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The impact of stroke on bone properties and muscle-bone relationship: A systematic review and meta-analysis

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Abstract

Purpose: To systematically review available evidence related to the characteristics of bone changes post-stroke and the relationship between various aspects of muscle function (e.g., strength, spasticity) and bone properties after stroke onset.

Methods: An extensive online database search was undertaken (last search in January 2019) Articles that examined the bone properties in stroke patients were included. The quality of the studies was evaluated with the National Institutes of Health (NIH) Study Quality Assessment Tools. Publication bias of meta-analyses was assessed using the Egger's regression asymmetry test. The selection and evaluation of the articles were conducted by two independent researchers.

Results: Fifty-nine studies were identified. In sub-acute and chronic stroke studies, the skeletal sites in the paretic limbs sustained a more pronounced decline in bone quality than their counterparts in the non-paretic limbs. The rate of changes showed a decelerating trend as post-stroke duration increased, but the timing of achieving the steady rate differed across skeletal sites. The magnitude of bone changes in the paretic upper limb was more pronounced than the paretic lower limb. There was a strong relationship between muscle strength/mass and bone density/strength index. Muscle spasticity seemed to have negative impact on bone integrity in the paretic upper limb, but its influence on bone properties in the paretic lower limb was uncertain.

Conclusions: Substantial bone changes in the paretic limbs occurred particularly in the first few months after stroke onset. Early intervention, muscle strength training and long term management strategies may be important to enhance bone health post-stroke. This review has also revealed the knowledge gaps which should be addressed in future research.

Key words: stroke; bone properties; muscle function; osteoporosis; muscle spasticity

1. Introduction

Stroke is one of the most prevalent chronic diseases among older adults[1]. One of the most common complications observed following stroke is secondary hemi-osteoporosis[2-4]. This area has been largely overlooked in research and clinical practice until the 2000s. Mounting evidence has demonstrated not only substantial reduction in bone mineral density (BMD), but also unfavorable changes in bone geometric properties on the hemi-paretic side after stroke[5-14]. Bone geometry is an important determinant of bone strength[15, 16]. Alterations in both bone mineral density and bone geometry have contributed to an exaggerated risk of fragility fractures in individuals with stroke[17-20]. For example, the relative risk of fractures after hospitalization for stroke is more than seven times the rate of fracture in age- and sex-matched populations[17]. Fragility fractures can lead to detrimental consequences, including prolonged hospital stay, as well as increased morbidity and mortality[21]. The medial cost related to the treatment of fracture also imposes an economic strain on the health care sector[22]. Thus, it is clinically important to search for proper therapeutic strategies to enhance bone health in individuals with stroke. In order to achieve this, there is a need to consolidate the knowledge on the characteristics (i.e., magnitude, time course, site-specific differences) of bone changes post-stroke.

Another important issue pertinent to post-stroke bone health is related to the muscle-bone link. According to Wolff's Law of transformation of bone, the skeletal system adapts itself to the external loads under which it is placed[23]. Muscle contractions provide a rich source of mechanical loading to bone, which may, in turn, induce bone adaptations. According to the muscle-bone unit theory proposed by Schoenau[24], muscle and bone are considered as a

functional unit. Muscle function and integrity of bone tissue may thus be closely linked. After stroke, morphological and functional changes occur in skeletal muscles, including reduced muscle mass and density[25, 26], intramuscular fat infiltration[27], muscle weakness[28], contracture[29] and spasticity[30]. These changes in muscle characteristics may have important influence on bone tissue.

To date, a comprehensive collation of the impact of stroke on bone properties has not been disseminated. Therefore, the primary objective of this systematic review was to synthesize the literature related to the impact of stroke on bone properties. The secondary objective was to summarize the research evidence on the relationship between muscle function and bone properties in individuals with stroke.

2. Methods

2.1 Study objectives

We systematically reviewed the literature to address the following questions: (1) What are the characteristics of bone changes in the paretic and non-paretic limbs after the onset of stroke (i.e., magnitude, time course, side-to-side differences, site-specific differences)? (2) Is there a relationship between different aspects of muscle function (e.g., muscle strength, spasticity) and bone properties (e.g., bone mineral density, bone geometry) in individuals with stroke? For the purpose of this review, acute, subacute and chronic stages of stroke were defined as occurring within one month after the onset of stroke, within six months after the onset of stroke, and more than six months after the onset of stroke, respectively. This systematic review was registered in PROSPERO (registration number: CRD42015026828).

2.2 Search strategy

The following databases were searched online through the university library from inception to January 2019: Cochrane, Ovid (Medline, Embase), CINAHL, Scopus and Pubmed. Search terms were based on the participants of interest (e.g. stroke, cerebrovascular accident, hemiplegia, hemiplegic, brain injury), and the construct of interest (e.g. bone density, bone mineral density, bone mineral content, bone geometry and bone loss). Search terms were truncated in accordance with each database and combined. The specific search strategy for the MEDLINE database is described in Appendix 1.

2.3 Selection criteria

Studies were included if they met the following criteria: (1) adult participants whose primary diagnosis was stroke, and (2) included measures of bone mass or geometry using single or dual photon absorptiometry, dual energy x-ray absorptiometry (DEXA), peripheral quantitative computed tomography (PQCT), magnetic resonance imaging (MRI) or ultrasound. Exclusion criteria were: (1) case reports, (2) articles written in languages other than English, (3) grey literature.

2.4 Data extraction and quality assessment

Two reviewers independently evaluated the list of potential articles. The titles and abstracts were first reviewed to screen out irrelevant articles. The remaining articles were then read in full to identify the eligible articles. The reference lists of the eligible articles were examined to identify more relevant articles. In addition, a forward search was conducted using Web of Science to obtain the potential relevant articles that had referenced the eligible articles identified using the above search strategy (last searched in February 2019). Any disagreements on article selection were resolved by involving a third reviewer, and consensus was reached after

discussion. Reporting quality of the selected articles was assessed using a standardized Study Quality Assessment Tool designed by the National Heart, Lung, and Blood Institute under the National Institutes of Health (NIH) [31]. Two reviewers independently appraised each study for risk of bias, and where disagreements occurred, a consensus was reached through discussion with the principal investigator. Each study was rated either as good (most methodological criteria met, low risk of bias), fair (some criteria met, low risk of bias), or poor (few criteria met, high risk of bias).

