



## Review Article

# Hip Fractures in Elderly Stroke Patients - The Role of Sarcopenia and Osteoporosis

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**Abstract:** Both hip fractures and stroke are common in elderly patients and hip fractures are especially prevalent in elderly stroke patients. This literature review is an attempt to explore the evidence for strategies to reduce hip fractures in stroke patients, the role of sarcopenia and osteoporosis in causing them and current and potential management strategies. A narrative approach was adopted in reviewing the evidence available on hip fractures in stroke patients, with regard to their incidence and prevalence, the role of sarcopenia and osteoporosis in their genesis and the evidence available for hip fracture prevention in stroke patients. I also attempt to explore the potential role of targeting muscle and bone as one unit in future therapeutic strategies. Although there are encouraging results from clinical trials on therapeutic interventions to prevent hip fractures in stroke patients, larger, more robustly designed studies are needed to validate many of the findings. Some evidence exists that suggest that hip fractures risk can be reduced in stroke patients but the findings need validation in larger more robust trials. Moreover it is clear that sarcopenia and osteoporosis are implicated in hip fractures in stroke and non-stroke elderly patients. A consensus on the definition of sarcopenia would also aid clarification of findings from studies.

**Keywords:** Stroke, Osteoporosis, Sarcopenia, Fractures, Osteosarcopenia

## 1. Introduction

Hip fractures and stroke are both common in elderly patients [1]. In addition, hip fractures are commoner in stroke patients than in age-matched controls [1]. Conversely, stroke is commoner in patients with hip fractures than in the general elderly population [2]. Both stroke and hip fractures are associated with a high mortality, significant morbidity and a huge burden of disability [1]. Therefore, the need to prevent hip fractures in stroke patients cannot be overstated.

The last ten years have seen an increase in understanding of post-stroke sarcopenia as distinct from sarcopenia of ageing [3]. It is postulated that the muscle changes that occur in elderly patients with stroke accelerates the age-related

reduction in cross-sectional muscle mass, muscle power and muscle quality leading to impaired motor function that is over and above that caused by ageing per-se [4]. Moreover, the effect of nutritional problems in stroke patients and the role of the resultant cachexia in contributing to sarcopenia has been recognized [5]. The subsequent impairment in motor function also impacts gait and balance, increasing the risk of falls and hip fractures in stroke patients [6].

The mechanical and humoral coupling (crosstalk) between muscle and bone is becoming an area of great research interest, and, in particular, the reciprocal impact of the factors secreted by myocytes on bone and by osteocytes on muscle [7]. The implication is that deterioration in bone mass and quality negatively impacts muscle mass and function and vice-versa

[7]. The term “osteosarcopenia” has been coined to describe the combined effect of osteoporosis/osteopenia and sarcopenia in causing frailty, falls, and fractures in non-stroke older patients as well as in older patients with stroke [7].

This article reviews the epidemiology and pathophysiology of hip fractures in stroke patients, the role of osteoporosis and sarcopenia in their genesis and the evidence base for hip fracture prevention strategies in stroke patients. It reviews the evidence, to date, on management strategies in patients with sarcopenia and osteopenia/osteoporosis post-stroke. It concludes with recommendations for future areas of research.

## 2. Epidemiology

Epidemiological data on hip fractures in stroke patients has been limited by geographical variation in the cohort of patients studied and the retrospective nature of most of the studies [8-13]. In addition, the findings have not been generalizable as they were mostly carried out on single population groups.

Kanis *et al* retrospectively examined the medical records of 273,888 Swedish patients with a stroke from 1987 to 1996 [8]. Compared with the general population, there was a 7-fold increase in all fracture risk and a 4-fold increase in the risk of hip fractures in the stroke group [8]. Pouwels *et al* conducted a case-control study of 6763 Dutch patients with a first hip/proximal femoral fracture [9]. They were matched, against controls, by age, gender and region [9]. They found a 2-fold increase in fracture risk in the stroke arm compared to the controls [9]. Female gender and a more recent stroke (less than 3 months) were associated with the highest risk. A Scottish cohort study showed an increased risk of hip fractures of 2% by the first year and 10.6% by 10 years after a Stroke [10]. Another study identified visual problems and poor spatial orientation, cognitive impairment and a previous fracture as factors that increased risk of hip fractures post-stroke [11]. Fisher *et al* found that about one in seven of hip fractures occurred in patients with previous stroke [12]. Longitudinal data on 1139 patients with stroke showed that the risk of hip fracture increased 3.8 times in those aged under 70 years and 2.1 times in those older than 79 years [9].

