Archives of Biochemistry and Biophysics 503 (2010) 153–159

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

Review

The complex mutual connection between stroke and bone health

Alireza Moayyeri [a,*], Yasir A. Alrawi [b], Phyo K. Myint [a,b,c]

[a] Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge, UK
[b] Department of Medicine for the Elderly, Norfolk and Norwich University Hospital, Norwich, UK
[c] Health and Social Sciences Research Institute, Faculty of Health, School of Medicine, Health Policy and Practice, University of East Anglia, Norwich, UK

ARTICLE INFO

Article history:
Available online 25 June 2010

Keywords:
Stroke
Osteoporosis
Hip fracture
Cardiovascular risk
Bisphosphonates
Physical activity
Falls
Ageing

ABSTRACT

Both stroke and osteoporosis are prevalent conditions among the elderly. With increasing life expectancy across the world, despite better preventative measures, the incidence of both conditions is set to rise in the ageing populations. Alongside with sharing several common risk factors, the current evidence suggests that these conditions are risk factors for each other albeit more clear support for the effects of stroke on bone health. In this article, we present aetiopathophysiology of these two conditions and the current evidence of impact on each other particularly the impact of stroke on bone health. We also provide suggestions for improving bone health in people living with stroke based on the currently available evidence.

Epidemiology and risk factors of stroke

The World Health Organisation (WHO)[1] defines stroke as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or longer, or leading to death, with no apparent cause other than of vascular origin' [1]. The clinical features of stroke could be any combination of locomotor, sensory, cognition, memory, visual and spatial orientation, vision, auditory, taste, and psychology (emotion). Stroke is classified pathophysiologically into two main types: ischaemic or haemorrhagic stroke. Prognosis following both forms of stroke varies widely and depends essentially on the extent of stroke, pre-morbid status and post-stroke complications [2].

The estimated number of new strokes each year is about 150,000 in the UK and 750,000 in the United States [3,4]. More than 900,000 people in England are disabled after stroke and half of these are dependent on other people with everyday activities [5]. In fact, stroke is a global health problem that is associated with high mortality and long-term disability [6]. There is a large variation in stroke mortality and burden worldwide [7]. National income is a strong predictor of stroke mortality with a 3.5-fold increase in lower income countries compared to middle-income ones [7]. In Western countries death from stroke has steadily declined in the past decades [8]. A recent review of large population-based studies showed that the age-adjusted incidence of stroke per 100,000 person-years ranges from 73 to 155 in the UK, 88–113 in the US, 153–375 in Japan, 48–151 in India and 100–367 in Finland [9]. Stroke is associated with significant economic burden; in the UK settings, for instance, the National Audit Office estimated the cost of caring for stroke to be approximately £7 billion per annum [5]. More recently it has been estimated to cost about £8.9 billion per year for the UK economy [10].

Recognised risk factors for stroke include age, hypertension, smoking, alcohol intake, diabetes, cardiovascular disease and atrial fibrillation [11,12]. Stroke incidence rises sharply with age as 95% of strokes occur in people aged 45 and more, and two-thirds of strokes occur in those over the age of 65 [13]. Current demographic trends project an increase in absolute numbers of strokes in the future. In contrast to coronary heart disease, almost half of strokes occur in women [13]. While hypertension and smoking as a risk factor for stroke are more established [14,15], the role of diabetes on stroke risk is somewhat conflicting [16]. More recent epidemiological evidence, for instance, suggests that optimum control of blood glucose for prevention of ischaemic and haemorrhagic stroke is not only an important issue for diabetics but also for the overall population [17]. It should be noted, however, that cardiovascular risk factors poorly predict stroke mortality and burden at the

* Corresponding author. Address: Department of Public Health and Primary Care, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, UK. Fax: +44 1223 740177.
E-mail addresses: am700@cam.ac.uk (A. Moayyeri), YASIR.AL-RAWI@nnuh.nhs.uk (Y.A. Alrawi), Phyo.K.Myint@uea.ac.uk (P.K. Myint).

[1] *Abbreviations used:* WHO, World Health Organisation; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; pQCT, peripheral quantitative computed tomography; 25-OHD, 25-hydroxyvitamin D; BMU, Bone Multi-cellular Unit; CIZ, Cas-interacting zinc finger; PTH, parathyroid hormone; BMP2, bone morphogenetic protein-2; RCTs, randomised controlled trials; HRT, Hormone replacement therapy; WHI, Women's Health Initiative.

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doi:10.1016/j.abb.2010.06.023

population level especially among low-income countries [7] and there are more genetic or environmental risk factors to be identified in future studies.

Common risk factors for stroke and osteoporosis

Although stroke presentation is neurological due to neuronal death, it is mainly caused by cardiovascular risk factors as described above. Many of these risk factors are common to other metabolic diseases including osteoporosis. Women with low bone mineral density are known to be at increased risk of stroke [18]. Moreover, NHANES III study showed that cardiovascular risk assessment using conventional cardiovascular risk factors can predict bone mineral density (BMD) among women [19]. Hypertension, which is a major preventable risk factor for stroke, has recently been suggested to be a risk factor for fracture [20]. A potential mechanism for this observation is that hypertensive subjects with high salt intake are prone to greater bone loss due to increased urinary calcium excretion [21]. The gene which encodes for the thiazide-sensitive sodium-chloride cotransporter (NCCT) represents a possible link between hypertension and osteoporosis. Recent observational clinical studies also support the benefit of several classes of anti-hypertensive drugs in reducing fracture risk or improving bone metabolism [21,22]. Use of these drugs for prevention of osteoporotic fractures, however, is still awaiting more evidence from randomised trials. There are other established risk behaviours (e.g., smoking and alcohol intake [11,12,23]) and suggested risk factors (e.g., obesity and low physical activity [24–27]) that increase the risk of both stroke and osteoporosis. High prevalence of these risk factors in the elderly population leads to high prevalence of both conditions and clinicians taking care of patients with one condition should be aware of the other and consider preventive measures for that [28].

