World Journal of Experimental Medicine

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5493/wjem.v6.i1.1

World J Exp Med 2016 February 20; 6(1): 1-8
ISSN 2220-315X (online)

EDITORIAL

Impact and risk factors of post-stroke bone fracture

Kang Huo, Syed I Hashim, Kimberley LY Yong, Hua Su, Qiu-Min Qu

Kang Huo, Syed I Hashim, Kimberley LY Yong, Qiu-Min Qu, Department of Neurology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China

Hua Su, Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA 94117, United States

Author contributions: Huo K, Hashim SI and Yong KLY analyzed the data and wrote the paper; Qu QM did critical editing; Su H designed the outline of the review and did critical editing; Hashim SI and Yong KLY contributed equally to this work.

Supported by National Institutes of Health, Nos. R01 NS027713, R01 HL122774 and R21 NS083788; the Michael Ryan Zodda Foundation and UCSF Research Evaluation and Allocation Committee (REAC).

Conflict-of-interest statement: The authors have no conflict of interests.

Correspondence to: Qiu-Min Qu, MD, PhD, Department of Neurology, the First Affiliated Hospital of Xi'an Jiaotong University, Yanta West road No. 277, Xi'an 710061, Shaanxi Province, China. quqiumin@medmail.com.cn
Telephone: +86-29-85324083
Fax: +86-29-85324083

Received: September 23, 2015
Peer-review started: October 3, 2015
First decision: October 27, 2015
Revised: January 6, 2016
Accepted: January 21, 2016
Article in press: January 22, 2016
Published online: February 20, 2016

Abstract

Bone fracture occurs in stroke patients at different times during the recovery phase, prolonging recovery time and increasing medical costs. In this review, we discuss the potential risk factors for post-stroke bone fracture and preventive methods. Most post-stroke bone fractures occur in the lower extremities, indicating fragile bones are a risk factor. Motor changes, including posture, mobility, and balance post-stroke contribute to bone loss and thus increase risk of bone fracture. Bone mineral density is a useful indicator for bone resorption, useful to identify patients at risk of post-stroke bone fracture. Calcium supplementation was previously regarded as a useful treatment during physical rehabilitation. However, recent data suggests calcium supplementation has a negative impact on atherosclerotic conditions. Vitamin D intake may prevent osteoporosis and fractures in patients with stroke. Although drugs such as teriparatide show some benefits in preventing osteoporosis, additional clinical trials are needed to determine the most effective conditions for post-stroke applications.

Key words: Bone fracture; Recovery; Bone mineral density; Stroke; Osteoporosis

Core tip: Post-stroke bone fracture negatively impacts stroke recovery, prolongs hospital stays, and increases economic cost. Stroke, osteoporosis and bone fracture share common risk factors. The main risk factors for post-stroke bone fracture include aging, osteoporosis, and loss of posture control. Bone mineral density measurement may identify patients who are at risk of post-stroke bone fracture. Drugs and supplements, such as vitamin D and teriparatide, can be tested in clinical settings for prevention of post-stroke bone fracture. Although bisphosphonate's incur side effects, they are considered first-line drugs to prevent post-stroke bone fracture.

Huo K, Hashim SI, Yong KLY, Su H, Qu QM. Impact and risk factors of post-stroke bone fracture. *World J Exp Med* 2016; 6(1): 1-8 Available from: URL: http://www.wjgnet.com/2220-315X/full/v6/i1/1.htm DOI: http://dx.doi.org/10.5493/wjem.v6.i1.1

INCIDENCE OF POST-STROKE BONE FRACTURE

Aging, smoking, hypertension and lack of physical activity contribute to osteoporosis bone fracture and stroke. Although strokes can occur at any age, they mostly occur in older age, which may due to reduction in bone density[1]. Only one fourth of strokes occur in people under the age of 65[2]. The prevalence of stroke more than doubles each decade after the age of 55.

Stroke and bone fracture share common risk factors. Individuals with a greater risk of stroke are also more prone to osteoporosis and fractures. Risk factors for post-stroke bone fracture include osteoporosis, aging, and loss of posture control. Osteoporosis is the main risk factor of bone fracture, with increasing prevalence worldwide. In the United Kingdom, over half of women, and one-fifth of men over age 50, will sustain a fragility fracture[3].

The risk of bone fracture post stroke is underestimated because it is often considered secondary to falling, especially among elderly. Previously, 534 elderly persons were assessed over 2 mo, results revealed that stroke was influenced by physical factors including falls[4]. A fracture post-stroke puts the patient at a greater disadvantage during rehabilitation, and greatly affects the quality of life after recovery.

RISK FACTORS OF POST-STROKE BONE FRACTURE

Stroke patients are highly susceptible to bone fracture[5]. They have a 2 to 4-fold increased risk of hip fractures, which carries a high mortality rate in the elderly[6]. Changes in walking posture, skeletal weight load, and bone maintenance have been studied as risk factors for poor post-stroke bone health[7]. Other factors include low bone mineral density (BMD), loss of balance, inappropriate gait, and muscle deformation[8]. In order to predict the risk of falls and fractures in stroke patients, we must take into account not only structural changes, but also functional disability.

Post-stroke fractures are of particular concern given the impact on functional outcomes of stroke rehabilitation. Functional impairment of stroke is commonly measured using two scales, the barthel index (BI) and modified Rankin scale (mRs). Both assessment scales place stroke patients with differing functional capabilities into categories, describing a level of independence or need for medical assistance. The BI is a measure of functional independence on ten activities of daily living (ADL). The mRs measures global disability of a patient. Harrison *et al*[9] studied the effectiveness and drawbacks of each scale and drew the conclusion that while all scales had weaknesses, certain types of disability were reliably assessed by these scales.

