

The effect of stem cells in repairing growth plate injury: a systematic review and meta-analysis

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Abstract

Background: Multiple studies have focused on stem cell-based therapies for growth plate injury. However, the results are not consistent.

Objectives: This systematic review and meta-analysis were performed to evaluate the effects of stem cells on growth plate healing.

Methods: A detailed search of relevant studies was conducted in three databases including Pub med, Cochrane library, and Embase databases, using the following keywords: "growth plate" or "physis" AND "stem cell" from inception to November 10, 2021. The standard mean difference (SMD) and 95% confidence interval (CI) for each individual study were extracted from the original studies based on relevant data and pooled to obtain integrated estimates using random effects modeling.

Results: A total of 6 studies were identified. The results demonstrated that the angular deformity in the stem cell group was significantly lower than that in the control group at 4, 8, 12 and 16 weeks. The length discrepancy represented the degree of shortening deformity. In the stem cell group, the shortening deformity was milder than that of the control group at 16 weeks. Meanwhile, at 16 weeks after surgery, the higher histologic scores in the stem cell group indicated that stem cell can significantly improve the repair quality of growth plate.

Conclusions: This systematic review and meta-analysis confirmed that stem cell improved the rehabilitation of growth plate injury. However, larger-scale studies are needed to further support these findings.

1. Introduction

The growth plate, also named as physis, is a band of hyaline cartilage located at the proximal and distal ends of the long bones of children, and is responsible for bone lengthening until closure at skeletal maturity. The physis is prone to injury due to its fragile nature but has poor regenerative capacity due to its avascular state [1]. Injury to growth plate cartilage often results in an undesirable repair response mechanism at the site of injury, where ossification of the damaged tissue may lead to formation a bone bridge [2]. Establishment of a bone bridge across the growth plate can have serious consequences in growing children, and may lead to limb length discrepancy and angular deformity. In children, an estimated 15% of all fractures reportedly involve the growth plate and 15% of these lead to growth disturbance [3].

In early studies, free growth plate as a implanted material was transferred from the iliac apophysis into the growth plate defect zone in animal experiment to inhibit bony bar formation. The results indicate that the transplanted growth plate demonstrated different degrees of apoptosis [4]. Early experimental works showed that ex vivo expanded chondrocytes can be successfully transplanted into a growth plate injury site and were able to form the growth plate-like columnar in rabbit [5, 6, 7, 8]. However, chondrocyte therapy for growth plate injury is controversial. In the other experiment, the researcher used a large animal (sheep) tibial growth plate injury model. He attempted transplanting chondrocytes directly into the growth plate injury site and did not produce any successful outcomes [9]. Hence, this highlights the unlikelihood of achieving successful growth plate cartilage regeneration with this chondrocyte transplantation approach. Moreover, using autologous chondrocytes clinically may be limited by the need to isolate cells from healthy pediatric cartilage tissue, thus creating secondary injury sites [4]. This has led to the investigation of alternative cell sources such as stem cells.

Stem cells are an attractive cell source for tissue engineering due to their availability and multipotent differentiation capacity, especially toward the bone and cartilage lineages [10, 11]. These cells include many types, such as bone marrow derived stem cells (BMSCs) [12, 13], adipose derived stem cells (ADSCs) [14, 15, 16], skeletal muscle derived stem cells [17, 18], umbilical cord blood derived mesenchymal stem cells (UCB-MSCs), periosteum derived stem cells [19, 20, 21], and synovial derived stem cells [22–24].

Stem cell therapy is an emerging therapeutic modality. The use of stem cells for growth plate repair have been studied by many researchers [22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33]. The main purpose of this meta-analysis was to summarize the best available evidence regarding the use of stem cells for the treatment of growth plate injury.

2. Materials And Methods

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement [34].

