Effects of Aerobic Exercise on Vascular Wall Thickness: A Meta-Analysis of Pre-Clinical Trials on Rat Model

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ABSTRACT

Exercise instigates adaptations in structural as well as functional organisation of the body at tissue and organ levels. However, the effect of exercise on vascular wall morphology is still under investigation. The objective of the review is to provide a meta-analysis of data from the previously published research to provide compiled analysis to determine the effect of exercise on the thickness of large-sized vessel walls. This meta-analysis was executed at the Ziauddin College of Rehabilitation Sciences with an extensive literature search using databases and search engines such as Pubmed, CINAHL, Web of Science, Scopus, and Google Scholar between September 2022 and January 2023. Studies were appraised according to an estimate of mean difference and pooled effect size was calculated using a random effect model. The risk of bias was also calculated using SYRCLE's risk of bias tool and CAMARADES. Overall, five eligible pre-clinical trials using rat models with pertinent data to determine the effect of exercise on vessel wall thickness were included in the meta-analysis. The results showed that aerobic exercise significantly reduced the vessel wall thickness (SMD -0.854 5%; CI: -1.365 to -0.344; p <0.001). Moreover, no significant publication bias was found through funnel plot and statistical test (Egger's p = 0.276; Begg's p = 0.624). However, an extensive review of the literature currently available on the topic has shown mixed findings that are consistent with the study and vice versa. Therefore, it indicated the need for sub-group analysis with different types of exercises for more peculiar clinical approaches.

Key Words: *Morphometry, Animal studies meta-analysis, Media thickness, Physical activity, Vascular morphology.*

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INTRODUCTION

Maintaining the health of blood vessels is vital for optimal cardiovascular function.[1] Therapeutic exercise has been used as an alternative to medicine for ages.[2] Undoubtedly, exercise provides various health benefits and impedes the onset of many chronic conditions.[3] Evidence advocates that any type of exercise culminates in modifications of the structural and functional organisation of the body at the tissue and organ levels. Thus, leading to many adaptations in metabolic, cardiovascular, and musculoskeletal systems.[4] In particular, the alterations in the cardiovascular systems in response to physical activity are of utmost significance since cardiovascular diseases are the leading cause of death globally. Statistics show that the global burden of cardiovascular diseases has crucially doubled from 271 million in 1990 to 523 million in 2019.

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Furthermore, cardiovascular mortality has also surged from 12.1 million in 1990 to 18.6 million in 2019.[5] Though expeditious technological advancement has equipped the human race with a more comfortable lifestyle, it has taken its toll on a healthy and more zestful life. Thus, leading to a more sedentary way of life with reduced daily physical activity.[6] The American Society for Preventive Cardiology (ASPC) Top Ten CVD Risk Factors 2021 Update has documented that physical inactivity is the second leading cause of cardiovascular diseases.[7] For instance, regular structured physical activity has been shown to subdue the formation of fatty plaques in the arteries. Furthermore, it supports the dilation of the vessels by increasing the availability of mediators of vasodilation, such as nitric oxide. In addition to this, regular physical activity has been shown to improve cardiac output and blood pressure.[8]

Along with physiological changes, many noteworthy changes are also contributed by exercise in the vascular histological architecture.[9] Consequently, causing alterations in the vascular diameter, vessel wall thickness, and overall perimetry.[10] Considering the histology, every vessel has three layers; tunica adventitia, tunica media, and tunica intima being the outer, middle, and innermost layer, respectively. Tunica adventitia comprises collagen fibres, tunica media has smooth muscles, and tunica intima contains endothelial cells.[11] According to studies conducted on lab animals, exercise can lead to variations in the thickness of vessel walls along with a change in the vascular luminal diameter.[12,13] Although many preclinical trials have been conducted to determine the effects of exercise on the histomorphometry of the vessels, the overall impact of exercise on all the vascular levels (arteries and arterioles) has not been studied; defining data on the topic is still scarce. Therefore, the objective of this study was to quantitatively evaluate the exercise's effects on vessel wall thickness. Thus, it provides a meta-analysis of the previous studies to evaluate the effects of exercise on vessel wall thickness statistically. The findings of this study will help to establish the quantitative correlation between exercise and vessel wall thickness through histomorphometric analysis. Thus, clinicians and rehabilitation experts can devise and re-evaluate vascular disorder regimes conscientiously.