2.5 Quantitative analysis

For outcomes that were measured in 4 studies or more, meta-analyses were performed using the review software package RevMan5 (The Nordic Cochrane Center, Copenhagen, Denmark). The generic inverse variance meta-analysis method was used as the data were paired (i.e., difference between the paretic and non-paretic side of the same individuals, or change over time within the same individuals)[32]. This required determining the mean inter-limb difference and the standard error of this difference. The standard error was calculated using the accepted formula[32] and involved imputing an assumed correlation of r=0.9 between the bone mass of the paretic and non-paretic limbs. It is reasonable to assume a high correlation between measures of bone mass taken bilaterally within subjects[33]. Statistical heterogeneity was assessed using the I^2 statistic. Where I^2 >50 %, a sensitivity analysis was performed to determine the source of heterogeneity. To assess publication bias, each meta-analysis was examined using Egger's regression asymmetry test (Comprehensive Meta-analysis version 3, Biostatc, Inc., Englewood, NJ, USA). A p-value of <0.1 (two-tailed test) was indicative of publication bias. Where meta-analyses were not appropriate, results were synthesized narratively.

3. Results

Figure 1 shows the flowchart of article selection. A total of 607 records were generated by the search strategy used, but only 59 articles fulfilled the criteria for review (intervention studies: n=4; observation studies: n=55; Online Resource 1). Among the observation studies, a total of 39 articles were cross-sectional, in which measures were taken from the paretic and non-paretic sides at one time point. In the remaining 16 observational studies, measures were taken from the same individuals at several time points relative to stroke onset. Of the measurement tools used, four articles used both DXA and PQCT, and one article used both Pixi densitometer and ultrasound. In the remaining 54 studies, only one measurement tool was used (DEXA, *n*=35; pQCT, *n*=13; CXD, *n*=3; Ultrasound, *n*=1; Dual photon absorptiometry, *n*=2).

Side-to-side differences in bone properties (cross-sectional analysis)

The differences in bone properties between the paretic and non-paretic side can be assessed by examining the data of cross-sectional observational studies, and baseline data of longitudinal observational studies and interventional studies. The results are reported separately below according to the chronicity of stroke (acute, subacute and chronic).

Acute stroke studies

Eleven articles studied bone properties in individuals with acute stroke (722 participants; Online Resource 2). The mean timing of bone measures relative to stroke ranged from 2 days to 17 days[3, 4, 34-38]. The level of stroke severity was reported in 6 studies (moderate to severe stroke: n=2, moderate stroke: n=4). DXA was used to measure areal bone mineral density (aBMD) and bone mineral content (BMC) in all of these studies[3, 4, 34-42], and the skeletal

sites measured included: proximal humerus (1 study)[37], total hip (3 studies)[38, 39, 41], femoral neck (5 studies)[4, 36, 39, 40, 42], and total body (3 studies)[3, 34, 35]. PQCT was used in one study to measure the volumetric BMD (vBMD) and bone geometry (7% of distal tibia)[34]. In terms of study quality, three studies were rated as fair [34, 35, 41], and the rest (n=8) were rated as good [3, 4, 36-40, 42]. In all 11 studies, there were no differences found in aBMD, BMC and vBMD between the paretic and non-paretic sides, regardless of the bone imaging techniques or skeletal sites measured.

Subacute stroke studies

There were 10 subacute stroke studies[2, 43-51] totaling 523 participants (Online Resource 3). The average timing of bone measurements ranged from 1 month to 4.2 months post-stroke onset. Five of those studies reported the level of stroke severity to be moderate to severe[43-47], and five of them moderate[2, 48-51]. DXA was used to measure aBMD and BMC in 10 studies[2, 43-51], with measurement sites including the humerus (2 studies)[2, 49], total arm (1 study)[2], forearm (1 study)[46], radius (4 studies)[2, 47-49], femoral neck (2 studies)[43, 45], femur (3 studies)[47, 49, 51], total femur (1 study)[2], proximal femur (1 study)[2], total hip (1 study)[48], calcaneus (1 study)[49], and total body (4 studies)[44, 48-50]. PQCT was used in one study[43] to measure the volumetric BMD (vBMD) and bone strength index (4 % and 20 % distal radius). Of the 10 studies, five were considered as having fair quality [45-47, 50, 51], and the other five were rated as good[2, 43, 44, 48, 49].

In the upper limbs, aBMD values measured at the proximal humerus (2 studies)[2, 49] and radius (3 studies)[47-49] on the paretic side were found to be significantly lower than the corresponding sites on the non-paretic side by 4.1-11.6% and 1.4-11.1% respectively. The

trabecular vBMD and bone strength index of the 4 % distal radius (1 study) derived from pQCT were significantly lower than the corresponding sites on the paretic side by 8.8 % and 11.5 %, respectively[43]. At the 20 % distal radius (1 study), the side-to-side difference in cortical vBMD and bone strength index was much smaller (by 1.3 % and 1.4 % respectively)[43].

In the lower limbs, aBMD values measured at the femur (3 studies)[47, 49, 51] and calcaneus (1 study)[49] on the paretic side were found to be significantly lower that the corresponding sites on the non-paretic side by 2.1-4.1% and 1.8% respectively.

Chronic stroke studies

There were 37 chronic stroke studies[5-9, 11-14, 25, 33, 52-77] totaling 1902 participants (Online Resource 4). The mean timing of bone measures ranged from 0.5 [68] to 13.5 years[56] after stroke onset. Only 15 studies reported the level of stroke severity, which was generally moderate[5, 6, 13, 14, 33, 53, 55, 60, 64, 65, 67, 69, 70, 72, 73]. The bone measurement techniques used included DXA[14, 25, 33, 52, 54-57, 60, 61, 63-67, 69, 74, 75] (18 studies), CXD[70, 72, 73] (3 studies), PQCT[5-9, 11-14, 53, 56, 58, 62, 68] (14 studies), dual photon absorptiometry (2 studies)[76, 77], Pixi densitometer and quantitative ultrasound (1 study)[59], and Lunar Achilles Plus ultrasound densitometer (1 study)[71]. Eight of the studies were considered as having good quality [5-8, 55, 61-63], and 29 were rated as fair[9, 11-14, 25, 33, 52-54, 56-60, 64-77].

In the upper limbs, the aBMD values measured at the total arm (2 studies)[63, 76] and second metacarpal[70] were significantly lower on the paretic side than that on the non-paretic side by 4.5-8 %, and 4.5% respectively.

