REVIEW ARTICLE

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Effects of Exercise on Cartilage Thickness and Chondrocytes Count: A Meta-Analysis of Pre-Clinical Randomized Controlled Trials Conducted on Rats

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Abstract

Background: The evidence regarding the effects of exercises on cartilage is enormous, but the literature on improving cartilage thickness and the number of chondrocytes is limited. To determine the cumulative effects of exercises on cartilage thickness and chondrocyte number by combining results from different randomized controlled trials.

Methods: Using MeSH terms like "cartilage thicknesses", "exercises", "chondrocytes", and "physical training", among others, multiple searches are conducted on exercise-based management approaches on cartilage thicknesses using search engines like Google Scholar, PEDro, MEDLINE, Cochrane Library, EMBASE, and Web of Science.

Results: The risk of bias assessment was performed based on the SYRCLE guidelines. The author-based judgment was performed on selection, performance, detection, attrition, reporting, and other biases. The quantitative analysis revealed that femoral cartilage thickness had increased in the exercise group (SMD=1.039, CI%= -0.64 to 2.72, p=0.225) while chondrocyte count had shown a mild increase in response to excises (SMD= -0.147, CI%= -2.161 to 1.866, p=0.883).

Conclusion: It has been concluded that although exercises have a potential impact on cartilage morphology, they must be performed within adaptive threshold limits.

Keywords

Exercises, Cartilage, Chondrocytes, Animal Physical Conditioning.

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Introduction

The most intricate structure in the human body is the knee joint., comprised of two joints and three bones[1]. The structural arrangement of the knee joint in the human body allows a degree of freedom of movement that can be broadly categorized into two components: the rotational component at the axes and the translational component along the axes[2,3]. The knee joint is anatomically designed to bear the weight of the body. Hence, the role of soft tissue structures is crucial to keep the joint pain-free and moveable[4]. Semilunar meniscal fibrocartilaginous menisci maintain congruity of the joint, particularly on the curved weight-bearing surface of the articular cartilage, preventing torsional forces generated during multidirectional stress from disrupting knee joint articulation[5,6].

A connective tissue that is present in many bodily components, including joints, is called cartilage, the ear, the nose, and the respiratory tract[7]. It comprises chondrocytes embedded in a matrix of collagen fibres and proteoglycans[8]. Cartilage performs various vital functions in the body. In joints, it acts as a cushion and shock absorber, helping to protect bones from wear and tear during movement[9,10]. In the ear and nose, it helps to maintain their shape and structure[10]. The respiratory tract helps open the airway and allows smooth breathing[10,11]. However, cartilage cannot repair and regenerate itself due to its avascular nature, meaning it has no direct blood supply[12,13]. Therefore, any cartilage damage can lead to problems such as osteoarthritis and degenerative joint diseases, where the cartilage in the joint wears away over time, causing pain and stiffness[14]. There are three main types of cartilage in the human body: a) Hyaline cartilage, the most common type of cartilage found in the body, and it is found in joints, the nose, the trachea, and the bronchi. It has a smooth, glassy appearance and a firm, rubbery texture[15]. Hyaline cartilage is crucial in cushioning and supporting joints, allowing for smooth and pain-free movement; b) Fibrocartilage, composed of dense collagen fibres and has a more rigid texture than hyaline cartilage, providing excellent shock absorption and support[15]; c)Elastic cartilage found in areas of the body that require strength and flexibility, such as the external ear and the epiglottis[15,16]. It is similar in appearance to hyaline cartilage but contains more elastic fibres, allowing it to be more flexible and resilient to deformation.

Each type of cartilage has its unique structure and function. However, all are important in maintaining the health and function of various tissues and organs in the body[17] as Hyaline cartilage has a various function ranging from weight bearing to lubrication and structural support depending upon the organizational arrangement of extracellular matrix (ECM), which is the primary determinant of its normal functioning[18,19]. Herefore, any disease affecting cartilage that brings changes in the ECM leads to rapid progression of the disease, as in the case of Osteoarthritis (OA) that enhances the leading indicators of disease like dwarfism occurs due to genetic/inherited mutation and also in disease in which collateral damages occurs due to pathological processes as observed in osteochondritis dissecans and inflammatory arthropathies[18,20]. Multiple factors that cause cartilage damage include age, trauma, repetitive stress, joint misalignment, or inflammatory disease, which can be managed by several therapeutic methods, from exercises to pharmacotherapy to surgery in severe conditions. However, many researchers have suggested that exercise is exceptional in restoring cartilage health after injuries, preventing cartilage from multiple injuries associated with mechanical stresses, particularly overload injuries and respective movement[17,21]. The impact of exercise on cartilage health depends on factors like type, intensity, and duration[21]. One possible effect of exercise on cartilage health is that it improves cartilage nutrition by improving blood flow to the joints, which can provide the necessary nutrients and oxygen to the chondrocytes. These cells produce and maintain cartilage. Exercise also increases the production of joint lubricants by stimulating the production of synovial fluid, which acts as a lubricant in the joint, helping to reduce friction and wear on the cartilage.