The level of functional impairment may be useful in estimating risk of falls. In a study of 135 elderly stroke patients, Nyberg *et al*[10] developed a fall prediction index that classifies patients into low-, intermediate-, and high-risk groups. The index includes male sex, poor ADL performance, urinary incontinence, bilateral motor impairment, impaired postural stability, visuospatial hemi-neglect, and use of diuretics, anti-depressants or sedatives as factors in increased falling[10]. A comprehensive index for assessing the risk of falls is vital to reliably predict the possibility of post-stroke bone fracture.

In addition, weak bones are a risk factor for post-stroke bone fracture. Hospitalization of stroke patients suffering adverse changes in motor function and body composition leads to long-term increase in fracture risk[11]. Although BMD decrease is common in stroke patients > 65 years, studies have demonstrated that BMD loss in paretic limbs are greater than their non-paretic counterparts, such as the arms. Interestingly, vitamin D deficiency causing osteopenia seems to be a possible mechanism[12]. Bone loss progresses rapidly in the acute stages of stroke[13], with the most dramatic changes seen in the first few months[14]. By measuring the magnitude of changes to volumetric BMD after stroke in a prospective study, Borschmann *et al*[15] found a 7% difference in total volumetric BMD between paretic and non-paretic distal tibiae 6 mo post-stroke, with lower density on the paretic side. Another study showed that while immobility does increase bone loss, stroke patients who maintained their ability to walk had a 3% decrease in BMD. This suggests that stroke itself is a risk factor for bone loss and fragile bones. Therefore, more studies are needed to better understand the influence and underlying mechanisms of stroke on BMD loss, as well as to develop preventive methods.

Biochemical markers related to bone turnover can be used to evaluate bone health and risk of bone fracture. Haddaway *et al*[16] showed that stroke patients older than 60 years displayed much earlier bone resorption (a process of bone breakdown) when compared with normal individuals, supporting the idea that bone remodeling is correlated with post-stroke bone fragility. Bone turnover in elderly women was inversely correlated with bone density at the hip on both hemiplegic and normal sides, which may adversely influence bone fracture. Serum biomarkers, such as osteocalcin (OC), bone alkaline phosphatase combined with BMD analysis better predict than physical exam alone. Early evaluation of bone turnover could help identify bone loss in stroke patients[17].

Motor changes, including posture, mobility and balance are also factors associated with bone loss. Chang *et al*[18] compared the femoral neck bone loss in hemi-

paretic patients with high or low weight-bearing on the paretic lower limb. The study showed that patients with lower standing weight placed on their paretic limb (< 50%) had faster bone loss and BMD reduction during the follow-up period (≥ 6 mo) compared with those who bore more weight (> 50%). The proportion of weight bore by the paretic leg was related to the BMD, indicating that reduced weight bearing is a predictor of bone loss in stroke patients[18]. Although results from a study by Melton *et al*[19] suggested that skeletal weight load is not an independent factor of bone loss, the effect of reduced skeletal weight load may be more pronounced in paresis. Immobility is also associated with increased bone loss in stroke patients, with wheelchair-bound patients showing a 4-fold loss in BMD (13% to 3%) compared with ambulating patients[20]. Together, these factors amplify the fragility of bones in patients undergoing rehabilitation, leading to osteoporosis[21].

Of course, some stroke patients are at a higher risk of having bone fractures than others. For example, a study by Ashburn *et al*[22] revealed that patients who were physically unstable (experienced near-falls), with upper-limb functional impairment, were at higher risk of falls. This suggests that proper arm function can prevent falls, as patients are able to support themselves using their arms. Interestingly, stroke survivors without functional impairment had significantly higher risk of fragility fractures in legs compared with arms. However, stroke survivors with functional impairment had no prevalence of fracture on any specific site of their body[23].

Prevention of fractures is of utmost concern, as post-fracture care can be long-term and strenuous, especially for stroke patients. Physical rehabilitation is essential for maximum motor recovery. Post-stroke rehabilitation includes re-learning of basic movement skills and other common activities. To perform daily activities, patients must recover balance, muscle strength, and movement. Early and consistent physical rehabilitation is key in achieving the most favorable results[24]. Having a fracture post or pre-stroke can put the patient at a greater disadvantage in their rehabilitation, and negatively affects their quality of life[25]. Bone fractures on the paretic side can be especially detrimental, as damage to the structure of the paretic limb complicates motor recovery.

There are many factors affecting the outcome of rehabilitation, including, but not limited to, the type of stroke lesion, age of the patient, previous lifestyle, rehabilitation, exercise and mobility[26]. Recent systematic reviews and meta-analyses show that in rat models, exercise was associated with decreased lesion volume and improved functional outcomes[27,28]. Studies also showed that early mobilization had a strong positive correlation with favorable outcomes in patients[29-31]. Despite the acceptance among studies on the positive effect of early mobilization, analyses of randomized-controlled trials comparing first-day and second-day mobilization on functional outcomes (good functional outcomes were mRs scores ≤ 2) showed little difference between the groups[32]. Future trials should define proper mobilization times at different functional impairment levels.

Patients with conditions that affect bone loss pre-stroke suffer more complications post-stroke. The effect of stroke on BMD has been independently observed in patients with pre-stroke osteoporosis[33]. Older women often experience bone loss after menopause, which is further exacerbated by stroke. In men, subjects with pre-stroke osteoporosis (due to aging or otherwise) suffer similar consequences of stroke, but given that most clinical trials have focused on menopausal women, male subjects are often neglected in studying osteoporosis.

The independent interaction of stroke on bone density may be difficult to observe due to the presence of multiple factors. Therefore, the multi-factorial character of post-stroke bone fracture needs to be studied deeper to determine possible interventions.

