CHAPTER II

REVIEW OF LITERATURES

Chapuy et al.(14), inspired many investigators to perform studies on the muscular effect of vitamin D. In the group of 3,270 elderly nursing home residents, supplementation with vitamin D (800 IU/d) and calcium (1200 mg/d) led to a 43% reduction in hip fracture risk after 18 months of treatment(14).The bone density at the proximal femur increased by 2.7% in vitamin D-calcium group and decreased by 4.6% in placebo group(14). This reduction in hip fracture incidence was somewhat surprising since the change in BMD was modest. Re-evaluation after 3 years continued to show a 25% reduction in the incidence of hip fracture. In addition, a study performed in men and women 65 years of age or older living in community, dietary supplementation with vitamin D and calcium increased BMD moderately, while significant reduction in non-vertebral fractures was observed(15). Twenty-six subjects in the placebo group compared with 11 subjects in calcium and vitamin D group had non-vertebral fractures ($p=0.02$) (15). It seems unlikely that the antifracture efficacy of vitamin D and calcium is attributable to their effect on BMD alone, since the reduction of fracture risk seemed to forward the improvement of bone mass induced by calcium and vitamin D. The action of vitamin D and calcium on decreased secondary hyperparathyroidism and decreased bone turnover were also considered, but another interesting explanation was the efficacy in reduction of falls by improves muscle function.

In the past few years, vitamin D receptors have been identified in a wide range of tissues, implying the hormone in effects not directly related to mineral metabolism only. Thus, $1,25(OH)_2D_3$, among various non-classical actions, may influence the proliferation and differentiation of various cell types(16). Several lines of evidence demonstrated that skeletal muscle was also a target tissue for vitamin

D(17). Classical VDR are existed in muscle cells. The analysis of binding showed that receptor proteins bind to $1,25(OH)_2D_3$ with high affinity(18). Recent data showed that $1,25(OH)_2D_3$ modulates the expression of genes related to the regulation of muscle calcium transport and phospholipid metabolism(17). There was a wealth of information showing that $1,25(OH)_2D_3$ also exerts the non-genomic actions, which mediate the fast effects of the hormone on muscular intracellular Ca^{2+} regulation(19,20).

Muscle biopsies obtained in severely vitamin D deficiency patients revealed selective atrophy of type-II muscle fibers with enlarged interfibrillar spaces and fat infiltration(21-23). These finding are not specific for hypovitaminosis D myopathy, but can be found only in a number of other of endocrine myopathy. However, in neuropathic myopathy, both type-I and type-II fibers are affected (19). In immobilization myopathy, type-I fibers were primary affected(24). Sato et al.(25), recently investigated muscle biopsies in hip fracture patients. The patients were divided into vitamin D-sufficient group [25(OH) D_3 > 39 nmol/L, n=20] and vitamin D-deficient group [25(OH) D_3 < 39 nmol/L, n=22]. In vitamin-deficient group, type-II fibers were significantly smaller (15.4 $\pm$ 4.2 μm) than in the vitamin D-sufficient group (38.7 $\pm$ 8.1 μm)($p<0.0001$)(25). Furthermore, in the vitamin D- deficient group, type-II muscle fiber diameters correlated with serum levels of 25(OH) D_3 ($r = 0.714$, $p=0.001$) (25). No such correlation was found in the vitamin D-sufficient group. Recently, Glerup(26) studies muscle biopsies of the vastus lateralis muscle from 8 patients with vitamin D deficiency before and after 3 months of vitamin D treatment. The Ca-ATPase content increased significantly during treatment (26) (before 3.4 $\pm$ 0.4, after 4.7 $\pm$ 0.2 nmol/g wet wt, $p < 0.02$). This increase is most likely explained by regeneration of type-II fibers, which have a higher overall Ca-ATPase content. During sudden movements, the fast and strong type-II muscle fibers are the first to be recruited to avoid falling(27). Thus, the selective type-II fibers atrophy may be closely associated with the tendency to fall in vitamin D deficiency individuals.

