Received: 16 November 2023 | Accepted: 1 May 2024

DOI: 10.1111/eci.14240

SYSTEMATIC REVIEW

WILEY

The acute effect of exercise on the endothelial glycocalyx in healthy adults: A systematic review and meta-analysis

Alicia Saz-Lara[1] | **Iván Cavero-Redondo**[2] | **Andrea del Saz-Lara**[3,4] | **Eva Rodríguez-Gutiérrez**[1] | **Bruno Bizzozero-Peroni**[1,5] | **Carlos Pascual-Morena**[1]

[1]Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca, Spain

[2]Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, Chile

[3]Laboratory of Epigenetics of Lipid Metabolism, Madrid Institute for Advanced Studies (IMDEA)-Food, CEI UAM + CSIC, Madrid, Spain

[4]Laboratory of Functional Foods, Madrid Institute for Advanced Studies (IMDEA)-Food, CEI UAM + CSIC, Madrid, Spain

[5]Departamento de Educación Físicay Salud, Instituto Superior de Educación Física, Universidad de la República, Rivera, Uruguay

Correspondence
Iván Cavero-Redondo, Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Talca, Chile.
Email: ivan.cavero@uclm.es

Abstract

Background: In recent years, it has been demonstrated that when the endothelial glycocalyx, composed of proteoglycans, glycosaminoglycans and glycoproteins, is altered or modified, this property is lost, playing a fundamental role in cardiovascular pathologies. Cardiovascular risk factors can destroy the endothelial glycocalyx layer. Exercise has a positive effect on cardiovascular risk factors, but little is known about its direct effect on the integrity of the endothelial layer.

Methods: The Cochrane Library, PubMed, Web of Science and Scopus databases were searched from their inception to June 30, 2022. The DerSimonian and Laird method was used to compute pooled effect size estimates and their respective 95% confidence intervals for the acute effect of exercise (within 24 h) on the endothelial glycocalyx and its components in healthy adults.

Results: Ten studies were included in the meta-analysis, with a total of 252 healthy subjects. The types of exercise included were resistance training, interval training, resistance training and maximal incremental exercise, with a duration range of 30–60 min. Glycocalyx assessment times included ranged from 0 to 90 min post-exercise. Our findings showed that endothelial glycocalyx increases after acute effect of exercise in healthy population (.56, 95% CI: .38, .74). The acute effect of exercise on endothelial glycocalyx components were .47 (95% CIs: .27, .67) for glycosaminoglycans, .67 (95% CIs: .08, 1.26) for proteoglycans and .61 (95% CIs: .35, .86) for glycoproteins.

Conclusions: In a healthy population, various types of exercise showed an acute improvement of the endothelial glycocalyx and its individual components.

KEYWORDS
endothelial glycocalyx, exercise, glycoproteins, glycosaminoglycans, proteoglycans

1 | INTRODUCTION

The endothelial glycocalyx, a carbohydrate-rich layer lining the vascular endothelium, is an important determinant of vascular permeability.[1–4] Furthermore, in healthy vessels, the endothelial glycocalyx attenuates interactions between blood cells and vessel walls, mediates shear stress sensing, enables balanced signalling and has a vasculoprotective function.[1] Proteoglycans are core proteins to which one or more glycosaminoglycan chains are attached and glycoproteins are considered the main connecting components between the endothelial glycocalyx and the endothelium.[5,6] These components form a network incorporating soluble molecules derived from the plasma or endothelium, which contributes greatly to the functional significance of the endothelial glycocalyx (Figure 1), as do endothelial markers such as syndecan, heparan sulfate, hyaluronic acid or selectins (Figure S1).[7,8]

In recent years, it has been demonstrated that when the endothelial glycocalyx is altered or modified, these properties are lost, playing a fundamental role in cardiovascular pathologies such as atherosclerosis, ischaemia and diabetes.[9] Currently, considering cardiovascular diseases (CVDs) as the main cause of morbidity and mortality worldwide, there are different strategies aimed at reducing the risk factors associated with this pathology[10]; however, only a 20%–30% reduction in cardiovascular events has been achieved.[11] Given the need for new strategies to improve cardiovascular outcomes, strategies focused on improving endothelial function have recently emerged, as increasing evidence reveals the critical role of the endothelial glycocalyx in vascular protection, modulation and haemostasis.[1]

Regular physical exercise offers a protective effect on cardiovascular health.[12–15] Moreover, there is evidence that exercise-based rehabilitation, prescribed on an individualized basis, improves the quality of life of patients with CVD.[16] In addition to reducing cardiovascular risk factors such as blood lipids, insulin resistance and hypertension,[17] which can destroy the endothelial glycocalyx layer,[1] the positive effects of exercise include the bioavailability of endothelium-derived nitric oxide. Nitric oxide bioavailability and production are associated with the integrity of the endothelial glycocalyx layer, which is essential for maintaining vascular homeostasis.[18] However, little is known about the effect of exercise on the integrity of the glycocalyx layer.

Although the protective effect of exercise on CVD has been described in several studies,[12–15] evaluating the possible acute beneficial or adverse effects of exercise on the endothelial glycocalyx seems necessary. Therefore, the objectives of this systematic review and meta-analysis were (i) to assess the acute effect of exercise on the endothelial glycocalyx in healthy adults, (ii) to assess the acute effect of exercise on endothelial glycocalyx components in healthy adults, and (iii) to assess the acute effect of exercise on markers of endothelial glycocalyx components in healthy adults.