It is also interesting to note that there is a two-way interaction between stroke and bone health. Stroke leads to low BMD, and low BMD increases the risk of stroke[34,35]. A prospective investigation conducted between 1997 and 2000 evaluated the relationship between BMD and incidence of stroke in 14290 participants. The study showed that the risk of stroke increased in low BMD individuals. The findings indicated that BMD predicted the risk of stroke, especially in women[36]. It has also been shown that vertebral fracture occurs more often in first time-stroke patients that have low pre-stroke BMD. Therefore, low pre-stroke BMD poses a greater risk of fracture, resulting in additional functional loss[37]. Hypertension is also a major risk factor for stroke. Elderly persons with shorter stature and lower BMD have been associated with increased arterial stiffness and hypertension. Therefore, this population could be at higher risk compared with the general population for post-stroke bone fracture[38].

Low estrogen level is correlated with reduced BMD. At menopause, decreased estrogen leads to a rapid loss of BMD and increased incidence of bone fracture in women. Estrogen plays a key role in regulating bone mass and strength by controlling the activity of bone-forming osteoblasts and bone-resorbing osteoclasts[39]. Therefore, post-menopausal women are more likely to develop osteoporosis, and thus have an increased risk of bone fractures. According to statistical data obtained from the International Osteoporosis Foundation, osteoporosis causes more than 8.9 million fractures worldwide annually, resulting in an osteoporotic fracture every three seconds[40].

Using anti-depressants on stroke patients may increase the possibility of post-stroke bone fracture. Stroke patients commonly suffer from secondary disorders, such as depression, that may affect bone health. Anti-depressants, in particular selective serotonin reuptake inhibitors (SSRIs), have been correlated with an increased risk for osteoporosis[41]. The association of fracture incidents and

antidepressants was studied using data from the Canadian Multicenter Osteoporosis Study in a prospective randomly selected population-based community cohort[42]. Among 6645 subjects, 192 (2.9%) were using SSRIs and/or serotonin and noradrenaline reuptake inhibitors (SNRIs) at baseline. During the 10-year study period, SSRI/SNRI use was associated with increased risk of fragility fracture (HE = 1.88; 95%CI: 1.48-2.39). Therefore, more attention and care should be given when prescribing antidepressant drugs to patients.

Although current evidence on the impact of stroke on bone health seems contradictory, what is clear is that risk of bone fracture and stroke are strongly correlated. However, whether stroke is an independent factor for BMD loss, due to motor function changes, is unknown. To prevent bone fracture, methods and treatments to reduce bone loss in stroke patients should be researched. A clear time frame for physical therapy, especially early mobilization, is important in long-term recovery. Patient fall prediction indexes can be developed further, and rehabilitative measures would function better when tailored to different risk grades. Ultimately, while evidence strongly supports the effectiveness of general rehabilitation, a deeper understanding of treatment response should be prioritized.

ASSESSMENT OF POST-STROKE BONE FRACTURE

In this section, we discuss treatment options available today as well as assessments to minimize the risk of bone fractures and to optimize post-stroke recovery. Given that osteoporosis is a predictor for stroke and bone fractures, the majority of the following discussion is focused on management of this condition.

Calcium is a major component of bone, supplementation of calcium is regarded as a possible solution for preventing post-stroke bone fracture. However, there is conflicting data on the effectiveness of calcium supplementation. Some evidence shows calcium intake has adverse cardiovascular effects, raising widespread concern. However, a recent study showed dairy products do not increase the risk of cardiovascular disease, particularly low fat versions. Therefore, dairy products could be a good resource for calcium intake[43].

Recent studies have shown that increasing the intake of calcium does not reduce osteoporotic fracture rates[44]. A prospective longitudinal cohort study revealed that gradual increases in dietary calcium intake above the first quintile in female population were not associated with further reductions to the risk of fracture or osteoporosis[45]. If these findings are true, then taking calcium will not prevent osteoporosis. Instead, it may increase the risk of developing cardiovascular problems long term.

Alternatively, other studies have shown that calcium supplementation does not increase carotid artery intimal medial thickness or carotid atherosclerosis[46]. Thus, the impact of calcium intake on osteoporosis is not clear. Until more confirmatory data are available, physicians should not stop prescribing calcium supplements to their patients[47]. The appropriate intake amount varies, ranging 800-1500 mg/d[48]. Some sources recommend calcium supplementation not exceed 1200-1500 mg/d. A study by Khan *et al*[49] found that to decrease fracture, non-fatal CVD, stroke, and all-cause mortality risks in both men and women, a specific dose of 1348 mg/d is optimal.

Given no clear consensus on proper calcium dosage, early screening and active management of osteoporosis at the acute stages of stroke are critical[37]. One of the best predictive factors for osteoporosis is BMD, and it should be measured on all stroke patients. Dual-energy X-ray absorptiometry (DXA) is a primary tool that accurately evaluates BMD. According to the United States Preventive Services Task Force, women over the age of 65 should get a DXA scan, men are recommended to get the scan at age 70[50]. At risk individuals should also get the scan performed. Risk is determined using the World Health Organization' s Fracture Risk Assessment Tool, a diagnostic that evaluates the 10-year probability of bone fracture risk. Clinical risk factors assessed include prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term use of glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and daily alcohol consumption[51].

There are 2 DXA scan methods, a central DXA that scans the hip and lower spine, and a peripheral DXA that most often scans the heel. A study showed the heel BMD can serve as a surrogate for hip BMD[52]. BMD measurements, used concomitantly with the Tinetti Test (TT), or Performance Oriented Mobility Assessment, provide a useful indication for those needing early prophylaxis against bone loss. The TT is a solid predictor to assess balancing ability of post-stroke patients. It was created to screen for balance and mobility skills (gait) in older adults, and determines the likelihood of falls. This is especially important in hemiplegic stroke patients. Using a 3-point scale, a score less than 19 indicates a high risk for falls, and scores between 19 and 24 indicate a moderate fall risk[53]. However, it is difficult to assess with specificity on a 3-point scale[54]. This test is not useful on post-stroke patients that are bed-ridden.

