through its comprehensive inclusion of available evidence.

Mechanistic insights

The efficacy of antidiabetic drugs, particularly metformin and GLP-1 receptor agonists, in improving WOMAC pain scores can be attributed to their dual anti-inflammatory and

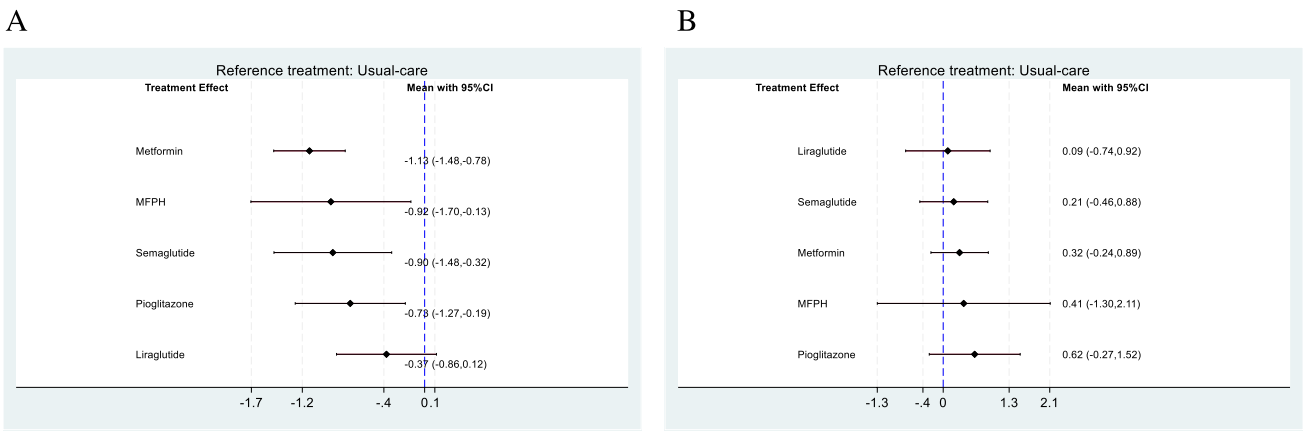

Fig. 3 Forest plot of treatment effects compared to usual care. **A** Mean differences (95% confidence intervals) for WOMAC pain score improvement. **B** Relative risks (95% confidence intervals) for serious adverse events