At the 4 % distal radius (i.e., distal radius epiphysis), the total vBMD, BMC, and bone strength index were significantly lower on the paretic side than that on the non-paretic side by 9.7-18.8 %, 9.5-18.0 %, and 15.4-31.3 %, respectively, whereas the total area consistently showed no significant differences between sides (4 studies)[5, 9, 12, 58]. The meta-analysis showed that (4 studies, 131 individuals)[5, 9, 12, 58] the BMC and total vBMD on the paretic side was significantly lower than that on the non-paretic side by 12.58 mg/mm (Fig. 2A) and 40.83 mg/cm^3 (Fig. 2B) respectively in individuals whose stroke onset was at least 12 months.

At the 30 % or 33 % distal radius (i.e., radius diaphysis), the meta-analysis showed that (4 studies, 147 individuals)[5, 6, 11, 12] the cortical vBMD and cortical area on the paretic side was significantly lower than that on the non-paretic side by 23.74 mg/cm^3 (Fig. 3A) and 5.7 mm^2 (Fig. 3B) respectively in individuals whose stroke onset was at least 12 months. However, there was a significant publication bias in the cortical vBMD analysis (Egger's regression asymmetry test, p=0.031). There was a trend for the bone strength index at radius diaphysis to be lower on the paretic side among individuals whose stroke onset was at least 12 months (Fig. 3C) but it did not reach statistical significance (p=0.09).

In the lower limbs, six studies[56, 57, 60, 66, 74, 75] demonstrated a significant side-to-side difference in femoral neck aBMD (by 2.2-16.1 %). The meta-analysis (6 studies, 400 individuals)[56, 57, 60, 66, 74, 75] revealed a significantly lower femoral neck aBMD by an average of 0.04 g/cm^2 in the paretic compared with the non-paretic limb in individuals who had sustained a stroke at least 6 months prior (Fig. 4).

At the 4 % tibial epiphysis, the total vBMD, trabecular vBMD, and bone strength index on the paretic side were significantly lower than their counterparts on the non-paretic side (6 studies) by 3.2-19.0 %, 2.8-4.7 %, and 6.6-31.0 %, respectively[8, 13, 14, 53, 56, 58]. The meta-

analysis revealed (4 studies)[8, 13, 14, 53] similar findings among individuals who had suffered the stroke for 12 months or more (Fig. 5A-C).

At the 50 % and 66 % tibial diaphysis, differences between cortical vBMD and bone strength index in paretic and non-paretic limbs were not consistent across studies. In 3 studies, the cortical vBMD was significantly lower on the paretic side than that on the non-paretic side by 1.6-2.2 %[13, 14, 53] but not in other 4 studies[7, 56, 58, 62]. Significant side-to-side differences in the bone strength index (4.3-10.3 %) was found in 4[13, 14, 53, 56] out of 6[13, 14, 53, 56, 58, 62] studies.

At the tibial diaphysis (66% site), the meta-analysis showed that the bone strength index of the paretic side was significantly lower than the non-paretic side by 304.11 mm^3 among individuals whose stroke onset was at 12 months ago or longer[13, 14, 26, 53, 56] (Fig. 6), but a publication bias was found (Egger's regression asymmetry test, p=0.086), and the heterogeneity of this analysis was high (I^2=59 %).

The amplitude dependent speed of sound measured by quantitative ultrasound was significantly lower in the paretic os calcis than the non-paretic site by 2.5 % (1 study)[59], but there was no side-to-side difference in the index stiffness measured by a lunar Achilles Plus ultrasound densitometer (1 study)[71].

Mixed subacute and chronic stroke studies

One study used a mixed sample of subacute and chronic stroke patients [26] (22 participants; Online Resource 5). The average timing of bone measurements were 3.2 months for subacute participants and 60 months for chronic particpants respectively. This study did not report the level of stroke severity. PQCT was used to measure the volumetric BMD (vBMD) and

bone strength index (66 % tibial). This study was rated as fair. Using pQCT, the side-to-side differences in bone variables measured at the tibial diaphysis were largely unremarkable, with only a small but significant side-to-side difference (1.5%) in bone strength index.

Actual bone changes over time (analysis of longitudinal data)

The actual changes in bone properties over time were assessed by comparing the baseline and follow-up data provided by the longitudinal observational studies.

Sixteen longitudinal studies[2-4, 11, 14, 34, 35, 37, 42-45, 47, 49, 50, 52] (592 participants) examined bone changes during a follow-up period (Online Resource 6). Only 8 studies reported the level of stroke severity, the overall level was moderate[2, 14, 34, 37, 45, 47, 49, 50]. The bone measurement techniques involved DXA (15 studies)[2-4, 14, 34, 35, 37, 42-45, 47, 49, 50, 52] and PQCT (4 studies)[11, 14, 34, 43]. Seven of these studies were rated as fair[14, 34, 35, 45, 47, 50, 52], and 9 were rated as good[2-4, 11, 37, 42-44, 49].

In the upper limbs, there was no significant reduction in humerus aBMD on both sides during a period between the 1- and 4-month post-stroke onset. However, with a longer follow-up period (from 1 to 7 months or from 1 to 12 months post-stroke), there was a significant reduction in humerus aBMD only on the paretic side by 7.4% and 12%-17.4% respectively[2, 49]. The non-paretic side showed no significant reduction in the same variable[2]. At the distal radius, the rate of reduction in aBMD on the paretic side was 1.8% (average duration of follow-up: 105.5 days; average time of first measurement post-stoke: 83 days)[49], and 12.4% (average duration of follow-up: 98 days; average time of first measurement post-stoke: 63 days)[47], whereas the non-paretic side showed only a significant reduction by 3.5% in the same variable [47].

At the 4% distal radius epiphysis, there was a significant reduction in the bone strength index on the paretic side by 25.6 % during a 1-year follow-up period in patients with subacute stroke (time of first measurement post-stoke: 3 months)[43] . However, the same variable showed less reduction (by 6.7 %) in one year among patients with long-standing stroke (average time of first measurement post-stoke: 45 months)[11] . At the 20 % or 33 % distal radius (radius diaphysis), a similar phenomenon occurred. One study[43] reported a significant reduction in cortical vBMD (3.3 % on the paretic side, 1.5 % on the non-paretic side) and bone strength index (7.2 % on the paretic side, 5.6 % on the non-paretic side) during the 1-year follow-up period among subacute stroke patients, but the changes in these variables were not significant among chronic stroke cases (average time of first measurement post-stoke: 45 months)[11].