2 | METHODS

This systematic review and meta-analysis was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[19] and was performed following the recommendations of the Cochrane Collaboration Handbook.[20] This study was registered in PROSPERO (Registration number: CRD4202235070).

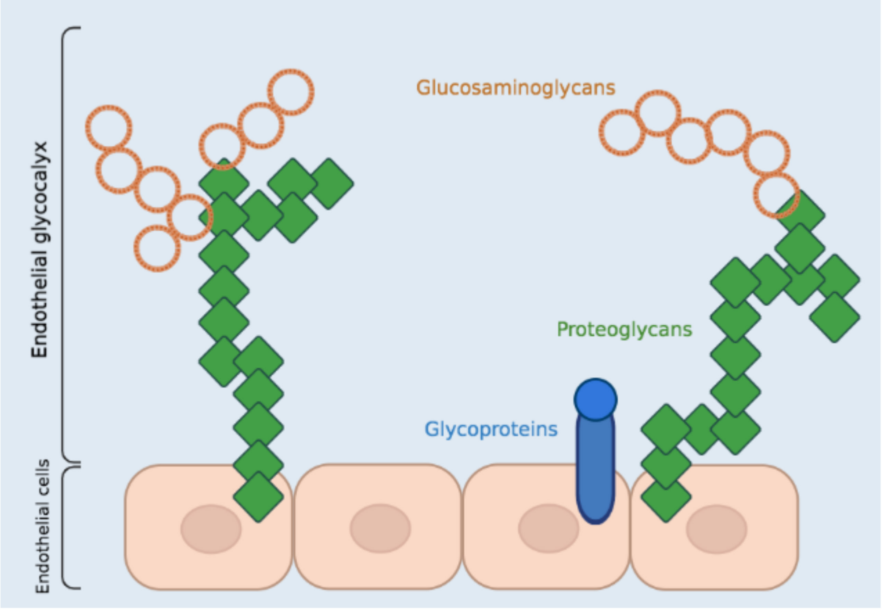

FIGURE 1 Structure and composition of the endothelial glycocalyx components.

2.1 | Search strategy

Two reviewers (A.S.-L. and I.C.-R.) independently conducted systematic searches of the Cochrane Library, PubMed (via Medline), Web of Science and Scopus databases from their inception to June 30, 2022. The following free terms were used in combination with Boolean operators following the PICO strategy (population, intervention, comparison, outcome): adults, 'adult population', 'adult subjects', exercise, 'physical exercise', 'physical activity', training, 'physical training', acute, 'acute effect', 'inmediate effect', 'endothelial glycocalyx', 'glycocalyx components', proteoglycan, syndecan, glypican, perlecan, mimecan, biglycan, versican, decorin, glycosaminoglycans, 'heparan sulfate', 'chondroitin sulfate', 'dermatan sulfate', 'keratan sulfate', 'hyaluronic acid', hyaluronan, glycoproteins, selectins, 'E-selectin', P-selectin', integrins, immunoglobulin, ICAM, VCAM, PCAM, 'functional complexes', 'glycoprotein Ib-IX-V complex' and 'von Willebrand factor'. Table S1 shows the search strategy used for the Medline database. Furthermore, we searched the reference lists of the included articles as well as previous systematic reviews or meta-analyses. A final search was performed just before the final analysis to include the most recently published studies.

2.2 | Eligibility and data extraction

Studies examining the acute effect of exercise on the endothelial glycocalyx were included in the systematic review and meta-analysis. The inclusion criteria were as follows: (i) population: healthy subjects older than 18 years; (ii) intervention: pre–post exercise (maximal incremental exercise, endurance training, interval training, resistance training); (iii) outcome: endothelial glycocalyx components (proteoglycans, glycosaminoglycans, glycoproteins); and (iv) study design: clinical trials. The following were excluded: (i) reports on the effect of exercise measured 24 h after the intervention; (ii) review articles, editorials, or case reports; (iii) studies including interventions combining exercise with supplements or diet; and (iv) articles that were not written in English.

The main characteristics of the included studies are summarized in Table 1, which includes the following information: (1) reference: first author and year of publication; (2) country in which the study data were collected; (3) study design (randomized clinical trial [RCT] or non-RCT); (4) population characteristics: sample size (percentage of males) and mean age; (5) intervention characteristics: exercise intervention (maximal incremental exercise, endurance training, interval training, resistance training), exercise characteristics and assessment points; and (6) outcome: endothelial glycocalyx components (proteoglycans, glycosaminoglycans, glycoproteins) and markers (syndecan-1, chondroitin sulfate, heparan sulfate, hyaluronic acid, E-selectin, P-selectin, VCAM-1, ICAM-1, von Willebrand factor) and measurement technology used.

2.3 | Quality assessment

The quality of the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Rob2).[21] This tool evaluates the Rob2 according to five domains: randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. Overall bias was considered 'low Rob2' if all domains were classified as 'low risk', 'some concerns' if there was at least one domain rated as 'some concern' and 'high Rob2' if there was at least one domain rated as 'high risk' or several domains rated as 'some concerns'.