METHODOLOGY

A meta-analysis of the published literature describing the effects of the exercise on the vessel wall thickness was conducted using pre-specified protocols (participants, interventions, comparisons, outcomes, and time) as per the guidelines specified in the preferred reporting items for systematic reviews and meta-analyses (PRISMA).[14]

An extensive literature search was conducted between September 2022 and January 2023 using databases and search engines of Pubmed, Google Scholar, CINAHL, Web of Science, and Scopus. The key terms such as exercise, blood vessels, and rats were used.

The first step in the data extraction process was to screen the articles based on title and abstract. Only the relevant full-text articles were retrieved and assessed, based on predefined eligibility criteria. The final step was to extract the data based on standardised data extraction, keeping in view the author's last name, year of publication, study design, country, setting of the study, species of the animal, gender, and methods of morphometric analysis. Only the studies conducted on male rats were included to keep the study precise. The vessel's morphology includes variables such as vessel diameter, wall thickness, and vessel wall area. However, the wall thickness is the most frequently reported variable. Thus, only the data, including the micrometre wall thickness / media thickness, were utilised for meta-analysis. In case of missing data, many authors were approached; however, no positive response was received. Studies with no figures and tables were also excluded.

Only *in vivo* animal studies that used aerobic exercise interventions and measured the vessel wall / media thickness in micrometre with an experimental study design were included. Studies that were not using exercise as an intervention, *in vitro* study models, human studies, abstracts without detail, and review articles were excluded.

The studies included in this review were assessed for quality and strength using the SYRCLE's risk of bias tool and CAMARADES checklist for quality of study, which is the gold standard publication checklist to improve the quality of animal studies. Thus, the percentage quality score of the studies was estimated and those with high scores were eventually used in sensitivity analysis.[15]

The statistical analysis was done using MedCalc Statistical Software (version 18.11.3). Heterogeneity and standardised mean difference (SMD) analysis between the intervention and the control groups were assessed with pooled standard deviation (SD) evaluated using a random effect model with 95% CI. With the use of Cohen's rule of thumb, effect size was determined as small (0.2 to 0.5), moderate (0.5 - 0.8), and large (>0.8). Heterogeneity among the studies was evaluated using I^2 and $p<0.05$ was considered significant.

RESULTS

The search strategy in the electronic databases generated 694 documents (Google Scholar 834, Pubmed 466, and Web of Science 39), of which 452 had quantitative data. Out of these, 220 were removed due to duplicity. Remaining 232 articles were screened on the basis of abstract and eligibility criteria. Eighty-two studies were consistent with the predefined criteria. However, 13 articles showed incomplete information, full-text was not available for 31, and 35 did not use appropriate exercise protocol. Only five studies were included in the meta-analysis (Figure 1).

The characteristics of the included studies are described in tabulated form. Five articles eligible for meta-analysis with fitting data were selected for statistical analysis. All the studies measured the wall thickness / media thickness of the vessels in control and the intervention groups of the same species in micrometres. There was some variation in the duration of intervention, sample size, and mode of exercise. However, all the studies were conducted on the male population of rats (Table I).

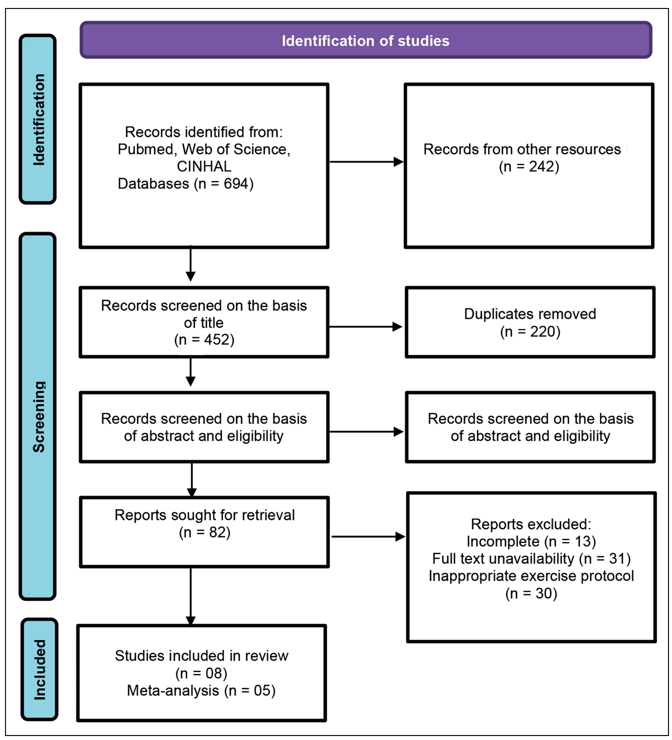

Figure 1: PRISMA flowchart.

