CHAPTER II

LITERATURE REVIEW

The search strategy was performed by searching PubMed database through December 2008 to find articles that studied effect of antiepileptic drugs (AEDs) on bone mineral density (BMD) in ambulatory epileptic patients, BMD reference in Thai ethnic people, daily calcium intake in Thai population, risk factors of osteoporosis, BMD measurement, bone turnover markers, pathophysiology of AED induced bone loss, prevention and management of osteoporosis. Book sections from standard text books, i.e. Epilepsy: a comprehensive textbook and Harrison's principle of internal medicine, were also reviewed.

Recently, several new and efficacious AED have been developed and widely distributed. Many of these new-generation AEDs are available in Thailand, such as lamotrigine, gabapentin, topiramate, oxcarbazepine, levetiracetam, etc. AED are classified in relation to metabolism of liver cytochrome P 450 enzyme into three groups that is cytochrome P 450 enzyme system inducing, inhibiting and neutralizing AEDs. Although there is sparse evidence of adverse effects on BMD of recent generation AED, all liver cytochrome P 450 enzyme system inducing, inhibiting and neutralizing AEDs can affect bone turnover and BMD, even when they are used for only 6-12 months (14-16).

Sato et al. did a cross-sectional survey in ambulatory Japanese epileptic patients, aged 20-50 years, without known factors affecting BMD, treated with monotherapy sodium valproate or phenytoin one year or longer (14). They found that valproate and phenytoin treated groups had 14% and 13% lower BMD than age-and sex-matched healthy controls respectively. In valproate group, 9 from total 40 patients (23%) were osteoporotic and 15 patients (37%) were osteopenic. In phenytoin group, 5 from total 40 patients (12%) were osteoporotic and 19 patients (48%) were osteopenic. They also found that female epileptic patients had lower BMD than male epileptic

patients in both groups, i.e. female 16% VS male 12% in valproate group; female 15% VS male 12% in phenytoin group. Likewise, female epileptic patients were found osteopenic and osteoporotic more than male patients in both valproate and phenytoin group. However, they measured BMD at the right second metacarpal bone that is not common osteoporotic fracture sites. In valproate group, serum calcium, BGP and ICTP were higher whereas serum parathyroid hormone, 1,25-$(OH)_2D$ and 25-OHD were lower than in control group. In phenytoin group, serum parathyroid hormone, BGP, ICTP and 1,25-$(OH)_2D$ were higher whereas serum calcium and 25-OHD were lower than in control group.

In a cross-sectional survey by Boluk et.al. in 50 ambulatory Turkish epileptic patients, aged 20-40 years, without factors affecting BMD, receiving monotherapy valproate for one year or longer, had BMD 9% lower than 60 age-and sex-match healthy controls (15). Epileptic patients were found osteopenia 52% and osteoporosis 16% whereas 22% and 0 in control group respectively. They also found 4.9% and 4.61% further bone loss at lumbar spine and femur in epileptic patients 6 months after first BMD measurement. Serum parathyroid hormone, alkaline phosphorus and phosphorus level in patient group were found significant higher than in control group whereas serum calcium level was similar.

A cross-sectional survey by Farhat et al. in Beirut was carried out in 71 ambulatory epileptic patients, aged 5-64 years, without known factors affecting BMD, receiving AED(s) for at least 6 months (16). They found that 59% of 42 adult patients had osteopenia. Subgroup analysis by sex (22 women and 20 men) was similar. However, they compared BMD with American BMD database rather than their own national database. They also included post menopausal and older than 50-year patients that were major factors of decreased BMD. In this study, 25-OHD was found deficiency in 34% and insufficiency in 43% of adult epileptic patients comparing to standard level.

Phabphal et.al. did a cross sectional survey in 130 ambulatory Thai epileptic patients, aged 15-50 years, without other chronic medical illness other than epilepsy, taking AED(s) more than 6 months, without hysterectomy, oophorectomy or history of

amenorrhea and not taking other drugs (17). They reported that 63 were male and 67 were female with mean age (± SD) 31.9 ± 9.7 years. Seventy nine were receiving monotherapy whereas 51 were taking polytherapy. 71 were taking enzyme-inducers only, 28 taking non-enzyme-inducers only and 31 were taking a combination of the two. Mean duration of AED used was 6.63 ± 4.63 years (range 0.5-25 years). Mean BMD of epileptic patients taking AED more than 6 months was lower than that of the sex and age-adjusted reference with mean BMD at femoral neck in Z-score – 0.15 ± 1.17 and that at lumbar spine – 0.56 ± 1.03. Thirty one patients had osteopenia at the spine and 30 patients at the femoral neck. Three patients had osteoporosis of the spine and 1 patient of the femoral neck. There was no significant correlation between age, sex, body mass index, duration of treatment and type of AED with BMD at the femur and spine.

