CHAPTER I

RATIONALE AND BACKGROUND

The pivotal roles of calcium and vitamin D in physiology of many systems in our body are generally known. Vitamin D_3 or cholecalciferol is synthesized from 7-dehydrocholesterol in the human skin in response to sunlight. The active hormone, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], is produced by sequential hydroxylations of vitamin D_3 in the liver (25-hydroxylation) and the kidney (1α-hydroxylation). $1,25(OH)_2D_3$ acting through the vitamin D receptor (VDR), by a genomic mechanism identical to the classical steroid hormones, to regulate target gene transcription. The traditional actions of $1,25(OH)_2D_3$ are to enhance calcium and phosphate absorption from the intestine in order to maintain normal concentration of these essential ions in serum and provide normal mineralization. Calcium and vitamin D deficiency is the most important risk factor in the pathogenesis of osteoporosis. As well, vitamin D deficiency also lead to secondary hyperparathyroidism, increase bone turnover and increase bone loss. Apart from the well-known effects on bone metabolism, this condition is also associated with decrease muscle strength. Increase bone fragility and increased number of falls due to impaired muscle function are known risk factors of hip fractures (1). Furthermore, postural instability has been identified as a risk factor for Colles' fracture (2). The percentage of elderly people who fall increases steeply in those older than 70 years, and over 90% of hip fractures in elderly people occur as a result of a fall. Impaired balance and increased body sway are important causes of fall (3).

Elderly women are prone to develop vitamin D deficiency because of various risk factors: decreased dietary intake, diminished sunlight exposure, reduced skin thickness, impaired intestinal absorption, and impaired hydroxylation in liver and kidneys. As mention above, $1,25(OH)_2D_3$ or active vitamin D metabolites acting on classical target organs through the genomic pathway via its nuclear receptor VDR, so

it is considered to be a hormone rather than a vitamin(4). The serum concentration of 25 hydroxyvitamin D_3 [25(OH) D_3], the circulating form of vitamin D metabolites, is 1,000 times that of serum 1,25$(OH)_2$ D_3, and this excess concentration constitutes a storage facility similar to that of other steroid hormones(4). Although it is generally agreed that vitamin D status is most accurately reflected by serum 25(OH) D_3 concentration, evidence regarding adequate serum concentration is inconclusive. The importances of the VDR gene polymorphisms in the development of osteoporosis have been increasing interest (5). The correlation between VDR gene polymorphisms to the muscle strength was also found. Geusens et al(6) ,with the use of specific restriction endonuclease, found that VDR gene polymorphisms have some correlation to muscle function. In non-obese, elderly women, a 23% difference in quadriceps strength and 7% difference in grip strength between the 2 homozygote types of a restriction site were found(6).

Recently, however, myopathy has been shown to be a prominent, and common symptom of vitamin D deficiency. New data indicate that severely impair muscle function may be present even before biochemical signs of bone disease develops(7). 1,25$(OH)_2$ D_3 affect muscle cell metabolism through various pathways. The genomic pathway, which results in changes in gene transcription and subsequences protein synthesis, was found to influence many functions of muscle cell, such as, calcium uptake, phosphate transport across the membrane, phospholipid metabolism and to mediate cell proliferation and subsequently differentiation (8-11). Evidence indicates that 1,25$(OH)_2D_3$ possibly also acting on membrane receptor, the non-genomic pathway, which rapidly cause further interacting with secondary messengers and subsequently activate muscle cell, result in enhance calcium uptake through the calcium channels (12-13). Although possible interaction between vitamin D status and muscle strength have been proposed for decades, only few human studies and clinical trials have been performed in this field.