CHAPTER IV

RESULTS

4.1 Basic Characteristics of Patients and Baseline Data

Fifty seven patients were eligible and invited to participate in the study. Seven patients were excluded with the following reasons: 2 patients having body mass index less than lower normal limit 18.5 kg/m^2, 1 patient having hyperthyroidism, 1 patient having estradiol (estrogen) less than lower normal limit 5 pg/ml, 2 patients having urine red blood cell more than 5 cells/high power field, 1 patient with missing BMD measure. Finally, fifty patients were included and their data were analyzed and compared with healthy controls.

Sixty three healthy eligible premenopausal women within the same age range were invited to the study as the control group. One did not return to have the study tests. Twelve subjects were excluded due to the following reasons: two with estradiol lower than normal limit 5 pg/ml, one with total bilirubin more than upper limit, one with persistent microscopic hematuria, six with parathyroid hormone higher than normal limit and another one with ionized calcium lower than normal limit. Therefore, there were fifty one normal controls left for comparing with the included patients.

Ratio of included patients to controls was 50 : 51 that was about 1:1. Table 5 displayed age and body mass index (BMI) of the patient and control group. Mean age (± SD) of patients and controls were similar : 32.86 ± 7.58 vs 32.75 ± 6.70 years (p-value = 0.936). The percentage of patients to controls in age range 20-30 years was 38.0 : 39.2, age 31 – 40 years = 46.0 : 43.1 and age 41 – 50 years = 16.0 : 17.6. Comparison of proportion of participants in each age range between patient and control group was not statistically significant with p-value = 0.953. Mean BMI in patients was 23.44 ± 3.88 kg/cm^2 whereas that in controls was 23.43 ± 4.10 kg/cm^2. Mean of BMI between the two groups was not statistically significantly different (p-value = 0.991).

Proportion of epilepsy type (generalized, localization-related, unclassified) proportion of number of AED (monotherapy, polytherapy), proportion of AED type (inducer, non-inducer) as well as mean and median of AED duration were reported in table 6. Of the total of included epileptic patients, 88% had localization-related epilepsy, 4% had generalized epilepsy and the rest 8% had unclassified epilepsy. Figure 2 displayed distribution of AED duration that was not normally distributed.

Table 5 Comparison of age and body mass index (BMI)

Characteristics	Mean (SD) or Number (%)		p-value
	Control (n=51)	Patient (n=50)	
Age (yrs)	32.75 (6.70)	32.86 (7.58)	0.936
20-30	20 (39.2)	19 (38.0)	0.953
31-40	22 (43.1)	23 (46.0)	
41-50	9 (17.6)	8 (16.0)	
BMI (kg/m^2)	23.43 (4.10)	23.44 (3.88)	0.991

Table 6 Proportion of epilepsy type and AED number and type as well as AED duration

	Number (%)
Epilepsy type	
Generalized	2 (4%)
Localization-related	44 (88%)
Unclassified	4 (8%)
Number of AED	
Monotherapy	19 (38%)
Polytherapy	31 (62%)
AED type	
Inducer	42 (84%)
Non-inducer	8 (16%)
AED duration (month)	
Mean (SD)	188.6 (119.5)
Median	144
Min, Max	40, 444

Figure 2 Distribution of antiepileptic drug duration
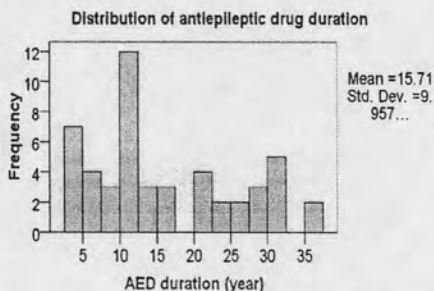
4.2 Outcomes

4.2.1 Primary Outcome

Bone mineral density (BMD) at three bone sites i.e. lumbar (L) 2-4, left femur (neck, trochanter, total) and left radius (radius UD, radius 33%) were reported by group (patients and controls) with T-score, Z-score and g/cm^2 in table 7. Figure 3-8 displayed distribution of BMD at three bone sites that were all normally distributed.

Comparison of BMD at three bone sites between patients and controls revealed that there was statistically significant difference only at femur neck measurement in T-score with p-value = 0.040, 95% CI 0.02 - 0.75 and in g/cm^2 with p-value = 0.042, 95% CI 0.00-0.09. However, if BMD at femur neck was compared in Z-score, it showed no statistically significant difference with p-value = 0.064, 95% CI -0.02 – 0.69.

Mean of BMD at L 2-4, femur trochanter, femur total and radius 33% in patients were lower than that in controls as they were shown in T-score, patients : controls as follows; L 2-4 = 0.26 ± 1.18 : 0.41 ± 0.91; femur trochanter = -0.39 ± 1.07 : -0.24 ± 0.72; femur total = 0.09 ± 1.04 : 0.24 ± 0.77 and radius 33% = -0.13 ± 0.70 : 0.09 ± 0.63. However, they were all not statistically significant. Analyses and comparison in Z-score and g/cm^2 were in the same direction.

Interestingly, radius UD was the only single site that mean of BMD in patients was higher than that in controls, i.e. in T-score = -0.54 ± 0.70 : -0.58 ± 1.04. However, it was not statistically significant.

Table 7 Comparison of bone mineral density at three bone sites between patients and controls

(a) T-score

| Bone site | Mean (SD) | | Mean difference (95% CI) | p-value |
	Control (n=51)	Patient (n=50)		
L2-4	0.41 (0.91)	0.26 (1.18)	0.15 (-0.27, 0.56)	0.481
Femur				
Neck	0.30 (0.86)	-0.08 (0.98)	0.38 (0.02, 0.75)	0.040
Trochanter	-0.24 (0.72)	-0.39 (1.07)	0.14 (-0.22, 0.51)	0.428
Total	0.24 (0.77)	0.09 (1.04)	0.15 (-0.22, 0.51)	0.428
Radius				
UD	-0.58 (1.04)	-0.54 (1.28)	-0.03 (-0.49, 0.43)	0.895
33%	-0.09 (0.63)	-0.13 (0.70)	0.04 (-0.22, 0.30)	0.764

(b) Z-score

| Bone site | Mean (SD) | | Mean difference (95% CI) | p-value |
	Control (n=51)	Patient (n=50)		
L2-4	0.00 (0.88)	-0.06 (1.13)	0.06 (-0.34, 0.46)	0.782
Femur				
Neck	0.20 (0.84)	-0.14 (0.95)	0.33 (-0.02, 0.69)	0.064
Trochanter	-0.44 (0.66)	-0.54 (1.00)	0.10 (-0.23, 0.44)	0.537
Total	0.09 (0.74)	-0.01 (0.99)	0.10 (-0.24, 0.45)	0.550
Radius				
UD	-0.56 (1.05)	-0.53 (1.27)	-0.03 (-0.49, 0.43)	0.888
33%	-0.08 (0.65)	-0.12 (0.70)	0.04 (-0.23, 0.31)	0.769