For the femoral neck and trochanter regions, the majority of studies showed a significant decline in aBMD within the first year post-stroke (1-year reduction in aBMD in femoral neck region: paretic side: 10-13%, non-paretic side: 5-10.9%; trochanter region: paretic side: 10-12.6%, non-paretic side: 5-10.9%), with most of the changes occurring during the first 6-7 months post-stroke (femoral neck region: 8-9% on paretic side, 2-8% on non-paretic side; trochanter region: 7-8% on the paretic side, 0-7.8% on non-paretic side)[42, 43, 45, 47].

Bone changes were less substantial in those whose stroke onset is more than one year. For example, for the total hip aBMD, Lam et al. [14] showed that chronic stroke patients exhibited a significant reduction by only 1.2 % on the paretic side in one year, while the non-paretic side displayed no significant reduction in the same parameter (average time of first measurement post-stoke: 48 months). However, the results may have differed across various bone sites. For example, at the 4 % tibial epiphysis, there was a significant reduction in the bone strength index by 2.7 % on the paretic side during the 1-year follow-up period among chronic

stroke patients (average time of first measurement: 48 months post-stroke) but the 66 % tibial diaphysis revealed no significant reduction in bone strength index during the same period[14].

Muscle-bone relationship

The results regarding the muscle-bone relationship are illustrated in Online Resource 7. The relationship between bone properties and muscle mass/strength was explored in 3 DXA studies[25, 35, 65] and 9 pQCT studies[5-9, 12-14, 26]. In the upper limb, the total arm BMC and total arm aBMD were significantly correlated with the composite arm muscle strength score (r=0.60-0.62)[35, 65] and arm lean mass (r=0.86)[65]. At the 4 % radial epiphysis, grip strength had a significant relationship with bone strength index (r=0.69)[9]. The strong relationship between muscle strength and bone strength index at the 33% radial diaphysis was also quite consistent (r=0.71-0.85)[5, 12].

In the lower limb, the proximal femur BMC and aBMD presented a significant relationship with isometric knee extension muscle strength (r=0.41 and r=0.39, respectively) and leg lean mass (r=0.78 and r=0.61, respectively)[25]. At the 4 % tibial epiphysis, there was a significant relationship between muscle strength/mass and bone strength index/BMD in two out of three studies (r=0.45-0.73)[8, 13, 14]. At the 66 % tibial diaphysis, there was a significant relationship between bone strength index and eccentric knee extensor muscle strength (r=0.45) but not concentric knee extensor muscle strength[13].

The relationship between bone properties and muscle spasticity was assessed in 3 DXA studies[3, 25, 65] and 7 pQCT studies[6-9, 12-14]. In the upper limb, one study [65] revealed that total arm BMC and total arm aBMD had no significant relationship with spasticity as measured by the Modified Ashworth Scale (MAS) (r=0.197, and r=0.068 respectively). At the

4 % radial epiphysis, spasticity had a significant relationship with bone strength index (r=0.465)[9]. However, the relationship between spasticity and bone strength index at the radius diaphysis was not clear as some work showed a significant association (r=0.356)[12], while other work found no relationship[6]. In the lower limb, the results were inconsistent. Some studies showed a significant correlation between MAS and proximal femur aBMD (r=-0.21, and r=-0.23 respectively)[25] and 4% tibial epiphysis (r=0.415)[8], other studies found no such relationship[7, 13, 14]. At the 66 % tibial diaphysis, one study found no significant relationship between bone strength index and spasticity[13].

Discussion

The overarching goal of this systematic review was to provide insight into the impact of stroke on bone properties as well as examine the association between muscle function and bone properties post-stroke. From this review, four main findings were consolidated: 1) the rate of change in bone properties in the affected limbs was slower in the chronic than subacute period after stroke; 2) the paretic upper limb exhibited more compromised bone properties compared with the paretic lower limb; 3) there was a strong relationship between muscle strength and bone quality in the upper and lower limbs; and 4) muscle spasticity seemed to have negative impact on bone integrity in the paretic upper limb, but its influence on the paretic lower limb was uncertain.

Rate of change in bone properties was slower in chronic than subacute stage

As revealed by the substantial side-to-side differences in bone properties found in cross-sectional studies, as well as the actual amount of bone changes in longitudinal studies, a consistent finding was that the skeletal sites in the paretic limbs sustained a more pronounced

decline in bone quality than their counterparts in the non-paretic limbs. However, the rate of change in bone properties showed a decelerating trend as post-stroke duration increased. Hamdy et al. (1995)[35] showed that most bone loss in the paretic upper and lower limbs occurred within the first 3-4 months post-stroke. After 1 year of stroke onset, the extent of bone change was minimal. For example, the decline in paretic total hip aBMD was 1.2% in 1 year for those whose stroke onset was more than one year ago[14]. This was much less than the 10% loss in femoral neck aBMD on the paretic side within the first year post-stroke[43]. This phenomenon was similar in the upper limbs. A good example is the radius diaphysis, in which the cortical vBMD showed a significant reduction in bone strength index by 7.2% during the period between 3 and 15 months post-stroke, but the chronic stroke cases (average onset: 45 months post-stroke) no longer sustained significant changes.

The exact time point at which the bone changes reached a steady state was unclear and may have differed depending on the specific bone site measured. Lam et al. further showed that even within the same bone, the timing at which the bone reaches steady state may differ. The trabecular bone density of the paretic tibial epiphysis did not reach steady state until 2 years post-stroke onset, but the cortical bone variables of the diaphysis region of the same bone showed no significant changes among those whose onset of stroke was earlier than 12-24 months ago[14]. The rate of change and timing of the plateau phase may also depend on the stroke severity as revealed by longitudinal studies[4]. For those who were wheelchair bound, the 1-year decline in hip BMD was much more severe (13%) than those who regained ambulatory function at 2-months post-stroke (8%) or had ambulatory function at stroke onset (3%)[4]. Nevertheless, the overall results suggest that the rate of change in bone properties between the paretic and non-paretic sides was slower in chronic than subacute stage. These results highlight the importance of

therapeutic interventions mitigating the rapid decline in bone integrity within the first year following stroke.

