The Egyptian Journal of Hospital Medicine (January 2019) Vol. 74 (7), Page 1491-1513

Limb Lengthening for Achondroplasia: Systematic Review and Meta-analysis

Yasser Ali Elbatrawy, Ashraf Mohammed Abdelaziz, Mohamed Ahmed Abdel-Meged Zidan
Department of Orthopedic Surgery, Faculty of Medicine, Al-Azhar University
Corresponding author: Mohamed Ahmed Abdel-Meged Zidan, **Mobile:** (+20) 01220427437,
E-Mail: drmohamedzidan@gmail.com

ABSTRACT

Background: Achondroplasia is the most common genetic skeletal dysplasia. It is characterized by a rhizomelic form of dwarfism, exaggerated lumbar lordosis, a prominent forehead and a low nasal bridge. The trunk is generally of near normal length. The incidence of achondroplasia is approximately 1 in 25000 people.

Objectives: In the present systematic review, we have aimed to synthesize evidence from the published literature about the safety and efficacy of limb lengthening in patients with achondroplasia. Also, we have aimed to assess which age is preferred to start the lengthening and effect of early management on natural growth and psychiatric health.

Methods: An electronic search was conducted from the inception till September 2018 in Medline via PubMed. Data entry and processing were carried out using a standardized Excel sheet and reviewers extracted the data from the included studies. We performed all statistical analyses using Review Manager (RevMan) 5.3 for windows.

Results: In the present study, 17 studies were included in the present systematic review and meta-analysis. In terms of gained length of femur, the overall effect estimate showed that limb lengthening procedure achieved a mean increase in femur length by 11.9 (95% CI 9.39 – 14.43) cm. In addition, the overall effect estimate showed that limb lengthening procedure achieved a healing index of femur 30.46 (95% CI 24.326 – 36.59) days/cm. Similarly, the overall effect estimate showed that limb lengthening procedure achieved a mean increase in tibia length by 9.5 (95% CI 8.169 – 10.927) cm. The overall effect estimate showed that limb lengthening procedure achieved a healing index of tibia of 32.09 (95% CI 18.65 – 25.52) days/cm

Conclusion: It could be concluded that limb lengthening is a reliable procedure with a relatively low complication rate in increasing the length of femur and tibia in patients with achondroplasia.

Keywords: Achondroplasia, Meta-analysis.

INTRODUCTION

Skeletal dysplasias are a group of genetic disorders that affect the size and shape of the limbs, trunk and skull, typically resulting in short stature [(1)]. On the basis of data from seven population-based birth defect-monitoring programs in the United States, the estimated prevalence of achondroplasia ranges from 0.36 to 0.60 per 10,000 live birth [(2)]. Achondroplasia creates an external appearance of disproportionate short stature in which extremities are too short relative to the trunk and head, due to inadequate enchondral ossification in the long bones, with an adult height that is below the third percentile [(3)]. In addition to the discomforting cosmetic appearance, achondroplasia often results in lumbar (lordosis) and spinal stenosis later in life, which may require surgery to correct [(1)].

Less commonly, achondroplasia may lead to neurological complications, craniofacial abnormalities, sleep-disordered breathing, thoracolumbar kyphosis, angular deformities of the knee and leg, otitis media, deafness, speech delay, weight gain and obesity [(4)].

Among the various surgical options that can be offered to those affected from achondroplasia, limb lengthening was proposed in order to increase height at maturity and restore normal body proportions in affected individuals [(5)]. The fundamental research conducted by Ilizarov led to a method allowing bilateral lengthening with acceptable risks [(6)].

Lengthening of the arms and legs of individuals with achondroplasia can potentially result in height gains of up to 30 cm and may improve limb function [(7)]. On the other hand, limb lengthening was reported to be associated with high incidence of serious complications. There is a growing body of evidence that lengthening is commonly associated with infection, pain, swelling of the limb, neurovascular complications, contractures of the soft tissues, subluxation and dislocation of adjacent joint, bone-related problems at the lengthened site and psychological problems [(8)].

Previous study by **Donaldson *et al.*** [(9)], on ten achondroplastic children underwent limb lengthening, reported an average total length gain of 20.5 cm, with a high rate of complications. Another report by **Kim *et al.*** [(10)] assessed whether patients were satisfied with leg lengthening using the AAOS lower limb, SF-36, and Rosenberg self-esteem scores. The minimum follow up was 4.5 years. They concluded that even with numerous complications, serial limb lengthening is a good option in terms of improvement in quality of life scores.

The aim of the current study was to synthesize evidence from the published literature about the safety and efficacy of limb lengthening in patients with

Received:25/10/2018
Accepted:14/11/2018

achondroplasia. Also, we have aimed to assess which age is preferred to start the lengthening and effect of early management on natural growth and psychiatric health.

MATERIALS AND METHODS

We performed this systematic review and meta-analysis in accordance to the recommendations of the Meta-analyses of Observational Studies in Epidemiology (MOOSE) statement. MOOSE is a reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. According to International committee of medical journal association (ICJME), reviewers must report their findings according to each of the items listed in this checklist (**Table 1**) [(11)].