Furthermore, it enhances joint stability by strengthening the muscles and ligaments surrounding the joint, providing better support and stability and reducing the load on the cartilage[22]. As the evidence regarding the effects of exercises on cartilage is enormous, the literature on improving cartilage thickness and the number of chondrocytes is limited. Therefore, this study aims to determine the cumulative effects of exercises on cartilage thickness and chondrocyte number by combining results from different randomized controlled trials (RCTs).

Materials and Methods

This study was conducted according to SYRCLE's laboratory animal experimentation guidelines, ensuring animals' ethical and humane treatment[23].

Databases and Searching Strategies

With the use of MeSH terms, several searches on exercise-based treatment strategies for cartilage thickness were carried out employing electronic databases like Google Scholar, PEDro, MEDLINE, Cochrane Library, EMBASE, and Web of Science, like ("Cartilage/Anatomy/Histology" OR "Thickness") AND ("Exercise" OR "Physical Exertion") AND ("Chondrocytes" OR "Cells/Cultured") AND ("Physical Training" OR "Exercise" OR "Resistance Training").

Criteria for Eligible Studies and Animal Models

Randomized experimental trials were selected based on control versus exercise intervention (treadmill and climbing ladder) on unhealthy and healthy rats published in English from 2012 to 2022. Studies in which the effect of exercise was assessed on the thickness of articular cartilage and chondrocyte count of the distal femur at the knee joint in healthy and unhealthy rats were included. In contrast, all trials in which assessments were performed for joints other than the knee and ankle were excluded. The insufficient number of full-text papers, studies that have yet to be made open access available despite email correspondence with authors and any research done in languages other than English were also disregarded.

Data Extraction and Management

The data was extracted from the articles based on the criteria of a self-designed evidence assessment form in which information like the first name of the author, title of publication, year of publication, study design, target population, nature of interventions provided to experimental and control groups, outcome measures for identifying the responses of treatment and essential findings were recorded. The data extraction process was utilized to generate the findings of this study and draw the corresponding conclusions.

Risk of Bias Assessment

The risk of bias in the included publications was assessed by two reviewers (K.Y. and J.R.) utilizing the SYRCLE risk of bias tool for animal studies24. The assessment was performed for selection bias (sequence generation, baseline characteristics, and allocation concealment), performance bias (random housing and blinding), detection bias (random outcome assessment and blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other types as determined by the author.

Quantitative Analysis

For the quantitative evaluation, MedCalc Statistical Software version 20.112 was used. In Continuous Measure Analysis, the pooled effect was calculated using the Standardized Mean Difference (SMD) with a 95% confidence interval (CI). Cohen's rule of thumb was used to categorize effect sizes based on three parameters: small (SMD values between 0.2 and 0.5), moderate (SMD values between 0.5 and 0.8), and significant (SMD values above 0.8). I^2 values (I^2<50 Fixed effect, I2>50 Random effect) were used to interpret heterogeneity in the random and fixed effect models.[25]

Results

The analysis of the results was based on qualitative and quantitative findings. For qualitative analysis, a risk of bias assessment was performed. For quantitative analysis, the SMD was estimated for the cumulative effects of the findings of randomized experimental studies included in this meta-analysis. The results regarding the search for evidence were illustrated in Figure-1, revealing that the search engines initially provided 90 articles which, after initial scrutiny that was

carried out through screening criteria, were reduced to n=20 studies that, after further selection, were reduced to 5 studies as shown in Figure-1, Table-1.