Stroke and bone density

Loss of areal BMD as assessed by dual-energy X-ray absorptiometry (DXA) is a common complication of stroke [29,30]. Other methods such as peripheral quantitative computed tomography (pQCT) have also shown a reduction of cortical thickness of bones due to stroke immobility [31]. Osteoporosis after stroke differs from age-related osteoporosis or bone loss secondary to endocrine diseases, nutritional disorders and drug-related factors, since it is more evident on the affected hemiplegic side (sometimes termed as *hemi-osteoporosis*) and correlates with the degree of paralysis [30]. The hemiplegic upper limb and proximal femur appear to be the most vulnerable sites for localised bone loss following stroke [29,30,32]. In comparison, the paretic upper limb tends to lose more bone than the lower limb [30,33]. This is in contrary to the bone loss seen in patients with spinal cord injury, where loss is more systemic but focussed on the lower limbs [34]. During the first year after stroke, bone loss in the hemiplegic arm in some patients is equivalent to more than 20 years of bone loss in healthy individuals of comparable age [29]. Different factors can be attributed to the change in BMD depending on the time-frame following the stroke. For instance, in one study determinants of BMD in the hemiplegic hand were age, severity of hemiplegia, duration of paresis, serum calcium concentration and 25-hydroxyvitamin D (25-OHD) levels during the first year after stroke; determinants in the second year were only severity of hemiplegia and 25-OHD levels [35]. There is, however, a paucity of studies on long-term (>12 months) effects of stroke on bone loss [30]. It should be noted that use of some bone measurement techniques such as DXA and pQCT is limited in many stroke patients due to limb tremor or spasticity that prevents proper positioning of patients.

Stroke and immobility

A number of potential mechanisms contribute to bone loss after stroke and immobility is one of the major factors implicated in this process. BMD studies on lower and upper limbs have consistently shown a reduction in bone mass on the immobile side more than the mobile side. The reason for this is not totally clear, but the association between immobility and bone loss has been known for a long time. In a key study published in 1984 by Schneider and McDonald, 90 healthy young men were subjected to continuous bed-rest for 5–36 weeks [36]. Both serum and urinary calcium rose quickly after immobility and plateaued by the sixth week for several weeks before coming down to a stable level that was above ambulatory baseline. This occurred even though the volunteers received vitamin D supplements throughout the study. The researchers found that calcium balance became negative after two weeks and by the end of the first month of immobility 200 mg of calcium per day was lost. The loss of calcium continued at this rate for at least 36 weeks, with a calcaneal mineral mass loss of 5% each month. Artificial attempts at halting this loss with mechanical and biochemical means, including a bisphosphonate, were unsuccessful [36]. How immobility causes this change in bone is still unclear; but the mechanism of action is considered to be similar in stroke patients. A number of factors including muscle strength, muscle atrophy, degree of motor recovery, cardiovascular fitness, ability to perform functional activities, walking ability, weight bearing ability and amount of skeletal loading have been found to be associated with loss of bone mass on the paretic side in stroke [37]. Some studies have shown that there is an actual increase in BMD in the non-paretic side, which may be a result of increased compensatory physical activity in the non-affected side and perhaps a redistribution of bone minerals from the paretic extremities [29,38].

Stroke and bone remodelling

It has been suggested that the bone remodelling balance at the Bone Multi-cellular Unit (BMU) is affected especially in the initial period post-stroke [39,40]. Prospective studies examining biochemical markers of bone turnover in hemiplegic patients suggest an early (within 7 days) increase in bone resorption after stroke [41]. Increased bone resorption is observed throughout the first year post-stroke but declines to normal or near-normal level by the end of the first year [42]. Factors such as the duration of hemiplegia, degree of functional recovery, reduced vitamin D status and the use of anticoagulants may determine the rate and extent of bone loss after stroke [41]. Research is still ongoing to identify the cellular mechanisms that underlie immobility-induced bone loss. Rubin and Lanyon [43] suggested that adaptive bone remodelling is extremely sensitive to alterations in both the magnitude and distribution of the strain generated within the bone tissue and that each region of bone can accept a particular amount and pattern of intermittent strain as normal. Any change to this amount and pattern will stimulate changes in the BMU remodelling balance, resulting in adaptive increases or decreases in bone mass [43].

One novel molecule that has been identified as contributing to immobility-induced osteoporosis is the Cas-interacting zinc finger (CIZ) protein, where Cas is protein p130^{cas} which is a docking protein that localises to focal adhesion plaques. Once this molecule is released from the focal adhesion plaque, it transfers into nuclear compartments, binds to consensus DNA sequences, and activates promoters of the genes encoding enzymes that degrade matrix proteins [44]. Hino et al. propose that this protein is an inhibitory factor on osteoblast activity and have shown, using CIZ-deficient