Table 1: MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation
1	Problem definition
2	Hypothesis statement
3	Description of study outcome(s)
4	Type of exposure or intervention used
5	Type of study designs used
6	Study population
7	Qualifications of searchers (eg, librarians and investigators)
8	Search strategy, including time period included in the synthesis and key words
9	Effort to include all available studies, including contact with authors
10	Databases and registries searched
11	Search software used, name and version, including special features used (eg, explosion)
12	Use of hand searching (eg, reference lists of obtained articles)
13	List of citations located and those excluded, including justification
14	Method of addressing articles published in languages other than English
15	Method of handling abstracts and unpublished studies
16	Description of any contact with authors
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results
22	Assessment of heterogeneity
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated
24	Provision of appropriate tables and graphics
25	Graphic summarizing individual study estimates and overall estimate
26	Table giving descriptive information for each study included
27	Results of sensitivity testing (eg, subgroup analysis)
28	Indication of statistical uncertainty of findings
29	Quantitative assessment of bias (eg, publication bias)
30	Justification for exclusion (eg, exclusion of non-English language citations)
31	Assessment of quality of included studies
32	Consideration of alternative explanations for observed results
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)
34	Guidelines for future research
35	Disclosure of funding source

Study Selection and Eligibility Criteria:

The present review included studies that fulfilled the following criteria:

(1) Studies that included patients with achondroplasia;

(2) Studies that assessed the efficacy and safety of limb lengthening for limb discrepancy associated with achondroplasia;

(3) Studies that compared limb lengthening with none or any comparison;

(4) Studies that reported any of the following outcomes: gained height of femur and tibia, percentage of gained height of femur and tibia, healing index in femur and tibia, satisfaction, complications, and quality of life assessed by SF-36 andRosenberg self-esteem score;

(5) Studies that were either prospective or retrospective studies.

We excluded non-English studies, theses, dissertations and conference abstracts.

Search Strategy and Screening

An electronic search was conducted from the inception till September 2018 in Medline via PubMed. We used different combinations of the following queries: achondroplasia, limb lengthening, and gained height**.**

Screening:

Retrieved citations were imported into EndNote X7 for duplicates removal. Subsequently, unique citations were imported into an Excel sheet and screened by two independent reviewers; the screening was conducted in two steps: title and abstract screening, followed by a full-texts screening of potentially eligible records.

Data Extraction:

Data entry and processing were carried out using a standardized Excel sheet and reviewers extracted the data from the included studies. The extracted data included the following domains: (1) Summary characteristics of the included studies; (2) Baseline characteristics of studied populations; and (3) Study outcomes. All reviewers' independently extracted data from the included articles and any discrepancies were solved by discussion.

Dealing with Missing Data:

Missing standard deviation (SD) of mean change from baseline was calculated from standard error or 95% confidence interval (CI).

Data Synthesis

Continuous outcomes were pooled as mean difference (MD) or standardized mean difference (SMD) using inverse variance method, and dichotomous outcomes will be pooled as relative risk (RR) using Mantel-Haenszel method. The random-effects method was used under the assumption of existing significant clinical and methodological heterogeneity. We performed all statistical analyses using Review Manager (RevMan) 5.3 for windows.

Assessment of Heterogeneity:

We assessed heterogeneity by visual inspection of the forest plots, chi-square, and I-square tests. According to the recommendations of Cochrane Handbook of Systematic Reviews and meta-analysis, chi-square p-value less than 0.1 denote significant heterogeneity while I-square values show no important heterogeneity between 0% and 40%, moderate heterogeneity from 30% to 60%, substantial heterogeneity from 50% to 100%.

RESULTS

Characteristics of the included studies

In the present study, 150 records were retrieved after online PubMed searching. We then retained 32 potentially eligible records for full-texts screening. Finally, 17 studies were included in the present systematic review and meta-analysis (**Figure 1**).

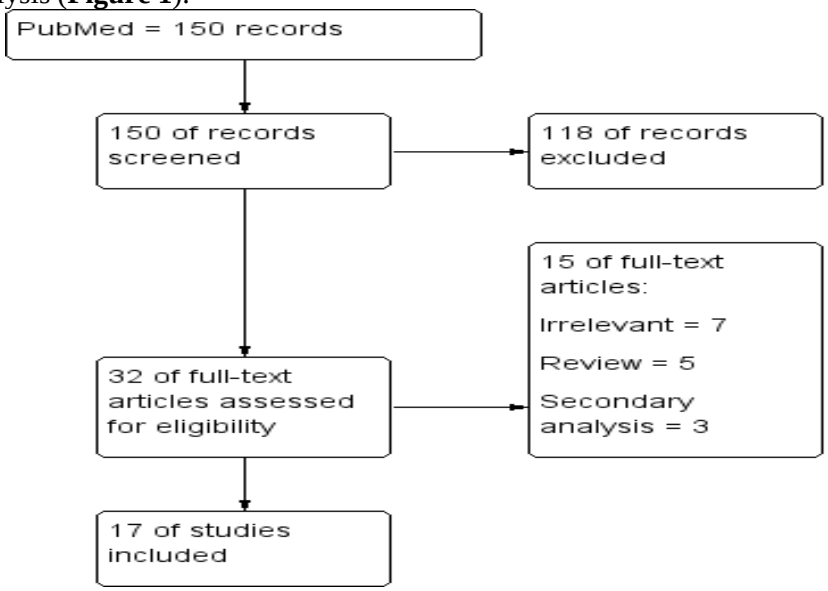

Figure 1: PRISMA flow-chart

Seventeen studies (No. of achondroplasia patients = 466) were included in the present review. Four studies were conducted in Italy, six studies were conducted in Korea, two in Japan, and one study in each of the following countries: US, UK, India, Spain, and France. The majority of the included studies (No. =14) were retrospective studies, one was prospective study, one was case-series study, and one was survey study. While most of included studies recruited heterogeneous group of patients who required lengthening of upper or lower limb, the majority of patients in all included studies were achondroplasia patients. The sample size of the included studies ranged from 8 to 140 patients and the duration of follow up ranged from 6 months to 23 years. Three studies assessed the effects of surgical correction of achondroplasia on psychologic aspects of patients using Rosenberg self-esteem score; the studies concluded that the quality of life increased significantly after limb lengthening. One study assessed the function of lengthened limbs, evaluated by physical strength tests, and reported that it was better at follow-up than before lengthening in the growing children. While the rest of included studies assessed the gained length of surgical correction (**Table 2**).