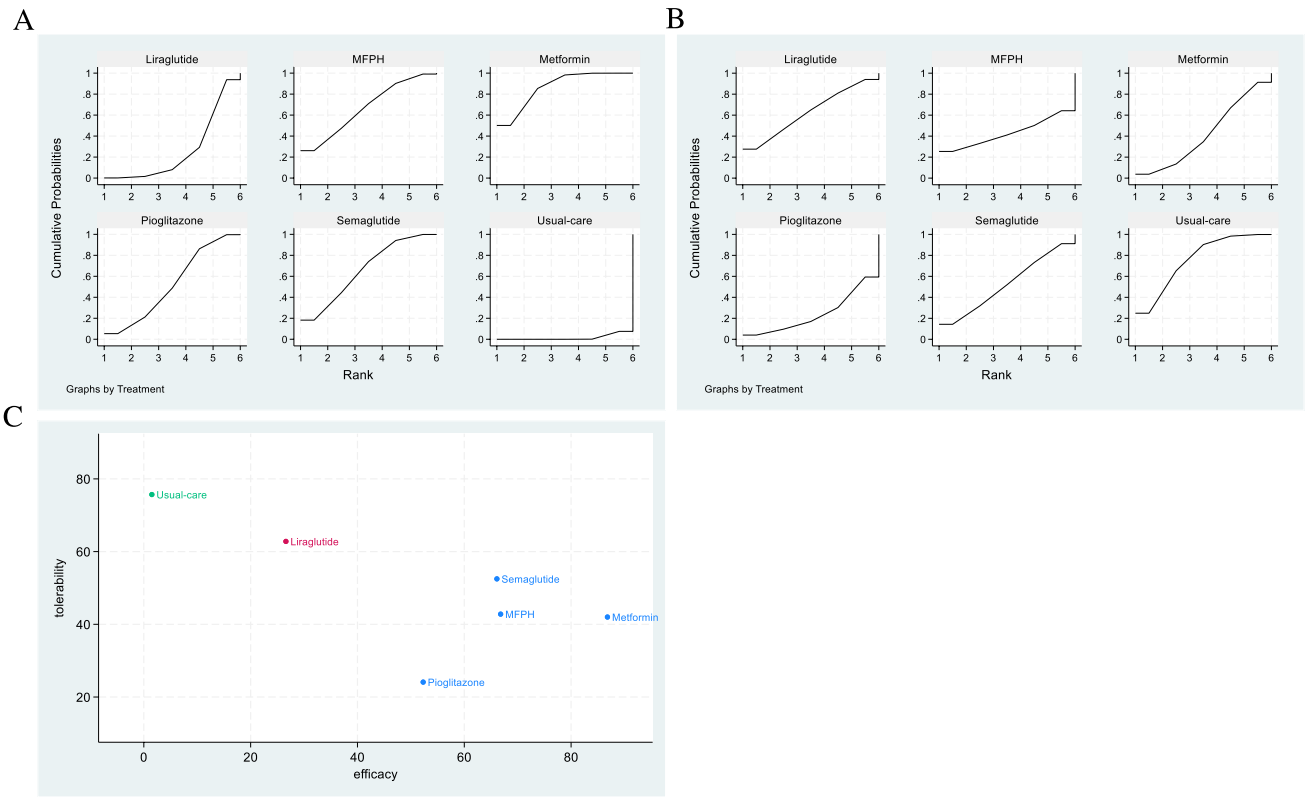

Fig. 4 SUCRA plots for efficacy and safety. **A** SUCRA rankings for WOMAC pain score improvement by treatment. **B** SUCRA rankings for serious adverse events. **C** Cluster plot showing the trade-off between efficacy and tolerability for each treatment, with treatments grouped based on their performance across both outcomes

weight-reducing effects. Metformin is known to inhibit pro-inflammatory pathways, including the nuclear factor kappa B (NF-κB) signaling pathway, and reduce the production of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) [18]. These mechanisms are particularly relevant in KOA, where inflammation plays a key role in disease progression and pain [20, 21]. Additionally, metformin's effects on glycemic control and insulin sensitivity may indirectly mitigate systemic inflammation, further contributing to pain relief [22]. GLP-1 receptor agonists, including semaglutide and liraglutide, exert their beneficial effects by promoting significant weight loss, which reduces mechanical stress on weight-bearing joints [9, 23]. Beyond their weight-reducing properties, GLP-1