Paretic upper limb sustains more pronounced changes in bone properties than paretic lower limb

Upon comparing the side-to-side differences in bone parameters of the upper limb and lower limb sites as well as the findings in longitudinal studies, it can be deduced that the magnitude of bone changes in the paretic upper limb was more pronounced than the paretic lower limb[43]. This observation could be partly explained by the difference in the course of recuperation between the hemiparetic upper and lower limbs post-stroke. Previous studies disclosed that only 44 % of stroke survivors with severe paralysis partially or completely recovered upper limb bone properties[14], while 75 % of stroke survivors recovered, in part or full, in the lower limbs[78]. It is also possible that because the affected lower limb was mechanically loaded during daily activities, such as standing and walking, a slower decline in function may have emerged relative to the upper site. Furthermore, the unaffected arm may have been used to compensate for the dysfunction of the paretic arm, thereby increasing the side-to-side differences in bone outcomes in the upper limbs. Altogether, a greater emphasis on recovering upper limb bone properties should be addressed in therapeutic interventions.

Association between muscle and bone properties post-stroke

Overall, there was a strong relationship between muscle strength/mass and bone density/strength index. This phenomenon was largely consistent in upper and lower limb skeletal sites. The results support the muscle-bone unit theory, which puts forward that muscle strength

and bone properties form a functional biological unit[24]. Mechanical strains from muscle contractions provide a potent stimulus for osteogenesis. Following the initial paralysis after the onset of stroke, there may be decrease in physical activity[79], as well as learned non-use of the affected limbs[80], resulting in further muscle weakness and atrophy[81] and ultimately, compromised integrity of bone tissue. The results also suggest that improving muscle strength may be a potentially effective method to enhance bone properties in this group. While no study has specifically examined the use of resistance/strength training on bone health post-stroke, Pang et al.[62, 63] did show in a chronic stroke exercise study that a mix of dynamic loading, resistance and aerobic exercises resulted in significant increases in paretic leg muscle strength and better bone outcomes in the hip and tibia on the affected side. Stroke is a chronic condition, thus long term care strategies in bone health management are essential. Health service providers, especially physiotherapists, should have a major role in formulating and implementing long term strategies to optimize bone health among chronic stroke survivors.

The relationship between muscle spasticity and bone outcomes, on the other hand, may not be straightforward, particularly in the affected lower limb. While some studies reported a negative relationship between spasticity and bone density/strength index[8, 9, 12], others did not show such a relationship[7, 13, 82]. It is likely that the relationship between spasticity and bone quality is a non-linear one. For example, individuals with mild spasticity may have better bone outcomes than those who have complete flaccid paralysis, as the tonic muscle contraction involved in spasticity may exert a protective effect on bone tissue. However, as spasticity level continues to increase, a negative effect on bone may ensue, as the functional use of the affected limb becomes severely impaired[6]. Also, the MAS, a scale that was used in the reviewed studies to measure spasticity, cannot measure hypotonia (flaccid paralysis). It is only a 6-point

ordinal scale and unable to provide a finer discrimination of different degrees of hypertonia. Overall, future studies with larger samples that cover the full spectrum of muscle tone changes (hypotonia and hypertonia) and use better spasticity measures (e.g., electromyography) are required to decipher the relationship between spasticity and bone health.

Limitations of the studies reviewed

The number of longitudinal studies were few relative to cross-sectional studies. Longitudinal studies are better designed to assess actual bone changes in each skeletal site after stroke onset, whereas the side-to-side difference values obtained from cross-sectional studies represent a combination of changes in the paretic and non-paretic sides. The number of chronic stroke studies was also much greater than those in the acute and subacute phases. The impact of stroke on microstructural properties of bone is unknown (e.g., trabecular thickness and spacing).

Limitations of this systematic review

In order to obtain a comprehensive understanding of the impact of stroke on bone properties, as well as the association of bone and muscle properties post-stroke, we included a variety of study designs in our review, including interventional, observational, cross-sectional, and longitudinal studies. Inherent limitations exist with variability in the length of stroke duration across studies. Additionally, most of the studies investigating the association between bone and muscle properties post-stroke conducted different statistical analyses and investigated different outcomes; thereby limiting the studies to be included in the meta-analyses. While the influence of stroke severity is addressed in this review, the impact of functional capacity is understudied.

Future research directions

The limitations identified above should provide opportunities for further research in various aspects of post-stroke bone health. More longitudinal studies with a long follow-up period after stroke onset are warranted. Future research should study changes in bone microproperties using bone measurement techniques such a high resolution pQCT. The impact of functional capacity of stroke patients on bone health should be addressed in future research.

Conclusion

In conclusion, significant changes in bone mass and macrostructure occurred after stroke, and these changes were more pronounced in the paretic limbs and in first few months post-stroke. The paretic upper limb sustained a substantial decline in bone quality relative to the paretic lower limb. There was a strong relationship between muscle strength/power and bone parameters, while the impact of muscle spasticity on bone quality remains unclear. The results of this review have important clinical implications, particularly for factors related to early intervention, muscle strength training and long term management strategies to enhance bone health post-stroke. This review has also revealed the knowledge gaps in the field which should be addressed in future research.

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Conflict of interest

The authors declare no competing financial or non-financial interests.

Author Contributions statement

Zhenhui Yang and Marco Pang: Conception of the work; Zhenhui Yang, Deborah Jehu, Huixi Ouyang and Freddy Lam: Data collection; Zhenhui Yang, Deborah Jehu, Huixi Ouyang, Freddy Lam: Data analysis and interpretation; Zhenhui Yang: drafting the article; Zhenhui Yang, Deborah Jehu, Huixi Ouyang, Freddy Lam, Marco Pang: Critical revision of the article and final approval of the version to be published.

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Appendix 1

Search strategy (MEDLINE)

1. Exp Cerebrovascular accident/
2. Exp Stroke/
3. Exp CVA/
4. Exp cerebral vascular/
5. Exp Brain injuries/
6. Exp Hemiplegia/
7. Exp Hemiplegic/
8. Or/1-7
9. Exp bone/ or exp bone density/
10. Exp bone mineral density/
11. Exp bone geometry/
12. Exp bone strength/
13. Exp bone mass/
14. Exp bone volume /or exp bone area/
15. Exp bone turnover/
16. Exp bone densitometry/
17. Or/ 9-17
18. Exp Dual-energy X-ray absorptiometry/or exp DXA/or exp DEXA
19. Exp Ultrasound/
20. Exp absorptiometry/
21. Exp peripheral quantitative computed tomography/or exp PQCT/or exp QCT/
22. Or/18-22
23. 8 and 17 and 23

FIGURE LEGENDS

Figure 1. Study flowchart

A total of 74 studies were included in the review.

Figure 2. Meta-analysis: side-to-side differences in bone parameters at the 4% radius site

At the 4% distal radius, the BMC and total vBMD on the paretic side were significantly lower than that on the non-paretic side by 12.58 mg/mm and 40.83g/cm^3 respectively in individuals whose stroke onset was at least 12 months. No significant publication bias was found in these analyses.