Table 2: Summary Characteristics of the included studies

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
Aldegheri et al.	2001	Rome, Italy	Retrospective review	Patients with achondroplasia	140	Orthofix fixator	31 months	The authors' recommendation is to start limb elongation of male patients with achondroplasia at the age of 8 years or older, but to delay limb lengthening in female patients with achondroplasia until approximately 15 years

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
								of age to allow for maximal skeletal growth
Barreto et al.	2006	Lyon, France	Retrospective review	Patients had limb discrepancy or short stature	57	Ilizarov procedure		There was no difference in the complications in leg lengthening using Ilizarov technique between the group of patients with leg length discrepancy and the group with short stature.

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
								A good knowledge of the Ilizarov technique is necessary to perform a lengthening programme with a low rate of complications.
Vaidya	2006	Seoul, South Korea	Retrospective review	Achondroplasia patients who underwent	24	Ilizarov procedure	1-4 years	The procedure is safe and efficacious if performed with strict

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
				lengthening before skeletal maturity				adherence to prescribed technique
Lie et al.	2009	Hong Kong	Retrospective review	Patients with short stature underwent distraction osteogenesis	8	ilizarov apparatus or the Orthofix fixator	4 - 14 months	Limb lengthening of up to 40% of the initial length of the bone segment can be achieved without significant longterm sequelae.

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
Venkatesh et al.	2009	Seoul, South Korea	Retrospective review	Achondroplasia patients who underwent lengthening before skeletal maturity	20	External fixator	2.1 - 6.7	Statistically, the incidence of stiffness in adjacent joints and regenerate bone fracture was significantly associated with the magnitude of lengthening.

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
Kim et al.	2011	Seoul, South Korea	Retrospective review	Patients diagnosed with achondroplasia who underwent bilateral lower and upper limb lengthenings.	12	External fixator	0.8 - 6.8 years	Humeral lengthening had a lower complication rate than lower-limb lengthening, and QOL increased significantly after humeral lengthening.
Kim et al.	2012	Seoul, South Korea	Retrospective review	Patients diagnosed with achondroplasia	44	ilizarov apparatus	4.5 - 6.9 years	Our data suggest that despite frequent complications, bilateral

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
				who underwent bilateral lower and upper limb lengthening between 2002 and 2005.				lower limb lengthening increases patients' QOL
Song et al.	2012	Seoul, South Korea	Retrospective review	Achondroplasia patients who underwent bilateral tibial	23	ilizarov apparatus	9.8	Physeal growth rate can be disturbed after tibial lengthening in achondroplasia, and a

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
				lengthening before skeletal maturity				close watch should be kept for such an occurrence—especially when lengthening of more than 50% is attempted.
Kitoh et al.	2014	Nagoya, Japan	Retrospective review	Patients with achondroplasia	25	External fixator	1.7 - 9 years	Radiological monitoring of the shape of the callus during distraction is important to prevent

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
								early and late fracture of lengthened limbs in patients with ACH or HCH
Donaldson et al.	2015	UK	Retrospective review	Patients with achondroplasia	10	External fixator	7.8	Although complication rates were high (70%), none were left with any long-term sequelae and all were pleased with the results.

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
Chilbule et al.	2016	Tamil Nadu, India	Retrospective review	Patients with achondroplasia	8	Ring fixator	58.5 months	Extensive limb lengthening (more than 50% over initial length) carries significant risk and should be undertaken only after due consideration.
Cattaneo et al .	1990	Lecco, Italy	Retrospective review	Patients required humeral lengthenings	29	Ilizarov technique.	2.7 years	lengthening can be safely performed with excellent

Author	Year	Country	Study Design	Population	Sample Size	Device	Follow-up range	Main Results
Lavinie et al.	1989	Rome, Italy	Survey Study	Male and female patients with achondroplasia who underwent limb lengthening procedure	72	ilizarov apparatus	NA	Long-term research is required to determine effects of surgical correction of achondroplasia from both psychologic and various physical points of view
Aldegheri et al.	1989	Rome, Italy	Prospective study	Patients with achondroplasia	140	Orthofix fixator	6 months - 2 years	Callotasis has yielded very favorable results. It is less complex than most lengthening methods and has a lower complication rate.
Peretti et al.	1995	NY, USA	Case-series	Patients with achondroplasia	28	NA	9 months	In 9 years 28 children have undergone limb lengthening, and six of these patients have now completed the first three stages, obtaining a total increase in length from 18 to 23 cm
Yasui et al.	1997	Saitama, Japan	Retrospective review	Patients with achondroplasia or hypochondroplasia	42		15 - 23 years	The function of lengthened limbs, evaluated by physical strength tests, was better at follow-up than before lengthening in the growing children, although the mechanical axes of the lengthened bones were not necessarily in correct alignment.
Noonan et al.	2001	Pamplona, Spain.	Retrospective review	Patients with achondroplasia or hypochondroplasia	121	Orthofix fixator		The results of the present review suggest that the use of healing indices to gauge the final outcome of distraction osteogenesis is questionable; we were unable to discern significance or clinical importance from appropriately adjusted values.
								clinical results using the Ilizarov

Regarding the baseline characteristics of the included studies, the total number of achondroplasia patients was 466 patients. The majority of patients were males and the average age at first operation ranged from 6 to 20 years old. All included studies operated on the femur and tibia except three studies; Kim et al, (2011) and Chilbule et al (2016) that operated on humerus as well, while Cattaneo et al (1990) operated on humerus only. The percentage of increased length of operated limbs ranged from 20.5% to 100.7%; while the healing index ranged from 26 to 48 days/cm (**Table 3**).