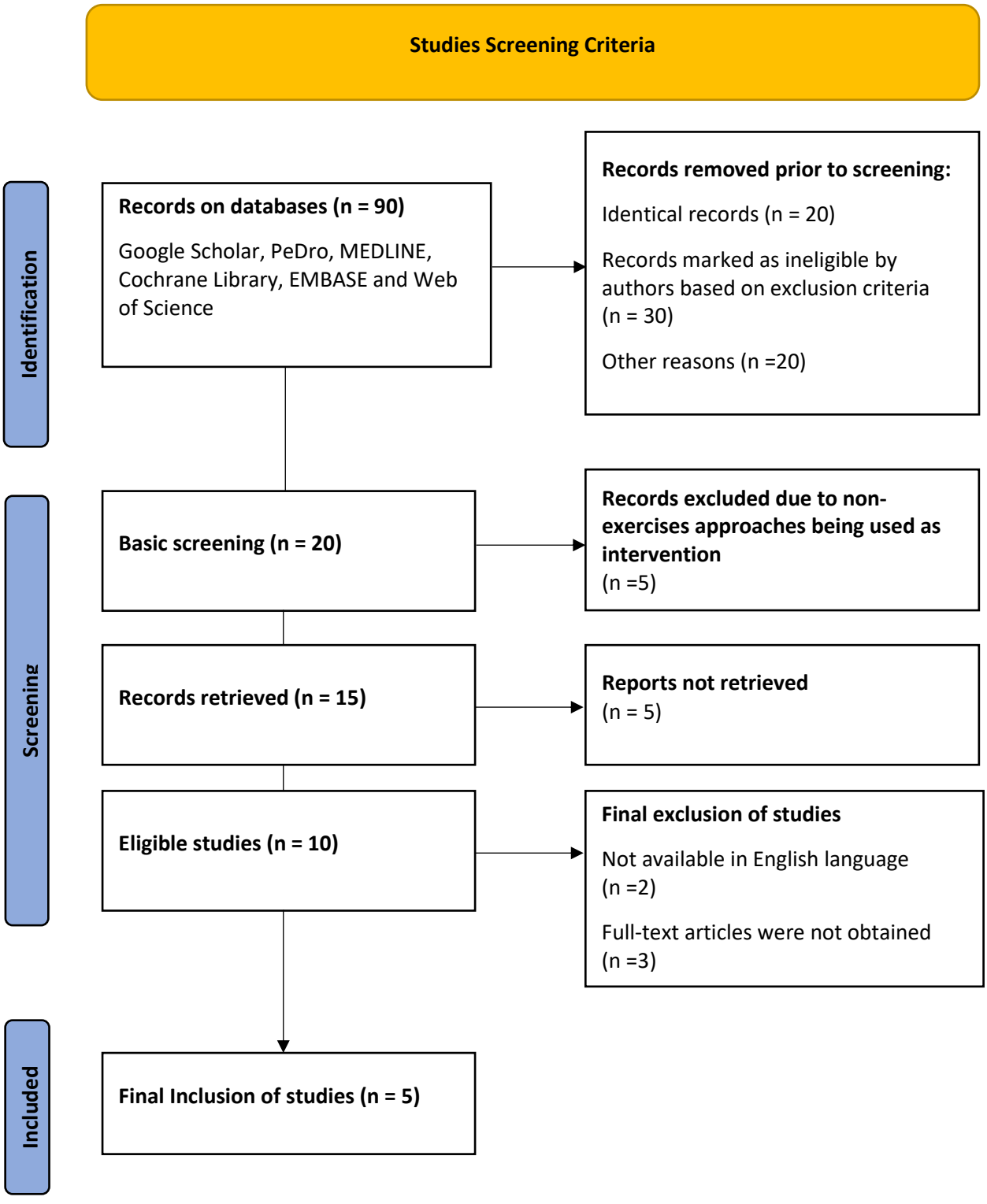

Table-1 Represents Characteristics Features of the Included Studies

Author' Year	Sample Size	Target Population	Study Design	Intervention		Duration	Outcomes
				Intervention Group	Control Group		
Neves et al. (2022)[26]	EG=8 CG=8	Male Wistar Rats	Randomized controlled trial	Climbing resistance exercises on stairs	No exercises	14 days	Cartilage thickness and chondrocyte count
Zhou (2021)[27]	EG=10 CG=10	Sprague-Dawley Rats	Randomized controlled trial	Moderate exercises group	No exercises	8 weeks	Cartilage thickness
Naeini et al. (2018)[28]	EG=10 CG=10	Male Wistar Rats	Randomized controlled trial	Running exercises on motor - driven rodent treadmill (Model T510, DRI Co., Taoyuan, Taiwan)	No exercises	6 weeks	Cartilage thickness and chondrocyte count
Qian et al. (2014)[29]	EG=20 CG=20	Sprague-Dawley Male Rats	Randomized controlled trial	PT98 electric animal treadmill	No exercises	6 weeks	Cartilage thickness
Ni et al. (2013)[30]	EG=6 CG=6	Male Wistar Rats	Randomized controlled trial	Treadmill running	No exercises	8 weeks	Cartilage thickness and chondrocyte count

EG Experimental group
CG Control Group

Qualitative Analysis

Risk of Bias Assessment: The risk of bias assessment was performed based on the guidelines of SYRCLE. The author-based judgement was performed on selection, performance, detection, attrition, reporting and other types of bias, as shown in Table-2.