More recently, Northius *et al*, in their review of a cohort of women obtained from the Women’s Health Initiative (WHI) register, found that the absolute 10 year probability of sustaining a hip fracture, calculated using the FRAX (UK) tool without a bone mineral density (BMD), was associated with increased radiological identification of index hip fractures at five years post-stroke [13]. The effect was independent of post-stroke mortality [13].

## 3. Pathogenesis and Pathophysiology of Hip Fractures in Stroke Patients

It is now a well-established fact that falls and reduced bone mass are implicated in hip fractures that occur in older patients [14]. More recently, the role of sarcopenia (reduced muscle

mass and function) in causing falls and increased risk of fractures has become widely accepted [15]. Age-related sarcopenia is well described but post-stroke sarcopenia, as an entity in itself, is becoming increasingly recognized [15]. Following a stroke, loss of central control of the alpha motor neurone leads to denervation and loss of motor units [15]. It is thought that remodelling occurs as re-innervation from surrounding neurones attempts to restore neuromuscular function [15, 16].

Unfortunately re-innervation tends to favour the relative increase in the slow twitch muscle fibre type I (which is weaker) compared to the fast twitch type II a and b (x) muscle fibres, which generate greater force of contraction and power, and are lost in much greater numbers [15, 16]. The overall effect is reduced muscle mass and muscle weakness [15, 16]. In addition poor nutrition due to neurogenic dysphagia following stroke can lead to significant weight loss (cachexia) and generalized loss of muscle mass further contributing to the sarcopenia [17]. Independently of denervation, apoptosis of motor units occurs at the neuromuscular junction due to increased accumulation of mitochondrial reactive oxygen radical species (mROS), further compromising muscle mass and function [18]. In normal circumstances, injury to muscle activates the maturation of satellite muscle stem cells which attempt to repair and replace damaged muscle tissue [19]. This compensatory mechanism is compromised following a stroke in elderly patients as well as in non-stroke older patients [3, 19]. Muscle and bone work together as a musculoskeletal unit [20]. During embryogenesis they develop together and there is evidence of crosstalk not only in the reciprocal mechanical interaction between them but they each secrete chemokines that impact the other [21, 22]. Reduced mass and function in the skeletal muscles is thought to reduce bone mass by reduced loading from skeletal muscle contraction [22]. In addition, de-innervated muscle secretes myokines such as myostatin which increase bone loss in addition to causing muscle atrophy [23]. Sarcopenia is also characterized by increased secretion, by skeletal muscle, of pro-inflammatory cytokines such as interleukins 1 (IL-1) and 6 (IL-6) and tumour necrosis factor alpha (TNF-alpha) which cause catabolic break down of muscle and increase activation of osteoclasts leading to bone resorption and bone loss [24, 25]. This induced, adverse, reciprocal paracrine effect of bone and muscle frequently leads to osteopenia/osteoporosis and sarcopenia occurring together with even greater risk of falls and hip fractures than would occur with either of them in isolation [24, 25]. Stroke patients have an increased risk of falls, most of it occurring on the hemi-paretic side [26]. Some studies suggest that as many as 73 percent of stroke patients fall within the first 6 months [26]. They also report an increased tendency to lose bone on the hemi-paretic side [26, 27]. This is thought to be due to disuse and lack of bone loading [27]. It is, therefore, not surprising that 80 percent of hip fractures occur on the hemi-paretic side [26, 27]. About 90 percent of hip fractures occur after a fall and so post-stroke falls impact significantly on the risk of hip fractures [26, 27]. Contributors to falls in stroke patients include asymmetrical

gait and balance, impaired visual and spatial awareness, sarcopenia and cognitive impairment [25, 26].

A lot of what is known about disuse osteoporosis has been gleaned from studying astronauts exposed to microgravity environments and spinal patients with paralysis [28, 29]. Very limited data on osteoporosis and bone loss are available from stroke patients per se and mostly consist of observational studies [30]. These data suggest that regional bone loss occurs rapidly in the immobilised limbs but generalised skeletal bone loss occurs more slowly over several years following immobilization [31]. The pattern of bone loss in patients post-stroke is uneven being greater in the hemiparetic upper limb than the lower limb on the same side [31]. This is due to lack of ground forces normally generated by gravity on the lower limb as opposed to the upper limb [31]. Some bone loss occurs on the non-paretic side but not to the same degree as the paretic side [31]. In addition, sarcopenia has been observed on both the hemiparetic and non-hemiparetic limbs in stroke patients though to a lesser degree in the non-hemiparetic limbs [15].