Study selection, data extraction and quality assessment were performed independently by two researchers (A.S.-L. and I.C.-R.), and disagreements were resolved by consensus or with the participation of a third researcher (C.P.-M.).

2.4 | Data synthesis and statistical analysis

The DerSimonian and Laird random effects method[22] was used to compute pooled estimates of effect size (ES) and their respective 95% confidence intervals (95% CIs) for the acute effect of exercise on the endothelial glycocalyx. Acute effect of exercise was considered as the effect of a single training session, which was not part of any physical training program.[23] In addition, pooled ES estimates were calculated for endothelial glycocalyx components (proteoglycans, glycosaminoglycans, glycoproteins). At least five studies were required for each exposure group in the meta-analyses.[24] Heterogeneity was assessed using the I^2 statistic, which ranges from 0% to 100%.[25] According to the I^2 values, heterogeneity was considered not important (0%–30%), moderate (30%–60%), substantial (60%–75%), or considerable (75%–100%). The corresponding p values were also considered.

Sensitivity analysis (systematic reanalysis removing studies one at a time) was also conducted to assess the robustness of the summary estimates. In addition, a sensitivity analysis was performed by removing studies that included resistance training to assess whether it influenced the robustness of the total effect of acute effect of exercise on the endothelial glycocalyx. Subgroup analysis according to the

TABLE 1 Baseline characteristics of the included studies.

Reference	Country	Study design	Population characteristics: Sample size (*n*, %male)	Population characteristics: Mean age (years)	Intervention characteristics: PE intervention	Intervention characteristics: PE characteristics	Intervention characteristics: Assessment points (min)	Outcome: Endothelial glycocalyx: Components	Outcome: Endothelial glycocalyx: Markers	Outcome: Endothelial glycocalyx: Measurement technology used
Smith et al, 2000[26]	United States	Non-RCT	6 (100)	23.7 ± 3.3	Resistance training	Eccentric phase of a bench press and a leg curl (4 sets, 12 repetitions/set) at an intensity equivalent to 100% 1RM	90	Glycoproteins	E-selectin P-selectin VCAM-1 ICAM-1	ELISA
Monchanin et al, 2007[27]	Cameroon	Non-RCT	G1: 6 (100) G2: 7 (100) G3: 7 (100)	G1: 29.5 ± 1.9 G2: 29.5 ± 2.7 G3: 29.4 ± 1.9	Maximal incremental exercise	An incremental test on a ergometer, the work rate was increased every minute by 30-Wsteps until exhaustion	0	Glycoproteins	VCAM-1 ICAM-1	ELISA
Monchanin et al, 2008[28]	Cameroon	Non-RCT	G1: 8 (100) G2: 5 (100) G3: 7 (100)	28 ± 2.5 30 ± 2.8 29 ± 1.9	Endurance training	60-min on cycloergometer with a workload set at 70% peak power	0	Glycoproteins	VCAM-1 ICAM-1	ELISA
Pruksakorn et al, 2013[29]	Thailand	Non-RCT	G1: 58 (41.4) G2: 24 (58.3)	18–25	Endurance training	Walk for 14 km with an incline of 5.97° or horizontal track	0	Glycosaminoglycans	Chondroitin sulfate Hyaluronic acid	ELISA
Majerczak et al, 2016[30]	Poland	Non-RCT	21 (100)	22.7 ± 1.37	Maximal incremental exercise	Bicycle ergometer, at a pedalling rate of 60 r.p.m., starting from a power output of 30 W and followed by a gradual increase by 30 W every 3 min until exhaustion	0	Proteoglycans Glycosaminoglycans Glycoproteins	Syndecan-1 Heparan sulfate Hyaluronic acid VCAM-1 ICAM-1	ELISA ELISA ELISA

TABLE 1 (Continued)

Reference	Country	Study design	Population characteristics: Sample size (n, %male)	Population characteristics: Mean age (years)	Intervention characteristics: PE intervention	Intervention characteristics: PE characteristics	Intervention characteristics: Assessment points (min)	Outcome: Endothelial glycocalyx: Components	Outcome: Endothelial glycocalyx: Markers	Outcome: Endothelial glycocalyx: Measurement technology used
Majerczak et al, 2017[31]	Poland	Non-RCT	11 (100)	22.4 ± 1.4	Maximal incremental exercise	Bicycle ergometer, at a pedalling rate of 60 r.p.m., starting from a power output of 30 W and followed by a gradual increase by 30 W every 3 min until exhaustion	0	Proteoglycans	Syndecan-1	ELISA
								Glycosaminoglycans	Heparan sulfate Hyaluronic acid	ELISA
								Glycoproteins	VCAM-1 ICAM-1	ELISA
Roberts et al, 2018[32]	United Kingdom	RCT	30 (5.0)	27.0 ± 5.0	Endurance training Resistance training	40 min of walking exercise (80%HRmax) and 40 min of lower-body resistance training, 15 repetitions (80% 1-RM)	0	Glycosaminoglycans	Hyaluronic acid	ELISA
Lee et al, 2019[33]	Norway	RCT	13 (100) 13 (100)	49.8 ± 7.4 52.5 ± 5.6	Endurance training Resistance training	Endurance bicycle sessions (60 min each), 70% VO2max, and whole-body resistance exercise sessions (60 min each),12–20 repetitions 1-RM	0	Proteoglycans	Syndecan-1 Syndecan-4	ELISA