Table 3: Baseline characteristic of the included studies

Author	Achondroplasia Patients, No (%)	Gender, No. (%)		Age at First Op, mean (SD)	Bone	Increased Length (%)	Range (%)	Healing Index (days/cm)	Implant	Approach
		Male	Female							
Lavinie et al.	72	33	39	15	Femur and Tibia	NA	NA	NA	NA	NA
Kitoh et al.	25	11	14	14.6 (4)	Femur and Tibia	44.70%	13.20%	34.7	Monolateral	NA
Aldegheri et al.	45			16	Femur and Tibia	24.60%	8 - 58%	39	Monolateral	NA
Aldegheri et al.	80			15.1	Femur and Tibia	20.5 cm	11 - 28 cm	NA	Monolateral	Longitudinal, cross-leg
Barreto et al.	22	9	13	20.2	Femur and Tibia	29.5	9.5 - 60%	NA	NA	NA
Kim et al.	22			12.7	Femur and Tibia	35.50%	14-65 %	34	Monolateral	Longitudinal
Kim et al.	12	6	6	11.8	Femur and humerus	35.20%	29 - 42%	34.4	Monolateral	Longitudinal
Lie et al.	3	2	1	20	Femur and Tibia	21%	7.9 - 40%	48	Monolateral and Circular	Longitudinal, cross-leg
Noonan et al.	28			11	Femur and Tibia	41%	9 - 100%	20.8	Monolateral,	Transverse
Peretti et al.	22	12	10	8.7	Femur and Tibia	40%	40 - 65%	NA	Monolateral, ring fixator	Transverse
Song et al.	23	11	12	8.2	Tibia	40%	40-50%	43	Monolateral	NA
Vaidya	24	14	10	12.9	Tibia	6.84 cm	3.5 - 10.3 cm	26.06	Ring fixator	Transverse
Venkatesh et al.	20	5	15	12.5	Femur	39.9%	14-65%		Monolateral	Longitudinal
Yasui et al.	35	21	14	14.5	Femur and Tibia	7.2 cm	4.5 - 12 cm	30.8	Monolateral	Longitudinal, cross-leg, Transverse
Donaldson et al.	10	NA	NA	5.9	Femur and Tibia	20.5%	NA	NA	NA	Crossed lengthening
Chilbule et al.	9	7	2		Femur, Tibia, and humerus	100.7%	67.3 – 153%	25.7		
Cattaneo et al.	14			18	Humerus	NA	NA	NA		

Table 4: Complications of limb lengthening

Author	Segments, No (%)	Total No. of complications	Knee contractures	Hip flexion contractures	Bony complication	Pin tract infection	Equinus contractures	Recurrent deformities	Malalignments	Fracture	Neuropraxia
Lavinie et al.	NA										
Kitoh et al.	72									17	
Aldeghe ri et al.	NA					3%				3%	
Aldeghe ri et al.	NA										
Barreto et al.	22	36									
Kim et al.	88	128	70	42	47						
Kim et al.	48										
Lie et al.	28	17	9			7		1	1	1	4
Noonan et al.	114	114	9	33		6			33	28	
Peretti et al.	22								3	1	
Song et al.	NA										
Vaidya	47	46				15	22	2	3		
Venkatesh et al.	40									36	
Yasui et al.	168					31	4			5	
Donaldson et al.	10*						2			4	1
Chilbule et al.	36	33				6	1	4		2	3
Cattaneo et al.	14					6					3

- Patients

Meta-analysis Results

1. Gain in length in femur

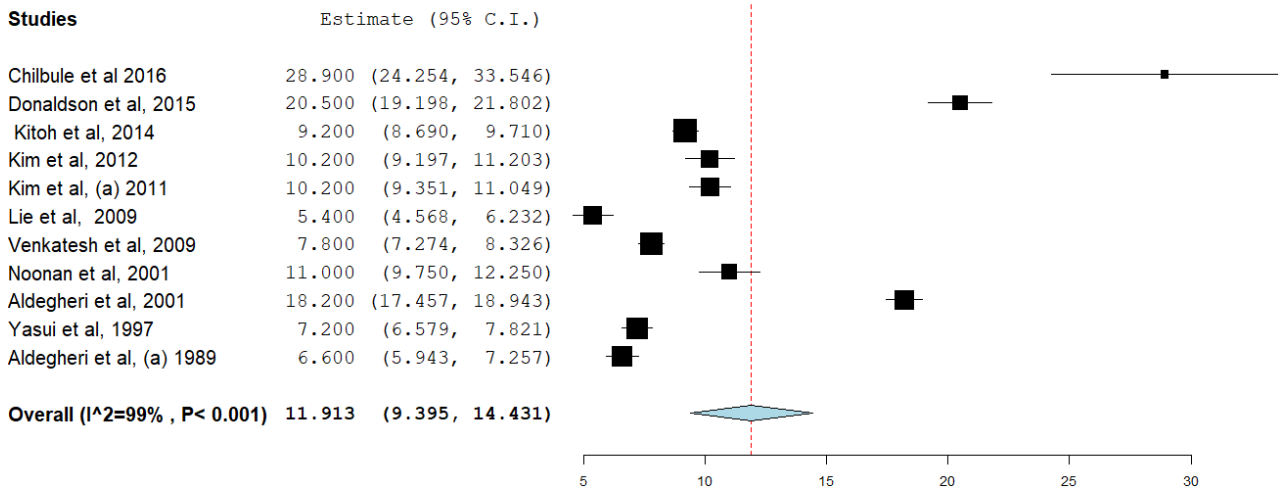

Figure 2: Forest plot of the pooled estimates of the change in gain length of femur

In terms of gained length of femur, eleven studies reported the average increase in femur length after limb lengthening procedure. The overall effect estimate showed that limb lengthening procedure achieved a mean increase in femur length by 11.9 (95% CI 9.39 – 14.43) cm.