A more reliable assessment is the Timed "Up and Go Test" (TUG). It is the shortest, simplest clinical balance test. A stop-watch timer is more objective compared with a rating scale used in the TT[55]. In a cross-sectional study performed by Ng and Hui-Chan, the TUG test showed excellent reliability (ICC > 0.95). Subjects with chronic stroke were found to have more significant spastic and weaker plantar flexors, slower walking speeds, and poorer walking endurance when compared to healthy elderly subjects (all $P < 0.003$)[56].

With the balancing ability assessed by either the TT or TUG, the severity of disuse on the hemiplegic side of

post-stroke patients can be determined. This disuse of the hemiplegic side in stroke patients results in bone-mass reduction, especially in the presence of vitamin D deficiency[57]. By comparing BMD, serum concentrations of intact parathyroid hormone (PTH), OC, tartrate-resistant acid phosphatase, 25-hydroxyvitamin D (25-OHD), and calcium levels between healthy and post-stroke patients, BMD values were lower on the hemiplegic side compared with the non-hemiplegic side. Vitamin D deficiency and compensatory secondary hyperparathyroidism stimulated skeletal turnover is an important cause of osteopenia in the hemiplegic limbs of stroke patients. This suggests that administration of vitamin D supplements is beneficial in stroke patients to reduce fracture risk.

In addition to increasing risk of bone fractures, vitamin D deficiency in post-stroke patients may also cause a variety of issues in non-stroke patients. Vitamin D deficiency impairs gastrointestinal absorption of calcium and bone mineralization, muscle strength, and is also associated with muscle mass loss, which contributes to an increased risk of fall[58]. Furthermore, vitamin D deficiency is a risk factor for strokes due to the associations of low 25-OHD levels, particularly in the presence of arterial hypertension[59]. Vitamin D also exhibits neuroprotective, as well as neuromuscular and osteo-protective effects, which may reduce cognitive and functional impairments in stroke patients. However, current evidence is too scarce to draw any conclusions. Further evaluations are needed to confirm the effect of vitamin D treatment in reducing stroke associated mortality and morbidity.

While vitamin D supplementation is important in patients who have osteoporosis, there is conflicting evidence showing that vitamin D does not prevent osteoporosis in healthy individuals. In a meta-analysis from 2014, the effects of vitamin D supplements on BMD were found to have no significance[60]. However, some studies showed that vitamin D with co-administration of calcium significantly improved BMD and thus, reduced the risk of falling in elderly patients[61].

Another strong indicator for osteoporosis is serum OC, which is associated with bone turnover. By examining serum total osteocalcin (TOC), carboxylated osteocalcin (COC), and their ratio (COC/TOC), data show serum COC concentrations, especially COC/TOC, predicted the occurrence of fractures in the elderly[62]. Thus, low COC/TOC is directly correlated with risk of fracture. Bone turnover can be further evaluated using serum urinary cross-linked N-telopeptide of type Ⅰ collagen (NTX), a reliable bone resorption marker in patients with metabolic bone disease. According to a study performed by Maeno *et al*[62], patients in the highest quartile of serum NTX concentrations exhibited rapid bone loss rates, with a sensitivity and specificity for detecting the rate of 48% and 83%, respectively.

Therefore, assessment instruments, such as the TT, TUG test, DXA scan, serum NTX, and COC/TOC levels, as well as supplements such as calcium and vitamin D, are important in identifying and preventing osteoporosis and fractures in patients with stroke. If preventive measures against osteoporosis are not well managed, or if a person already has osteoporosis, the treatment goals should be to minimize further bone loss and prevent osteoporotic fractures.

PREVENTION AND ADDITIONAL MANAGEMENT

Osteoporosis is a devastating disorder that impairs bone strength, causing an increased risk of fracture. It is usually diagnosed by assessing BMD *via* the DXA scan, and is defined by the World Health Organization criteria as a BMD T-score of 2.5 standard deviations or more below the average of a young, healthy person[63].

Most studies show that mitigation of osteoporosis prevents post-stroke bone fracture. Hemiplegic patients and severe stroke patients will experience bone remodeling. A study by Ramnemark *et al*[64] in 1999, with 24 extensive paresis stroke patients, found that during the first year after severe stroke, patients developed pronounced hemi-osteoporosis. This was not associated with general changes in lean or fat mass. The development of hemi-osteoporosis was independent of weight changes after stroke[65].

Currently, bisphosphonates are used to treat osteoporosis because these drugs slow bone breakdown due to their strong affinity to skeleton, low toxicity to other tissues and organs in the body, and ease of frequency of administration[66]. Alendronate, risedronate, ibandronate, and zoledronate were found to reduce fracture risk by 50% within the first year of therapy in both men and women[67]. However, some studies suggest that bisphosphonates may increase the risk of esophageal cancer and cardiovascular diseases[68], osteonecrosis of the jaw, and subtrochanteric fractures[69,70]. These side effects seem likely to hinder the use and benefits of bisphosphonates. Thus, bisphosphonates use should be determined on a case-to-case basis.