(Continues)

TABLE 1 (Continued)

			Population characteristics		Intervention characteristics			Outcome: Endothelial glycocalyx		
Reference	Country	Study design	Sample size (n, %male)	Mean age (years)	PE intervention	PE characteristics	Assessment points (min)	Components	Markers	Measurement technology used
Sapp et al, 2019[34]	United States	Non-RCT	10 (100)	22.0 ± 2.0	Interval training Endurance training	30-min moderate continuous (60% PPO) and high-intensity interval cycling exercise bouts (3-min intervals at 85% PPO interspersed with 4-min intervals at 40% PPO)	10	Proteoglycans Glycoproteins	Syndecan-1 von Willebrand factor	ELISA ELISA
Pranskuniene et al, 2020[35]	Lithuania	RCT	18 (100)	23 (22–28)	Interval training	Each sprint interval exercise bout comprised 12 repeats of 5 seg on a cycle ergometer	0	Proteoglycans	Syndecan-1	ELISA
Kropfl et al, 2021[36]	Switzerland	Non-RCT	18 (100)	29.7 ± 4.0	Interval training	Bouts of 4 min high-intensity cycling/running intersped by 3 minof low intensity exercise		Proteoglycans Glycosaminoglycans	Syndecan-1 Heparan sulfate Hyaluronic acid	ELISA ELISA

Note: Data are shown as mean ± standard deviation (SD) or interquartile range.

Abbreviations: ELISA, enzyme-linked immunosorbent assay; ICAM-1, intercellular adhesion molecule-1; PE, physical exercise; RCT, randomized clinical trial; VCAM-1, vascular adhesion molecule-1.

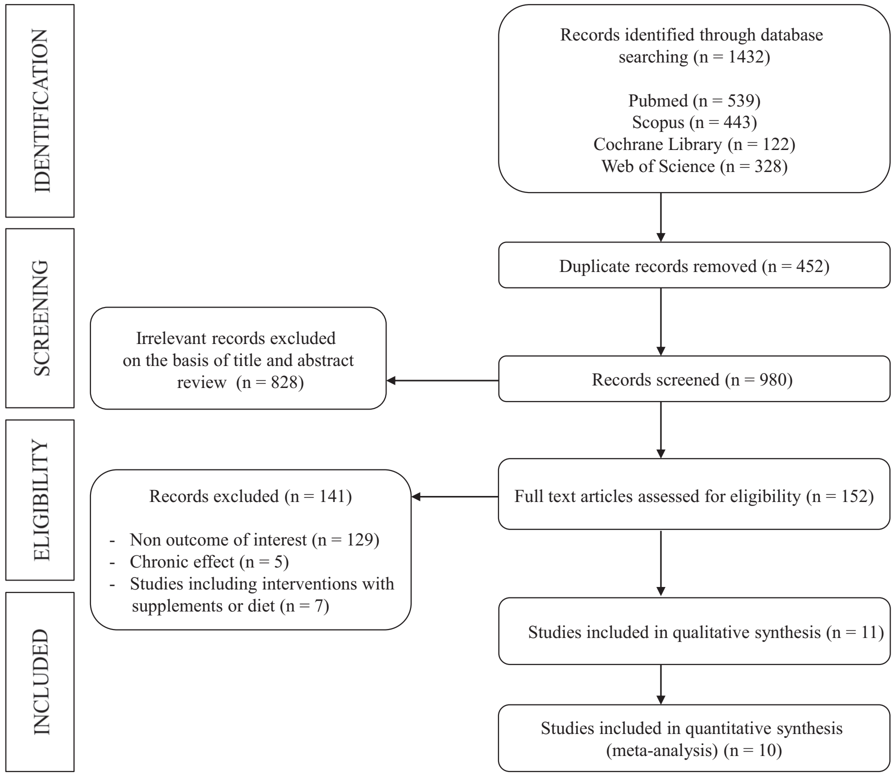

FIGURE 2 Flowchart: Search strategy.

acute effect of exercise on the expression of the endothelial glycocalyx components (syndecan-1, chondroitin sulfate, heparan sulfate, hyaluronic acid, E-selectin, P-selectin, VCAM-1, ICAM-1, and von Willebrand factor) was performed. Randomeffects meta-regressions were used to assess whether mean age, percentage of males or assessment points, as continuous variables, modified the acute effect of exercise on the endothelial glycocalyx. Finally, publication bias was evaluated using Egger's regression asymmetry test.[26] A level of <.10 was used to determine whether publication bias was present.

Statistical analyses were performed using STATA SE software, version 15 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Baseline characteristics