Figure 3. Meta-analysis: side-to-side difference in bone variables at the radius diaphysis

At the 30 % or 33 % distal radius, the cortical vBMD (Fig. 3A) and cortical area (Fig. 3B) on the paretic side was significantly lower than that on the non-paretic side respectively in individuals whose stroke onset was at least 12 months prior. No significant side-to-side difference in the bone strength index at radius diaphysis was found among individuals whose stroke onset was at least 12 months (Fig. 3C). A significant publication was found in the cortical vBMD analysis ($p<0.1$).

Figure 4. Meta-analysis: side-to-side difference in femoral neck areal bone mineral density (g/cm^2)

The femoral neck aBMD was significantly lower than that on the non-paretic side in individuals who had sustained a stroke for at least 6 months. No significant publication bias was found.

Figure 5. Meta-analysis: side-to-side difference in bone variables of the tibial epiphysis

At the 4 % tibial epiphysis, the total vBMD (Fig. 5A), trabecular vBMD (Fig. 5B), and bone strength index (Fig. 5C) on the paretic side were significantly lower than the non-paretic side among individuals who had suffered the stroke for 12 months or more. No significant publication bias was found in these analyses.

Figure 6. Meta-analysis: side-to-side difference in polar stress-strain index (p-SSI, mm^3) at the tibial diaphysis

At the tibial diaphysis, the bone strength index of the paretic side was significantly lower than the non-paretic side among individuals whose stroke onset was at 12 months ago or longer. A significant publication bias was found ($p<0.1$). Macintyre et al [26] is a study containing both subacute and chronic stroke patients. In this meta-analysis, only the data collected from chronic stroke patients were used.

Figure 1. Study flowchart

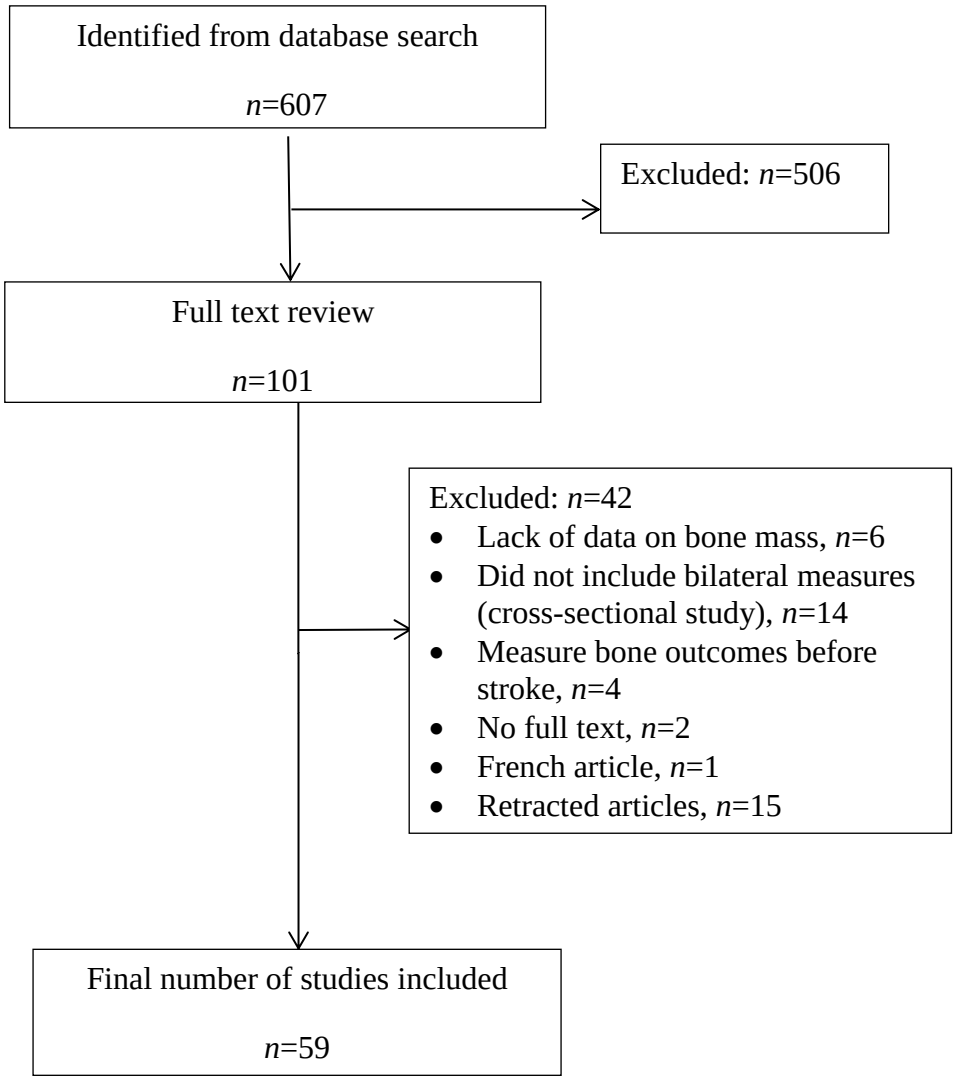
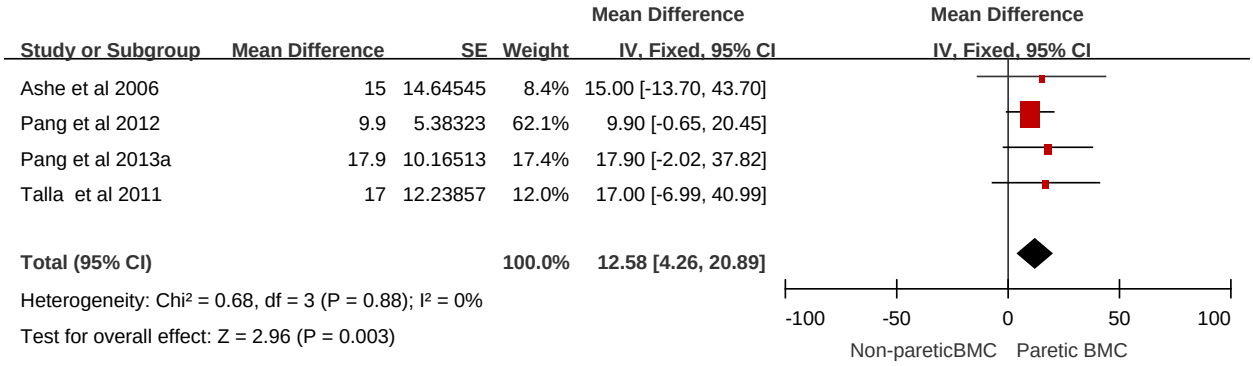