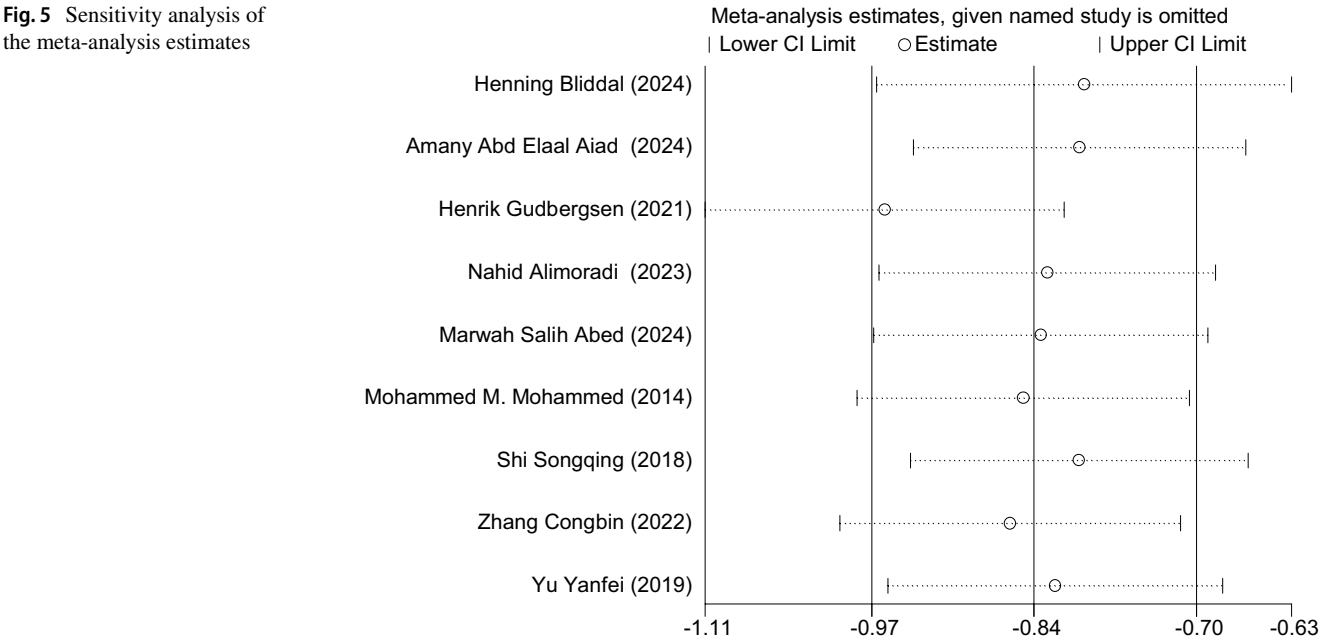

Fig. 5 Sensitivity analysis of the meta-analysis estimates

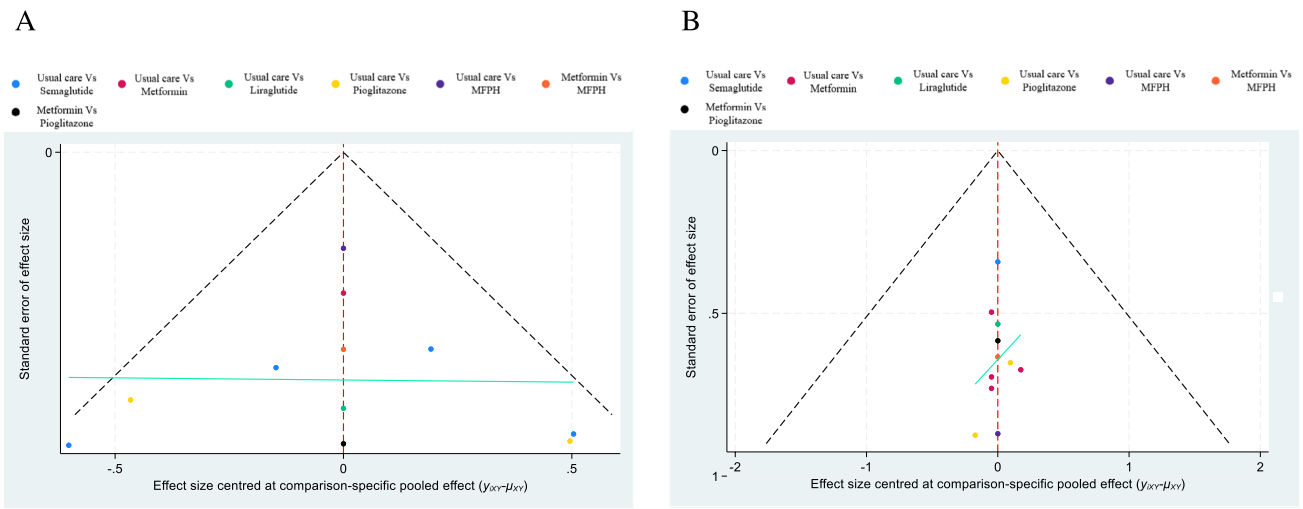

Fig. 6 Funnel plots for publication bias. **A** Funnel plot for WOMAC pain score improvement. **B** Funnel plot for serious adverse events

receptor agonists also have anti-inflammatory effects, mediated by reductions in circulating inflammatory markers and improved metabolic profiles [24]. These combined mechanisms help address both mechanical and metabolic contributors to KOA, leading to improved clinical outcomes in obese patients.