A total of 11 studies[27–37] were included in the systematic review and 10 studies[27–33,35–37] were included in the meta-analysis (Figure 2). All included studies were non-RCTs,[27–32,35,37] except for three that were RCTs.[33,34,36] The records were published between 2000 and 2021 and were obtained from eight countries: two in the United States,[27,35] Cameroon[28,29] and Poland[31,32] and one in Thailand,[30] the United Kingdom,[33] Norway,[34] Lithuania[36] and Switzerland.[37] The sample sizes of the studies ranged from 9 to 58 healthy adults (aged 18.0–52.5 years). The included assessment time points ranged from 0 to 90 min after exercise. The most common type of exercise was endurance training (five studies),[29,30,33–35] followed by interval training (three studies),[35–37] resistance training (three studies)[27,33,34] and maximal incremental exercise (three studies).[28,31,32] Regarding endothelial glycocalyx components, six studies included glycoproteins,[27–29,31,32,35] six studies included proteoglycans[31,32,34–37] and five studies included glycosaminoglycans.[30–33,37] Finally, in reference to markers of endothelial glycocalyx components, six studies reported data on syndecan-1,[31,32,34–37] five studies on VCAM-1,[27–29,31,32] ICAM-1[27–29,31,32] and hyaluronic acid[30–33,37]; three studies on heparan sulfate[31,32,37]; and one study on syndecan-4,[34] von Willebrand factor,[35] chondroitin sulfate,[30] E-selentin[27] and P-selectin.[27] Finally, all included studies used an enzyme-linked immunosorbent assay (ELISA) for the measurement of endothelial glycocalyx markers. Table 1 shows the characteristics of the included studies.

3.2 | Quality assessment

The overall Rob2 for records showed a high Rob2 in 72.7% of the included studies and some concerns in 27.3% of the included studies. Regarding the specific domains, we identified one main reason for the high Rob2: (i) most of the included studies were not randomized. In addition, none of the studies provided information on whether the investigators were blinded to the intervention of the participants (Figure S2).

3.3 | Acute effect of exercise on the endothelial glycocalyx

The pooled ES of the acute effect of exercise on the endothelial glycocalyx was .56 (95% CIs: .38, .74). Heterogeneity between studies was not important (I^2=27.7%; p=.118) (Figure 3).

3.4 | Acute effect of exercise on endothelial glycocalyx components

ES estimates of the acute effect of exercise on endothelial glycocalyx components were .47 (95% CIs: .27, .67) for glycosaminoglycans, .67 (95% CIs: .08, 1.26) for proteoglycans and .61 (95% CIs: .35, .86) for glycoproteins. Heterogeneity between studies was not important for glycosaminoglycans and glycoproteins (I^2=7.0%; p=.372 and I^2=.0%; p=.630, respectively), and heterogeneity was substantial for proteoglycans (I^2=72.0%; p=.007) (Figure 3).