At a molecular level, evidence suggests that immobilisation of the paretic limb results in bone loss with dissolution of calcium from bone leading to hypercalcaemia and hypercalciuria [32]. In elderly patients the hypercalcaemia may not necessarily be evident on measuring total serum calcium but the ionized serum calcium is raised in this situation [32]. The hypercalcaemia results in inhibition of parathyroid hormone (PTH) secretion, which, in turn, impairs the conversion of 25-hydroxy vitamin D to 1,25 di-hydroxy vitamin D by alpha-hydroxylation in the proximal renal tubules [32]. However, because 1,25-dihydroxyvitamin D normally exerts a negative feedback on PTH production the reduced production of the 1,25-dihydroxy vitamin D diminishes

the negative feedback on PTH production, thus over-riding the hypercalcaemia-mediated PTH inhibition [32]. The resultant hyperparathyroidism causes increased bone resorption and bone loss [32]. Moreover the immobility imposed by the stroke reduces outdoor exposure to sunlight leading to low levels of 25 (OH) vitamin D, muscle weakness, impaired calcium absorption from the gut and secondary hyperparathyroidism [33]. Other molecular mechanisms have been postulated as contributing to hip fractures in stroke patients including hyper-homocysteinaemia which occurs in both stroke and hip fractures [34]. Elevated homocysteine levels are known to impair bone quality rather than bone mass and this may, in part, explain its association with hip fractures [34].

#### 4. Strategies to Reduce Hip Fractures in Older Stroke Patients

Data on risk reduction of hip fractures in stroke patients is sparse [35-37]. Studies looking at interventions to reduce falls in stroke patients have been conflicting and limited by poor quality of the trials and heterogeneity between the groups studied [36]. Some evidence exists to support strategies that

might prevent bone loss post-stroke [36, 37]. Unfortunately due to the small sample sizes, the trials were not sufficiently powered to demonstrate statistical significance [36, 37]. Many of them were performed on single cohort groups and are not generalizable to the wider population [36, 37]. Larger, multi-centre studies are needed to replicate their findings [37].

The most recent cochrane systematic review of falls interventions in post-stroke patients found that most of the trials were of low or very low quality but suggested that falls interventions led to a reduction in rate of falls [36]. There was no evidence of reduction in the number of fallers [36]. The variation in definition of falls, as well as, small sample sizes and heterogeneity of the cohorts studied have made it difficult to be definitive in recommending these interventions [36]. Moreover, the timing of the interventions post-stroke, was not explicitly stated in many of the trials [36]. Vitamin D supplementation was shown to have a significant reduction in the rate of falls in hospitalized female patients after stroke [36].

A study by Pang et al, on stroke patients, showed promising results following fitness and mobilisation exercises (FAME) in the intervention group [38, 39]. Unfortunately, the sample size was small and, therefore, not sufficiently powered to detect statistically significant results [39]. The study randomized 63 community-dwelling chronic stroke patients into two groups: 32 for intervention and 31 for usual care [39]. The intervention group received fitness and mobilisation exercises (FAME) while the control group received chair based exercises [39]. After 19 weeks, the intervention group showed increased benefit in cardiovascular fitness, mobility and paretic muscle strength when compared with the control group [39]. In addition, the femoral neck bone mineral density (BMD) was maintained in the paretic limb whereas there was significant decline in the paretic limb BMD in the control arm [39]. Other studies have shown improved tibial bone quality with FAME exercises [40]. Vitamin D deficiency has been shown to be more prevalent in acute and chronic stroke patients when compared to the general elderly population [41]. The reduction in mobility and the consequent increase in time spent indoors is likely to play a part in further depletion of vitamin D stores long term [41]. Measuring the 25- hydroxy vitamin D levels and treating vitamin D deficiency and insufficiency is important early on post-stroke [41]. However, the evidence for improved outcomes, following routine administration of vitamin D in post-stroke patients, remains ambiguous [41]. The intravenous bisphosphonate, Zolendronic acid, has also been studied in stroke patients [42]. Post-stroke patients randomized to a single dose of 4mg of Zolendronic acid infusion showed significant reduction in bone loss when compared to the placebo group [42]. These results need to be more widely replicated in larger, randomized, controlled, multicentre trials and their role in prevention of hip fractures in stroke further clarified, before they can be recommended as standard treatment in this context [42, 43].