The adverse event profiles observed for certain drugs, such as pioglitazone, can be explained by their known side effects. Pioglitazone, a thiazolidinedione, is associated with fluid retention and an increased risk of heart failure due to its effects on sodium reabsorption in renal tubules and altered vascular permeability [25]. These adverse effects are particularly concerning in obese patients, who may already have a higher baseline risk of cardiovascular complications. In contrast, GLP-1 receptor agonists and usual care demonstrated more favorable safety profiles, likely due to the absence of such systemic side effects and their well-tolerated mechanisms of action.

Clinical implications

The findings of this study suggest a promising role for antidiabetic drugs, particularly metformin and GLP-1 receptor agonists like semaglutide, in the management of KOA for obese patients. These drugs offer a dual benefit of targeting both the mechanical and metabolic factors contributing

to KOA, making them uniquely positioned to address the multifactorial nature of the disease. By reducing systemic inflammation and body weight, these therapies not only alleviate symptoms such as pain but may also slow disease progression, which current standard treatments often fail to achieve. Metformin and semaglutide stand out as particularly promising candidates for integration into future clinical guidelines. Metformin, with its robust efficacy in reducing pain (as indicated by its superior SUCRA ranking), is a cost-effective option that has been widely studied in various populations. Semaglutide, on the other hand, combines substantial weight loss benefits with a favorable safety profile, offering a strong alternative for obese patients who may not tolerate metformin or require additional weight reduction to manage KOA progression. Both drugs demonstrated a balance between efficacy and safety that supports their use as part of comprehensive KOA management strategies.

However, while antidiabetic drugs, particularly metformin and GLP-1 receptor agonists, may have potential as treatment options for KOA in obese patients, caution is advised given the limited and heterogeneous evidence base. The modest differences in treatment effects observed across studies, combined with the variability in side effects, suggest that these therapies should not yet be universally recommended for inclusion in clinical guidelines. Within-class treatment effect differences for antidiabetic drugs are often modest, and composite adverse-event outcomes do not fully capture the severity or patient impact of side effects. As such, clinicians should be cautious when considering these treatments, especially given the heterogeneity in both efficacy and safety profiles observed across studies. A more nuanced understanding of side effect profiles, along with patient-reported outcomes, is needed to guide clinical decision-making.

Further high-quality studies with diverse populations and long-term follow-up are needed to better assess the role of antidiabetic drugs in KOA management. These studies should aim to clarify the magnitude of treatment effects, identify subgroups of patients who may benefit most, and provide a more comprehensive evaluation of safety profiles. Until such evidence is available, the integration of metformin and semaglutide into clinical guidelines should be approached with careful consideration, balancing their potential benefits against the uncertainties in their efficacy and safety.

Strengths and limitations

Strengths

This study has several notable strengths. First, the comprehensive inclusion of multiple antidiabetic drugs allowed for a comparative evaluation of their efficacy and safety outcomes in managing KOA among obese patients. While this approach provides valuable insights, it is important to acknowledge the limitations of the analysis, including potential biases and confounding factors that may affect the interpretation of the results. The use of a network meta-analysis framework allowed the integration of both direct and indirect evidence, increasing the reliability and scope of the findings. Second, the application of SUCRA rankings and cluster analysis provided actionable insights, facilitating the identification of treatments that balance efficacy and safety. Although there are some limitations in the study design, such as the relatively small number of included studies for certain treatments, the methods provide a reasonable basis for guiding treatment decisions in the context of available evidence.