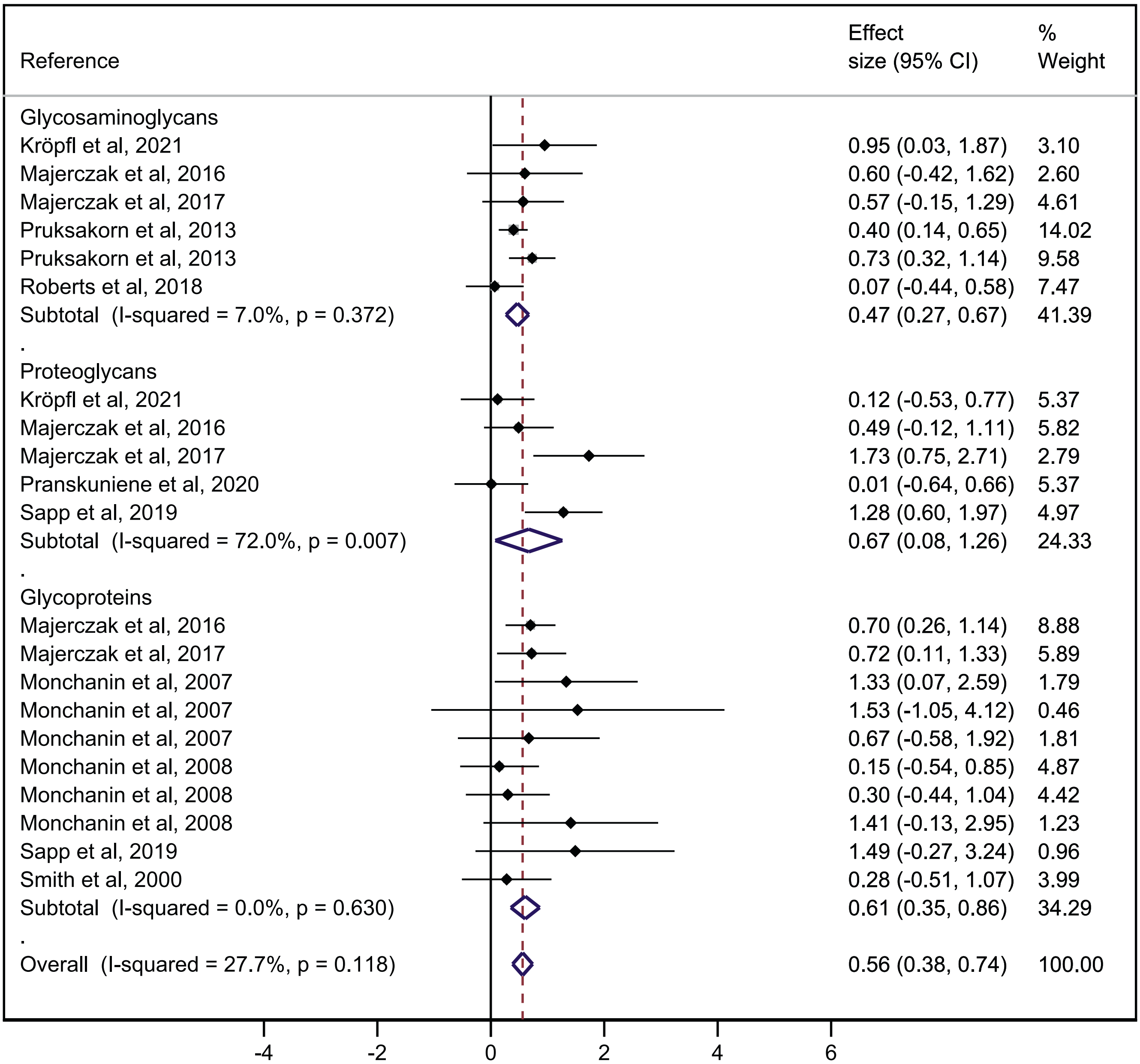

FIGURE 3 Forest plot for the acute effect of exercise on endothelial glycocalyx components (Proteoglycans, glycosaminoglycans and Glycoproteins).

3.5 | Sensitivity analysis

The pooled ES estimate for the acute effect of exercise on the endothelial glycocalyx and its components was not significantly modified (in magnitude or direction) when the data from individual studies were removed one at a time from the analysis. In addition, when a sensitivity analysis was performed by removing studies that included resistance training, the acute effect of exercise on the endothelial glycocalyx and its components was also not significantly modified.

3.6 | Subgroup analysis and meta-regression models

When analyses based on markers of endothelial glycocalyx components (syndecan-1, chondroitin sulfate, heparan sulfate, hyaluronic acid, E-selectin, P-selectin, VCAM-1, ICAM-1 and von Willebrand factor) were performed to estimate the acute effect of exercise, pooled ES estimates showed significant results for syndecan-1 (ES: .73; 95% CIs: .19–1.27, $I^2=65.6\%$), hyaluronic acid (ES: .67; 95% CIs: .30–1.04, $I^2=58.0\%$), ICAM-1 (ES: .54; 95% CIs: .21–.87, $I^2=.0\%$), and VCAM-1 (ES: .93; 95% CIs: .45–1.41, $I^2=46.6\%$) (Table S2).

Random-effects meta-regression models showed that mean age, percentage of males, and assessment points were not related to pooled ES estimates (Table S3).

3.7 | Publication bias

Finally, evidence of publication bias was found by Egger's test for the endothelial glycocalyx estimate ($p=.065$) but not for its components (proteoglycans, $p=.175$; glycosaminoglycans, $p=.524$; and glycoproteins, $p=.163$).

4 | DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis evaluating the acute effect of exercise on the endothelial glycocalyx and its components in healthy adults. Our findings provide a synthesis of evidence showing positive effects of acute effect of exercise on the endothelial glycocalyx and its components in a healthy population, showing a greater effect on proteoglycans. Additionally, syndecan-1, hyaluronic acid, ICAM-1 and VCAM-1 showed positive effects on endothelial function after acute effect of exercise.

Recently, the endothelial glycocalyx has been attributed, among other functions, a mechanotransduction function whereby endothelial cells (endothelial glycocalyx-coated) exposed to flow stress produce nitric oxide, which is an important determinant of vascular tone.[38,39] In particular, heparan sulfate, hyaluronic acid and glycosaminoglycans appear to play a role in sensing and amplifying flow stress forces. Previous evidence has shown that acute effect of exercise produces changes in blood flow patterns characterized by increases in flow stress on artery walls, which in turn triggers NO synthesis.[40,41] Our findings could shed light on the mechanism by which exercise leads to improvements at the vascular level by eliciting specific cell signalling processes (such as nitric oxide synthesis) that act directly on glycosaminoglycans.[42]

Furthermore, previous evidence has shown that acute effect of exercise restricts oxidative phosphorylation, allowing oxygen to diffuse to peripheral tissues.[43] This could occur because, as suggested by our findings, exercise stimulates proteoglycans, which in turn bind oxygen radical inactivators, such as extracellular superoxide dismutase, reducing oxidative stress and maintaining nitric oxide bioavailability.[44]

Finally, glycoproteins act as enzyme receptors and favour the adhesion of plasma-derived molecules and important anticoagulant mediators, such as tissue factor inhibitory factor, to promote endothelial thromboembolism resistance.[45] Therefore, the described effect of exercise on homeostasis could be mediated by the effect of acute effect of exercise on glycoproteins, as acute effect of exercise has been observed to improve coagulation and fibrinolysis and thus decrease endothelial thrombo-resistance.[46]

This systematic review and meta-analysis has several limitations that should be acknowledged. First, different markers were included in the endothelial glycocalyx. Second, the limited number of samples included in the evaluation of several markers of endothelial glycocalyx components may have modified the results of the meta-analysis. Third, some interventions showed a considerable level of heterogeneity, possibly due to the inclusion of some samples who exercised regularly, so the results should be interpreted with caution. Fourth, the results of this meta-analysis were obtained after some data manipulation (ESs of the raw data of the included studies), which could generate some bias. Fifth, 72.7% of the studies included in the systematic review showed a high Rob2. Sixth, there was evidence of publication bias for the use of the endothelial glycocalyx and unpublished results could have modified the results of this meta-analysis. Seventh, only a healthy population was included in the meta-analysis. Eighth, because of the limited number of studies that included different exercise modalities, the overall analysis was performed and included different types of exercise. Finally, because of the limited number of studies, it was not possible to evaluate the long-term effect of exercise on the endothelial glycocalyx. Therefore, randomized controlled trials of high methodological quality with large sample sizes testing these findings in populations with different characteristics are needed to further elucidate the acute effect of exercise on the endothelial glycocalyx and its components, in addition to assessing the long-term effect of different exercise modalities on the endothelial glycocalyx.