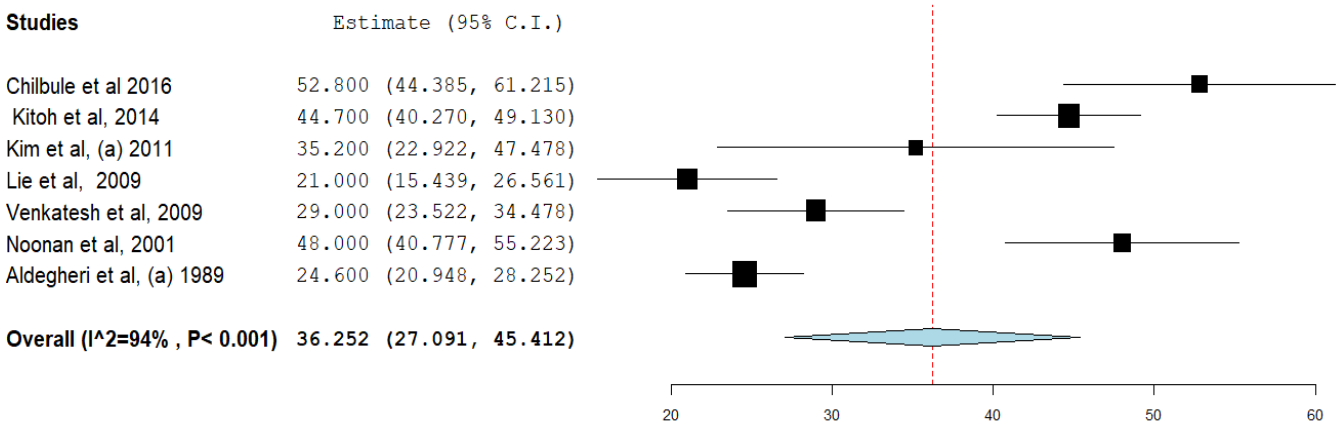

Figure 3: Forest plot of the pooled estimates of the change in percentage of gained length of femur

In terms of percentage increase in gained length of femur, seven studies reported the percentage increase in femur length after limb lengthening procedure. The overall effect estimate showed that percentage limb lengthening procedure achieved a mean increase in femur length by 36.25 (95% CI 27.09 – 45.4) %.

2. Healing Index in femur

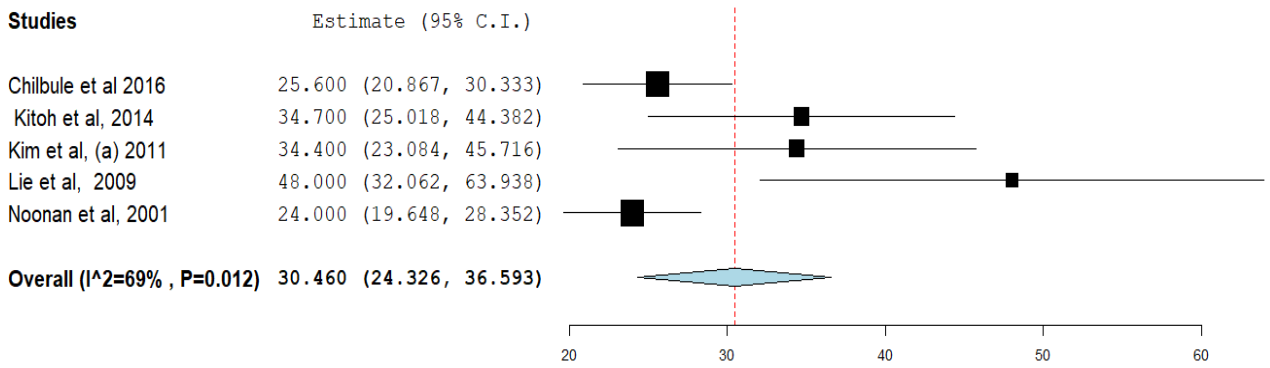

Figure 4: Forest plot of the pooled estimates of the healing index of femur

In terms of healing index of femur, five studies reported the average increase in healing index of femur after limb lengthening procedure. The overall effect estimate showed that limb lengthening procedure achieved anhealing index of femur 30.46 (95% CI 24.326 – 36.59) days/cm.