(c) g/cm^2

| Bone site | Mean (SD) | | Mean difference (95% CI) | p-value |
	Control (n=51)	Patient (n=50)		
L2-4	1.17 (0.11)	1.15 (0.14)	0.02 (-0.03, 0.07)	0.481
Femur				
Neck	0.94 (0.10)	0.89 (0.12)	0.04 (0.00, 0.09)	0.042
Trochanter	0.72 (0.08)	0.71 (0.12)	0.02 (-0.02, 0.06)	0.428
Total	0.96 (0.09)	0.95 (0.12)	0.02 (-0.03, 0.06)	0.425
Radius				
UD	0.423 (0.05)	0.424 (0.06)	-0.002 (-0.02, 0.02)	0.864
33%	0.841 (0.06)	0.839 (0.06)	0.003 (-0.02, 0.03)	0.775

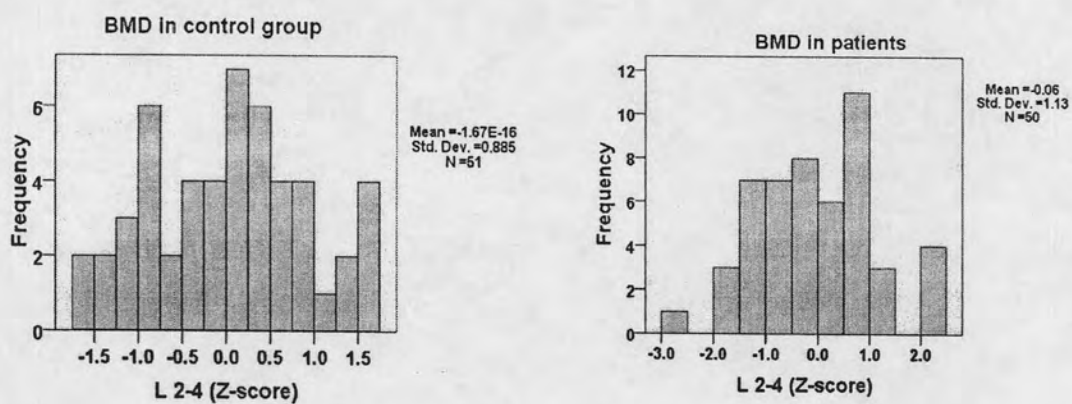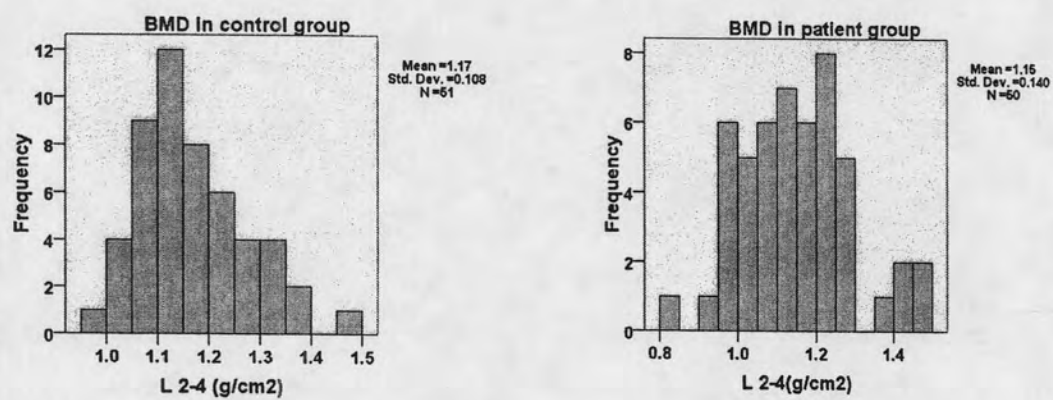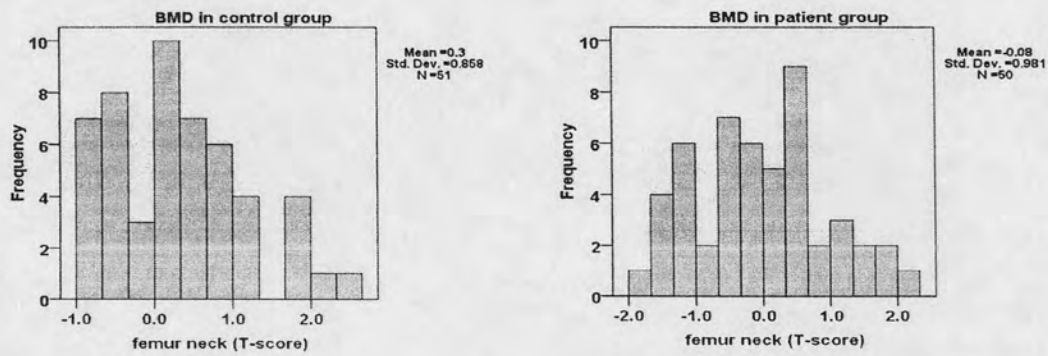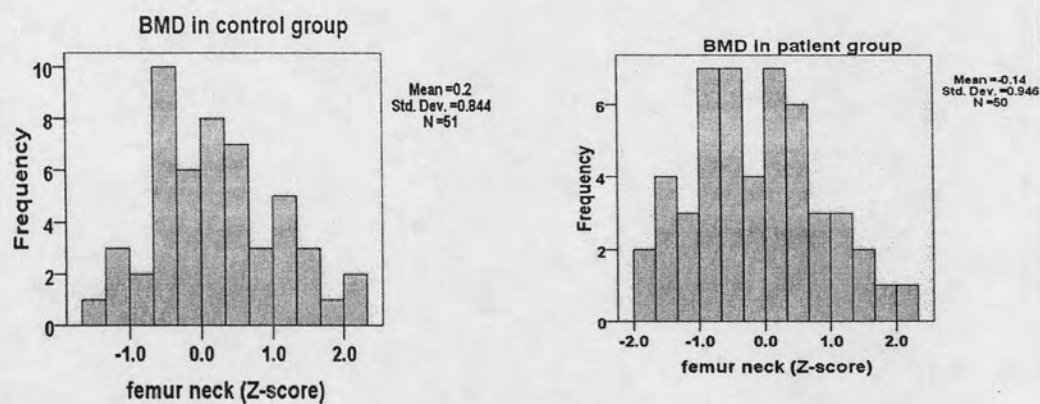Figure 3 Distribution of bone mineral density at L2-4

(a) T-score

BMD in control group

Mean =0.41
Std. Dev. =0.91...

Frequency axis, L 2-4 (T-score)

BMD in patient group

Mean =0.26
Std. Dev. =1. 175...

Frequency axis, L 2-4 (T-score)

(b) Z-score

BMD in control group

Mean =-1.67E-16
Std. Dev. =0.885
N =51

Frequency axis, L 2-4 (Z-score)

BMD in patients

Mean =-0.06
Std. Dev. =1.13
N =50

Frequency axis, L 2-4 (Z-score)

(c) g/cm^2

BMD in control group

Mean =1.17
Std. Dev. =0.108
N =51

Frequency axis, L 2-4 (g/cm2)

BMD in patient group

Mean =1.15
Std. Dev. =0.140
N =50

Frequency axis, L 2-4(g/cm2)