Table I: Characteristics of the given studies.

Authors' name	Species of the animal	Age (months)	Sample Size		Intervention duration (weeks)	Exercise	Vessel
Niederhoffer *et al.* 2000 [21]	Rats	6	9	10	8	Treadmill	Aorta
Horta *et al.* 2005[22]	Rats	6	5	5	20	Treadmill	Aorta
de Andrade *et al.* 2010[23]	Rats	3	8	8	20	Treadmill	Aorta
Jordao *et al.* 2011[24]	Rats	2	5	5	12	Treadmill	Aorta
Potora *et al.* 2018[25]	Rats	4-5	10	10	2	Swimming	Aorta

Table II: CAMARADES checklist.

Criteria	Niederhoffer, 2000	Horta, 2005	Jessica de Andrade, 2010	Maria Tereza Jordao, 2011	Cristian Simion Potora, 2018
Publication in peer-reviewed journal	Y	Y	Y	Y	Y
Statement of control of temperature	NM	Y	Y	NM	NM
Randomisation to treatment and control	NM	NM	Y	N	NM
Allocation concealment	NM	NM	NM	NM	NM
Blinded assessment of outcome	NM	NM	NM	NM	NM
Sample size calculation	NM	NM	NM	NM	NM
Statement of compliance with regulatory requirements	Y	Y	Y	Y	Y
Statement regarding possible conflict of interest	NM	NM	NM	NM	Y
Prespecified inclusion and exclusion criteria	Y	Y	NM	Y	Y
Reporting animals excluded from analysis	NM	NM	NM	NM	NM
Total score (out of 10)	3	4	4	3	4

Y = Yes, N = No, NM = Not mentioned.

Table III: SYRCLE's risk of bias tool for animal studies.

Author	Selection			Performance		Detection		Attrition	Reporting	Other
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding of caregiver	Random outcome assessment	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other source
Niederhoffer *et al.* 2000 [21]	-	+	-	-	-	-	-	-	-	-
Horta *et al.* 2005[22]	-	+	-	?	?	-	-	-	-	-
de Andrade *et al.* 2010[23]	+	+	-	+	-	-	-	-	-	-
Jordao *et al.* 2011[24]	-	+	-	-	-	+	-	-	-	-
Potora *et al.* 2018[25]	-	+	-	-	-	-	-	-	-	-

+ = low risk of bias, - = high risk of bias,?=Unclear.

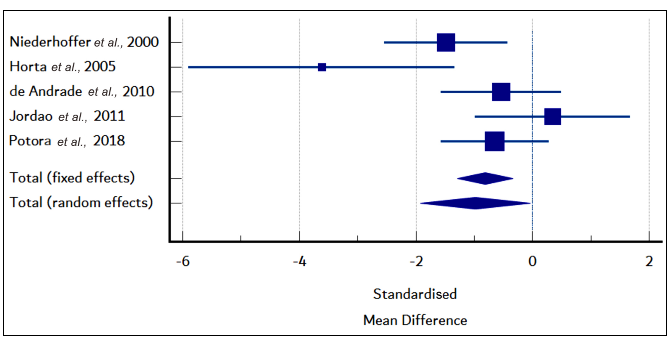

Figure 2: Forest plot of standardised mean difference (SMD) and 95% confidence interval (CI).

The comprehensive meta-analysis included five studies which used exercise as an intervention. The results for meta-analysis showed significant difference between means of the vessel wall thickness in control and intervention animal groups. The overall pooled SMD was -0.981 (95% CI: 1.921 to -0.0414) and p-value was 0.041, while using the random effect model with 72.07 heterogeneity. As per the Cohen's rule of thumb, the results indicated that the exercise intervention had a large effect on the vessel wall thickness. The impact of exercise intervention was also evaluated using the forest plot to identify the pool effects in a random effects model at 95% confidence interval (CI) (Figure 2).

The quality assessment in the study consisted of the items taken from CAMARADES (Table II) and SYRCLE's risk of bias tool (Table III) for animal study quality assessment. Sensitivity analysis was performed by removing the studies one by one from the meta-analytical model in order to find the effect of each on the overall estimate. Omission of each study confirmed that total findings were not influenced by any particular study. The risk of bias due to missing results was identified using funnel plot (Figure 3) and Egger's test ($p = 0.276$) and Begg's test (0.624) which showed non-significant results suggesting no strong evidence due to publication bias.