Figure 2. Meta-analysis: side-to-side differences in bone parameters at the 4% radius site

A. Bone mineral content (BMC in mg/mm)



B. Total volumetric bone mineral density (vBMD in mg/cm^3)

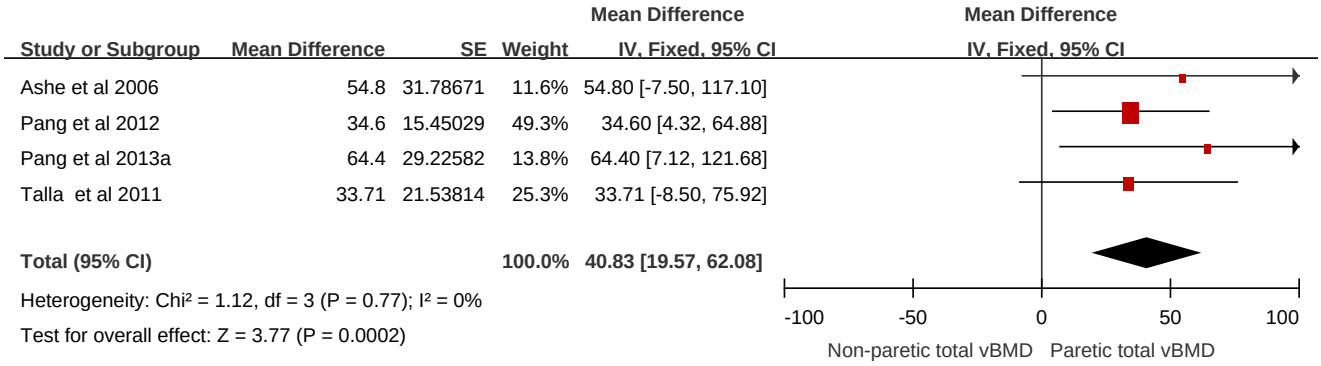
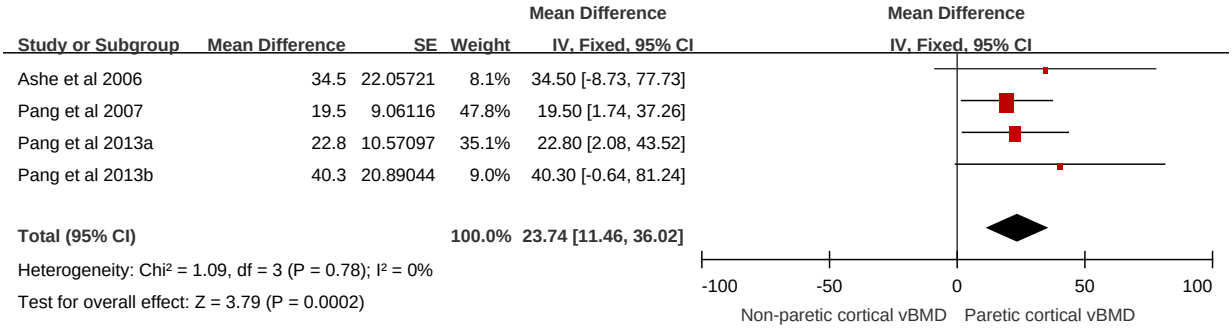
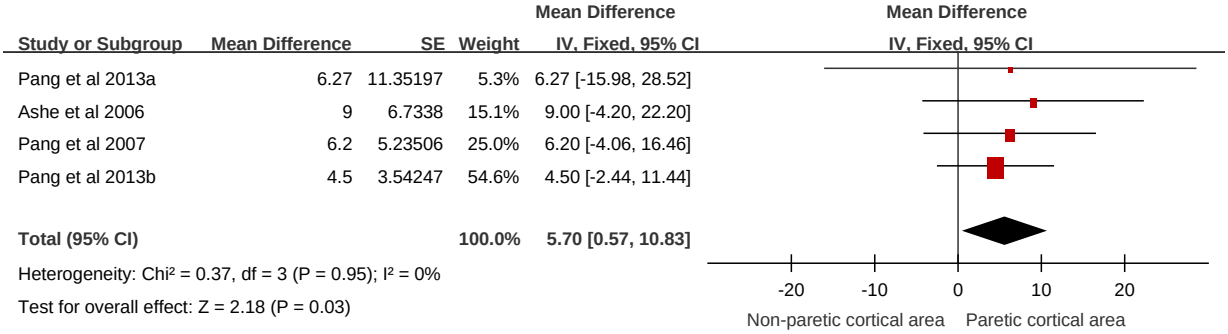


Figure 3. Meta-analysis: side-to-side difference in bone variables at the radius diaphysis

A. Cortical volumetric bone mineral density (vBMD in mg/cm^3)



B. Cortical area (mm^2)



C. Polar stress-strain index (p-SSI, mm^3)

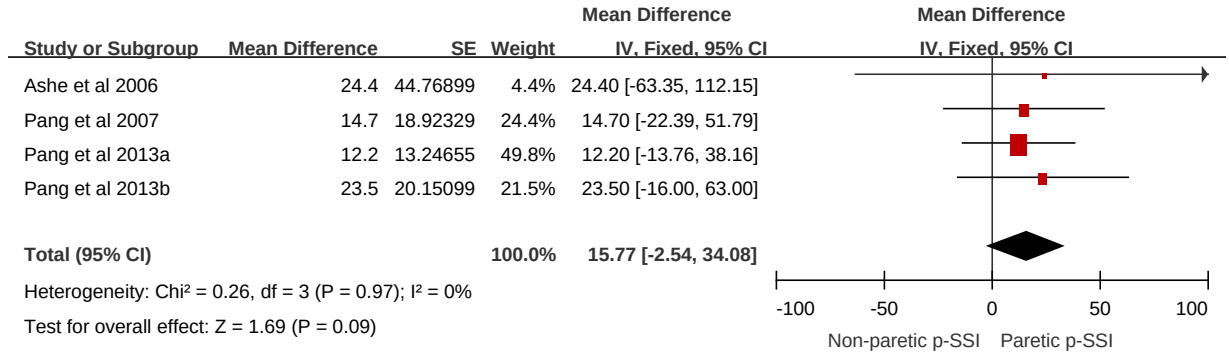


Figure 4. Meta-analysis: side-to-side difference in femoral neck areal bone mineral density (g/cm^2)