5 | CONCLUSIONS

Our findings provide a synthesis of evidence showing a positive acute effect of exercise on the endothelial glycocalyx and its components in a healthy population. These findings are of research and clinical importance, as they could generate new hypotheses as to why exercise improves different vascular parameters and could therefore be implemented in the preclinical phases of CVDs to slow their progression and prevent major complications.

AUTHOR CONTRIBUTIONS

Conceptualization: A.S.-L. and I.C.-R.; *Methodology*: A.S.-L., A.dS.-L. and I.C.-R.; Software, I.C.-R. and A.dS.-L.; *Validation*: C.P.-M. and E.R.-G.; *Formal analysis*: A.S.- L. and A.dS.-L.; *Investigation*: A.S.-L. and I.C.-R.; *Resources*: A.S.-L., C.P.-M and E.R.-G.; *Data curation*: I.C.-R. and B.B.-P.; *Writing—Original draft preparation*: A.S.-L. and I.C.-R.; *Writing—Review & Editing*: B.B.-P.; *Visualization*: C.P.-M. and E.R.-G.; *Supervision*: I.C.-R. and B.B.-P. All of the authors revised and approved the final version of the article.

ACKNOWLEDGEMENTS

Not applicable.

FUNDING INFORMATION

This study was funded by the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III and cofunded by the European Union (ERDF/ESF), grant numbers PI21/00008 and RD21/0016/0025. A.dS.-L. is supported by a predoctoral fellowship (N° 2021–01- PhD GRANT) from the International Olive Council. B.B.-P. was supported by a grant from the Universidad de Castilla-La Mancha co-financed by the European Social Fund (2020-PREDUCLM-16746).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ORCID

Iván Cavero-Redondo https://orcid.org/0000-0003-2617-0430

REFERENCES

1. Reitsma S, Slaaf DW, Vink H, van Zandvoort MA, Egbrink MG. The endothelial glycocalyx: composition, functions, and visualization. *Pflugers Arch*. 2007;454(3):345-359.
2. Vink H, Duling BR. Capillary endothelial surface layer selectively reduces plasma solute distribution volume. *Am J Physiol Heart Circ Physiol*. 2000;278:285-289.
3. Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. *Annu Rev Biomed Eng*. 2007;9:121-167.
4. Alphonsus CS, Rodseth RN. The endothelial glycocalyx: a review of the vascular barrier. *Anaesthesia*. 2014;69(7):777-784.
5. Fransson LA, Belting M, Cheng F, Jonsson M, Mani K, Sandgren S. Novel aspects of glypican glycobiology. *Cell Mol Life Sci*. 2004;61:1016-1024.
6. Curry FE, Adamson RH. Endothelial glycocalyx: permeability barrier and mechanosensory. *Ann Biomed Eng*. 2012;40:828-839.
7. Krüger-Genge A, Blocki A, Franke RP, Jung F. Vascular endothelial cell biology: an update. *Int J Mol Sci*. 2019;20(18):4411.
8. Huxley VH, Curry FE. Differential actions of albumin and plasma on capillary solute permeability. *Am J Phys*. 1991;260:1645-1654.
9. Machin DR, Phuong TT, Donato AJ. The role of the endothelial glycocalyx in advanced age and cardiovascular disease. *Curr Opin Pharmacol*. 2019;45:66-71.
10. Celermajer DS, Chow CK, Marijon E, Anstey NM, Woo KS. Cardiovascular disease in the developing world: prevalences, patterns, and the potential of early disease detection. *JACC*. 2012;60(14):1207-1216.
11. Arnold N, Lechner K, Waldeyer C, Shapiro MD, Koenig W. Inflammation and cardiovascular disease: the future. *Eur Cardiol*. 2021;16:e20.
12. Dimmeler S, Zeiher AM. Exercise and cardiovascular health: get active to 'AKTivate' your endothelial nitric oxide synthase. *Circulation*. 2003;107(25):3118-3120.
13. Myers J. Exercise and cardiovascular health. *Circulation*. 2003;107(1):e2-e5.
14. Shiroma EJ, Lee IM. Physical activity and cardiovascular health: lessons learned from epidemiological studies across age, gender, and race/ethnicity. *Circulation*. 2010;122(7):743-752.
15. Vanhees L, Geladas N, Hansen D, et al. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR. *Part II Eur J Prev Cardiol*. 2012;19(5):1005-1033.
16. Swift DL, Lavie CJ, Johannsen NM, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J*. 2013;77:281-292.
17. Joyner MJ, Green DJ. Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J Physiol*. 2009;587:5551-5558.
18. Yen W, Cai B, Yang J, et al. Endothelial surface glycocalyx can regulate flow-induced nitric oxide production in microvessels in vivo. *PLoS One*. 2015;10(1):e0117133.