Figure 4 Distribution of bone mineral density at femur neck

(a) T-score

(b) Z-score

(c) g/cm^2
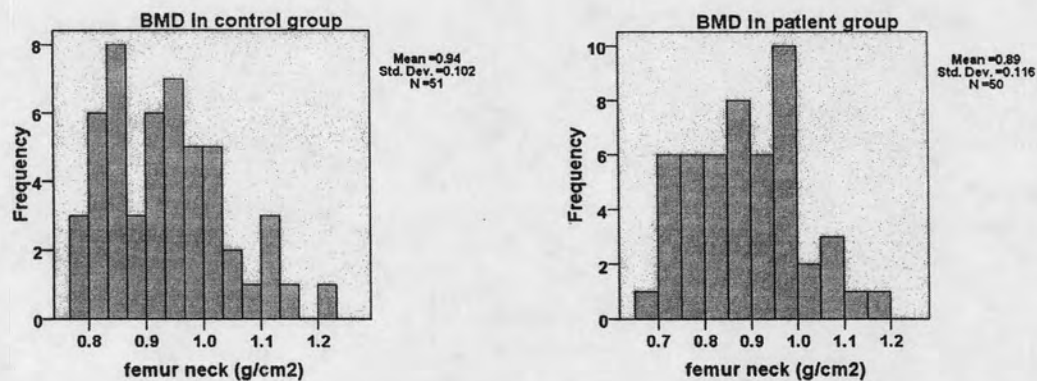
Figure 5 Distribution of bone mineral density at femur trochanter

(a) T-score
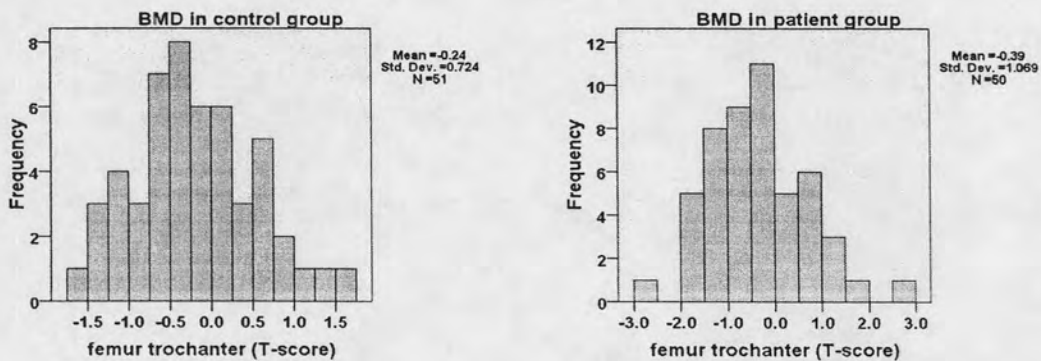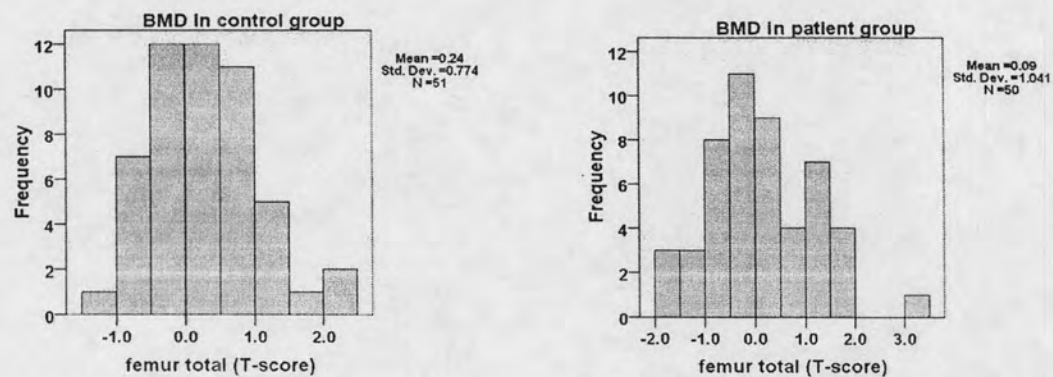

(b) Z-score
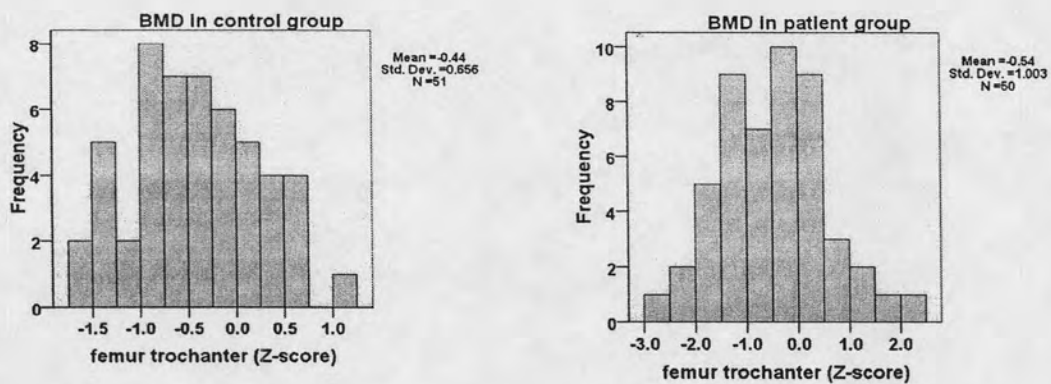
(d) g/cm^2
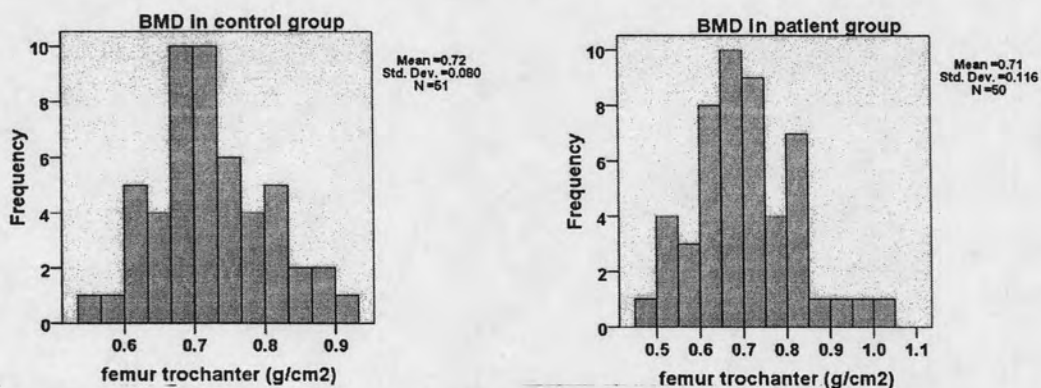
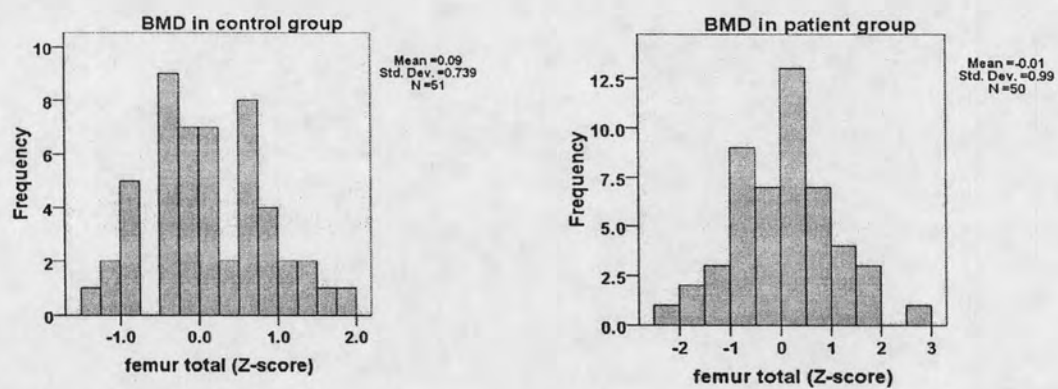Figure 6 Distribution of bone mineral density at femur total
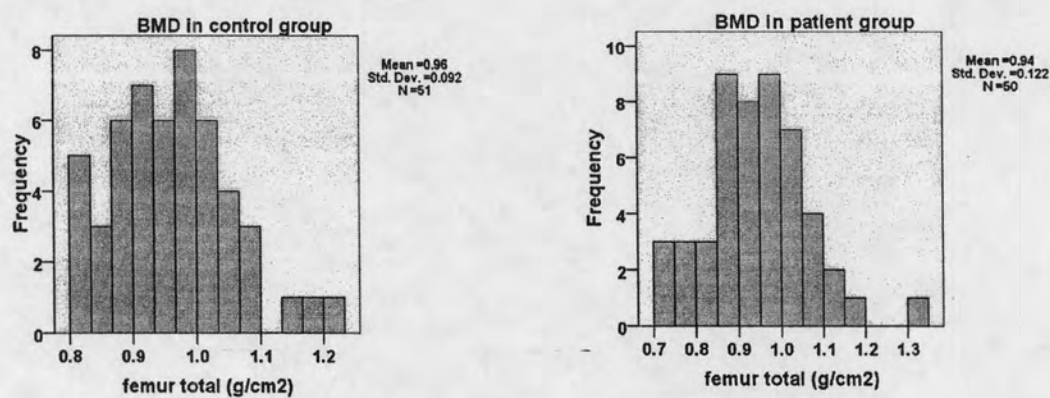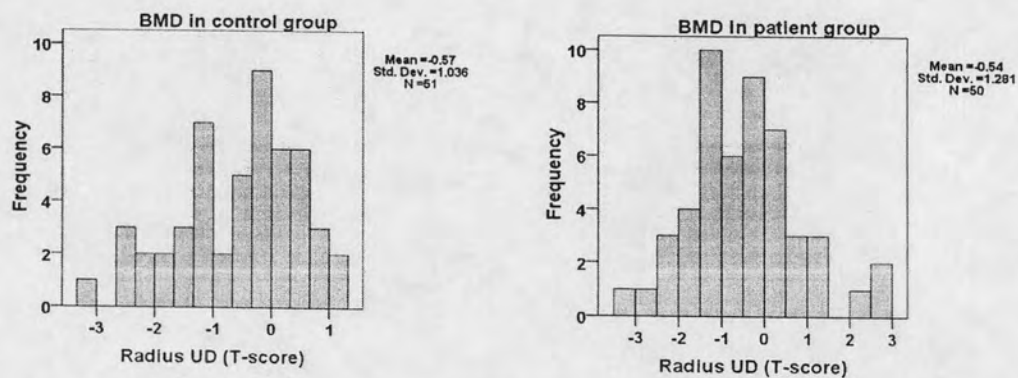
(a) T-score