- **Selection Bias:** Selection bias assessment was performed on three parameters: sequence generation, baseline characteristics, and allocation concealment, and it was identified that all studies fulfilled the criteria. However, a low risk of biases was observed in all five studies.26-30

- **Performance Bias:** SYRCLE's guidelines provide two evaluation parameters for performance bias assessment: random housing and blinding. As per the evaluation of

findings, all studies included in this analysis fulfil the criteria and hence are marked for low risk of bias[26-30].

- **Detection Bias:** The criteria for detection bias include random outcome assessment and blinding. The evaluation of the studies revealed that detection bias for two studies, Qian et al.[29] and Ni et al.[30], were found to have high risk as both of these studies have not provided criteria for detection bias. In contrast, the remaining studies were considered at unknown risk of bias.

- **Attrition Bias:** Attrition bias was evaluated based on incomplete outcome data. The evaluation revealed that two studies, Neves et al.[26] and Zhou[27], had shown a low risk of biases. In contrast, Qian et al.[29] and Ni et al.[30] showed a high risk of bias, whereas Naeini et al.[28] showed an unknown risk.

- **Reporting and Other Biases:** Reporting bias was performed on selective outcome reporting. The Naeini et al.[28] study had an unknown risk of bias, whereas the remaining four showed a low risk. Moreover, publication bias was identified using Egger's and Begg's tests, illustrated in quantitative analyses.

Table-2 Assessing risk of bias using a Cochrane collaboration's tool

Studies	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
Neves et al. (2022)[26]	+	+	?	+	+
Zhou (2021)[27]	+	+	?	+	+
Naeini et al. (2018)[28]	+	+	?	?	?
Qian et al. (2014)[29]	+	+	-	-	+
Ni et al. (2013)[30]	+	+	-	-	+

–, high risk
+, low risk
? , unknown risk

Quantitative Analysis

The analysis was performed to determine the cumulative effects on two outcome measures which were femoral cartilage thickness and chondrocytes number.

Femoral Cartilage Thickness

The findings revealed that femoral cartilage thickness had increased in the exercises group on a random effect model with high SMD of 1.039 (CI % -0.64 to 2.72, p=0.225), as depicted in the Table-3, Figure-2.

Table-3 Femoral cartilage thickness

Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Neves et al. (2022)[26]	8	8	16	0.145	0.473	-0.870 to 1.161			22.75	20.36
Zhou (2021)[27]	10	10	20	3.478	0.697	2.013 to 4.942			10.49	18.97
Naeini et al. (2018)[28]	10	10	20	-1.687	0.505	-2.747 to -0.627			20.02	20.19
Qian et al. (2014)[29]	20	20	40	2.303	0.403	1.488 to 3.119			31.39	20.72
Ni et al. (2013)[30]	6	6	12	1.076	0.576	-0.208 to 2.360			15.35	19.76
Total (fixed effects)	54	54	108	0.948	0.226	0.501 to 1.396	4.201	<0.001	100.00	100.00
Total (random effects)	54	54	108	1.039	0.851	-0.649 to 2.726	1.220	0.225	100.00	100.00

Test for Heterogeneity	
Q	54.68
DF	4
p-value	0.001
I^2	90.08%
95% of CI	85.9 to 96.2

