

Online Resource

Journal Name: Drugs

Title: GLP-1 Receptor Agonists and musculoskeletal outcomes: a systematic literature review and meta-analysis

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Online Resource 1

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	6
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	9
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	10
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	12
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	11
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Online material
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	12
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	13
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	13
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	13
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	13
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	13-14
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	13-14
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	14-15

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	14-15
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	13-15
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	14
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	14
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	14
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	15
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	16
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	16
Study characteristics	17	Cite each included study and present its characteristics.	43-59
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	17 and Online material
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	61-63 + OSF platform
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	17-18
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	18-22
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	18-22
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	18-22
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	18-22
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	22
DISCUSSION			

Section and Topic	Item #	Checklist item	Location where item is reported
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	23-28
	23b	Discuss any limitations of the evidence included in the review.	30-31
	23c	Discuss any limitations of the review processes used.	30-31
	23d	Discuss implications of the results for practice, policy, and future research.	29-30
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	11
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	11
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	4
Competing interests	26	Declare any competing interests of review authors.	4
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	3-4

Online Resource 2

Database: Ovid MEDLINE(R) ALL <1946 to March 2025>

Search Strategy:

- 1 glucagon-like peptide-1 receptor agonists/ or exenatide/ or liraglutide/ (5999)
- 2 GLP 1.ti,ab,kf. (17617)
- 3 "glucagon like peptide 1".ti,ab,kf. (18625)
- 4 (Lixisenatide or exenatide or liraglutide or Dulaglutide or Semaglutide or Tirzepatide).ti,ab,kf. (9133)
- 5 (incretin adj1 mimetics).ti,ab,kf. (295)
- 6 (Byetta or Adlyxin or Lyxumia or Bydureon or "Bydureon BCise" or Victoza or Saxenda or Trulicity or Ozempic or Wegovy or Rybelsus or Mounjaro or Zepbound).ti,ab,kf. (412)
- 7 or/1-6 (28327)
- 8 Osteoporosis/ (53896)
- 9 Bone Diseases, Metabolic/ (9551)
- 10 Bone Density/ (63951)
- 11 Bone Demineralization, Pathologic/ (372)
- 12 Osteoporotic Fractures/ (9098)
- 13 osteoporo*.ti,ab,kf. (102795)
- 14 osteopeni*.ti,ab,kf. (13688)
- 15 (bone* adj2 (densit* or content)).ti,ab,kf. (74559)
- 16 (bone* adj2 (demineralization or demineralisation of loss* or decreas* or deterioration*)).ti,ab,kf. (14191)
- 17 metabolic bone disease*.ti,ab,kf. (3548)
- 18 (osteoporo* adj1 fracture*).ti,ab,kf. (10261)
- 19 or/8-18 (177621)
- 20 Osteoarthritis/ (46525)
- 21 exp Joints/ (291700)
- 22 (osteoarthr* or OA or WOMAC).ti,ab,kf. (125646)
- 23 ((knee or hip or pain or function or replacement) adj2 joint*).ti,ab,kf. (75361)
- 24 arthriti*.ti,ab,kf. (230876)
- 25 or/20-24 (590628)
- 26 muscles/ or muscle, skeletal/ (321846)
- 27 sarcopenia/ (12191)
- 28 sarcopeni*.ti,ab,kf. (21632)
- 29 ((muscle or lean or appendicular or fat-free) adj2 mass).ti,ab,kf. (54528)
- 30 (muscle adj2 (strength or skeletal or performance)).ti,ab,kf. (166851)
- 31 exp physical functional performance/ (4966)
- 32 Walking Speed/ (3204)
- 33 ((walk or gait) adj1 speed).ti,ab,kf. (9109)
- 34 ("short physical performance battery" or SPPB).ti,ab,kf. (3077)
- 35 "chair stand test".ti,ab,kf. (1146)
- 36 or/26-35 (452395)
- 37 19 or 25 or 36 (1174377)
- 38 7 and 37 (788)
- 39 38 not (exp animals/ not humans.sh.) (595)

40 limit 39 to english language (568)
 41 (protocol* or review* or comment*).ti. (1062076)
 42 40 not 41 (523)