Recent studies show that teriparatide, a synthetic peptide that mimics the action of PTH, rebuilds bone and reverses osteoporosis. A large, randomized, placebo-controlled clinical trial found that postmenopausal women with severe osteoporosis had reduced spinal and non-vertebral fractures by more than 50% when using teriparatide[71]. However, this trial was stopped after controversy that teriparatide caused osteosarcoma, a type of bone cancer, when injected into laboratory rats[72]. Retrospective studies have found no significant association between osteosarcoma and teriparatide, and only 2 cases of osteosarcoma in PTH-treated patients have been reported. The prevalence of osteosarcoma in rats is likely due to the ever-growing epiphysis in rats. Thus, teriparatide is contraindicated in children and young adults whose epiphysis has not closed. Adults that are pregnant, have risk of renal failure, or have a history of radiation therapy should also refrain from using teriparatide. Currently, teriparatide should be limited to 2 years, and is not encouraged to prevent osteoporosis,

to treat mild osteoporosis, or by people who can take other osteoporosis treatment[73]. The post-treatment effect of bone loss is prevented by adding an anti-resorptive drug after stopping teriparatide. Based on the researches we already have, benefits of bisphosphonates surpass disadvantages for not using them. Regardless of bisphosphonate's side effects, it is still a first-line drug choice to prevent post-stroke bone fracture. However, large scale randomized double blind clinical trials still should be conducted in the further to explore a safe preventive method for reducing bone fracture on post-stroke patients.

ACKNOWLEDGMENTS

The authors thank Dr. Mitradas Panicker for the useful discussions, Mr. Alan Alfieri for proofreading and editing, and Dr. Austin Cape the ASJ Editors for critical reading.

REFERENCES

1 **Jørgensen L**, Engstad T, Jacobsen BK. Bone mineral density in acute stroke patients: low bone mineral density may predict first stroke in women. *Stroke* 2001; **32**: 47-51 [PMID: 11136913 DOI: 10.1161/01.STR.32.1.47]
2 **Poole KE**, Reeve J, Warburton EA. Falls, fractures, and osteoporosis after stroke: time to think about protection? *Stroke* 2002; **33**: 1432-1436 [PMID: 11988628 DOI: 10.1161/01.STR.0000014510.48897.7D]
3 **van Staa TP**, Dennison EM, Leufkens HG, Cooper C. Epidemiology of fractures in England and Wales. *Bone* 2001; **29**: 517-522 [PMID: 11728921 DOI: 10.1016/S8756-3282(01)00614-7]
4 **Yoo JS,** Kim CG, Yim J, Jeon MY. Factors influencing falls in the frail elderly individuals in urban and rural areas. *Aging Clin Exp Res* 2015 Oct 13; Epub ahead of print [PMID: 26462845 DOI: 10.1007/s40520-015-0469-2]
5 **Whitson HE**, Pieper CF, Sanders L, Horner RD, Duncan PW, Lyles KW. Adding injury to insult: fracture risk after stroke in veterans. *J Am Geriatr Soc* 2006; **54**: 1082-1088 [PMID: 16866679 DOI: 10.1111/j.1532-5415.2006.00769.x]
6 **Frost SA**, Nguyen ND, Black DA, Eisman JA, Nguyen TV. Risk factors for in-hospital post-hip fracture mortality. *Bone* 2011; **49**: 553-558 [PMID: 21689802 DOI: 10.1016/j.bone.2011.06.002]
7 **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**: 330-335 [PMID: 21967614 DOI: 10.1111/j.1747-4949.2011.00645.x]
8 **Yavuzer G**, Ataman S, Süldür N, Atay M. Bone mineral density in patients with stroke. *Int J Rehabil Res* 2002; **25**: 235-239 [PMID: 12352178 DOI: 10.1097/00004356-200209000-00010]
9 **Harrison JK**, McArthur KS, Quinn TJ. Assessment scales in stroke: clinimetric and clinical considerations. *Clin Interv Aging* 2013; **8**: 201-211 [PMID: 23440256 DOI: 10.2147/CIA.S32405]
10 **Nyberg L**, Gustafson Y. Fall prediction index for patients in stroke rehabilitation. *Stroke* 1997; **28**: 716-721 [PMID: 9099185 DOI: 10.1161/01.STR.28.4.716]
11 **Kanis J**, Oden A, Johnell O. Acute and long-term increase in fracture risk after hospitalization for stroke. *Stroke* 2001; **32**: 702-706 [PMID: 11239190 DOI: 10.1161/01.STR.32.3.702]
12 **Sato Y**, Maruoka H, Oizumi K, Kikuyama M. Vitamin D deficiency and osteopenia in the hemiplegic limbs of stroke patients. *Stroke* 1996; **27**: 2183-2187 [PMID: 8969777 DOI: 10.1161/01.STR.27.12.2183]
13 **Beaupre GS**, Lew HL. Bone-density changes after stroke. *Am J Phys Med Rehabil* 2006; **85**: 464-472 [PMID: 16628156 DOI: 10.1097/01.phm.0000214275.69286.7a]
14 **Hamdy RC**, Moore SW, Cancellaro VA, Harvill LM. Long-term effects of strokes on bone mass. *Am J Phys Med Rehabil* 1995; **74**: 351-356 [PMID: 7576411 DOI: 10.1097/00002060-199509000-00006]
15 **Borschmann K**, Pang MY, Iuliano S, Churilov L, Brodtmann A, Ekinci EI, Bernhardt J. Changes to volumetric bone mineral density and bone strength after stroke: a prospective study. *Int J Stroke* 2015; **10**: 396-399 [PMID: 24373530 DOI: 10.1111/ijs.12228]
16 **Haddaway MJ**, Bainbridge NJ, Powell DE, Davie MW. Bone resorption in stroke and institutionalized subjects. *Calcif Tissue Int* 2009; **84**: 118-125 [PMID: 19142679 DOI: 10.1007/s00223-008-9203-9]
17 **Melton LJ**, Khosla S, Atkinson EJ, O'Fallon WM, Riggs BL. Relationship of bone turnover to bone density and fractures. *J Bone Miner Res* 1997; **12**: 1083-1091 [PMID: 9200008 DOI: 10.1359/jbmr.1997.12.7.1083]
18 **Chang KH**, Liou TH, Sung JY, Wang CY, Genant HK, Chan WP. Femoral neck bone mineral density change is associated with shift in standing weight in hemiparetic stroke patients. *Am J Phys Med Rehabil* 2014; **93**: 477-485 [PMID: 24508925 DOI: 10.1097/phm.0000000000000053]
19 **Melton LJ**, Riggs BL, Achenbach SJ, Amin S, Camp JJ, Rouleau PA, Robb RA, Oberg AL, Khosla S. Does reduced skeletal loading account for age-related bone loss? *J Bone Miner Res* 2006; **21**: 1847-1855 [PMID: 17002566 DOI: 10.1359/jbmr.060908]
20 **Jørgensen L**, Jacobsen BK, Wilsgaard T, Magnus JH. Walking after stroke: does it matter? Changes in bone mineral density within the first 12 months after stroke. A longitudinal study. *Osteoporos Int* 2000; **11**: 381-387 [PMID: 10912838 DOI: 10.1007/s001980070103]
21 **Carda S**, Cisari C, Invernizzi M, Bevilacqua M. Osteoporosis after stroke: a review of the causes and potential treatments. *Cerebrovasc Dis* 2009; **28**: 191-200 [PMID: 19571530 DOI: 10.1159/000226578]
22 **Ashburn A**, Hyndman D, Pickering R, Yardley L, Harris S. Predicting people with stroke at risk of falls. *Age Ageing* 2008; **37**: 270-276 [PMID: 18456791 DOI: 10.1093/ageing/afn066]
23 **Benzinger P**, Rapp K, König HH, Bleibler F, Globas C, Beyersmann J, Jaensch A, Becker C, Büchele G. Risk of osteoporotic fractures following stroke in older persons. *Osteoporos Int* 2015; **26**: 1341-1349 [PMID: 25572044 DOI: 10.1007/s00198-014-3005-x]
24 **Knecht S**, Hesse S, Oster P. Rehabilitation after stroke. *Dtsch Arztebl Int* 2011; **108**: 600-606 [PMID: 21966318 DOI: 10.3238/arztebl.2011.0600]
25 **Poplingher AR**, Pillar T. Hip fracture in stroke patients. Epidemiology and rehabilitation. *Acta Orthop Scand* 1985; **56**: 226-227 [PMID: 4036571]
26 **Austin MW**, Ploughman M, Glynn L, Corbett D. Aerobic exercise effects on neuroprotection and brain repair following stroke: a systematic review and perspective. *Neurosci Res* 2014; **87**: 8-15 [PMID: 24997243 DOI: 10.1016/j.neures.2014.06.007]
27 **Egan KJ**, Janssen H, Sena ES, Longley L, Speare S, Howells DW, Spratt NJ, Macleod MR, Mead GE, Bernhardt J. Exercise reduces infarct volume and facilitates neurobehavioral recovery: results from a systematic review and meta-analysis of exercise in experimental models of focal ischemia. *Neurorehabil Neural Repair* 2014; **28**: 800-812 [PMID: 24553105 DOI: 10.1177/1545968314521694]
28 **Zhang P**, Yu H, Zhou N, Zhang J, Wu Y, Zhang Y, Bai Y, Jia J, Zhang Q, Tian S, Wu J, Hu Y. Early exercise improves cerebral blood flow through increased angiogenesis in experimental stroke rat model. *J Neuroeng Rehabil* 2013; **10**: 43 [PMID: 23622352 DOI: 10.1186/1743-0003-10-43]
29 **Dean CM**, Rissel C, Sherrington C, Sharkey M, Cumming RG, Lord SR, Barker RN, Kirkham C, O'Rourke S. Exercise to enhance mobility and prevent falls after stroke: the community stroke club randomized trial. *Neurorehabil Neural Repair* 2012; **26**: 1046-1057 [PMID: 22544817 DOI: 10.1177/1545968312441711]