Some investigators recommend pharmacological and non-pharmacological approaches that can target bone and

muscle simultaneously in an effort to reduce sarcopenia and osteoporosis with the same approach [44-46]. However there are, as yet, no randomized controlled trials (RCTs) to address this [45, 46]. There is a suggestion from some studies that higher daily intake of protein greater than 1 kg per kg body weight per day is associated with less muscle loss and maintenance of spinal bone mineral density (BMD) and a reduced risk of hip fracture [47]. However, these need further clarification with larger studies and the findings need to be validated in other clinical trials [47]. Other studies including meta-analysis have demonstrated that resistance exercise training has dual positive effects in both bone and muscle [48].

Bonnet *et al* tested Denosumab on animals and post-menopausal women [49]. They found that muscle expresses Receptor Activator of Nuclear Kappa B (RANK) just like osteoclast precursors in bone [49]. Denosumab is a monoclonal antibody that binds to RANK ligand (RANKL) preventing it from binding to and activating RANK [49]. This has the effect of inhibiting maturation of osteoclast precursors reducing bone resorption and osteoporosis [49]. The Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial showed significant reduction of risk of vertebral, non-vertebral and hip fractures in post-menopausal women [49]. Bonnet and his colleagues found that knocking off RANK in animals improved their muscle strength and Denosumab showed improved muscle strength in the post-menopausal women they studied [49]. Moreover, a recent Phase I study showed that deletion of RANK in muscle was associated with preservation of force in de-innervated fast-twitch muscle fibres [49]. The impact of this in preventing post-stroke sarcopenia and bone loss needs further clarification with specific studies looking at this population group.

Other treatment modalities such as statin use, use of biomechanical vibrators and robot-assisted physiotherapy in immobile stroke patients have shown some evidence of reduced hip fracture in stroke patients [50-52]. For the most part these were small studies [50-52]. Larger, randomized control trials are needed to clarify treatment strategies to reduce hip fractures in stroke patients. Although trials are currently underway looking at prevention of sarcopenia in older patients, future trials may need to target elderly stroke patients specifically. At present, routine screening of patients for osteoporosis is not included in most guidelines for stroke management [53]. This may, in part, be due to limited evidence on fracture prevention strategies in this population group as well as the logistics of measuring bone mineral density using axial bone densitometry (DXA) scans [53]. Moreover the definition of sarcopenia as an entity in itself that clarifies and simplifies its diagnosis has only just become established [54]. It is hoped that consensus on its diagnostic criteria by all the different working groups will help with diagnosing and managing it in routine clinical practice. Smith *et al* have proposed the use of a clinical fracture screening tool (FRAC-stroke) to identify stroke patients for DXA or treatment to prevent fractures [53]. The tool has been validated in Canadian patients but may need wider validation

analogous to the way the Fracture Risk Assessment (FRAX) tool has been validated in different population groups around the world [53].

## 5. Conclusion

Hip fractures are common in older stroke patients. They worsen outcomes and prolong functional recovery in these patients. Falls and bone loss, particularly on the hemiplegic side, are largely implicated in their pathogenesis. Although there are encouraging results from clinical trials on therapeutic interventions to prevent hip fractures in stroke patients, larger, more detailed studies are needed to validate many of the findings.

More recently, with the definition of sarcopenia becoming clearer and more unified as a concept with focus on muscle mass and quality, as well as its impact on function, it is hoped that this will galvanize more research into prevention of sarcopenia in attempt to match the preponderance of data already available on osteoporotic fracture prevention. Perhaps the biggest paradigm shift is an approach that can target muscle and bone simultaneously in reducing falls, frailty and fractures in older people, in general, and older stroke patients in particular.

## Conflict of Interest

All the authors do not have any possible conflict of interest.