A survey in rural Thai adults, 181 men and 255 women, living in Khon Kaen Province (northeastern) of BMD at distal radius, femoral neck and lumbar spine classified by sex and age group were shown in table 1 (10). It also revealed that Thai adults had decreased BMD with advancing age. The rate of decline is greater in women particularly after 60 years old. BMD in women was also less than that in men at distal radius and femoral neck at all age groups.

Table 1 Mean and standard deviation of bone mineral density (BMD) by sex and age group in rural Thai adults in Khon Kaen

BMD	Sex	Age group (year)					
(g/cm^2)		20-29	30-39	40-49	50-59	60-69	>70
Distal	M	0.46±0.06	0.43±0.05	0.42±0.04	0.40±0.05	0.36±0.06	0.35±0.07
radius	F	0.36±0.04	0.35±0.05	0.34±0.05	0.30±0.05	0.25±0.05	0.21±0.05
Femoral	M	1.18±0.14	1.02±0.13	0.96±0.11	0.94±0.16	0.84±0.11	0.82±0.14
neck	F	1.01±0.12	1.05±0.14	0.95±0.12	0.87±0.14	0.73±0.15	0.63±0.10
Lumbar	M	1.24±0.11	1.11±0.14	1.06±0.14	1.09±0.16	1.05±0.12	1.10±0.22
spine	F	1.15±0.09	1.17±0.13	1.11±0.16	1.01±0.21	0.85±0.15	0.76±0.17

Nititham et al. (13) analysed 5 consecutive daily diets of 10 male and 10 female volunteers in rural area (Ubon Ratchathani) and those in urban area (Bangkok) by using duplicate portion technique. The diets were blended, aliquoted, mixed, freeze-dried and homogenized then analysed for calcium by atomic absorption spectrophotometer. It was reported that calcium intakes were 524.6 ± 259.9, 379.9 ± 111.4 for males and females in Ubon Ratchathani and 366.5 ± 150.5, 286.7 ± 68.7 mg/d for males and females in Bangkok. The daily intakes of calcium in these rural and urban areas were low compared to Thai RDA 800 mg/d.

Multiple factors contribute to low BMD and osteoporotic fractures (11, 18). These factors can be classified into two groups that are modifiable and non-modifiable factors. Modifiable factors contributing to reduced BMD are low calcium intake, low vitamin D intake/low sunlight exposture, sedentary lifestyle, glucocorticoid therapy, surgical or drug induced hypogonadism, low body weight, smoking, stress/depression. Non-modifiable factors contributing to reduced BMD are advanced age, female sex, White/Asian race, family history of osteoporosis, family history of hip fracture, lactose intolerance, metabolic disorders affecting skeleton, certain malignancies such as myeloma, lymphoma. Common causes of secondary osteoporosis are some endocrine disorders, nutritional deficiency, chronic drug therapy and miscellaneous (18). Endocrine disorders causing secondary osteoporosis are hypogonadism, hyperthyroidism, anorexia nervosa, type 1 diabetes mellitus. Nutritional deficiency includes malabsorption syndrome, vitamin D deficiency/resistance, calcium deficiency, alcoholism. Chronic drug therapy includes glucocorticoids, thyroxine, anticonvulsants, loop diuretics, GnRH agonists, aromatase inhibitors. Miscellaneous factors leading to secondary osteoporosis are hypercalciuria, COPDE, rheumatoid arthritis, organ transplantation. Risk factors for osteoporotic fractures in postmenopausal women are classified by Canadian task force on preventive health care into major and minor factors (11). Major risk factors are age $\geq$ 65 years, vertebral compression fracture, fragility fracture after age 40 years, family history of osteoporotic fracture especially hip fracture in mother, systemic glucocorticoid therapy $\geq$ 3 months, malabsorption syndrome,

primary hyperparathyroidism, propensity to fall, appearance of osteopenia on radiograph, and hypogonadism and early menopause (<45 years). Minor risk factors are rheumatoid arthritis, history of clinical hyperthyroidism, long term anticonvulsant therapy, weight loss > 10% of body weight at age 25 years, weight < 57 kg. smoking, excess alcohol intake, excess caffeine intake, low dietary calcium intake, long-term heparin therapy.

Bone is the dynamic tissue and undergoes remodeling, a continuous process of bone resorption and formation, throughout life (19, 20). Bone turnover continuously occur in discrete areas all over the skeleton by coordinated actions of osteoclasts in bone resorption and osteoblasts in bone formation. Bone is the metabolic reservoir of calcium, phosphorus, magnesium, sodium and other necessary ions. Bone, therefore, plays a central role in mineral homeostasis particularly ionized calcium that regulates many vital cell functions.

In bone formation, osteoblasts synthesize and secrete the organic matrix (soft bone) which is then mineralized with calcium and phosphorus (hard bone). Parathyroid hormone and 1,25-dihydroxyvitamin D activate osteoblast precursor to active osteoblast and also activate receptors expressed by osteoblasts to assure mineral homeostasis.