(b) Z-score

(c) g/cm^2

Figure 7 Distribution of bone mineral density at radius UD

(a) T-score

(b) Z-score
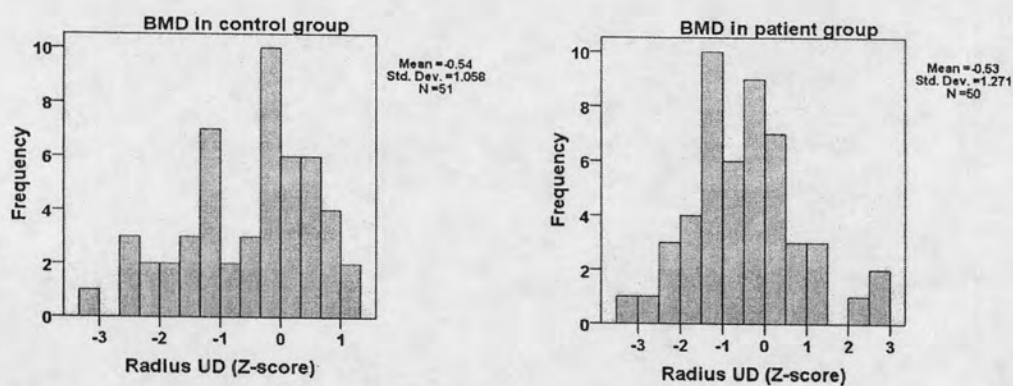
(c) g/cm^2

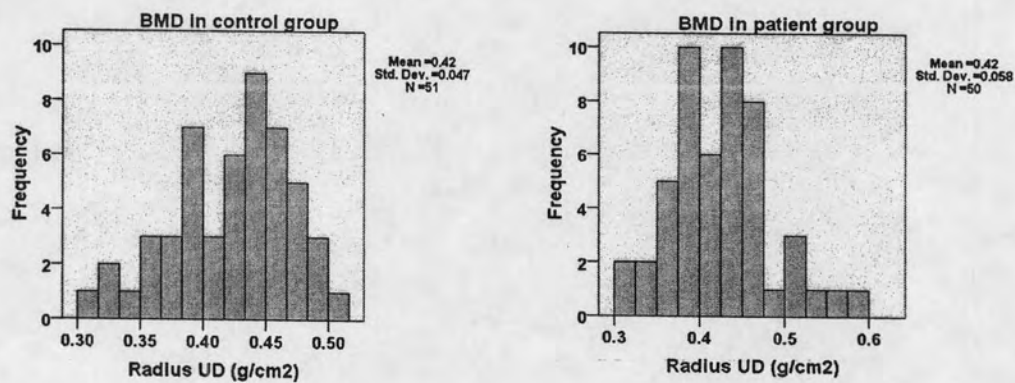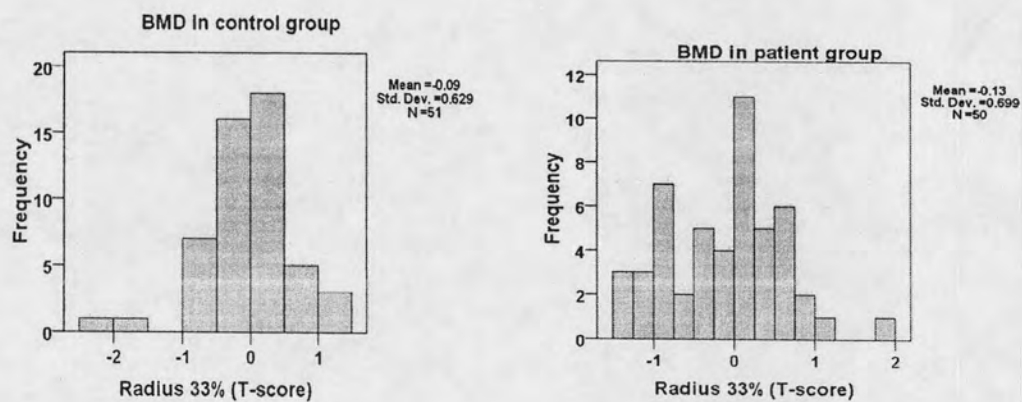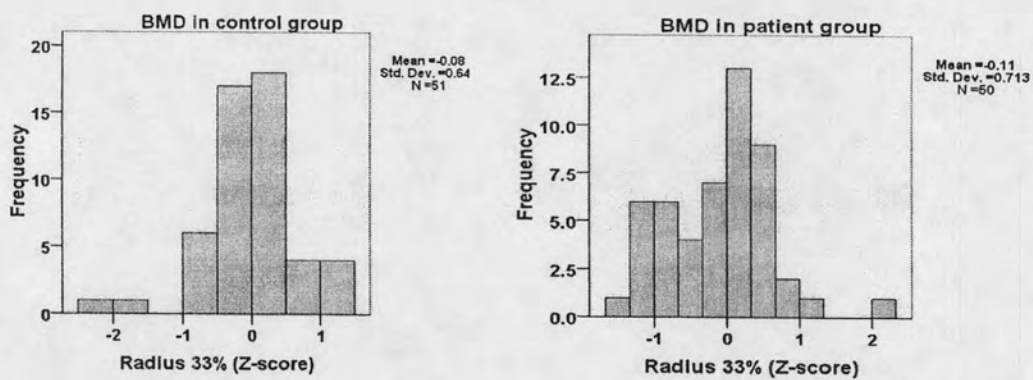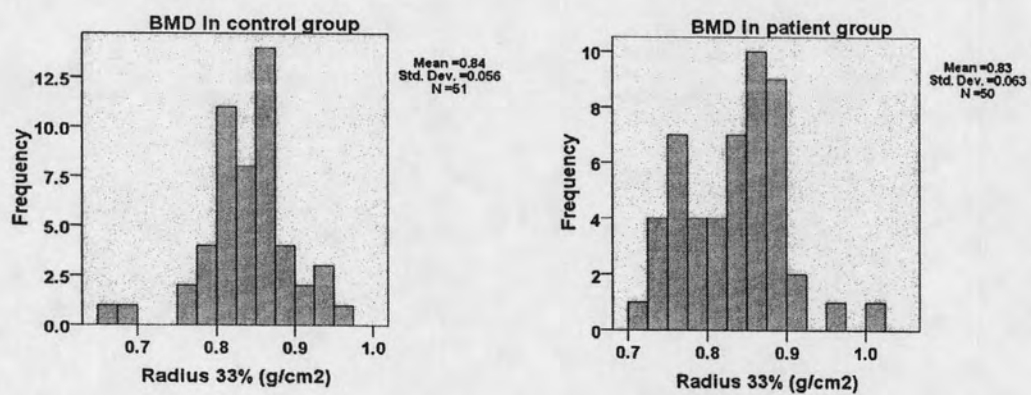Figure 8 Distribution of bone mineral density at radius 33%