## References

- [1] Anderson A. G, Seiger A., Appelos P. Hip fractures In Persons with Stroke. *Stroke resource Treatment*: 954279. Doi: 10.1155/2013/954279.
- [2] Kang J, Chung S, Xirasager S, Jaw F, Lin H. Increased Risk Of Stroke In The Year After A Hip Fracture: A population-based follow up study. *Stroke* 2011; 42: 336-341.
- [3] Scherbakov N, Sandek A, Doehner W. Stroke-related Sarcopenia: Specific characteristics. *J Am Mrd Dir Assoc* 2015; 16 (4): 272-276.
- [4] Hunnicutt J. L, Gregory C. M. Skeletal Muscle Changes Following Stroke: a systematic review and comparison to healthy individuals. *Topics In Stroke Rehabilitation* 2017; 24 (6): 463-471.
- [5] Yoshimura Y, Wakabayashi H, Bise T, Tanoue M. Prevalence of Sarcopenia and its association with activities of daily living and dysphagia in convalescent Ward Patients. *Clinical Nutrition* 2018; 37 (6): 2022-2028.
- [6] Foster E. J, Barlas R. S, Bettencourt-Silva J. H, Clark A. B *et al*. Longterm Factors Associated With Falls and Fractures Post-Stroke. *Frontiers in Neurology* 2018; doi.org/10.3389/fneur.2018.00210.
- [7] Greco E. A, Pietschmann P, Migliaccio S. Osteoporosis and Sarcopenia Increase Frailty Syndrome In The Elderly. *Frontiers in Endocrinology* 2019; doi: 10.3389/fendo.2019.00253.