Clinical studies of correlation between vitamin D status and muscle function were well demonstrated. One study of an elderly population (age 65-95 yr) of whom 12% of women and 18% of men had a serum 25(OH) D_3 concentration < 30

nmol/L(12 ng/ml), a significant correlation was found between vitamin D metabolites and leg extension power(28). This finding agreed with that study by Mowe et al (29), in which the association between serum vitamin D metabolites, $25(OH)D_3$, and muscle function was examined. In this study, serum $25(OH)D_3$ concentrations were significant lower in those subjects whom have less handgrip strength, unable to climb stairs, without any outdoor activity, and who had fallen in the previous month(29). On the other hand, Boonen et al.(30), investigated the correlation between muscle function and serum levels of $1,25(OH)_2D_3$ in 245 elderly women (70-90 years). No correlation could be demonstrated. $25(OH)D_3$ levels were not reported in this study.

Several studies have shown clinical improvement in muscle strength and function following vitamin D therapy, but some studies not. In one treatment study by Grady et al (31), failed to demonstrate any muscular effects of treatment with 0.5 μg calcitriol daily in 98 men and women volunteers over 69 years old. However, serum levels of 25(OH) D_3 among these participants were above 60 nmol/L (24 ng/ml). Another study performed a contrary result, Verhaar et al(32), study in 10 vitamin D deficient (serum 25(OH) D_3 < 20 nmol/L or 8 ng/ml) , elderly women(mean age 76 yr) who were treated with 0.5 μg /d of alfacalcidol. Both knee extension strength and walking distance improved significantly in those women. Bischoff et al.(33), demonstrated a reduction in falls after treatment with vitamin D and calcium in elderly institutionalized women. The women, with a mean age of 85 years received either 1200 mg of elemental calcium or 1200 mg of elemental calcium plus 800 IU of vitamin D. The number of falls before treatment subtracted from the number of falls during treatment period was significantly lower in calcium and vitamin D group ($p<0.01$) (33). Glerup et al. (7), studied the treatment effect of vitamin D in veiled Arab women living in Denmark (n=55)(25(OH) D_3 = 6.7 ± 0.6 nmol/L). They demonstrated a 34% reduction in muscle power determined by voluntary knee extension (MVC), when compared to controls (n=22) with normal vitamin D levels[7]. A series of ergocalciferol injections(100,000 IU weekly for one month follow by 100,000 IU monthly for six months) and daily calcium supplement of 1,200 mg were given. MVC increased by 13% after three months and by 24% after six months ($p< 0.02$) (7). Further, MVC correlated significantly with serum levels of 25(OH) D_3 ($r=0.34, p<0.01$) and PTH (r=-

0.33,p < 0.001), but not with $1,25(OH)_2D_3$. In multivariate regression analysis, only 25(OH) D_3 was found to be significant (7).

Very few studies in effect of hypovitaminosis D have been conducted in Thailand. Chailurkit et al (34), reported in 158 normal Thai volunteers, 81 women and 77men, age between 20 and 80 years. They found that mean level of serum 25(OH) D_3 was 42.2 ng/ml(106 nmol/L), and they concluded that no evidence of vitamin D deficiency in ambulatory Thais. But only 39 cases of postmenopausal women were enrolled in this study. Another study by Soontrapa et al. (35), in elderly Thai women living in Khon Kaen province (mean age of 69 year old) found a significantly inverse relationship between serum 25(OH) D_3 and PTH concentration. Serum PTH concentration started to increase steeply when serum 25(OH) D_3 concentration declined < 30 ng/ml. As a result, the prevalence of hypovitaminosis D in this population would be at least 34.9 %(35). The authors discussed that, the belief that there are no hypovitaminosis D or vitamin D deficiency in tropical or subtropical countries should be reconsidered (35). This result was corresponded to some studies in other tropical Asian area(36-38). If hypovitaminosis D has a significant prevalence in Asian people and causes a significant effect on muscle strength, it can increase additional risk to fall and subsequence fractures. Study to evaluate the correlation between serum 25(OH) D_3 concentration and muscle strength in these elderly women population as well as a solid study to evaluate the response of them to the treatment with vitamin D metabolite in term of muscle strength have not been established.