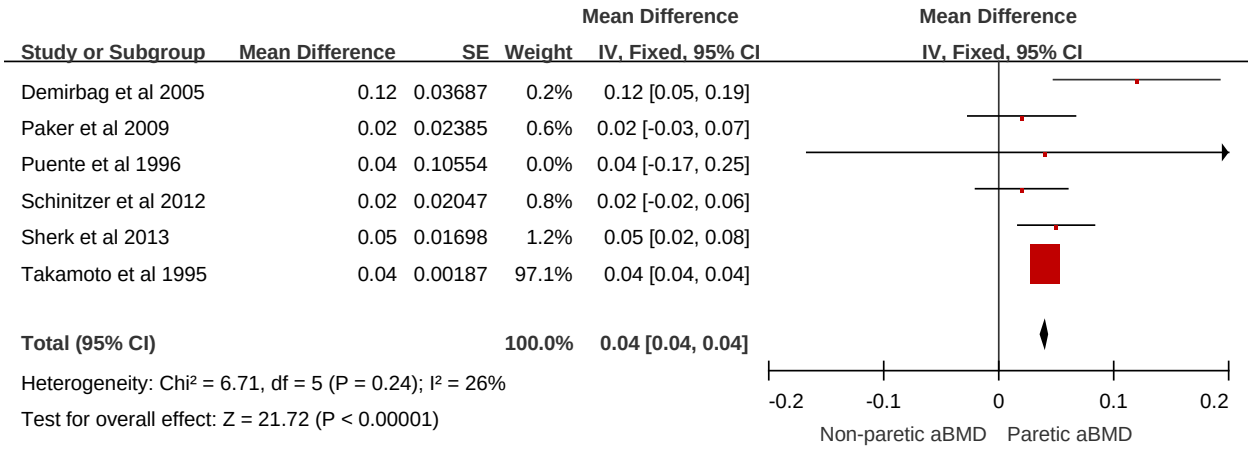
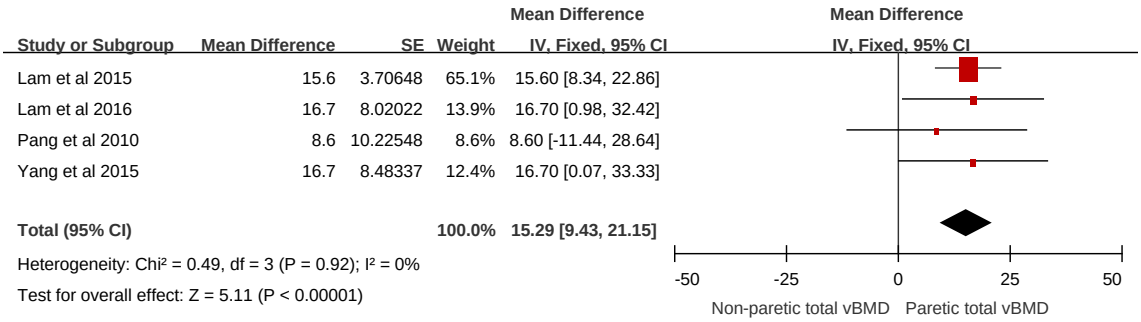
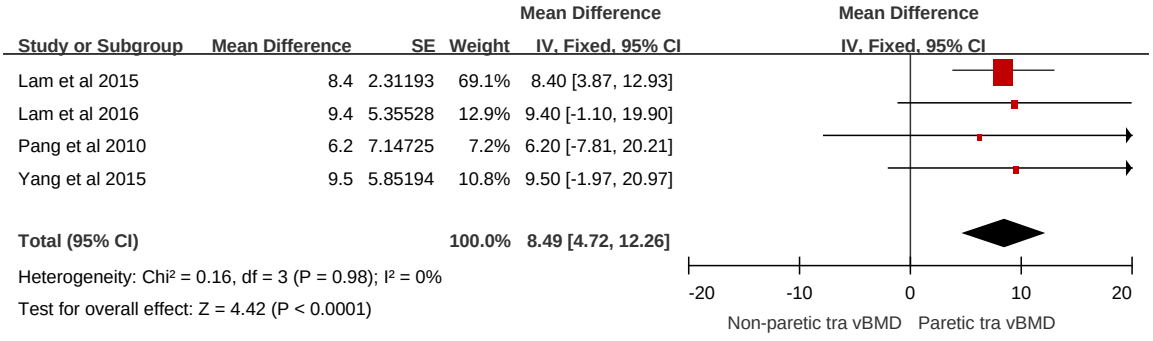


Figure 5. Meta-analysis: side-to-side difference in bone variables of the tibial epiphysis

A. Total volumetric bone mineral density (vBMD)(mg/cm^3)



B. Trabecular volumetric bone mineral density (vBMD)(mg/cm^3)



C. Bone strength index (BSI, g^2/cm^4)

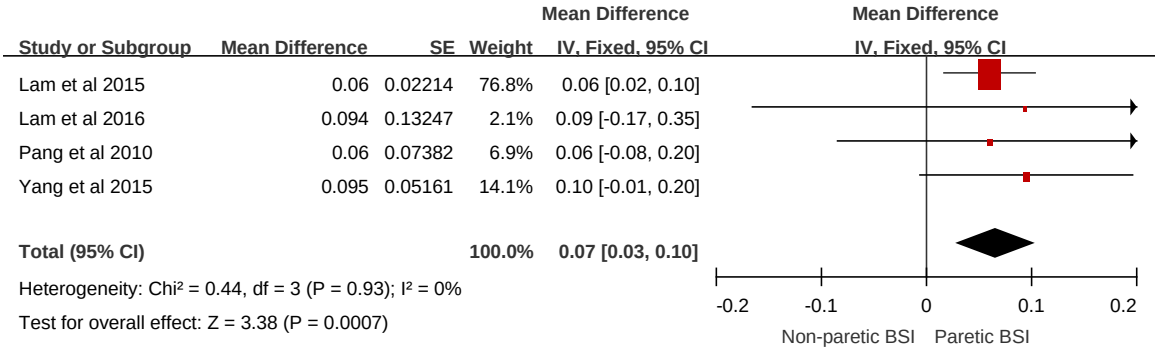


Figure 6. Meta-analysis: Side-to-side difference in polar stress-strain index (p-SSI, mm^3) at the tibial diaphysis