(a) T-score

(b) Z-score

(c) g/cm^2

Proportion of normal BMD, osteopenia and osteoporosis at three bone sites in patient and control groups were presented in table 8. The percentage of osteopenia plus osteoporosis in patients : controls measured at L 2-4 was 16 : 2 and at femur neck was 22 : 0. Comparison of proportion of osteopenia plus osteoporosis at L 2-4 and femur neck between patients and controls were both statistically significantly different with p-value = 0.014 and p-value < 0.001 respectively.

In addition, comparison of BMD at the rest bone sites also demonstrated that the percentage of osteopenia plus osteoporosis in patients were more than in controls, i.e. patients : controls at femur trochanter = 28 : 15.7; at femur total = 12 : 2; at radius UD = 38 : 33.4 and at radius 33 % = 12 : 3.9. However, they were all not statistically significant different.

Table 8 Proportion of normal bone mineral density, osteopenia and osteoporosis at three bone sites in patient and control groups

Bone site	BMD	Number (%)		Exact p-value[#]
		Control (n=51)	Patient (n=50)	
L 2-4	Normal	50 (98)	42 (92)	0.014
	Osteopenia	1 (2)	7 (14)	
	Ostoporosis	-	1 (2)	
Femur neck	Normal	51 (100)	39 (78)	< 0.001
	Osteopenia	-	11 (22)	
	Ostoporosis	-	-	
Femur trochanter	Normal	43 (84.3)	36 (72)	0.120
	Osteopenia	8 (15.7)	13 (26)	
	Ostoporosis	-	1 (2)	
Femur total	Normal	50 (98)	44 (88)	0.060
	Osteopenia	1 (2)	6 (12)	
	Ostoporosis	-	-	
Radius UD	Normal	34 (66.7)	31 (62.0)	0.744
	Osteopenia	14 (27.5)	16 (32)	
	Ostoporosis	3 (5.9)	3 (6)	
Radius 33%	Normal	49 (96.1)	44 (88)	0.160
	Osteopenia	2 (3.9)	6 (12)	
	Ostoporosis	-	-	

Linear-by-Linear Association Test

4.2.2 Secondary Outcome

Mean and comparison of bone mineral density (BMD) (in T-score, Z-score, g/cm^2) between epileptic patients receiving long-term antiepileptic drug (AED) monotherapy and polytherapy by unpaired t-test were shown in table 9. Mean of BMD at L 2-4, femur trochanter, femur total and radius UD was lower in polytherapy group while those at femur neck and radius 33% was lower in monotherapy group. No significant difference between monotherapy and polytherapy was demonstrated at all.

Comparison of BMD (in T-score, Z-score, g/cm^2) between epileptic patients receiving long-term CYP 450 inducing AEDs (inducer) and non-inducing AEDs (non-inducer) were shown in table 10. Since BMD in each group was not normally distributed, comparison between inducer and non-inducer group was done by Mann-Whitney U test and showed no statistically significant difference at all. Mean of BMD in inducer group was lower than that in non-inducer group at nearly all bone sites except at radius 33%. Median of BMD in inducer group was lower at femur trochanter, femur total and radius UD whereas it was higher at L 2-4, femur neck, and radius 33%.

Relationship between duration of AEDs therapy and BMD (T-score, Z-score and g/cm^2) in epileptic patients was shown by scatter plot in figures 9-14. Since the duration of AEDs therapy was not normally distributed, Spearman rank correlation was applied and reported in table 11. There was no correlation between duration of AEDs therapy and BMD with correlation coefficients between -0.183 and 0.131 in T-score; -0.168 and 0.129 in Z-score and -0.193 and 0.155 in g/cm^2.

Mean BMD (T-score, Z-score, g/cm^2) among patients with localization-related epilepsy, generalized epilepsy and unclassified type was displayed in table 12. Comparison of BMD between localization-related epilepsy group and generalized epilepsy group was not done since there were only 2 patients (4%) in generalized epilepsy group which was very small.