Embase

No.	Query Results	Results	Date
#24.	#10 AND #21 AND [humans]/lim AND [english]/lim AND [article]/lim	655	
#23.	#10 AND #21 AND [humans]/lim AND [english]/lim	1,755	
#22.	#10 AND #21	2,182	
#21.	#16 OR #17 OR #20	1,359,642	
#20.	#18 OR #19	311,488	
#19.	'sarcopeni*':ti,ab,kw OR 'muscle mass':ti,ab,kw OR 'muscle strength':ti,ab,kw OR 'lean mass':ti,ab,kw OR 'fat free mass':ti,ab,kw OR 'skeletal muscle*':ti,ab,kw OR 'physical performance':ti,ab,kw OR 'muscle performance':ti,ab,kw OR 'walk* speed':ti,ab,kw OR 'gait speed':ti,ab,kw OR sppb:ti,ab,kw OR 'short physical performance battery':ti,ab,kw OR 'chair stand test':ti,ab,kw	308,579	
#18.	'sarcopenia'/exp	26,707	
#17.	osteoarthritis:ti,ab,kw OR 'knee joint*':ti,ab,kw OR 'hip joint*':ti,ab,kw OR 'replacement joint*':ti,ab,kw OR arthriti*:ti,ab,kw	502,163	
#16.	#11 OR #12 OR #13 OR #14 OR #15	603,543	
#15.	('metabolic bone disease'/exp OR 'bone mineral density':ti,ab,kw OR 'bone density':ti,ab,kw OR 'bone mineral content':ti,ab,kw OR 'bone loss*':ti,ab,kw OR 'bone deterioration':ti,ab,kw OR 'bone demineralisation':ti,ab,kw) AND 'bone demineralization':ti,ab,kw OR fracture*:ti,ab,kw	418,708	
#14.	osteopeni*:ti,ab,kw	23,421	
#13.	osteoporos*:ti,ab,kw	145,868	
#12.	'bone density'/exp	124,225	
#11.	'osteoporosis'/exp	168,312	
#10.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	63,720	
#9.	'liraglutide'/exp	14,828	
#8.	'exendin 4'/exp	13,108	
#7.	lixisenatide:ab,kw,ti OR exenatide:ab,kw,ti OR liraglutide:ab,kw,ti OR dulaglutide:ab,kw,ti OR semaglutide:ab,kw,ti OR tirzepatide:ab,kw,ti OR byetta:ab,kw,ti OR adlyxin:ab,kw,ti OR	17,104	

lyxumia:ab,kw,ti OR bydureon:ab,kw,ti OR
 'bydureon bcise':ab,kw,ti OR victoza:ab,kw,ti OR
 saxenda:ab,kw,ti OR trulicity:ab,kw,ti OR
 ozempic:ab,kw,ti OR wegovy:ab,kw,ti OR
 rybelsus:ab,kw,ti OR mounjaro:ab,kw,ti OR
 zepbound:ab,kw,ti

#6. 'glucagon like peptide 1':ab,kw,ti	25,558
#5. 'glp1r':ab,kw,ti	3,958
#4. 'glp-1':ab,kw,ti	29,052
#3. 'glp1':ab,kw,ti	30,260
#2. 'glucagon like peptide 1 receptor agonist':ab,kw,ti	2,830
#1. 'glucagon like peptide 1 receptor agonist'/exp	58,431

Database: EBM Reviews - Cochrane Central Register of Controlled Trials (March 2025)

Search Strategy:

- 1 "glucagon-like peptide-1 receptor agonists".ti,ab. (379)
 - 2 GLP1.ti,ab. (276)
 - 3 "glucagon like peptide 1".ti,ab. (3854)
 - 4 GLP-1.ti,ab. (4790)
 - 5 (Lixisenatide or exenatide or liraglutide or Dulaglutide or Semaglutide or Tirzepatide or Byetta or Adlyxin or Lyxumia or Bydureon or "Bydureon BCise" or Victoza or Saxenda or Trulicity or Ozempic or Wegovy or Rybelsus or Mounjaro or Zepbound).ti,ab. (5921)
 - 6 or/1-5 (9770)
 - 7 (osteoporos* or "bone densit*" or "bone mineral densit*" or "bone loss*" or "bone content*" or "bone demineralization" or "bone demineralisation" or "bone decreas*" or "bone deterioration" or fracture*).ti,ab. (42734)
 - 8 (osteoarthrit* or arthriti* or "knee joint*" or "hip joint*" or "joint* replacement").ti,ab. (49188)
 - 9 (sarcopeni* or "mucle mass" or "lean mass" or "fat free mass" or "skeletal muscle" or "muscle performance" or "muscle strength" or "physical performance" or "gait speed" or "walk* speed" or "sppb" or "short physical performance battery" or "chair stand test").ti,ab. (36315)
 - 10 or/7-9 (121405)
 - 11 6 and 10 (251)
 - 12 limit 11 to english language (248)
-