- [8] Kanis J, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke*. 2001; 32 (3): 702–706.
- [9] Pouwels S, Lalmohamed A, Leufkens B, et al. Risk of hip/femur fracture after stroke: a population-based case-control study. *Stroke*. 2009; 40 (10): 3281–3285.
- [10] Dennis MS, Lo KM, McDowall M, West T. Fractures after stroke: frequency, types, and associations. *Stroke*. 2002; 33 (3): 728–734.
- [11] Vadas D, Kalichman L. Post-stroke hip fracture in older people: A narrative review. *International Journal of Therapy and Rehabilitation* 2016; 23 (2): 1759–1779.
- [12] Fisher A, Srikusalanukai W, Davis M and Smith P. Post-stroke Hip Fracture: Prevalence, Clinical Characteristics, Mineral-Bone Metabolism, Outcomes and Gaps in Prevention. *Stroke Research and Treatment* 2013; doi.org/10.1155/2013/641943.
- [13] Northius C, Crandall C. J, Margolis K. L., Diem S. J, Ensrud K. E, Wactawski-Wende J, Lakshminarayan K. Association Between Post-stroke Disability and 5-year Hip-fracture Risk: the Women's Health Initiative. *Circulation*. 2019; 139 (1): doi.org/10.1161/circ.139.
- [14] Huo K, Hashim S. I, Yong K. I. Y, Su H, Ou O. Impact and risk factors of post-stroke bone fracture. *World Journal Of Experimental Medicine* 2016; 6 (1): 1-8.
- [15] Scherbakov N, von Haehling S, Anker SD, Dirnagl U, Doehner W. Stroke- induced Sarcopenia: muscle wasting and disability after stroke. *Int J Cardiol*. 2013; 170 (2): 89-94. Epub 2013 Oct 14.
- [16] Yao B, Klein C. S, Hu H, Li S, Zhou P. Motor Unit Properties Of The First Dorsal Interosseous In Chronic Stroke Subjects: Concentric Needle and Single Fibre EMG Analysis. *Frontiers In Physiology* 2018; doi.org/10.3389/phys.2018.01587.
- [17] Wakabayashi H, Sakuna K. Rehabilitation nutrition for Sarcopenia with disability: a combination of both rehabilitation and nutrition care management. *J Cachexia Sarcopenia Muscle*. 2014 Dec; 5 (4): 269–277.
- [18] Jou M. J. Pathophysiology and Pharmacological implications of mitochondrial targeted reactive oxygen species generation in astrocytes. *Advanced Drug Delivery Reviews* 2008; 60 (13-14): 1512-1526.
- [19] Yin H, Price F, Rudnicki MA. Satellite cells and the muscle stem cell niche. *Physiol Rev*. 2013; 93 (1): 23-67. doi: 10.1152/physrev.00043.2011.
- [20] Reginster J, Beaudart C, Buckinx F and Bruyere O. Osteoporosis and sarcopenia: two diseases or one? *Current Opinions on Clinical Nutrition and Metabolic Care* 2016; 19 (1): 31-36.
- [21] Locquet M, Beaudart C, Durieux N, Reginster J and Bruyere O. Relationship between the changes over time of bone mass and muscle health in children and adults: a systematic review and meta-analysis. *BMC Musculoskeletal Disorders* 2019; 20 (429).
- [22] Yang FZ, Jehu DAM, Ouyang H, Lam FMH, Pang MYC. The impact of stroke on bone properties and muscle-bone relationship: a systematic review and meta-analysis. *Osteoporos Int*. 2020; 31 (2): 211-224. doi: 10.1007/s00198-019-05175-4. Epub 2019.
- [23] Gandolfi M, Smania N, Vella A, Chirumbolo S. Assessed and Emerging Biomarkers in Stroke and Training-mediated Stroke Recovery: State of the Art. *Neural Plasticity* 2017; doi.org/10.1155/2017/1389475.
- [24] Brotto M & Johnson M. L. Endocrine crosstalk between and muscle. *Current Osteoporosis Reports* 2014; 12: 135–141.
- [25] Cardozo C. P., Graham Z. A. Muscle-bone interactions: Movement in the field of mechano-humoral coupling of muscle and bone. *Ann. N. Y. Acad. Sci*. 2017 doi: 10.1111/nyas.13411.
- [26] Alemdaroglu, E.; Ucan, H.; Topcuoglu, A. M.; Sivas, F. In-hospital predictors of falls in community-dwelling individuals after stroke in the first 6 months after a baseline evaluation: A prospective cohort study. *Arch. Phys. Med. Rehabil*. 2012, 93, 2244–2250.
- [27] Ciobanu N, Ciobanu S. Femoral neck fractures in patients with stroke sequelae. *The Moldovan Medical Journal* 2017; 60 (2) DOI: 10.5281/zenodo.1050980.
- [28] Axpe E, Chan D, Abegaz MF, Schreurs A-S, Alwood JS, Globus RK, et al. A human mission to Mars: Predicting the bone mineral density loss of astronauts. *PLoS ONE* (2020); 15 (1): e0226434. <https://doi.org/10.1371/journal.pone.0226434>.
- [29] Varacallo M, Pizzutillo P. Osteoporosis in Spinal Cord Injuries. [Updated 2020 Jan 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK526109/>.
- [30] Borschmann K, Pang MY, Bernhardt J, Iuliano-Burns S. Stepping towards prevention of bone loss after stroke: a systematic review of the skeletal effects of physical activity after stroke. *Int J Stroke*. 2012; 7 (4): 330-5.
- [31] Lazoura O, Groumas N, Antoniadou E, Papadaki P. J, Papadimitriou A, Thriskos P, Fezoulidis I, Viychou M. Bone Mineral Density Alterations in Upper and Lower Extremities 12 Months after Stroke measured by Peripheral Quantitative Computed Tomography and DXA. *Journal of Clinical Densitometry* 2008; 11 (4): 511-517.
- [32] Maimoun L, Fattal C, Sultan C. Bone remodelling and calcium homeostasis in patients with spinal cord injury: a review. *Metabolism* 2011; 60 (12): 1655-1663.
- [33] Selim F. O, Fahmi R. O, Ali A. E, Raafat N and Elsaied A. F. Serum Vitamin D levels in acute stroke patients. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery* 2019; 55 (80): doi.org/10.1186/s41983-019-0129-0.
- [34] Gommans J, Yi Q, Eikelboom JW, Hankey GJ, Chen C, Rodgers H. The effect of homocysteine-lowering with B-vitamins on osteoporotic fractures in patients with cerebrovascular disease: substudy of VITATOPS, a randomised placebo-controlled trial. *BMC Geriatr*. 2013; 13 (1): 1.
- [35] Pang M. Y. C, Zhang M, Li L. S. W, Jones A. Y. M. Changes in bone density and geometry of the radius in chronic stroke and related factors: A one-year prospective study. *J Musculoskeletal Neuronal Interact* 2013; 13 (1): 77-88.
- [36] Denissen S, Staring W, Kunkel D, Pickering R, Lennon S. G, Alexander C. H., Weerdesteyn, V and Verheyden G. Interventions for preventing falls in people after stroke. *Cochrane Database of Systematic Reviews* 2019; doi: 10.1002/14651858. CD008728.pub3.