30 **Askim T**, Bernhardt J, Salvesen O, Indredavik B. Physical activity early after stroke and its association to functional outcome 3 months later. *J Stroke Cerebrovasc Dis* 2014; **23**: e305-e312 [PMID: 24529353 DOI: 10.1016/j.jstrokecerebrovasdis.2013.12.011]

31 **Sundseth A**, Thommessen B, Rønning OM. Early mobilization after acute stroke. *J Stroke Cerebrovasc Dis* 2014; **23**: 496-499 [PMID: 23680682 DOI: 10.1016/j.jstrokecerebrovasdis.2013.04.012]

32 **Kutlubaev MA**, Akhmadeeva LR. The early post-stroke mobilization. *Vopr Kurortol Fizioter Lech Fiz Kult* 2015; **92**: 46-50 [PMID: 25876435]

33 **Poole KE**, Warburton EA, Reeve J. Rapid long-term bone loss following stroke in a man with osteoporosis and atherosclerosis. *Osteoporos Int* 2005; **16**: 302-305 [PMID: 15197547 DOI: 10.1007/s00198-004-1682-6]

34 **Nordström A**, Eriksson M, Stegmayr B, Gustafson Y, Nordström P. Low bone mineral density is an independent risk factor for stroke and death. *Cerebrovasc Dis* 2010; **29**: 130-136 [PMID: 19955736 DOI: 10.1159/000262308]

35 **Minn YK**, Suk SH, Do SY. Osteoporosis as an independent risk factor for silent brain infarction and white matter changes in men and women: the PRESENT project. *Osteoporos Int* 2014; **25**: 2465-2469 [PMID: 25011984 DOI: 10.1007/s00198-014-2785-3]

36 **Myint PK**, Clark AB, Kwok CS, Loke YK, Yeong JK, Luben RN, Wareham NJ, Khaw KT. Bone mineral density and incidence of stroke: European prospective investigation into cancer-norfolk population-based study, systematic review, and meta-analysis. *Stroke* 2014; **45**: 373-382 [PMID: 24399373 DOI: 10.1161/strokeaha.113.002999]