<u>Study (in intention-to-treat analysis)</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>	
Astrup, 2011	+	+	+	+	+	+	
Bliddal, 2024	+	+	+	+	+	+	+
Bunck, 2011	+	+	+	+	+	!	!
Cai, 2021	+	!	+	+	!	!	
Gerstein, 2019	+	+	+	+	+	+	
Golubic, 2024	+	+	+	+	+	+	D1 Randomisation process
Gudbergesen, 2021	!	+	+	+	+	!	D2 Deviations from the intended interventions
Hansen, 2024	+	+	+	+	+	+	D3 Missing outcome data
Heise, 2023	+	+	+	+	+	+	D4 Measurement of the outcome
Hygum, 2019	+	+	+	+	+	+	D5 Selection of the reported result
Iepsen, 2015	!	!	+	+	+	!	
Jendle, 2009	+	+	+	+	+	+	
Johansen, 2022	+	+	+	+	+	+	
Jorsal, 2017	+	+	+	-	+	-	
Kadouh, 2020	+	+	+	+	+	+	
Kushner, 2024	+	+	+	+	+	+	
Lundgren, 2021	!	+	+	+	+	!	
Margulies, 2025	+	+	+	+	+	+	
McCrimmon, 2020	+	+	+	+	+	+	
Mensberg, 2017	+	+	+	+	+	+	
Mok, 2023	!	+	+	+	+	!	
Nakaguchi, 2020	+	+	+	+	+	+	
Schmidt, 2022	+	+	+	+	+	+	
Silver, 2023	+	+	+	+	+	+	
Wadden, 2020	+	+	+	+	+	+	
Wagner, 2019	+	+	+	+	+	+	
Wilding, 2021	+	+	+	+	+	+	

Online Resource 3. Risk of bias assessment of randomized controlled trials using the Cochrane Risk of Bias 2.0 tool (intention-to-treat analyses)

<u>Study (in per-protocol analysis)</u>		D1	D2	D3	D4	D5	Overall		
Per-protocol	Akyay, 2023	+	-	+	+	!	-	+	Low risk
	Bartholdy, 2022	!	+	+	+	+	+	!	Some concerns
	Bouchi, 2017	!	+	+	+	+	!	-	High risk
	Bunck, 2010	!	+	!	-	+	-	D1	Randomisation process
	Corbin, 2023	!	-	+	+	+	-	D2	Deviations from the intended interventions
	Feng, 2019	+	+	+	+	+	+	D3	Missing outcome data
	Ghanim, 2020	+	+	+	+	+	+	D4	Measurement of the outcome
	Gilbert, 2015	+	+	+	+	+	+	D5	Selection of the reported result
	Harder, 2004	+	+	+	+	+	+		
	Jastreboff, 2022	!	+	+	+	+	!		
	Kondo, 2024	-	+	+	+	+	-		
	Ludvik, 2018	+	+	+	+	+	+		
	Neeland, 2021	+	+	+	+	+	+		
	Shoemaker, 2022	+	+	+	+	+	+		
	van Eyk, 2020	!	+	+	+	+	!		
	Yin, 2018	!	+	-	+	+	-		

Online Resource 4. Risk of bias assessment of randomized controlled trials using the Cochrane Risk of Bias 2.0 tool (per-protocol analyses)

Intention-to-treat	<u>Study</u>	D1	D2	D3	D4	D5	Overall		
	Dubé, 2018	!	+	+	+	+	!	+	Low risk
Per-protocol	<u>Study</u>	D1	D2	D3	D4	D5	Overall	!	Some concerns
	Blundell, 2017	!	+	+	+	!	!		
	Gibbons, 2021	!	+	+	+	+	!		
								D1	Randomisation process
								D5	Bias arising from period and carryover effects
								D2	Deviations from the intended interventions
								D3	Missing outcome data
								D4	Measurement of the outcome
								D5	Selection of the reported result

Online Resource 5. Risk of bias assessment of randomized crossover trials using the Cochrane Risk of Bias 2.0 tool for crossover trials

