CHAPTER V

DISCUSSION

In the clinical aspect, the relationship between vitamin D to the health status of adults or elderly subjects had been largely ignored for a long time. Studies on vitamin D status of the elderly began only after mid-1970s when assays for serum 25(OH) D_3 became available. Severe and prolonged deficiency in vitamin D is associated with osteomalacia characterized by defective mineralization of bone and decrease bone strength. On the other hand, hypovitaminosis D or vitamin D insufficiency that is not severe enough to cause osteomalacia may nevertheless contribute to hip fracture risk especially in elderly. Although hip fracture among these elderly peoples may have a several numbers of etiology, increased in number of falls due to impaired muscle function is one of the most fascinating issues today.

Several studies have shown a high prevalence of hypovitaminosis D in elderly population (30%-60%), especially in European countries (40,41). In Thailand, as well as many countries in topical zone, this point of debate still controversy. As mention earlier, one study (34) in Bangkok reported a normal level of serum 25(OH) D_3 in 158 volunteers age 20-80 years, while in Khon Kaen province, a study(35) in 106 elderly women mean age of 69.4 years, reported a high prevalence of hypovitaminosis D. It is a problem of defining the term hypovitaminosis D, which still debate about the clinically appropriate cut point. According to a study by Soontrapa et al(35), serum PTH concentration started to increase steeply when serum 25(OH) D_3 concentration declined $\leq$ 30 ng/ml. By this criteria, hypovitaminosis D have to defined as those population which serum 25(OH) D_3 equal or less than 30 ng/ml. This value was corresponded with a study by Chapuy et al.(40), in which serum level of PTH in their study population increased when serum 25(OH) D_3 value was lower than 31 ng/ml (78 nmol/L). In the present study, our percent of hypovitaminosis D was as high as 63.9 %,

if we used this cut off point. It may be due to our study population were the outpatients who usually came to the hospital for some medical problems, these women did not routinely exercise or walking outside their houses. In this present study, we could not found any correlation between the serum level of 25(OH) D_3 or serum intact PTH (serum iPTH) and the muscle strength. We also explored into the subgroup of serum 25(OH) $D_3 \leq 30$ ng/ml, and again no significant correlation was found. One possible reason for this inconsistency is our study sample was too small for detect these correlations. Since this study population was calculated based on the primary research question, which is the improvement of muscle strength compare to placebo after intervention. Another possible reason is may be due to this level of 25(OH) D_3 are still in physiologic range, which muscle strength still no clinical deteriorate. Studies by some other experts, such as Ooms et al.(42), defined level of serum 25(OH) D_3 below 12 ng/ml (30 nmol/L) was associated with secondary hyperparathyroidism. The Denish study by Glerup et al.(7), a serum 25(OH) D_3 level below 8 ng/ml (20 nmol/L) was associated with severely impaired muscle function. Bischoff et al.(28), also found a lower muscle strength in men and women with a serum 25(OH) D_3 level below 12 ng/ml.

It is well known that vitamin D is needed for strong bones, without enough vitamin D, the body can not adequately absorb the calcium crucial to bone strength. What less well known is that vitamin D is also critical to proper muscle function. Striated muscles contain vitamin D receptors (VDR), and vitamin D has been shown to stimulate the synthesis of several important muscle proteins (troponin C, actin, Ca-ATPase) in the sarcoplasmatic reticulum and inner membrane of mitochondria. In the study by Geusens et al (6), statistically significant association between the VDR genotypes and quadriceps strength was observed only in non-obese, elderly women. A 23% difference in quadriceps strength between the two homozygote bb and BB genotypes were found. In our study, no correlation between serum 25(OH) D_3 to quadriceps muscle strength in any genotype groups. Because of the distribution of these three genotypes in Asian population are not similar to the Caucasian. We have only a small numbers of BB genotype in our population, so we could not compared the baseline muscle strength as the study by Geusen et al.

For the primary outcome of this study, we have demonstrate that the muscle strength are significantly improved in the group that taken alfacalcidol compared to the group that taken placebo. In the placebo group, only taken calcium carbonate cannot improved the muscle strength, on the other hand, muscle strength had decreased, especially in muscle strength at 60°/sec angular velocity, which slightly more decrease than the 30°/sec. The muscle strength at 60°/sec angular velocity is represent the strength in normal walking velocity in elderly peoples(60° - 90° /sec), while, the 30°/sec angular velocity is represent the strength in very slow walking velocity. The reasons why muscle strength deteriorated in the group that take only calcium are doubtfulness. One possibility is that intestinal absorption of calcium in these subjects was not good enough. Among various calcium compounds used as supplements, calcium carbonate was thought to be absorbed less efficiently than other calcium compounds, especially in the elderly people(43). Since we did not allow all the subjects to take any vitamin supplements or any other calcium supplements during the study period, so these women may develop subclinical hypocalcemia and some fatigue of muscle occurred. We did not measure the biochemical blood tests in the end of 12 weeks, so it may be mysterious to what happen to these subjects.

In our treatment group, who have received alfacalcidol and calcium carbonate significant increase the muscle strength compared to placebo in both angular velocity. The muscle strength at 60°/sec angular velocity is much better increase in this aspect. As we already mention earlier, the muscle fibers, which is responsibility for fast and strong action, are type-II muscle fibers. The muscle biopsy study by Sato et al., clearly demonstrate that type-II muscle fibers were the main defect in vitamin D deficient myopathy. Theoretically, if we give vitamin D to those subjects, who have hypovitaminosis D, the muscle fibers that will be response better might be the type-II fibers. These are correspond to our finding that muscle strength in 60°/sec angular velocity, which type-II muscle fibers are responsible, is actively react to a given or not given of alfacalcidol.

Three possible mechanism whereby vitamin D can improved muscle strength have been purposed. Firstly, that we call the "calcemic action". Vitamin D may act by controlling ionized calcium concentrations. As we known that calcium ions are the

important factor in muscle contraction processes. Secondly, it may have a direct action on muscle cells on induce expression of specific genes. Since we discovered the VDR in muscle cells, we find many "genomic action" of vitamin D that induced expression of many proteins such as vitamin D binding protein, troponin C and actin. Finally, the "non-genomic action" , which are rapid and mediated through a membrane-bound receptors. The binding to this receptor initiates a cascade leading to the formation of second messenger or phosphorylation of intracellular proteins.

Although our result corresponds to the results in many studies (7,32,33), which demonstrate that supplement with vitamin D in the elderly population can improved muscle strength, some limitation of this study is the size of sample. which may be too small to demonstrate the significant of secondary outcomes. Further studies to confirmed our results in bigger sample size may be properly perform.