2.1. Search strategy

Three databases including PubMed, Cochrane library, and Embase databases have been searched for related studies from inception to November 10, 2021. To build up the literature, we selected the following terms: “growth plate” or “growth plate injury” or “physis” or “physis injury” or “physeal” and “stem cell” or “stem cells” or “progenitor cell”. The articles are limited to preclinical studies and published in English. Processes including online searching, reference lists screening, study selection, data extraction, and assessment of the risk of bias were performed by two investigators independently.

2.2. Study screening and eligibility criteria

The selection criteria for the studies were prespecified as follows: (1) the study applies stem cells for growth plate repair; (2) the study needs to use animal model; (3) a qualitative or quantitative outcome to determine if stem cells have provided improvement in growth plate repair, and (4) English language. Studies were excluded on the following criteria: (1) the study does not involve the use of any types of stem cell; (2) study protocols, letters, correspondence, and conference addressing; or (3) studies do not involve qualitative outcomes to determine if the stem cells have provided any improvement in growth plate repair.

2.3. Data extraction

The studies that did not meet the inclusion criteria were excluded after screening all the articles searched. The following details were recorded from the included articles: (1) the first author, year of publication, and country of studies; (2) the species and number of animals in the trial groups; (3) types and sources of stem cells; (4) intervention measures of treatment group and control group; and (5) evaluation of endpoint outcomes of interest: deformity angle, length discrepancy and histological scores. Standardized mean difference (SMD) and its 95% confidence interval (CI) were directly extracted from the articles or calculated according to the relevant data.

2.4. Assessment of the risk of bias

The quality assessment was performed by two research experts (SJ Lu and SG Chen) independently, and any disagreement was settled through discussion or judgement of a third investigator (QM Liao) when consensus could not be reached. The quality assessment was carried out using the modified Cochrane Collaboration tool to assess the risk of bias for randomized controlled trials. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).

2.5. Statistical analysis

All analyses were implemented using the Review Manager V.5.3 software. Outcomes were continuous data and presented as standardized mean difference (SMD) with 95% confidence interval when the scales of data are inconsistent. The results of the meta-analysis are presented with forest diagram. The I^2 statistic was used to assess heterogeneity. When $I^2 > 50\%$, indicating that the included studies have significant heterogeneity. Explore the source of the heterogeneity when heterogeneity was obvious. Then sensitivity analyses were conducted by omitting studies one by one to assess the stability of the results and subgroup analyses were performed to address the source for heterogeneity.

3. Results

3.1. Selection Process

A total of 797 potential articles were obtained in the initial search through the database and references. Fig. 1 shows the stepwise selection procedure and reasons for exclusions. After excluding 11 reduplicated studies, the remaining 786 studies were further screened. After screening of the title and abstract of the remaining studies and a careful reading of the full text, 780 studies were excluded for the following reasons: (1) review article, (2) irrelevant studies, (3) inappropriate therapy method, (4) no available information, (5) growth factors are involved, and (6) comparison of different cells. Finally, 6 studies met the predefined inclusion criteria and therefore were included in the meta-analysis. All included 6 articles were reviewed thoroughly and the main characteristics of all these articles are summarized in Table 1.

3.3. Study characteristic and quality assessment

These studies were published in English. As for animal experiments, 5 studies used rabbits, 1 used pigs. Sample sizes of these studies ranged from 20 to 72. For the types of the stem cell, 3 studies used bone marrow mesenchymal stem cells, 2 used periosteum derived stem cells, and only 1 used synovial mesenchymal stem cells. For experimental model, 3 studies involved femoral growth plate defect model, 3 studies involved tibial growth plate defect model. For outcome measures, angle deformity and length discrepancy were used in all studies, histologic score in only two studies. All included studies were rated as high-quality in the risk of bias assessment.