- [37] Borschmann K. Exercise Protects Bone after Stroke, or Does It? A Narrative Review of the Evidence. *Stroke Research and Treatment* 2012; <https://doi.org/10.1155/2012>.
- [38] Pang M. Y, Eng J. J, Dawson A. S, Gylfadottir S. The use of aerobic exercise training in improving aerobic capacity in individuals with stroke: a meta-analysis. *Clin Rehabil.* 2006 Feb; 20 (2): 97-111.
- [39] Pang M, Eng J. J, Ashe M, McKay H. A. A 19 week exercise program for people with chronic stroke enhances bone geometry at the tibia: A peripheral quantitative computed tomography study. *Osteoporosis International* 2006; 17 (11): 1615-25.
- [40] Eng J. J, Pang M. Y. C, Ashe M. C. Balance, falls, and bone health: Role of exercise in reducing fracture risk after stroke. *Journal Of Rehabilitation, Research and Development* 2008; 45 (2): 297-314.
- [41] Momosaki R, Abo M, Urashima M. Vitamin D Supplementation and Post-Stroke Rehabilitation: A Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* 2019; 11 (6): 1295. Doi.org/10.3390/nu 11061295.
- [42] Poole KE, Loveridge N, Rose CM, Warburton EA, Reeve J. A single infusion of zoledronate prevents bone loss after stroke. *Stroke.* 2007; 38 (5): 1519-25.
- [43] Hsieh C, Sung S and Huang H. Drug treatment strategies for osteoporosis in stroke patients. *Expert Opinion On Pharmacotherapy* 2020; 21 (7): 811–821.
- [44] Tagliaferri C, Wittrant Y, Davicco MJ et al. Muscle and bone, two interconnected tissues. *Ageing Res Rev* 2015; 21: 55–57.
- [45] Kaji H. Interaction between Muscle and Bone. *Journal of Bone Metabolism* 2014; 21 (1): 29.
- [46] Demontiero O, Boersma D, Suriyaarachchi P, Duque G. Clinical outcomes of impaired muscle and bone interactions. *Clin Rev Bone Miner Metab* 2014; 12: 86–92.
- [47] Carbonel J. W and Pasiakos S. M. Dietary Protein and Muscle Mass: Translating Science to Application and Health Benefit. *Nutrients.* 2019; 11 (5): 1136. doi: 10.3390/nu11051136.
- [48] Hong A. R, Kim S. W. Effects of Resistance Exercise on Bone Health. *Endocrinol Metab (Seoul).* 2018; 33 (4): 435–444. doi: 10.3803/EnM.2018.33.4.435.
- [49] Bonnet N, Bourgoin L, Biver E, Douni E, Ferrari S. RANKL inhibition improves muscle strength and insulin sensitivity and restores bone mass. *J Clin Invest.* 2019; 129 (8): 3214-3223. doi: 10.1172/JCI125915.
- [50] Lin S, Wang J, Liang C, Huang H. Statin Use Is Associated With Decreased Osteoporosis and Fracture Risks in Stroke Patients. *The Journal of Clinical Endocrinology & Metabolism* 2018; 103 (9): 3439–3448.
- [51] Park Y. J, Park S. W, Lee H. S. Comparison of the Effectiveness of Whole Body Vibration in Stroke Patients: A Meta-Analysis. *Biomed Res Int.* 2018; 2018: 5083634. doi: 10.1155/2018/5083634.
- [52] Guo, S; Wang, Y; Kun, W; Long, J; Xing, L; Huang, Z; Yi, Y; Miramini, S; Zhang, L, Robot-assisted weight-bearing exercise for stroke patients with limited mobility, *Journal Of Low Frequency Noise Vibration And Active Control* 2019; 38 (2): 879-892.
- [53] Smith E. E, Fang. J, Alibhai S. M, Cram P, Cheung A. M, Casaubon L. K, Kapoor E., Austin P. C., Kapral M. K et al. Derivation and External Validation of a Scoring System for Predicting Fracture Risk After Ischemic Stroke in a Canadian Cohort. *JAMA Neurol.* 2019; 76 (8): 925-931. doi: 10.1001/jamaneurol.2019.1114.
- [54] Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer A. A, Schneider S. M, Sieber C. C, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing.* 2019; 48 (1): 16-31. doi: 10.1093/ageing/afy169.