Table 9 Comparison of BMD between patients receiving monotherapy and polytherapy

(a) T-score

| Bone site | Mean (SD) | | p-value |
	Monotherapy (n=19)	Polytherapy (n=31)	
L2-4	0.45 (0.88)	0.15 (1.33)	0.342
Femur			
Neck	-0.12 (0.91)	-0.06 (1.04)	0.820
Trochanter	-0.30 (1.01)	-0.44 (1.12)	0.661
Total	0.23 (0.88)	0.01 (1.14)	0.487
Radius			
UD	-0.48 (1.12)	-0.58 (1.39)	0.782
33%	-0.31 (0.65)	-0.02 (0.71)	0.155

(b) Z-score

| Bone site | Mean (SD) | | p-value |
	Monotherapy (n=19)	Polytherapy (n=31)	
L2-4	0.174 (0.86)	-0.20 (1.26)	0.223
Femur			
Neck	-0.20 (0.83)	-0.10 (1.02)	0.744
Trochanter	-0.45 (0.94)	-0.60 (1.05)	0.627
Total	0.12 (0.79)	-0.90 (1.10)	0.481
Radius			
UD	-0.48 (1.12)	-0.56 (1.37)	0.827
33%	-0.31 (0.65)	0.003 (0.71)	0.124

(c) g/cm^2

| Bone site | Mean (SD) | | p-value |
	Monotherapy (n=19)	Polytherapy (n=31)	
L2-4	1.17 (0.10)	1.14 (0.16)	0.349
Femur			
Neck	0.88 (0.11)	0.89 (0.12)	0.780
Trochanter	0.72 (0.11)	0.70 (0.12)	0.701
Total	0.96 (0.10)	0.94 (0.14)	0.519
Radius			
UD	0.43 (0.05)	0.42 (0.06)	0.782
33%	0.82 (0.06)	0.85 (0.06)	0.156

Table 10   Comparison of bone mineral density between patients receiving CYP-450 inducing
antiepileptic drug (inducer) and non-inducing antiepileptic drug (non-inducer)

(a) T-score

| Bone site | Inducer (n=42) | | Non-inducer (n=8) | | Exact |
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	p-value[#]
L 2-4	25.44 (1.17)	0.20 (5.4)	25.81 (1.25)	0.20 (3.8)	0.953
Femur neck	25.15 (0.97)	0.10 (3.8)	27.31 (1.07)	-0.30 (3.0)	0.711
Femur trochanter	23.88 (1.03)	-0.50 (5.1)	34.00 (1.07)	0.20 (2.8)	0.072
Femur total	24.82 (1.06)	0.00 (5.0)	29.06 (0.97)	0.20 (2.5)	0.461
Radius UD	24.73 (1.33)	-0.90 (6.0)	29.56 (1.00)	-0.45 (3.5)	0.400
Radius 33%	26.75 (0.70)	0.00 (3.3)	18.94 (0.67)	-0.65 (1.8)	0.161

[#] Mann-Whitney U test

(b) Z-score

| Bone site | Inducer (n=42) | | Non-inducer (n=8) | | Exact |
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	p-value[#]
L 2-4	25.82 (1.13)	-0.10 (5.2)	23.81 (1.21)	-0.25 (4.0)	0.730
Femur neck	25.08 (0.95)	-0.30 (3.8)	27.69 (0.96)	-0.20 (2.8)	0.654
Femur trochanter	24.02 (0.97)	-0.60 (4.8)	33.25 (1.04)	0.50 (2.9)	0.103
Femur total	24.86 (1.01)	0.50 (4.9)	28.88 (0.92)	0.15 (2.5)	0.486
Radius UD	24.75 (1.32)	-0.80 (6.0)	29.44 (1.00)	-0.45 (3.5)	0.415
Radius 33%	26.85 (0.70)	0.00 (3.3)	18.44 (0.66)	-0.65 (1.8)	0.138

[#] Mann-Whitney U test

(c) g/cm^2

| Bone site | Inducer (n=42) | | Non-inducer (n=8) | | Exact |
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	p-value[#]
L 2-4	25.48 (1.14)	1.15 (0.64)	25.62 (1.15)	1.14 (0.46)	0.985
Femur neck	25.18 (0.12)	0.89 (0.46)	27.19 (0.13)	0.86 (0.35)	0.731
Femur trochanter	23.88 (0.11)	0.69 (0.56)	34.00 (0.12)	0.77 (0.31)	0.073
Femur total	24.88 (0.13)	0.94 (0.60)	28.75 (0.12)	0.96 (0.30)	0.503
Radius UD	24.74 (0.06)	0.41 (0.27)	29.50 (0.04)	0.43 (0.16)	0.408
Radius 33%	26.75 (0.06)	0.85 (0.29)	18.94 (0.05)	0.80 (0.16)	0.170

[#] Mann-Whitney U test

Figure 9 Relation between bone mineral density at L 2-4 and duration of antiepileptic
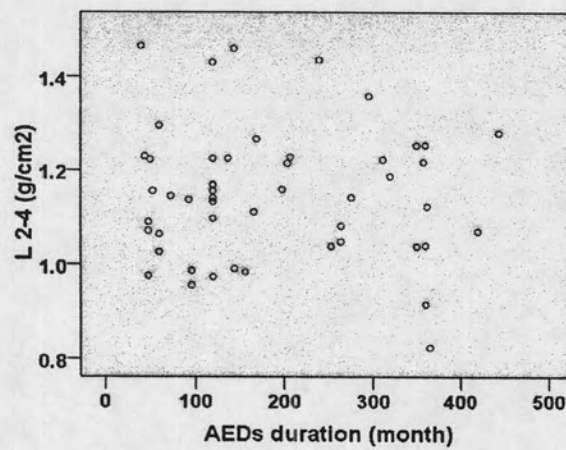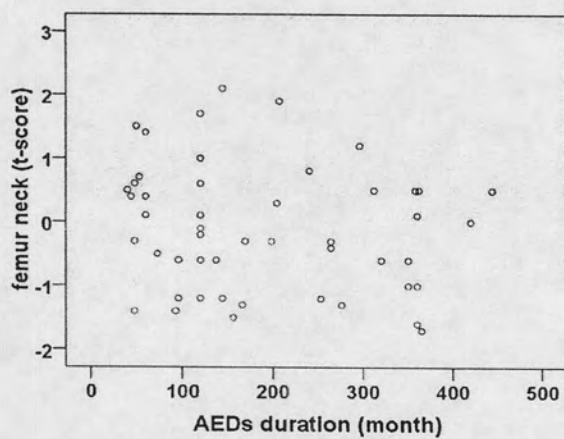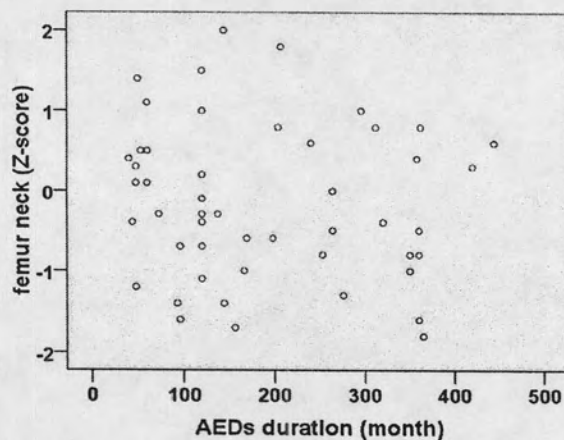drugs (AEDs)
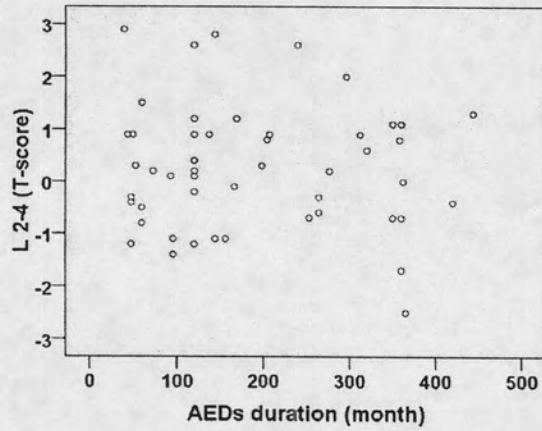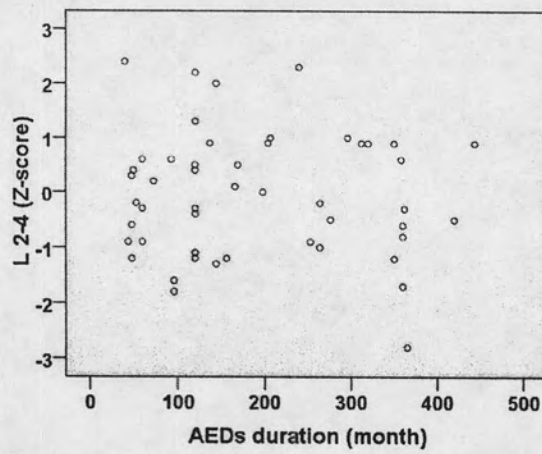
(a) T-score