37 **Kim HW**, Kang E, Im S, Ko YJ, Im SA, Lee JI. Prevalence of pre-stroke low bone mineral density and vertebral fracture in first stroke patients. *Bone* 2008; **43**: 183-186 [PMID: 18420478 DOI: 10.1016/j.bone.2008.02.016]

38 **El-Bikai R**, Tahir MR, Tremblay J, Joffres M, Šeda O, Šedová L, Awadalla P, Laberge C, Knoppers BM, Dumas P, Gaudet D, Ste-Marie LG, Hamet P. Association of age-dependent height and bone mineral density decline with increased arterial stiffness and rate of fractures in hypertensive individuals. *J Hypertens* 2015; **33**: 727-735; discussion 735 [PMID: 25915877 DOI: 10.1097/HJH.0000000000000475]

39 **Johnell O**, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; **17**: 1726-1733 [PMID: 16983459 DOI: 10.1007/s00198-006-0172-4]

40 **Rauma PH**, Pasco JA, Berk M, Stuart AL, Koivumaa-Honkanen H, Honkanen RJ, Hodge JM, Williams LJ. The association between use of antidepressants and bone quality using quantitative heel ultrasound. *Aust N Z J Psychiatry* 2015; **49**: 437-443 [PMID: 25586753 DOI: 10.1177/0004867414565475]

41 **Moura C**, Bernatsky S, Abrahamowicz M, Papaioannou A, Bessette L, Adachi J, Goltzman D, Prior J, Kreiger N, Towheed T, Leslie WD, Kaiser S, Ioannidis G, Pickard L, Fraser LA, Rahme E. Antidepressant use and 10-year incident fracture risk: the population-based Canadian Multicentre Osteoporosis Study (CaMoS). *Osteoporos Int* 2014; **25**: 1473-1481 [PMID: 24566587 DOI: 10.1007/s00198-014-2649-x]

42 **Cheng ML**, Gupta V. Teriparatide - Indications beyond osteoporosis. *Indian J Endocrinol Metab* 2012; **16**: 343-348 [PMID: 22629497 DOI: 10.4103/2230-8210.95661]

43 **Rozenberg S**, Body JJ, Bruyère O, Bergmann P, Brandi ML, Cooper C, Devogelaer JP, Gielen E, Goemaere S, Kaufman JM, Rizzoli R, Reginster JY. Effects of Dairy Products Consumption on Health: Benefits and Beliefs-A Commentary from the Belgian Bone Club and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases. *Calcif Tissue Int* 2016; **98**: 1-17 [PMID: 26445771]

44 **Seeman E**. Evidence that calcium supplements reduce fracture risk is lacking. *Clin J Am Soc Nephrol* 2010; **5** Suppl 1: S3-11 [PMID: 20089500 DOI: 10.2215/cjn.06160809]

45 **Warensjö E**, Byberg L, Melhus H, Gedeborg R, Mallmin H, Wolk A, Michaëlsson K. Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. *BMJ* 2011; **342**: d1473 [PMID: 21610048 DOI: 10.1136/bmj.d1473]

46 **Lewis JR**, Zhu K, Thompson PL, Prince RL. The effects of 3 years of calcium supplementation on common carotid artery intimal medial thickness and carotid atherosclerosis in older women: an ancillary study of the CAIFOS randomized controlled trial. *J Bone Miner Res* 2014; **29**: 534-541 [PMID: 24155106 DOI: 10.1002/jbmr.2117]

47 **Chrysant SG**, Chrysant GS. Controversy regarding the association of high calcium intake and increased risk for cardiovascular disease. *J Clin Hypertens* (Greenwich) 2014; **16**: 545-550 [PMID: 24890035 DOI: 10.1111/jch.12347]

48 **van der Velde RY**, Brouwers JR, Geusens PP, Lems WF, van den Bergh JP. Calcium and vitamin D supplementation: state of the art for daily practice. *Food Nutr Res* 2014; **58** [PMID: 25147494 DOI: 10.3402/fnr.v58.21796]

49 **Khan B**, Nowson CA, Daly RM, English DR, Hodge AM, Giles GG, Ebeling PR. Higher Dietary Calcium Intakes Are Associated With Reduced Risks of Fractures, Cardiovascular Events, and Mortality: A Prospective Cohort Study of Older Men and Women. *J Bone Miner Res* 2015; **30**: 1758-1766 [PMID: 25828852 DOI: 10.1002/jbmr.2515]

50 **Kanis JA**, Oden A, Johnell O, Johansson H, De Laet C, Brown J, Burckhardt P, Cooper C, Christiansen C, Cummings S, Eisman JA, Fujiwara S, Glüer C, Goltzman D, Hans D, Krieg MA, La Croix A, McCloskey E, Mellstrom D, Melton LJ, Pols H, Reeve J, Sanders K, Schott AM, Silman A, Torgerson D, van Staa T, Watts NB, Yoshimura N. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007; **18**: 1033-1046 [PMID: 17323110 DOI: 10.1007/s00198-007-0343-y]

51 **Bainbridge NJ**, Davie MW, Haddaway MJ. Bone loss after stroke over 52 weeks at os calcis: influence of sex, mobility and relation to bone density at other sites. *Age Ageing* 2006; **35**: 127-132 [PMID: 16495292 DOI: 10.1093/ageing/afj045]

52 **Tinetti ME**, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities. *Am J Med* 1986; **80**: 429-434 [PMID: 3953620]

53 **Maki BE**, Holliday PJ, Topper AK. A prospective study of postural balance and risk of falling in an ambulatory and independent elderly population. *J Gerontol* 1994; **49**: M72-M84 [PMID: 8126355]