3. Gain in length in tibia

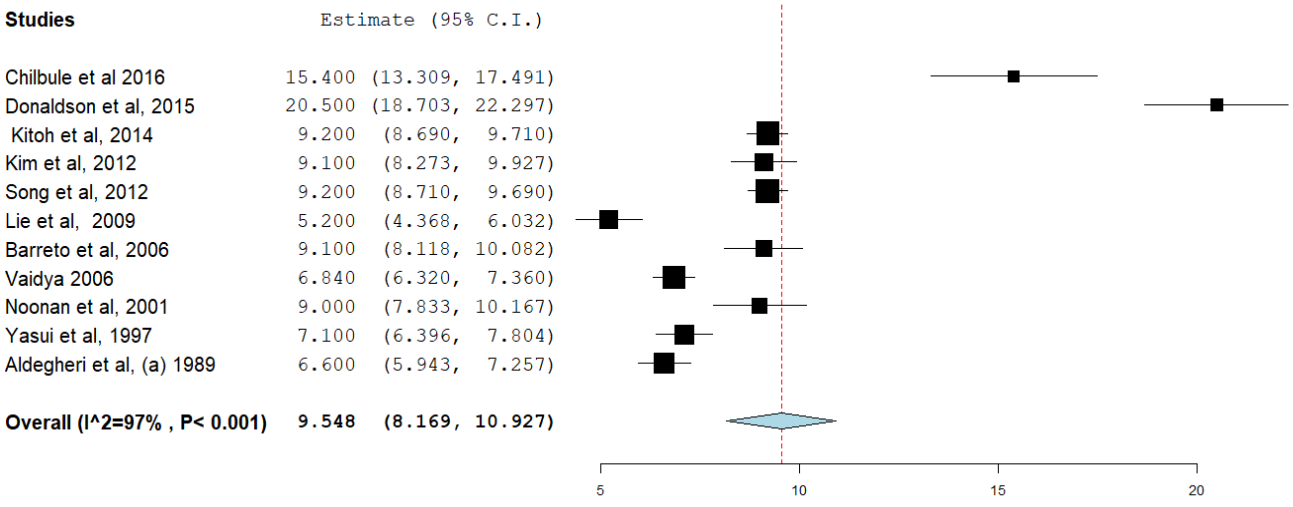

Figure 5: Forest plot of the pooled estimates of gained length of tibia

In terms of gained length of tibia, eleven studies reported the average increase in tibia length after limb lengthening procedure. The overall effect estimate showed that limb lengthening procedure achieved a mean increase in tibia length by 9.5 (95% CI 8.169 – 10.927) cm.

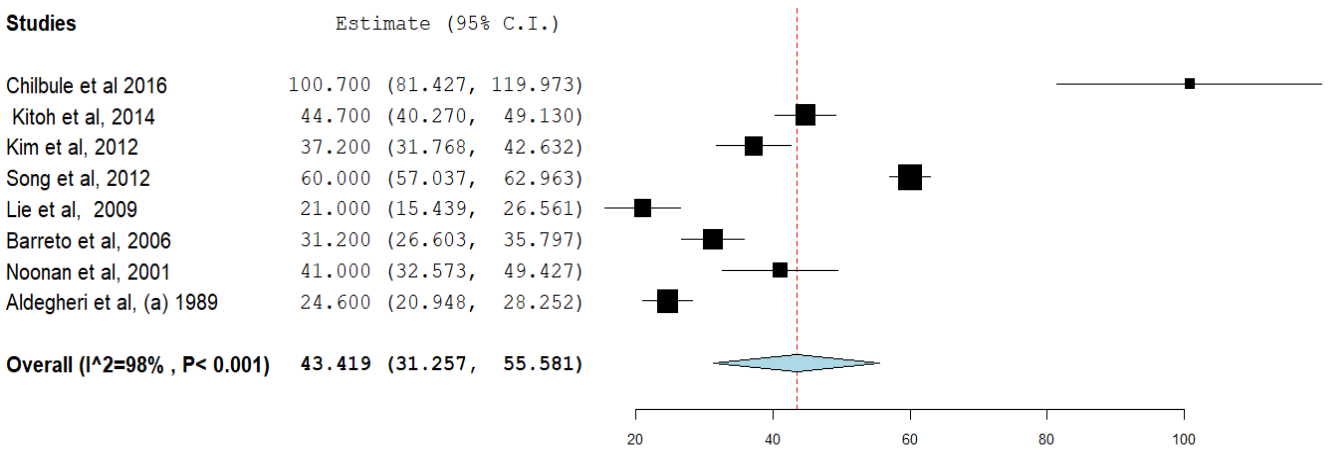

Figure 6: Forest plot of the pooled estimates of percentage gained length of tibia

In terms of percentage increase in gained length of tibia, eight studies reported the percentage increase in tibia length after limb lengthening procedure. The overall effect estimate showed that percentage limb lengthening procedure achieved a mean increase in tibia length by 43.49 (95% CI 31.25 – 55.58) %.

4. Healing Index in tibia

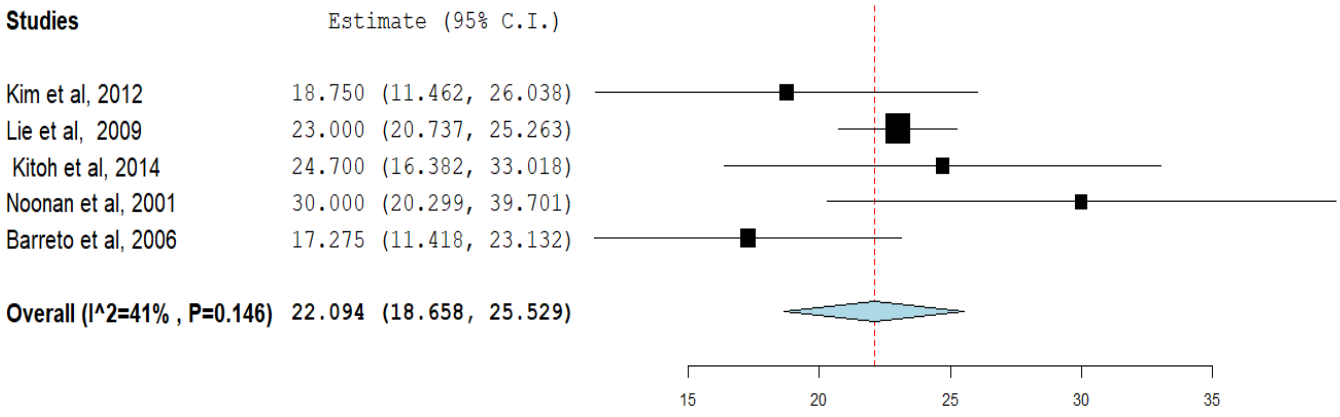

Figure 7: Forest plot of the pooled estimates of healing index of tibia

In terms of healing index of tibia, five studies reported the average increase in healing index of tibia after limb lengthening procedure. The overall effect estimate showed that limb lengthening procedure achieved ahealing index of tibia of 32.09 (95% CI 18.65 – 25.52) days/cm.