Table 1
Characteristics of the included studies

Author	Year	Country	Animal (number)	Stem cell	Tissue of origin	Experimental model	Groups	Outcome index
Chen[26]	2003	Singapore	New Zealand rabbits 36	MSCs	Periosteum	Excised medial half of the proximal growth plate of the tibia	1.Control 2.Periosteum flap 3.Agarose scaffold with MSCs	1.Varus angle 2.Length
Li[27]	2004	Singapore	New Zealand rabbits 72	MSCs	Periosteum	Excised medial half of the proximal growth plate of the tibia	1.Control 2.Chitin scaffold alone 3.Chitin scaffold with MSCs	1.Varus angle 2.Length
Plánka [28]	2007	Czech Republic	New Zealand rabbits 20	MSCs	Bone marrow	Excised lateral portion of the distal growth plate of the femur	1.Control 2.MSCs alone 3.Gel scaffold with MSCs	1.Valgus angle 2.Length
Plánka [30]	2009	Czech Republic	Pigs 20	MSCs	Bone marrow	Excised lateral portion of the distal growth plate of the femur	1.Control 2.Collagen-chitosan scaffold with MSCs	1.Valgus angle 2.Length
Kiyoshi [32]	2012	Japan	New Zealand rabbits 34	MSCs	Synovial membrane	Excised medial half of the proximal growth plate of the tibia	1.Control 2.Bone wax 3.MSCs with extracellular matrix	1.Varus angle 2.Length 3.Histologic Score
Azarpira[33]	2015	Iran	New Zealand rabbits 28	MSCs	Bone marrow	Excised lateral portion of the distal growth plate of the femur	1.Control 2.Chitosan scaffold 3.Chitosan scaffold with MSCs	1.Valgus angle 2.Length 3.Histologic Score
<i>MSCs</i> mesenchymal stem cells								

3.3.The varus angle of tibial or valgus angle of femur

A total of 6 studies [26, 27, 28, 30, 32, 33] assessed the deformity angle of tibial or femur at 4, 8, 12, 16 weeks. The outcomes revealed that the deformity angle of tibial in the stem cell group was significantly lower than that in the control group at 4, 8, 16 weeks (SMD = -3.49, 95% CI: -5.54 to -1.43; SMD = -2.61, 95% CI: -5.19 to -0.03; SMD = -8.18, 95% CI:

-14.95 to -1.42, respectively) (Fig. 2). However, for the deformity angle of femur, the results indicated that the deformity angle at middle stage (12 weeks) showed no significant difference between the two groups (SMD = -0.88, 95% CI: -2.09 to 0.33). At longer follow-up (16 weeks), the deformity angle of femur in the stem cell group was significantly lower than that in the control group (SMD = -1.69, 95% CI: -2.55 to -0.83) (Fig. 3).

3.4. The difference in medial/lateral height of tibial plateau or the length of femur

The analysis of data from 4 studies [26, 27, 28, 30] evaluated the difference in medial/lateral height of tibial plateau or the length of femur. It demonstrated that the stem cell group had a significant smaller discrepancy in medial/lateral height of tibial plateau than control group at 8 and 16 weeks (SMD = -3.31, 95% CI: -5.28 to -1.34; SMD = -3.10, 95% CI: -4.73 to -1.48, respectively) (Fig. 4). Also, the difference about the femur length in the experimental group was significantly longer than that in the control group at 16 weeks (SMD = 0.45, 95% CI: 0.37 to 0.52) (Fig. 5).

3.5. The histological scores

Only 2 studies [32, 33] assessed the histological scores at 4, 8 and 12 weeks, confirming that there were no significant difference between the two groups in early and middle stages (SMD = 1.13, 95% CI: -0.14 to 2.4; SMD = 1.15, 95% CI: -0.18 to 2.48, respectively) (Fig. 6). While in later stage (12 weeks), the histological scores in the stem cell group was significantly higher than that in the control group (SMD = 1.45, 95% CI: 0.12 to 2.79) (Fig. 6).

4. Discussion

Due to accidents in sports and play, skeletal fracture are becoming more common in children, with up to 50% children experiencing a bone fracture [35]. It has been estimated that around 20% childhood bone fractures involve growth plate [36]. When such an injury happens, the ability of spontaneous repair is very limited, which results in significant orthopaedic problems such as limb length discrepancy and angular deformity [37, 38, 39]. In clinical practice, all of these available treatments so far are extremely invasive, time consuming, or may be ineffective [39, 40]. Currently, finding a better treatment to promote growth plate repair have drawn researchers much interest.