Limitations

Despite its strengths, this study has several limitations that warrant careful consideration. First, potential heterogeneity across the included studies, such as variations in patient populations, baseline characteristics, drug dosages, and treatment durations, may have influenced the results. These differences could contribute to variability in treatment effects and limit the generalizability of the findings. For example, the findings for semaglutide in this study are based on data from a single RCT that evaluated a distinct patient population—obese individuals with KOA who had a mean baseline BMI of 40.5 kg/m^2 and a mean WOMAC pain score above 70. These characteristics, particularly the high disease severity, differ significantly from those typically reported in other KOA studies, raising concerns about the generalizability of the results to patients with less severe KOA or those with different comorbidities. While the trial demonstrated promising efficacy for pain relief and functional improvement, the conclusions drawn for semaglutide are based on limited evidence and may reflect its effects in a more severe subset of KOA patients. Caution is therefore warranted when extrapolating these findings to the broader KOA population. Second, the limited number of trials available for certain drugs, such as pioglitazone, reduces confidence in the precision of estimates for these treatments. Additionally, we acknowledge that the criteria for study inclusion and exclusion may have further constrained the number of eligible trials, particularly for semaglutide and liraglutide. The decision to exclude studies was based on clear and predefined eligibility criteria that ensured the included studies were directly relevant to our research question. Specifically, studies were excluded if they did not focus on obese patients with KOA, evaluated non-antidiabetic drugs or interventions, or did not measure outcomes aligned with our analysis objectives. While these

criteria were necessary to maintain the focus and rigor of the meta-analysis, they inevitably resulted in a smaller pool of eligible studies, particularly for GLP-1 receptor agonists. This limitation impacts the robustness of the conclusions for these interventions, and future research with a broader scope of trials and more diverse patient populations is needed to strengthen the evidence base for their use in managing KOA. Third, the lack of long-term follow-up data restricts the ability to evaluate the sustainability of both the efficacy and safety profiles of the drugs analyzed. This is particularly relevant for semaglutide, as additional trials with extended follow-up are needed to assess the durability of its effects and to determine whether similar results can be achieved in a wider, more diverse group of patients. Finally, while efforts were made to account for heterogeneity and variability across studies, residual inconsistencies cannot be entirely ruled out. Future research addressing these gaps—including larger, more diverse trials with long-term follow-up—is needed to build a more comprehensive evidence base and to validate the findings of this study.

Future directions

To build on the findings of this study, further research should focus on validating these results in larger and more diverse populations. Trials with broader inclusion criteria and representation from different geographic, ethnic, and clinical settings will improve the generalizability of the findings. Additionally, there is a need for studies exploring the long-term benefits and risks of antidiabetic drugs in KOA management. Mechanistic studies could provide deeper insights into how these drugs modulate disease pathways, further elucidating their potential as disease-modifying agents.

Future research should also prioritize evaluating the cost-effectiveness and quality-of-life impacts of these treatments. Such studies would help determine whether the observed benefits justify the cost of integrating these drugs into routine clinical practice. Lastly, trials designed to explore combination therapies, including antidiabetic drugs alongside standard KOA treatments, could identify synergistic effects and optimize therapeutic strategies.

Conclusion

This study suggests that antidiabetic drugs, particularly metformin and GLP-1 receptor agonists like semaglutide, may have potential in managing knee osteoarthritis in obese patients. However, due to the limited number of randomized controlled trials, especially for GLP-1 receptor agonists, the evidence is insufficient to firmly establish their efficacy and safety for this indication. Further research is needed to validate these findings and to explore the long-term effects of these treatments in the context of knee osteoarthritis. Metformin showed the highest efficacy for pain relief, while semaglutide balanced efficacy with a favorable safety profile. The findings highlight the importance of integrating these drugs into personalized treatment strategies that address both mechanical and metabolic contributors to KOA. Future research should focus on validating these results, exploring long-term outcomes, and assessing cost-effectiveness to support their broader adoption in clinical practice.

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Data availability All data generated or analysed during the present study are included in this published article.

Declarations

Conflict of interests The authors declare that they have no competing interests.

Human and animal rights As this is a systematic review and meta-analysis exclusively based on de-identified aggregate data from previously published studies, formal ethical approval and animal/human subject declarations are not required in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Consent for publication Not applicable.

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