19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-1012.
20. Higgins JPT, Green S. Selecting studies and collecting data. *Cochrane Handbook of Systematic Reviews of Interventions; Version 5.1..; the Cochrane Collaboration*; 2011.
21. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomized trials. *BMJ*. 2019;366:l4898.
22. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28:105-114.
23. Beltrami FG, Roos E, von Ow M, Spengler CM. Cardiorespiratory responses to constant and varied-load interval training sessions. *Int J Sports Physiol Perform*. 2021;16(7):1021-1028.
24. Jackson D, Turner R. Power analysis for random-effects meta-analysis. *Res Synth Methods*. 2017;8:290-302.
25. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
26. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323:101-105.
27. Smith LL, Anwar A, Fragen M, Rananto C, Johnson R, Holbert D. Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise. *Eur J Appl Physiol*. 2000;82(1–2):61-67.
28. Monchanin G, Serpero LD, Connes P, et al. Effects of progressive and maximal exercise on plasma levels of adhesion molecules in athletes with sickle cell trait with or without alpha-thalassemia. *J Appl Physiol*. 2007;102(1):169-173.
29. Monchanin G, Serpero LD, Connes P, et al. Plasma levels of adhesion molecules ICAM-1 and VCAM-1 in athletes with sickle cell trait with or without alpha-thalassemia during endurance exercise and recovery. *Clin Hemorheol Circ*. 2008;40(2):89-97.
30. Pruksakorn D, Tirankgura P, Luevitoonvechkij S, et al. Changes in the serum cartilage biomarker levels of healthy adults in response to an uphill walk. *SMJ*. 2013;54(12):702-708.
31. Majerczak J, Duda K, Chlopicki S, et al. Endothelial glycocalyx integrity is preserved in young, healthy men during a single bout of strenuous physical exercise. *Physiol Res*. 2016;65(2):281-291.
32. Majerczak J, Grandys M, Duda K, et al. Moderate-intensity endurance training improves endothelial glycocalyx layer integrity in healthy young men. *Exp Physiol*. 2017;102(1):70-85.
33. Roberts HM, Moore JP, Thom JM. The effect of aerobic walking and lower body resistance exercise on serum COMP and hyaluronan, in both males and females. *Eur J Appl Physiol*. 2018;118(6):1095-1105.
34. Lee S, Kolset SO, Birkeland KI, Drevon CA, Reine TM. Acute exercise increases syndecan-1 and -4 serum concentrations. *Glycoconj J*. 2019;36(2):113-125.
35. Sapp RM, Evans WS, Eagan LE, et al. The effects of moderate and high-intensity exercise on circulating markers of endothelial integrity and activation in young, healthy men. *J Appl Physiol*. 2019;127(5):1245-1256.
36. Pranskuniene Z, Belousoviene E, Baranauskiene N, et al. Modulation of endothelial glycocalyx and microcirculation in healthy young men during high-intensity Sprint interval cycling-exercise by supplementation with pomegranate extract. *A Randomized Controlled Trial IJERPH*. 2020;17(12):4405.
37. Kröpfl JM, Beltrami FG, Rehm M, Gruber HJ, Stelzer I, Spengler C. Acute exercise-induced glycocalyx shedding does not differ between exercise modalities, but is associated with total antioxidative capacity. *J Sci Med Sport*. 2021;24(7):689-695.
38. Davies PF. Flow-mediated endothelial mechanotransduction. *Physiol Rev*. 1995;75:519-560.
39. Mochizuki S, Vink H, Hiramatsu O, et al. Role of hyaluronic acid glycosaminoglycans in shear-induced endothelium-derived nitric oxide release. *Am J Physiol Heart Circ Physiol*. 2003;285:722-726.
40. Green D, Cheetham C, Reed C, Dembo L, O'Driscoll G. Assessment of brachial artery blood flow across the cardiac cycle: retrograde flows during cycle ergometry. *J Appl Physiol*. 2002;93:361-368.
41. Green D, Cheetham C, Mavaddat L, et al. Effect of lower limb exercise on forearm vascular function: contribution of nitric oxide. *Am J Physiol Heart Circ Physiol*. 2002;283:899-907.
42. Tarbell JM, Pahakis MY. Mechanotransduction and the glycocalyx. *J Intern Med*. 2006;256:339-350.
43. Groschner LN, Waldeck-Weiermair M, Malli R, Graier WF. Endothelial mitochondria–less respiration, more integration. *Pflugers Arch*. 2012;464:63-76.
44. Li Q, Bolli R, Qiu Y, Tang XL, Murphree SS, French BA. Gene therapy with extracellular superoxide dismutase attenuates myocardial stunning in conscious rabbits. *Circulation*. 1998;98:1438-1448.
45. Kato H. Regulation of functions of vascular wall cells by tissue factor pathway inhibitor: basic and clinical aspects. *Arterioscler Thromb Vasc Biol*. 2002;22:539-548.
46. Menzel K, Hilberg T. Coagulation and fibrinolysis are in balance after moderate exercise in middle-aged participants. *Clin Appl Thromb Hemost*. 2009;15(3):348-355.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Saz-Lara A, Cavero-Redondo I, del Saz-Lara A, Rodríguez-Gutiérrez E, Bizzozero-Peroni B, Pascual-Morena C. The acute effect of exercise on the endothelial glycocalyx in healthy adults: A systematic review and meta-analysis. *Eur J Clin Invest*. 2024;00:e14240. doi:10.1111/eci.14240