Recently, biological therapies using stem cells to boost growth plate healing has become a hot researched topic. Mesenchymal stem cells are multipotent cells that are capable of differentiating into multiple cell types including osteoblasts, adipocytes, and chondrocytes. Many studies have focused on the application of mesenchymal stem cell treatments for growth plate. Our meta-analysis including 6 studies [26, 27, 28, 30, 32, 33] provided evidence that stem cells can improve the repair of the growth plate injury by radiological examination and histological analysis. Currently, stem cell therapy in combination with various scaffolds showed positive effects on growth plate healing. Stem cells have the ability to self-replicate through mitosis and reserve the capacity to differentiate into mature committed cells of various lineages [41].

The optimistic criteria for assessing growth plate repair are bone angular deformity, length discrepancy and histological assessment. Follow-up studies in the animal model were conducted at 4, 8, 12 and 16 weeks. Differences in angular deformity, limb length and histological score between therapy and control groups became significant beginning from 4, 8, 12 weeks respectively. This was observed to last up till 16 weeks post-implantation, after which the physis would close.

For the angular deformity, the varus angle of tibia in experimental groups was much milder than in control group from 4 weeks after surgery. However, the valgus angle of femur showed no significant difference between the two groups at 12 weeks after surgery. At 16 weeks postoperatively, the valgus deformity of femur was significantly improved. The discrepancy in medial/lateral height of tibial plateau or the length of femur were used to assess the therapeutic effectiveness of stem cells. The femur length in the experimental group was significantly longer than that in the control group at 16 weeks. Also, in the experimental, growth plate injury had little effect on tibial medial/lateral plateau height at 8,

16 weeks. Therefore, stem cells based therapy could relieve bone angular deformity and length discrepancy. Histological study for evaluation of regeneration of physis was also done in 2 studies. Histologic analyses at 4, 8 and 12 weeks after surgery were evaluated using two similar histologic grading scales. At 4 and 8 weeks after surgery, histologic scores for the repaired growth plate showed no significant difference between the two groups. However, the histologic scores of stem cell group at 12 weeks were significantly higher than that of control group. Taken together, stem cells were transferred into an experimental growth plate defect zone can promote growth plate healing, reduce bone bridge formation, prevent bone shortening and angular deformity.

For the clinical application of stem cells in patients, several major concerns need to be addressed. Currently, the most researched and applied stem cells types for growth plate repair were derived from bone marrow, periosteum, and synovial membrane. Previous studies have demonstrated that MSCs derived from various compartments possess different regenerative potentials [42]. Therefore, it is necessary to define the most practical way to promote the growth plate repair for clinical applications among all the available sources. Subsequently, another challenge for growth plate regeneration is to find the most appropriate carrier support systems (scaffolds) for MSC transplantation. The scaffolds should be biodegradable, biocompatible, promoting cell attachment, as well as allowing for tissue formation.

Nevertheless, this investigation still exist some potential limitations. First of all, although our analysis does prove the significant efficacy of stem cell-based treatments on growth plate, the heterogeneity between studies has to be mentioned. Therefore, we deal with the heterogeneity by random-effect model, standardized mean difference and subgroup analysis. Second, due to the small number of studies in the analysis, sensitivity analysis and publication bias were not conducted for the secondary outcomes. Third, the lack of some important data in several studies poses a barrier to more detailed subgroup analysis.

Conclusion

In conclusion, the meta-analysis indicates that stem cell-based therapy was a promising method to repair growth plate injury. However, more preclinical studies are needed to further confirm the benefits and to produce the most suitable stem cells for future clinical study. Our further study will focus on the comparison between the improvements by different types of stem cells. And other impact factors such as scaffold can also be included in the comparison. Additional larger-scale and prospective studies are still needed to confirm our results.