5. Quality of life:

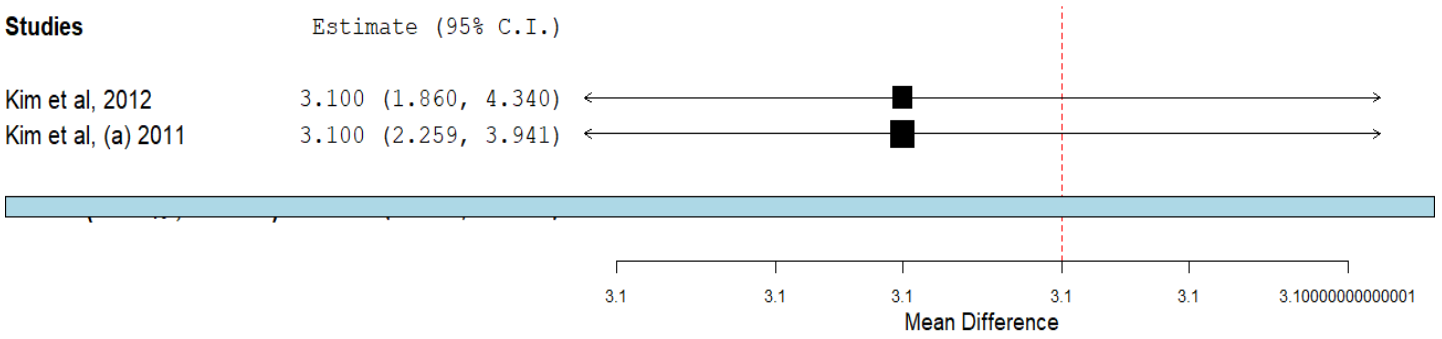

Figure 8: Forest plot of the pooled estimates of Rosenberg self-esteem score

In terms of Rosenberg self-esteem score, two studies compared limb lengthening to no treatment control group The overall effect estimate showed that limb lengthening significantly improved the quality of life (MD 3.1 95% CI 2.25 – 3.94).

DISCUSSION

Achondroplasia is the most common genetic skeletal dysplasia. It is characterized by a rhizomelic form of dwarfism, exaggerated lumbar lordosis, a prominent forehead and a low nasal bridge. The trunk is generally of near normal length. The incidence of achondroplasia is approximately 1 in 25000 people [(12)].

Limb lengthening remains controversial in patients with achondroplasia. Bilateral lower-limb lengthening has been commonly performed for patients with achondroplasia, as it improves the quality of life (QOL) in selected patients [(13)].

Limb lengthening is associated with a high complication rate, particularly stiffness of adjacent joints and fractures leading to a poor outcome. Many authors suggest a goal of lengthening a bone segment to 20% of its original length [(5)].

The high risk of complications needs to be carefully balanced against any potential cosmetic gains. Improved techniques and understanding of distraction osteogenesis in limb lengthening has led to an increase in the number of limb lengthening procedures and more successful outcomes. In addition the rhizomelic pattern of dwarfism in achondroplasia lends itself favorably to limb lengthening to restore more normal body proportionality [(12)].

In this systematic review and meta-analysis study, we included 17 studies (No. of achondroplasia patients = 466). Four studies were conducted in Italy, six studies were conducted in Korea, two in Japan, and one study in each of the following countries: US, UK, India, Spain, and France. The majority of the included studies (No. =14) were retrospective studies, one was prospective study, one was case-series study, and one was survey study. While most of included studies recruited heterogeneous group of patients who required lengthening of upper or lower limb, the majority of patients in all included studies were achondroplasia patients. The sample size of the included studies ranged from 8 to 140 patients and the duration of follow up ranged from 6 months to 23 years. Three studies assessed the effects of surgical correction of achondroplasia on psychologic aspects of patients using Rosenberg self-esteem score; the studies concluded that the quality of life increased significantly after limb lengthening. One study assessed the function of lengthened limbs, evaluated by physical strength tests, and reported that it was better at follow-up than before lengthening in the growing children. While the rest of included studies assessed the gained length of surgical correction.

This was in concordance with the previous meta-analysis conducted by **Jauregui *et al.*** [(14)], which included seven studies evaluated a total of 192

cases of limb lengthening and averaged 27 limbs lengthened per study. One hundred fifty-three patients comprised of 118 males and 35 females with a mean weighted age of 26 years (range of means 8 to 39 years) underwent limb lengthening procedure. The included studies operated on tibiae 155 cases, femora 25 cases, and humeri 12 cases.

In another systematic review and meta-analysis performed by **Schiedel *et al.*** [15], who included 12 studies dating from the last 20 years;three tibial study groups and two groups with only femoral lengthening while the remaining eight studies are reporting about femoral and tibial lengthening procedures. . The range of average ages in 12 reports, independently of the absolute numbers of patients, was 8.7–16.7 years. Overall, using the age ranges at the time of the first operation given in 11 of the 12 reports, patients with achondroplasia underwent the first lengthening procedure at ages of between 3 and 35 years. The authors recommend that the operation should be carried out starting at the age of 8 in boys and later in girls, so that at the age of 15 another treatment step for lengthening can take place.

In our study, the percentage of increased length of operated limbs ranged from 20.5% to 100.7%; while the healing index ranged from 26 to 48 days/cm.