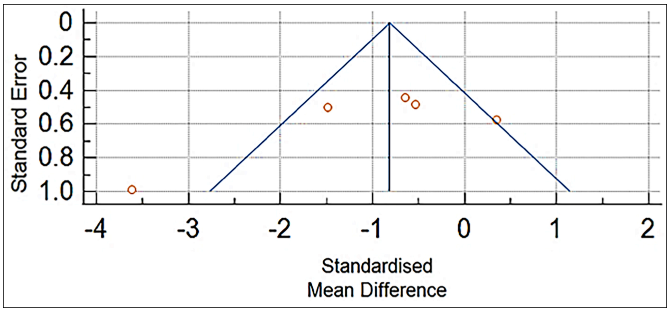

Figure 3: Funnel plot for standardised mean difference.

DISCUSSION

Exercise has multiple effects on the microstructure of the blood vessels, such as altered morphology of endothelial cells, smooth muscle cells, and extracellular matrix components.[16] As shown previously, the endothelial cells' number is increased in response to regular physical exercise and their function is boosted. This increased proficiency of endothelial cells is attributed to increased nitric oxide production by these cells, which subsequently leads to vasodilation, thus maintaining enhanced blood supply to exercising muscles and ensuring improved oxygen and nutrient delivery.[17] Regular physical activity has also shown changes in the contractile properties of smooth muscle cells of blood vessels. Improved contraction and the number of smooth muscles regulate blood pressure during physical activity.[18] Similarly, exercise can lead to modifications in composition, such as the increased elastin and collagen proteins making the vessels stiffer and aiding in maintaining blood pressure during exercise.[19] In the same manner, vessel wall thickness is altered by regular physical exercise. As discussed above, nitric oxide (NO) production by the endothelial cells increases in the luminal diameter causing the dilation of the vessel; after this dilation, vessel walls are stretched, culminating in the alteration of vessel wall thickness.[20]

Therefore, this meta-analysis reported the effects of physical activity on the thickness of vessel walls using rat models. The random effect model was used to evaluate the heterogeneity among the included studies, and the Higgins test was acquired.[13] The vessel wall thickness was the outcome measure evaluated in the study. The forest plot of the studies showed a significant effect of exercise on the vessel walls of the intervention as compared to the control group. Similarly, the pooled estimate of SMD of vessel wall thickness in micrometres showed significant changes. Four studies reported decreased vessel wall thickness after the exercise intervention.[20-23]

On the contrary, however, one study reported an increase in the wall thickness.[24] All the studies used aerobic exercise and a treadmill as an intervention; however, one study incorporated swimming exercise.[25] Aorta was the vessel of interest in all studies. Meta-analysis data showed that aerobic exercise reduces the thickness of the vessel wall. However, the review of the literature on the topic has shown mixed findings, where few studies indicated an increase in the wall thickness while others proved vice versa. Therefore, this study indicates the need for sub-group analysis with different types of exercises for more peculiar clinical approaches.

Various studies have reported vessel wall thickness alterations after exercise.[26,27] However, these changes are subjected to the type of intervention used, since different types of exercises are expected to generate different outcomes. Further, diverse types of vessels may show contrary results depending on their location, size, and the relative composition of their walls.

Various limitations were identified during the quantitative analysis of the exercise intervention on the vessel wall morphology, such as the variations in the duration of intervention used, which ranged from 2 to 20 weeks. Further, the aorta was studied at different levels, i.e. thoracic and abdominal, which may lead to changes in the shear pressure as per the location and affect the outcome, thus leading to selection bias. While searching the data for the correlation between exercise and vessels there were very limited studies that elaborated the effects of exercise on the veins. Therefore, this study is only limited to arteries. However, it is recommended for the future that there should be more studies involving multiple vessels since microstructure of the veins significantly differ from the other vessels.

CONCLUSION

Meta-analysis data showed that aerobic exercise reduces the thickness of the vessel wall. However, the literature review of the literature available on the topic has shown mixed findings where few studies indicated an increase in the wall thickness while others proved vice versa. Therefore, this study indicates the need for sub-group analysis with different types of exercises for more precise results.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

FH: Drafting and framework and acquisition of the data.
NNS: Interpretation of the data.
AAK: Analysis.
SIF: Critical revision of the manuscript for important intellectual content.
KJJB: Final approval.
All authors approved the final version of the manuscript to be published.

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