Abbreviations

SMD

standard mean difference

CI

confidence interval

BMSCs

bone mesenchymal stem cells

ADSCs

adipose derived stem cells

UCB-MSCs

umbilical cord blood derived mesenchymal stem cells

PRISMA

Preferred Reporting Items for Systematic Reviews and Meta Analyses

Declarations

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Not applicable.

Authors' contributions

All authors contributed to all parts of the study. XLX, SJL, HP, SGC, and QML designed the study. XLX, SJL, and SGC collected the data and performed all analysis. XLX wrote the manuscript. QML supervised the work and revised the manuscript. All authors read and approved the final manuscript

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow diagram for the selection of studies, with article search strategy results

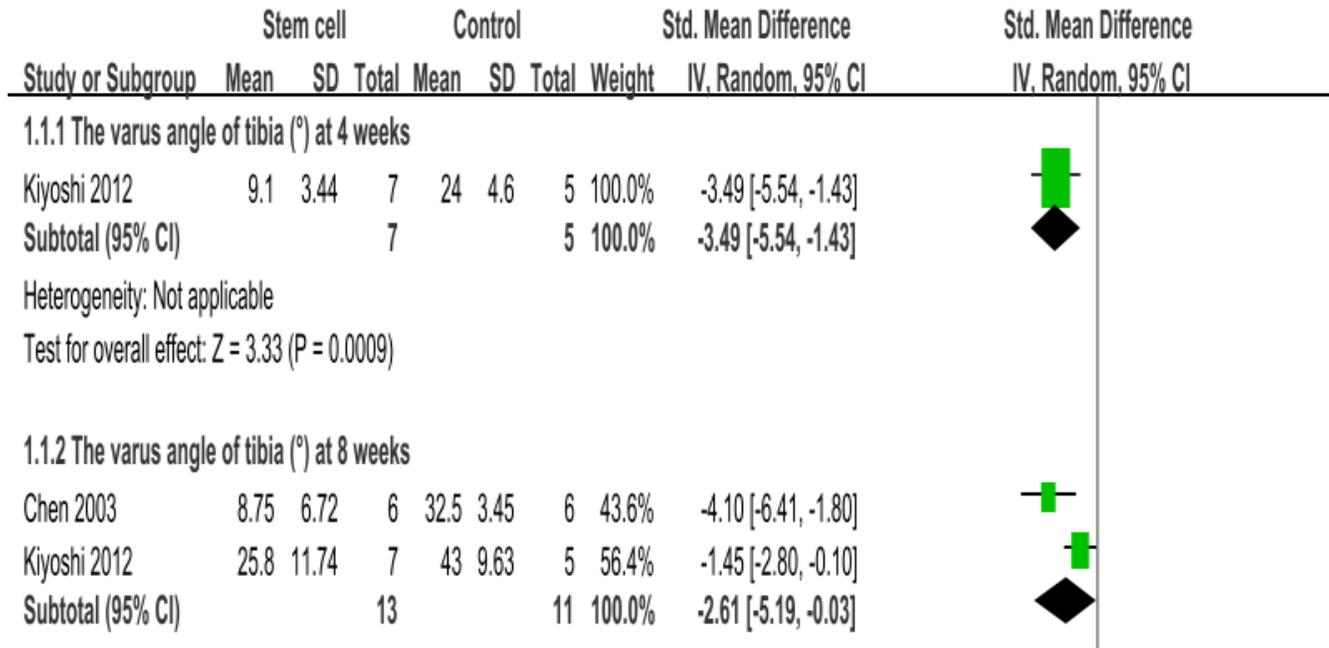
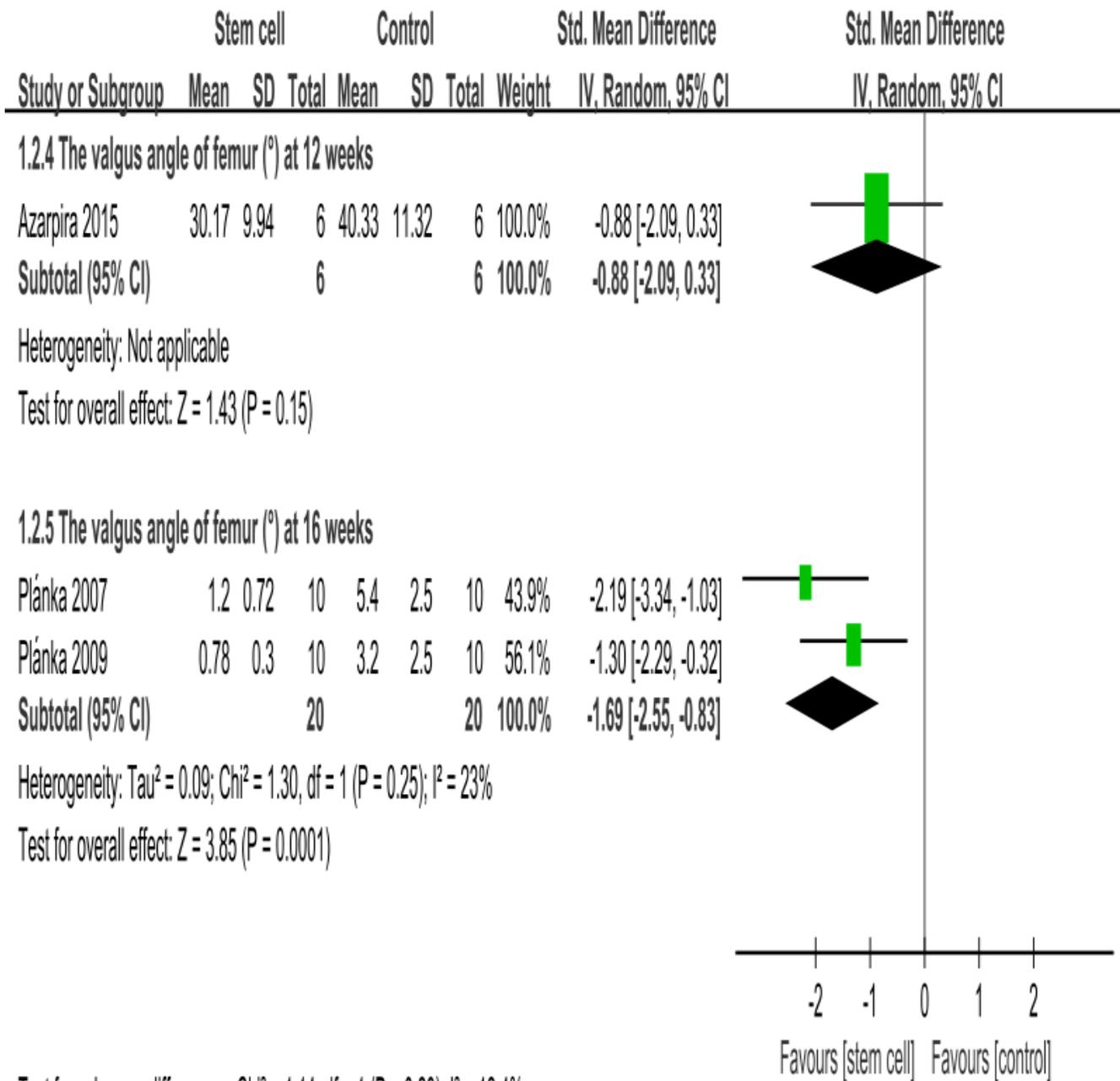


Figure 2

The forest plot: the effects of stem cells therapy for alleviating the varus deformity of tibial compared with controls.



Test for subgroup differences: Chi² = 1.14, df = 1 (P = 0.29), I² = 12.4%

Figure 3

The forest plot: the effects of stem cells therapy for alleviating the valgus deformity of femur compared with controls.