(b) Z-score

(c) g/cm^2

Figure 10 Relation between bone mineral density at femur neck and duration of antiepileptic drugs (AEDs)
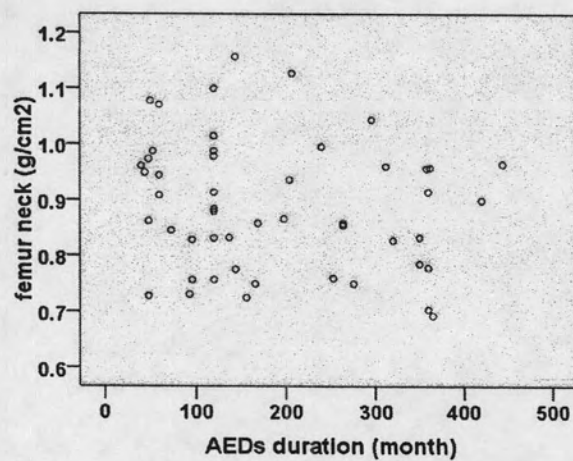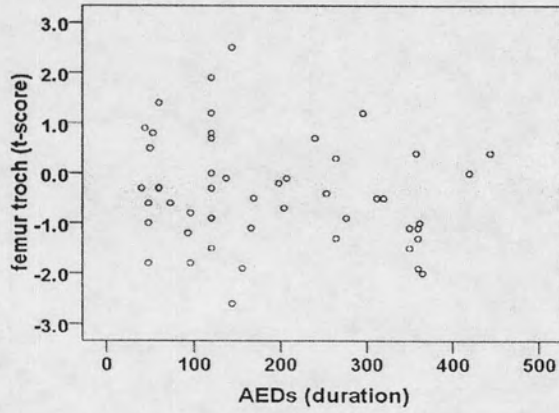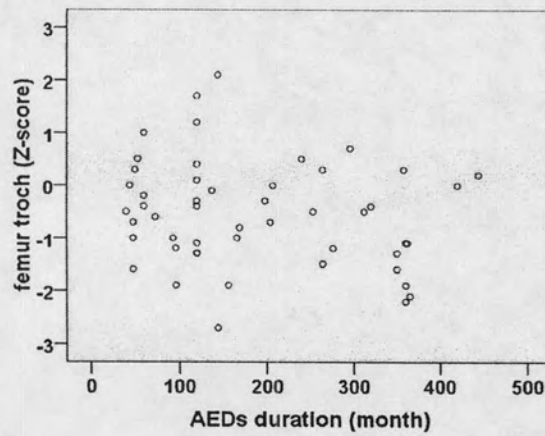
(a) T-score

(b) Z-score

(c) g/cm2

Figure 11 Relation between bone mineral density at femur trochanter and duration of antiepileptic drugs (AEDs)
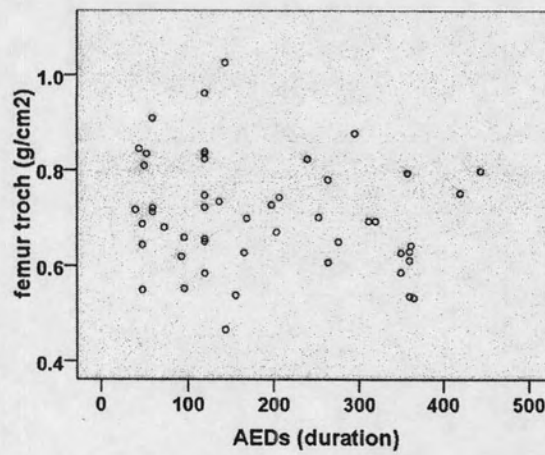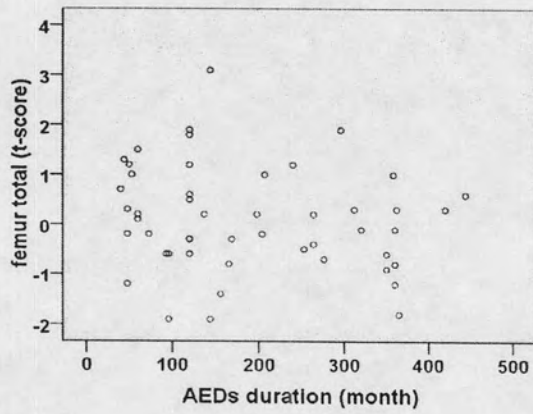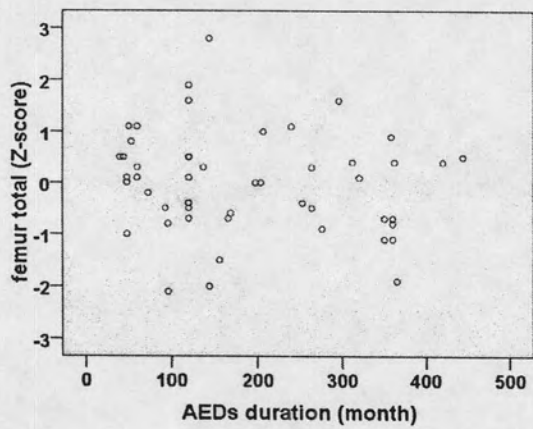
(a) T-score

(b) Z-score

(c) g/cm2

Figure 12 Relation between bone mineral density at femur total and duration of antiepileptic drugs (AEDs)

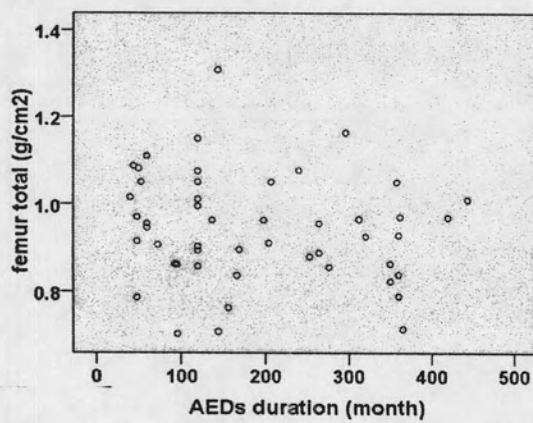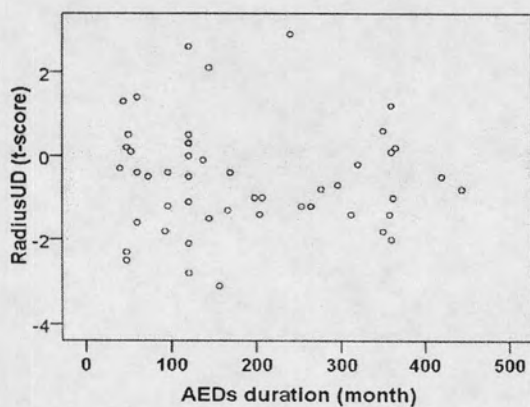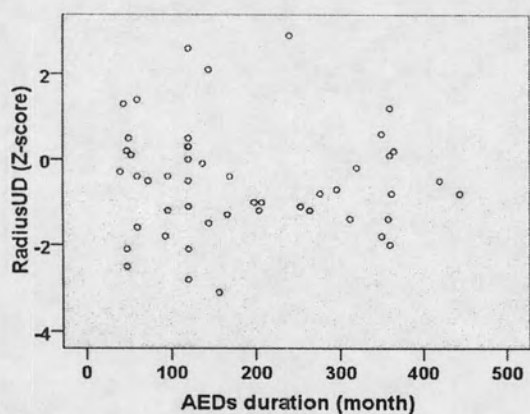(a) T-score