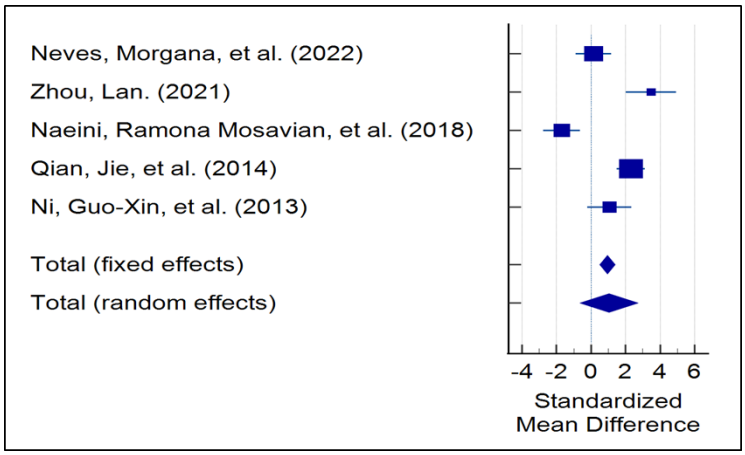

Figure-2 Forest plot of studies on femoral cartilage thickness

Publication Bias of Studies on Cartilage Thickness

Egger's and Begg's test was applied to identify publication bias, and the analysis revealed that studies had shown an intercept value of 1.85 (-32.11 to 35.81), p=0.87 hence suggesting no evidence for publication bias as shown in Table-4.

Table-4 Estimation of publication biases on the outcome of cartilage thickness

Egger's test	
Intercept	1.8543
95% CI	-32.1110 to 35.8196
Significance level	P = 0.8731
Begg's test	
Kendall's Tau	0.0000
Significance level	P = 1.0000

Femoral Chondrocyte Counts

The findings based on cumulative effects revealed that three studies out of five that were included in the meta-analysis had estimated femoral chondrocyte count and had shown a mild increase in chondrocyte count in response to excises in terms of SMD=0.147 (CI % -2.161 to 1.866). The values are illustrated in Table 5; a forest plot of findings is depicted in Figure-3.

Table-5 Chondrocytes Count										
Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%)	
									Fixed	Random
Neves et al. (2022)[25]	8	8	16	-0.845	0.496	-1.909 to 0.218			39.60	34.15
Zhou (2021)[26]	10	10	20	-1.562	0.494	-2.600 to -0.523			39.82	34.16
Naeini et al. (2018)[27]	6	6	12	2.129	0.688	0.597 to 3.661			20.58	31.69
Total (fixed effects)	24	24	48	-0.518	0.312	-1.146 to 0.110	-1.662	0.103	100.00	100.00
Total (random effects)	24	24	48	-0.147	1.000	-2.161 to 1.866	-0.147	0.883	100.00	100.00
Test for Heterogeneity										
Q	19.717									
DF	2									
p-value	0.001									
I^2	89.86%									
95% of CI	72.80 to 96.22									

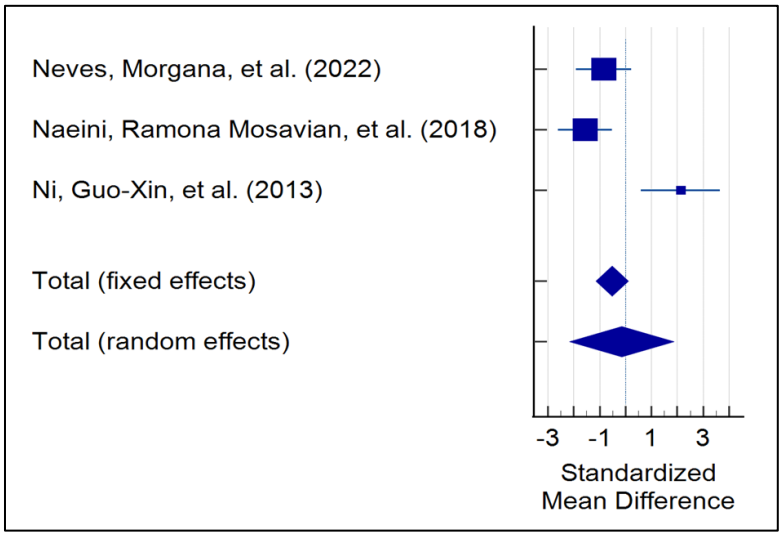

Figure-3 Forest plot of studies on femoral chondrocytes count

Publication Bias of Studies on Chondrocytes Count

Egger's and Begg's test was applied to identify publication bias, and the analysis revealed that studies had shown an intercept value of 17.34 (95% of CI -33.01 to 67.71), p=0.14 suggesting no evidence of publication bias values illustrated in Table-6.