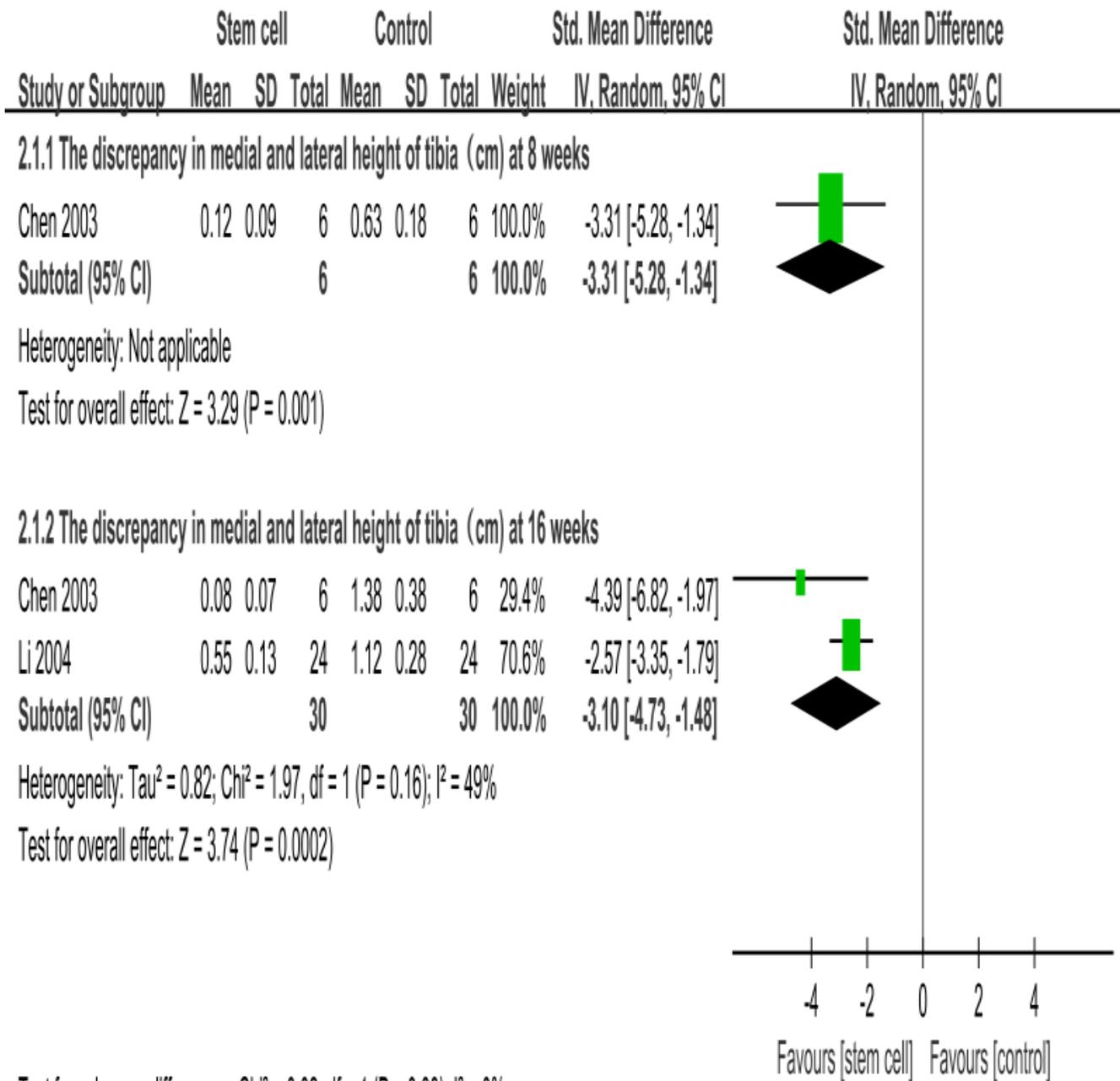


Figure 4

The forest plot: the effects of stem cells therapy for reducing the impact of growth plate injury on the height of the medial tibial plateau.