Bone resorption is mainly carried out by osteoclasts. Both parathyroid hormone and 1,25-dihydroxyvitamin D indirectly increase osteoclast number and activity, whereas estrogen indirectly decreases osteoclast number and activity. Calcitonin binds to osteoclast receptor and directly inhibit its function.

Bone turnover and bone mass are dependent on various factors affecting bone metabolism or homeostasis of calcium or phosphorus. These factors include serum level of 25 hydroxy-vitamin D (25[OH]D), 1,25 dihydroxy-vitamin D (1,25-$[OH]_2$D), total calcium, ionized calcium, exposure to sunlight, optimum physical activity, disorders or substances affecting bone metabolism or homeostasis of calcium or phosphorus, etc (20)]. Furthermore, genetics is probably one of important influencing factors on adverse effects of AEDs on bone turnover and BMD (21).

The products of osteoblast and osteoclast activity, bone markers, can assist in the diagnosis and management of bone diseases. Osteoblast activity, in bone formation, can be assessed by measuring serum bone-specific alkaline phosphatase, total osteocalcin (including the intact molecule and the large N-mid fragment) and the procollagen type I N-terminal propeptide (P1NP) which are the most sensitive and specific markers of bone formation. For osteoclast activity in bone resorption, it can be assessed by measurement of products of collagen degradation. Collagen molecules are covalently linked to each other in the extracellular matrix through the formation of hydroxypiridinium crosslinks. Serum level of these cross-linked peptides represent osteoclast activity. Among the various markers of bone resorption, measurements of the urinary excretion of N- and C-terminal cross-linked telopeptides) and of serum C-terminal cross-linked telopeptides (β-Cross Laps) are the most sensitive and specific (8, 22, 23).

Since the metabolism of vitamin D, one of important regulating factors of BMD, into inactive metabolites is mainly via liver cytochrome P 450 enzyme system, it was, therefore, believed that adverse effect of AED was caused by alteration of liver cytochrome P 450 enzyme system induced by AEDs (20). However, there is recent evidence that valproate, a liver cytochrome P 450 enzyme system inhibiting AED, can also cause increased bone turn over and decreased bone mass in adult patients with epilepsy (14, 15, 24, 25). Thus, the mechanism of AED on bone turnover and BMD is not simply only on metabolism of vitamin D but, in fact, is multi-factorial. Many mechanisms and hypotheses have been proposed including increased induction of hepatic cytochrome P 450 enzyme system, increased catabolism of vitamin D resulting in hypocalcemia and secondary hyperparathyroidism, direct effects of AED on bone cells, resistance to parathyroid hormone, calcitonin deficiency, impaired calcium absorption, etc (20).

Prevention and management of osteoporosis are composed of various options including adequate calcium and vitamin D intake, adequate exposure to sunlight, optimum weight-bearing activity, controlling disorders and substance affecting bone

metabolism or homeostasis of calcium or phosphorus and taking one of anti-resorptive agents such as bisphosphonate, calcitonin, estrogen, parathyroid hormone, etc (26). Anti-resorptive agents were recommended in guideline for post-menopausal osteoporosis management, however, there was no definite guideline for treatment of AED induced osteoporosis. Some of these options are expensive such as parathyroid hormone, bisphosphonate. Moreover, some carry serious side effects.

To prevent osteoporosis and to treat osteoporotic fracture in post menopausal women, the Canadian task force on preventive health care recommend screening postmenopausal women aged $\geq$ 65 years or aged > 60 years with fracture risk by dual energy x-ray absorptiometry to prevent fragility fractures (no or low trauma fracture) (grade B recommendation) (11). For women with osteoporosis, therapy with bisphosphonate, i.e. alendronate, risedronate or raloxifene is recommended to prevent osteoporotic fracture (grade A to B recommendation). For women with severe osteoporosis (osteoporosis plus at least 1 fragility fracture), alendronate, risedronate, parathyroid hormone (limited duration), raloxifene, etidronate and oral pamidronate therapy are recommended (grade A to B recommendation). If not tolerable, hormone replacement therapy or calcitonin can be used. For women with or without osteoporosis, lifestyle assessment is recommended (grade B recommendation), i.e. adequate intake of calcium (1,000 – 1,500 mg/d) and vitamin D (400 – 800 IU/d), exercise 3 times per week, for at least 20-30 min. each time, decrease caffeine intake to fewer than 4 cups of coffee a day, stop smoking.

To date, data on cost-benefit, cost effectiveness or health resource utility related to prevention and management of AED induced osteopenia-osteoporosis were not available. There was no consensus, recommendation or guideline on BMD check up strategy, prevention and management of AED induced bone loss. And also, there was no data in term of adverse effect on BMD from long-term AED therapy in Thai pre-menopausal epileptic patients available for the decision of prevention and intervention recommendation.