54 **Mancini M**, Horak FB. The relevance of clinical balance assessment tools to differentiate balance deficits. *Eur J Phys Rehabil Med* 2010; **46**: 239-248 [PMID: 20485226]

55 **Ng SS**, Hui-Chan CW. The timed up & amp; go test: its reliability and association with lower-limb impairments and locomotor capacities in people with chronic stroke. *Arch Phys Med Rehabil* 2005; **86**: 1641-1647 [PMID: 16084820 DOI: 10.1016/j.apmr.2005.01.011]

56 **Fisher A**, Srikusalanukul W, Davis M, Smith P. Poststroke hip fracture: prevalence, clinical characteristics, mineral-bone metabolism, outcomes, and gaps in prevention. *Stroke Res Treat* 2013; **2013**: 641943 [PMID: 24187647 DOI: 10.1155/2013/641943]

57 **Body JJ**, Bergmann P, Boonen S, Devogelaer JP, Gielen E, Goemaere S, Kaufman JM, Rozenberg S, Reginster JY. Extraskeletal benefits and risks of calcium, vitamin D and anti-osteoporosis medications. *Osteoporos Int* 2012; **23** Suppl 1: S1-23 [PMID: 22311111 DOI: 10.1007/s00198-011-1891-8]

58 **Pilz S**, Tomaschitz A, Drechsler C, Zittermann A, Dekker JM, März W. Vitamin D supplementation: a promising approach for the prevention and treatment of strokes. *Curr Drug Targets* 2011; **12**: 88-96 [PMID: 20795935]

59 **Reid IR**, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet* 2014; **383**: 146-155 [PMID: 24119980 DOI: 10.1016/s0140-6736(13)61647-5]

60 **Lazzari AA**, Dussault PM, Thakore-James M, Gagnon D, Baker E, Davis SA, Houranieh AM. Prevention of bone loss and vertebral fractures in patients with chronic epilepsy--antiepileptic drug and osteoporosis prevention trial. *Epilepsia* 2013; **54**: 1997-2004 [PMID:

24010637 DOI: 10.1111/epi.12351]
61 **Luukinen H**, Käkönen SM, Pettersson K, Koski K, Laippala P, Lövgren T, Kivelä SL, Väänänen HK. Strong prediction of fractures among older adults by the ratio of carboxylated to total serum osteocalcin. *J Bone Miner Res* 2000; **15**: 2473-2478 [PMID: 11127212 DOI: 10.1359/jbmr.2000.15.12.2473]
62 **Maeno Y**, Inaba M, Okuno S, Yamakawa T, Ishimura E, Nishizawa Y. Serum concentrations of cross-linked N-telopeptides of type I collagen: new marker for bone resorption in hemodialysis patients. *Clin Chem* 2005; **51**: 2312-2317 [PMID: 16223890 DOI: 10.1373/clinchem.2005.051524]
63 **Kanis JA**. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos Int* 1994; **4**: 368-381 [PMID: 7696835 DOI: 10.1007/BF01622200]
64 **Ramnemark A**, Nyberg L, Lorentzon R, Olsson T, Gustafson Y. Hemiosteoporosis after severe stroke, independent of changes in body composition and weight. *Stroke* 1999; **30**: 755-760 [PMID: 10187874 DOI: 10.1161/01.STR.30.4.755]
65 **Imai Y**, Youn MY, Kondoh S, Nakamura T, Kouzmenko A, Matsumoto T, Takada I, Takaoka K, Kato S. Estrogens maintain bone mass by regulating expression of genes controlling function and life span in mature osteoclasts. *Ann N Y Acad Sci* 2009; **1173** Suppl 1: E31-E39 [PMID: 19751412 DOI: 10.1111/j.1749-6632.2009.04954.x]
66 **Riek AE**, Towler DA. The pharmacological management of osteoporosis. *Mo Med* 2011; **108**: 118-123 [PMID: 21568234]
67 **Green J**, Czanner G, Reeves G, Watson J, Wise L, Beral V. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. *BMJ* 2010; **341**: c4444 [PMID: 20813820 DOI: 10.1136/bmj.c4444]
68 **Drake MT**, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. *Mayo Clin Proc* 2008; **83**: 1032-1045 [PMID: 18775204 DOI: 10.4065/83.9.1032]
69 **Vasikaran SD**. Association of low-energy femoral fractures with prolonged bisphosphonate use: a case--control study. *Osteoporos Int* 2009; **20**: 1457-1458 [PMID: 19436933 DOI: 10.1007/s00198-009-0955-5]
70 **Kawai M**, Mödder UI, Khosla S, Rosen CJ. Emerging therapeutic opportunities for skeletal restoration. *Nat Rev Drug Discov* 2011; **10**: 141-156 [PMID: 21283108 DOI: 10.1038/nrd3299]
71 **Ascott-Evans BH**, Guanabens N, Kivinen S, Stuckey BG, Magaril CH, Vandormael K, Stych B, Melton ME. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. *Arch Intern Med* 2003; **163**: 789-794 [PMID: 12695269 DOI: 10.1001/archinte.163.7.789]
72 **Orwoll ES**, Scheele WH, Paul S, Adami S, Syversen U, Diez-Perez A, Kaufman JM, Clancy AD, Gaich GA. The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003; **18**: 9-17 [PMID: 12510800 DOI: 10.1359/jbmr.2003.18.1.9]
73 **Hodsman AB**, Bauer DC, Dempster DW, Dian L, Hanley DA, Harris ST, Kendler DL, McClung MR, Miller PD, Olszynski WP, Orwoll E, Yuen CK. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. *Endocr Rev* 2005; **26**: 688-703 [PMID: 15769903 DOI: 10.1210/er.2004-0006]

P- Reviewer: Hamet P, Ohishi T **S- Editor**: Kong JX **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com