(b) Z-score

(c) g/cm2

Figure 13 Relation between bone mineral density at radius UD and duration of antiepileptic drugs (AEDs)

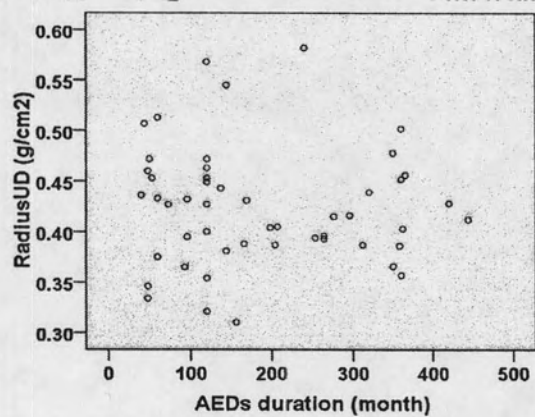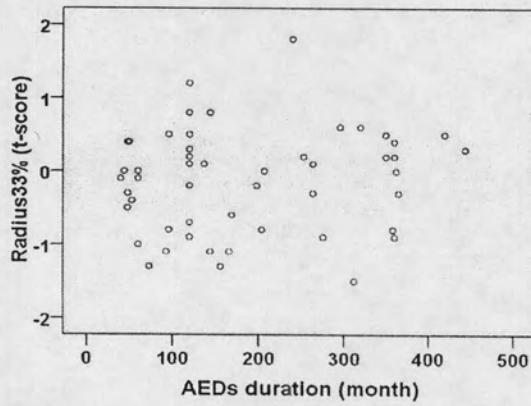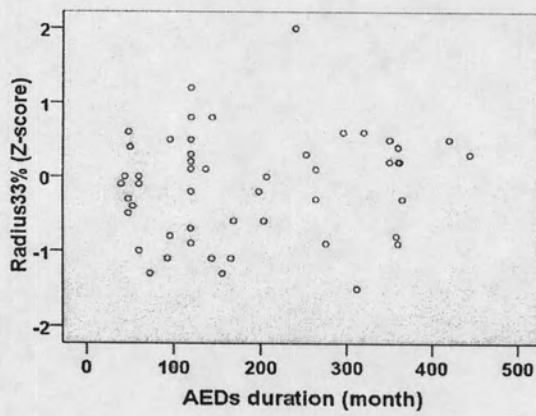(a) T-score

(b) Z-score

(c) g/cm^2

Figure 14 Relation between bone mineral density at radius 33% and duration of antiepileptic drugs (AEDs)

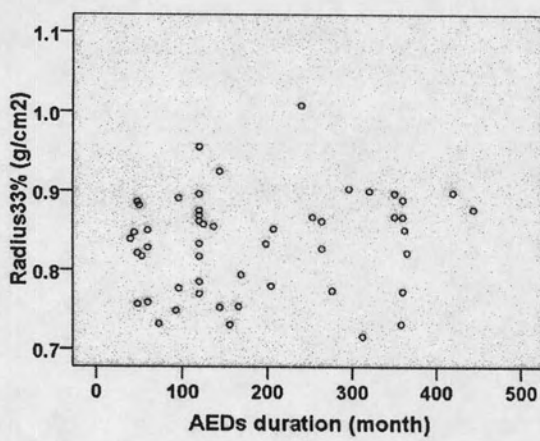(a) T-score

(b) Z-score

(c) g/cm^2

Table 11 Correlation between duration of antiepileptic drug therapy and bone mineral density

Bone site	Spearman rank correlation between AEDs duration and BMD		
	T-score	Z-score	g/cm^2
L 2-4	-0.008 (p=0.958)	0.011 (p=0.939)	-0.013 (p=0.926)
Femur neck	-0.183 (p=0.203)	-0.119 (p=0.409)	-0.181 (p=0.209)
Femur trochanter	-0.171 (p=0.235)	-0.168 (p=0.240)	-0.193 (p=0.180)
Femur total	-0.176 (p=0.222)	-0.161 (p=0.263)	-0.174 (p=0.227)
Radius UD	-0.076 (p=0.601)	-0.073 (p=0.613)	-0.081 (p=0.577)
Radius 33	0.131 (p=0.366)	0.129 (p=0.373)	0.155 (p=0.284)

Table 12 Bone mineral density in patients with generalized, localization-related and unclassified epilepsy type

(a) T-score

Bone site	Mean (SD)		
	Generalized (n=2)	Localization-related (n=45)	Unclassified (n=4)
L 2-4	-0.50 (0.99)	0.31 (1.20)	0.13 (1.01)
Femur neck	-0.55 (0.07)	-0.04 (1.02)	-0.28 (0.67)
Femur trochanter	-0.45 (0.21)	-0.32 (1.07)	-1.08 (1.21)
Femur total	-0.25 (0.07)	0.16 (1.06)	-0.50 (0.95)
Radius UD	-0.50 (0.00)	-0.51 (1.35)	-1.00 (0.74)
Radius 33%	-1.10 (0.28)	-0.56 (0.68)	-0.45 (0.66)

(b) Z-score

Bone site	Mean (SD)		
	Generalized (n=2)	Localization-related (n=45)	Unclassified (n=4)
L 2-4	-0.50 (0.99)	-0.009 (1.16)	-0.35 (0.95)
Femur neck	-0.50 (0.28)	-0.11 (0.97)	-0.28 (0.92)
Femur trochanter	-0.45 (0.21)	-0.475 (0.98)	-1.33 (1.38)
Femur total	-0.30 (0.14)	0.057 (1.00)	-0.63 (1.03)
Radius UD	-0.50 (0.00)	-0.493 (1.34)	-0.95 (0.71)
Radius 33%	-1.10 (0.28)	-0.45 (0.69)	-0.40 (0.63)

(d) g/cm^2

Bone site	Mean (SD)		
	Generalized (n=2)	Localization-related (n=45)	Unclassified (n=4)
L 2-4	1.06 (0.12)	1.16 (0.14)	1.14 (0.12)
Femur neck	0.84 (0.01)	0.89 (0.12)	0.87 (0.07)
Femur trochanter	0.70 (0.03)	0.71 (0.12)	0.63 (0.13)
Femur total	0.90 (0.01)	0.95 (0.13)	0.88 (0.11)
Radius UD	0.43 (0.00)	0.43 (0.06)	0.40 (0.03)
Radius 33%	0.75 (0.03)	0.84 (0.06)	0.81 (0.06)