Kim *et al.* [12], who performed a retrospective study on 48 segments (24 humeral and 24 femoral) in 12 patients with achondroplasia. All included patients had bilateral lower-limb lengthening two to three years before bilateral humeral lengthening with mean age at the time of the initial surgery was 11.8 years (6.2 to 19.8) to compare the complications of humeral lengthening with those of femoral lengthening. They found that mean gain in length in the femur was 10.2 cm (7.9 to 12.6). The mean lengthening percentage (LP) was 35.2% (29% to 42%) in the femur. The mean healing index (HI) was 34.4 days/cm (17 to 80) in the femur**.**

In terms of gained length of tibia, eleven studies reported the average increase in tibia length after limb lengthening procedure. The overall effect estimate showed that limb lengthening procedure achieved a mean increase in tibia length by 9.5 (95% CI 8.169 – 10.927) cm and the percentage increase in gained length of tibia, the overall effect estimate showed that percentage limb lengthening procedure achieved a mean increase in tibia length by 43.49 (95% CI 31.25 – 55.58) %. While the healing index of tibia, the overall effect estimate showed that limb lengthening procedure achieved a healing index of tibia of 32.09 (95% CI 18.65 – 25.52) days/cm.

Vaidya *et al.* [16], performed a study between 2000 and 2004 on 24 achondroplastic patients with average age at the time of surgery was 12.9 ± 7.48 years (4-35 years), with bifocal tibial osteotomy with gradual deformity correction and lengthening by application of Ilizarov ring fixator in 47 tibiae. They found that the average tibial length at the time of surgery was 16.2 ± 2.3 cm (11.5- 20.8 cm). The total amount of tibial lengthening exceeded 40% and the average tibial healing index was 26.06 ± 3.27 days/cm (range, 21- 35 days/cm).

Regarding complications, they were many complications reported after limb lengthening procedure.

Our study reported some of these complications such as knee contractures, hip flexion contractures, bony complication, pin tract infection, equinus contractures, recurrent deformities, malalignments, fracture, neuropraxia.

In terms of Rosenberg self-esteem score, two studies compared limb lengthening to no treatment control group The overall effect estimate showed that limb lengthening significantly improved the quality of life (MD 3.1 95% CI 2.25 – 3.94).

Similarly, **Kim *et al.*** [12]**,** reported in their retrospective study that the Rosenberg score was higher ($p < 0.001$) for the surgical than for the nonsurgical group: 22.1 ± 2.5 versus 19 ± 1.6, respectively which means there was a significant improvement in the quality of life between the surgical and nonsurgical groups.

CONCLUSION

In conclusion, limb lengthening is a reliable procedure with a relatively low complication rate in increasing the length of femur and tibia in patients with achondroplasia. The limb lengthening significantly increase the length of both femur and tibia. Moreover, the procedure significantly improve the quality of life of the patients. Nevertheless, the quality of included studies were low and further high quality studies are still needed.

RECOMMENDATIONS

- Limb lengthening is a reliable procedure with a relatively low complication rate
- Therefore. The procedure can be used to increase the length of femur and tibia in patients with achondroplasia. and improve their quality of life.

REFERENCES

1. **Carter EM, Davis JG and Raggio CL (2007):** Advances in understanding etiology of achondroplasia and

review of management. Curr Opin Pediatr.,19:32–7.
2. **Waller DK, Correa A, Vo TM *et al.* (2008):** The population-based prevalence of achondroplasia and thanatophoric dysplasia in selected regions of the US. Am J Med Genet Part A.,146:2385–9.
3. **Horton WA (2006):** Recent milestones in Achondroplasia research. Am J Med Genet., 140 :166–9.
4. **Song D, Maher CO (2007):** Spinal disorders associated with skeletal dysplasias and syndromes. Neurosurg Clin N Am., 18:499–514.
5. **Venkatesh KP, Modi HN, Devmurari K *et al.* (2009):** Femoral lengthening in achondroplasia: magnitude of lengthening in relation to patterns of callus, stiffness of adjacent joints and fracture. J Bone Joint Surg Br., 91:1612–7.
6. **Ilizarov GA (1990):** Clinical application of the tension-stress effect for limb lengthening. Clin Orthop Relat Res., 8–26. doi:10.1097/00003086-199001000-00003.
7. **Kashiwagi N, Suzuki S, Seto Y *et al.* (2001):** Bilateral humeral lengthening in achondroplasia. Clin Orthop Relat Res., 15: 251–7.
8. **Di Russo F, Committeri G, Pitzalis S *et al.* (2006):** Cortical plasticity following surgical extension of lower limbs. Neuroimage, 30:172–83.
9. **Donaldson J, Aftab S and Bradish C (2015):** Achondroplasia and limb lengthening: Results in a UK cohort and review of the literature. J Orthop., 12:31–4.
10. **Kim SJ, Balce GC, Agashe MV *et al.* (2012):** Is bilateral lower limb lengthening appropriate for achondroplasia?: Midterm analysis of the complications and quality of life. Clin Orthop Relat Res., 470: 616–21.
11. **Stroup D, Berlin J, Morton S (2000):** MOOSE Checklist for Meta-analyses of Observational Studies. Jama., 28315:14–5.
12. **Park KW, Garcia RAN, Rejuso CA, Choi JW, Song HR**. Limb lengthening in patients with achondroplasia. Yonsei Med J **.,**56:1656–62.
13. **Chaudhary M (2008):** Limb lengthening over a nail can safely reduce the duration of external fixation. Indian J Orthop., 42:323-330.
14. **Jauregui JJ, Ventimiglia AV, Grieco PW *et al.* (2016):** Regenerate bone stimulation following limb lengthening: a meta-analysis. BMC Musculoskelet Disord., 17:1–8.
15. **Schiedel F, Rödl R (2012):** Lower limb lengthening in patients with disproportionate short stature with achondroplasia: A systematic review of the last 20 years. Disabil Rehabil., 34:982–7.
16. **Vaidya SV, Song H-R, Lee S-H *et al.* (2006):** Bifocal Tibial Corrective Osteotomy With Lengthening in Achondroplasia. J Pediatr Orthop., 26:788–93.