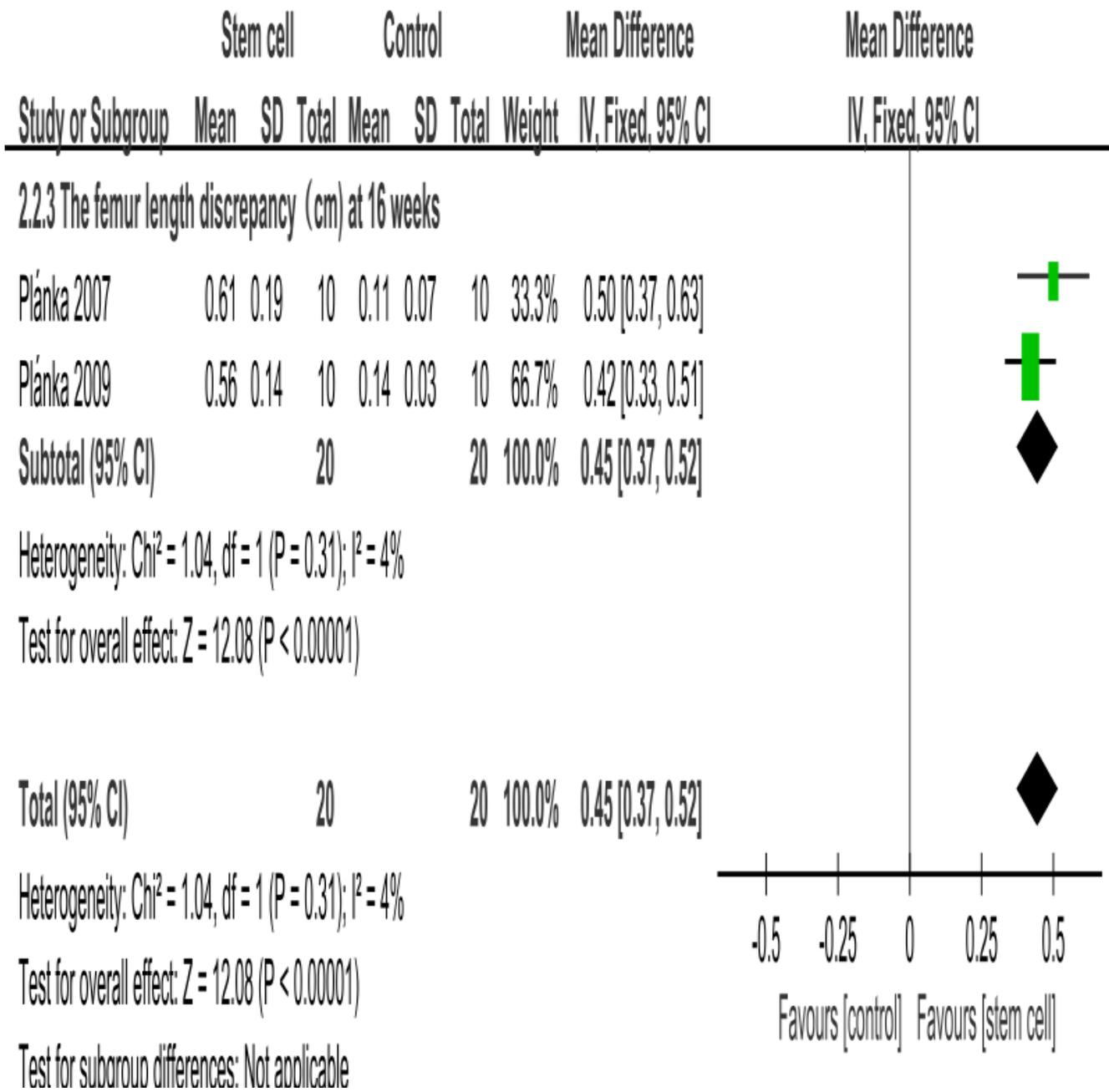


Figure 5

The forest plot: the effects of stem cells therapy for reducing the impact of of growth plate injury on the length of femur.

Figure 6

The forest plot: the effects of stem cells therapy for improving the repair quality of growth plate.