Online Resource 6. Quality assessment of real-world evidence studies using the Newcastle–Ottawa Scale

Study	Selection (4 stars)	Comparability (2 stars)	Outcome (3 stars)	Total score (9 stars)
Agcakaya, 2023	3 stars	1 star	2 stars	6 stars
Al-Mashhadi, 2022	4 stars	2 stars	3 stars	9 stars
Al-Mashhadi, 2022	4 stars	2 stars	3 stars	9 stars
Driessen, 2015	4 stars	2 stars	3 stars	9 stars
Keskin, 2022	4 stars	0 star	3 stars	7 stars
Ko, 2023	4 stars	2 stars	3 stars	9 stars
Osaka, 2023	4 stars	1 star	3 stars	8 stars
Patil, 2023	3 stars	2 stars	3 stars	8 stars
Patorno, 2021	4 stars	2 stars	3 stars	9 stars
Song, 2018	3 stars	1 star	3 stars	7 stars
Ueda, 2018	4 stars	2 stars	3 stars	9 stars
Zhu, 2023	4 stars	2 stars	3 stars	9 stars
Zhuo, 2021	4 stars	2 stars	3 stars	9 stars

Online Resource 7. GRADE assessment per outcomes

Treatments	n. studies / no of participants	Start of grading de evidence	Quantitative analysis possible		GRADE assessment					
			Leave-one-out sensitivity analysis	Publication bias assessment	Risk of bias (high in more than 75% of included studies)	Inconsistency (i.e. unexplained heterogeneity)	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
Lumbar spine BMD	k=5 RCTs, n=245 individuals	High	YES	NO	Not serious	Not serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕ ⊕ ⊕
Femoral neck BMD	k=5 RCTs, n=245 individuals	High	YES	NO	Not serious	Serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕ ⊕
Total hip BMD	k=4 RCTs, n=265 individuals	High	YES	NO	Not serious	Serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕ ⊕
Total body BMD	k=5 RCTs, n=254 individuals	High	YES	NO	Not serious	Serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕ ⊕
Hip fractures	k=4 RWE studies, n=472,054 individuals	Moderate	YES	NO	Not serious	Serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕
MOF fractures	k=3 RWE studies, n=315,778 individuals	Moderate	YES	NO	Not serious	Serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕
Any fractures	k=7 RWE studies, n=972,713 individuals	Moderate	YES	NO	Not serious	Serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕
	K=3 RCTs, n=11,070 individuals	High	YES	NO	Not serious	Not serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕ ⊕ ⊕
Vertebral fractures	k=3 RWE studies, n=401,360 individuals	Moderate	YES	NO	Not serious	Not serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕ ⊕
Lean mass / fat free mass	k=27 RCTs, n=1,765 individuals	High	YES	YES	Not serious	Serious	Serious	Not serious	Not serious	⊕ ⊕
Skeletal muscle mass	k=3 RWE studies, n=370 individuals	Moderate	YES	NO	Not serious	Not serious	Serious	Serious	Not measurable but not suspected	⊕
	k=2 RCTs, n=65 individuals	High	YES	NO	Not serious	Serious	Serious	Serious	Not measurable but not suspected	⊕
WOMAC function	k=3, n=2,331 individuals	High	YES	NO	Not serious	Serious	Not serious	Not serious	Not measurable but not suspected	⊕ ⊕ ⊕

WOMAC pain	k=2 RCTs, n= 563 individuals	<i>High</i>	<i>YES</i>	<i>NO</i>	<i>Not serious</i>	<i>Serious</i>	<i>Serious</i>	<i>Serious</i>	<i>Not measurable but not suspected</i>	⊕
WOMAC stiffness	k=2 RCTs, n=563 individuals	<i>High</i>	<i>YES</i>	<i>NO</i>	<i>Not serious</i>	<i>Serious</i>	<i>Serious</i>	<i>Serious</i>	<i>Not measurable but not suspected</i>	⊕
WOMAC total	k=2 RCTs, n=563 individuals	<i>High</i>	<i>YES</i>	<i>NO</i>	<i>Not serious</i>	<i>Serious</i>	<i>Serious</i>	<i>Serious</i>	<i>Not measurable but not suspected</i>	⊕

Certainty of evidence is graded as follows: High: ⊕⊕⊕⊕; Moderate: ⊕⊕⊕⊖; Low: ⊕⊕⊖⊖; Very low: ⊕⊖⊖⊖.