Table-6 Estimation of publication biases on the outcome of chondrocytes count	
Egger's test	
Intercept	17.34
95% CI	-33.01 to 67.71
Significance level	P = 0.14
Begg's test	
Kendall's Tau	1.0000
Significance level	P = 0.117

Discussion

Several studies have provided evidence that different forms of exercise have a beneficial impact on the musculoskeletal system and physiological component, as endurance exercises are mainly responsible for improving cardiac and respiratory components; likewise, on the other hand, resistant exercises bring about a change in muscular thickness and increase in the overall strength of the muscles[31, 32, 33]. It is also evident from several kinds of literature that combining forms of exercises that incorporate both endurance and resistance training brings about various effects within the physiological and structural components of the body depending upon the composition of training like frequency, speed, duration mode etc and the training protocol (combination of one or more than one component of exercise composition) used for combine exercises protocol[34, 35].

The findings of the meta-analysis revealed that exercises had impacted femoral thickness (SMD= 1.039), favouring the interventional group over the control group. However, the effect was not significant (p=0.20). The effect was mild on several chondrocytes (SMD= -0.14, p=0.883), suggesting no such effects in increasing the number of chondrocytes compared to the control group. Individual analysis of the studies included in this meta-analysis was performed, concluding that the findings from Neves et al.[26] revealed that animals in the exercise group had responded better after 14 days of intervention to improve cartilage thicknesses and increase the number of chondrocyte counts. However, the difference between the two groups was slight, and the same was reflected in our study. A study by Zhou[27] focused on determining the effects of exercises on cartilage cell metabolism. It concluded that compared to the control group, the exercise group had shown significant improvement in cartilage thickness after eight weeks of training. It further determined that exercises improve cartilage thickness but should be performed within the

adaptation limit as crossing the barrier of adaptation limit during exercises may directly aggravate cartilage damage. Naeini et al.[28] aimed to determine the effects of running on an inclined treadmill on knee joint osteoarthritis (OA) and determined the effects on cartilage thickness and chondrocyte number after six weeks of training. The findings revealed that as compared to the control group, the exercises group had shown lesser femoral thicknesses and less number of chondrocytes count and hence concluded that exercises beyond the limit of adaptive threshold had a deleterious effect rather than beneficial and must be performed within the adaptive threshold limits. Qian et al.[29] determined the effects of passive motions on articular cartilage in osteoarthritic rats and identified its effects on cartilage thickness at different intervals. The findings revealed that compared to the control group, the passive exercises group had shown a significant increase in cartilage thickness in the sixth week. Thus, the passive motion exercises not only had to repair effects on degenerative cartilage but also improved the morphology of degenerating structures and reduced the occurrence of OA in the long run. Ni et al.[30] determined the intensity-dependent effects of treadmill running on knee articular cartilage in a rat model after eight weeks of training, revealing that cartilage thicknesses and chondrocyte numbers were increased significantly in the moderate-intensity running group compared to the control group. Hence, it was concluded that regular aerobic exercise brought about multiple positive changes in the body. However, other studies suggested determining the optimum dose of exercise. They recommended that a precise and apposite evaluation must be done before inducing exercises as a mode of treatment among cartilaginous degenerative diseases, as exercises beyond optimal limits could have potentially deleterious effects.

This study's strengths include the thorough analysis of several studies, which strengthens the validity of the conclusions. The inclusion of various studies also enables a broader comprehension of the subject. Additionally, the individual analysis of the studies offers a complex viewpoint on how exercise affects chondrocyte count and cartilage thickness. However, there are some limitations to consider. The findings' generalizability may be constrained by the few studies eligible for inclusion in the meta-analysis.

Furthermore, the heterogeneity of the included studies, which differs in the exercise protocols and measurement approaches, could introduce bias and impact the final results. Also, the findings' direct applicability to human populations may be constrained by the dearth of human studies and the sole emphasis on rat models. Nevertheless, several approaches could be taken to address these restrictions and open the door for additional studies. First, more pre-clinical randomized controlled trials using various animal models, such as larger mammals or disease-specific models, may help us better understand how exercise affects cartilage health. Additionally, incorporating human studies into meta-analysis would make it possible to evaluate the effect of exercise on the cartilage in clinical populations through standardized exercise protocols, measurement approaches, and outcome evaluations across studies that would improve comparability and reinforce the findings' validity.

Conclusion

This meta-analysis has concluded that although exercises potentially impact cartilage morphology, they must be performed within adaptive threshold limits. High-intensity strenuous exercises could have a deleterious effect rather than curative and rehabilitating. Further studies determining the dose-response effects of exercises on cartilage thickness, chondrocyte number, and morphological appearance must be conducted to gather concrete evidence at a larger scale.

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Conflict of Interest
None.

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None.

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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.