CHAPTER V

DISCUSSION

The present research was a study of long-term adverse effect of antiepileptic drug (AED) on bone mineral density (BMD) in Thai ethnic, pre-menopausal epileptic female patients receiving AED three years or more in comparison with age-matched healthy controls. Since human being can live longer, some will suffer from ostepenia-osteoporosis and some may finally have osteoporotic fracture. Therefore, there were growing concerns and studies on the negative effect of AED on BMD particularly in older or menopausal women (33, 34). It was the fact that age, sex, ethnic, body weight, socioeconomic status, physical activity and menopause were major risks of osteoporosis and older women suffered from osteoporotic fracture more than older men (21). Thus, this study explored the effect of AED on BMD only in women. Additionally, to exclude the strong effect of menopause, the study excluded post menopausal women with serum estradiol level lower than normal 5 pg/ml. Most studies compared BMD with the standard laboratory reference rather than healthy controls (14, 16, 17, 34). This study was designed to compare with healthy participants and to control several major factors affecting on BMD, i.e. ethnic, age, menopause, body mass index, socioeconomic status, physical activity, drugs and other disorders affecting on BMD. However, it was not able to recruit healthy subjects living in the same environment as patients. Instead, all controls were nurses and paramedics within the same economic status as patients. The study did not design to control daily calcium and vitamin D intake as well as sunlight exposure and exact amount of physical activity as it was intended to be a study for widely application. The study aimed to compare BMD at the three bone sites, i.e. lumbar 2-4; left femur neck, trochanter, total; and left radius UD, 33% for the reason that these bone areas were common osteoporotic fracture sites. Though, T-score was commonly used in literature. However, sometimes other researchers or applicants required BMD in term of g/cm^2 or Z-score, the study displayed and compared BMD in T-score, Z-score and g/cm^2 all together.

The majority of the included epileptic patients had pharmacologically resistant epilepsy. Their AEDs were adjusted and changed throughout the treatment duration. The type of AEDs (cytochrome P 450 inducer or non-inducer) and number of AEDs (monotherapy or polytherapy) were classified by the current AEDs that were taking continuously more than one year.

The study found that one patient and two healthy participants, who still had regular menstruation, had serum estradiol less than lower normal limit 5 pg/ml and were excluded as they were regarded as menopause. Thus, to be certain that any study recruited pre-menopausal women, it may necessary to have serum estradiol level tested as well.

The sample size in the study design was calculated with the expectation of 10% difference of BMD between patients and controls. It was 55 persons with the ratio of patients to controls = 1 : 1. The study was able to recruited 50 patients and 51 controls that nearly met the planned sample size and ratio.

There was no statistically significant difference between patients and controls in mean of age (p-value = 0.936), proportion of participant in each age range (p-value = 0.953) and mean of body mass index (p-value = 0.991). As a result, the included patients and controls were similar in their baseline characteristics.

Most of included patients that was 88% had localization-related epilepsy and only 4% had generalized epilepsy. The rest 8% had unclassified epilepsy. The AEDs duration was not normally distributed. Consequently, any statistic tests related to AEDs duration were applied with non-parametric tests.

For primary outcome, the study found that BMD measured at three bone sites were all normally distributed. Statistic tests related to BMD were applied with parametric methods. Comparison of BMD at three bone sites between patients and controls revealed that there was statistically significantly difference only at femur neck measurement (in T-score: p-value = 0.04, 95% CI 0.02 - 0.75) whereas BMD at lumbar 2-4, femur trochanter, femur total, radius UD and radius 33% were all not statistically significantly different. However, when it was analyzed and compared in term of normal BMD, osteopenia and osteoporosis. It showed that the proportion of osteopenia plus osteoporosis measured at lumbar 2-4 and femur neck was statistically significantly higher in the patient group with p = 0.014 and p < 0.001 respectively. In addition, the proportion of osteopenia plus osteoporosis measured at femur trochanter, femur total and radius 33 % were also higher, although, it was not statistically significant. The percentage of osteopenia plus osteoporosis in patient to control group at femur trochanter was 28 : 15.7, at femur total = 12 : 2, at radius33% = 12 : 3.9. The study result was in consistent with the previous studies (14-17, 24, 25, 34) that AEDs had a negative effect on BMD resulting osteopenia or osteoporosis. Interestingly, the study showed significant lower BMD in patients only at femur neck despite significantly higher proportion of osteopenia-osteoporosis at femur neck and lumbar 2-4. In addition, measurement at the rest areas also revealed that there was higher proportion of osteopenia plus osteoporosis in patient group though not statistically significant. This study results could be explained that the study expectation of 10% difference in BMD possibly was higher than reality. In fact, BMD in physically active pre-menopausal epileptic women possibly decreased very slightly over the time even though there was definitely a negative effect of AEDs. Probably, BMD was not a sensitive outcome for comparison. The proportion of osteopenia and osteoporosis may be more sensitive in evaluation and would be a better outcome analysis.

For the first secondary outcome, the comparison of the effect on BMD between monotherapy and polytherapy AEDs, it was found that mean of BMD in polytherapy AEDs was lower at lumbar 2-4, femur trochanter, femur total and radius UD, though, they were all not statistical significant. Interestingly, mean BMD at femur neck and radius 33% was, in contrast, lower in monotherapy group. Theoretically, it was expected that polytherapy would have more negative effect on BMD. However, the study result did not support the expectation. It was possibly because the number of patients was too small to demonstrate the stronger effect on BMD of polytherapy AEDs.

Anothor secondary outcome, the analysis of effect of inducer and non-inducer AEDs revealed that mean of BMD of patients receiving inducer AEDs was lower than that in non-inducer group at nearly all bone sites except radius 33%. Although they were all not statistically significant, there was a trend of more negative effect of inducer AEDs on BMD. This tendency could possibly be statistically significant if sample size was adequately large. Median of BMD was not in agreement with mean of BMD as femur trochanter, femur total and radius UD was lower while L 2-4, femur neck and radius 33% was higher in inducer AEDs group. This phenomenon could be due to the small sample size and asymmetrical data distribution.

The last secondary outcome, effect of epilepsy type on BMD, could not evaluate, since there were a very small proportion of generalized epilepsy type.

Conclusion

The study of long-term AED effect on bone density in Thai pre-menopausal epileptic patients comparing with age-matched healthy controls proved that AED had an adverse effect on bone density resulting in decreased bone mass after continuously receiving three years or more in Thai ethnic pre-menopausal epileptic female patients who had no other disorders or drugs with bone density decreasing effect. The study could not draw a conclusion on the effect on bone density of number of AED, type of AED, duration of AED receiving and type of epilepsy.