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RESEARCH ARTICLE

"VITAMIN D LEVELS IN PATIENTS WITH FRACTURES AROUND THE HIP....A HOSPITAL BASED STUDY".

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Abstract

Introduction: Assessment and treatment of osteoporosis are recommended following hip fracture. Osteoporosis treatment assumes an adequate calcium intake and a normal vitamin D plasma level. The authors conducted a study in three phases.

Materials and Methods: The authors conducted a study in three phases. Phase I : circulating 25-hydroxyvitamin D levels were retrospectively recorded from in the case records of 381 consecutive patients with 387 hip fractures, between May 2015 and November 2016. Only 27 patients had sufficient (>75 nmol/L) circulating vitamin D, and of these 22 were taking vitamin D supplements. The remainder, 354 patients, had abnormally low vitamin D levels, with a mean value of 26.4 nmol/L. These findings confirmed literature data, and gave rise to the prospective Phase II (December 2016) : 14 consecutive patients with a hip fracture received rapid substitution therapy with 50,000 IU cholecalciferol (vitamin D3) daily for 3 days. Patients with corrected calcium level (calcium level based on the serum albumin level) > 2.60 mmol/L were excluded from phase II (and phase III), in order to avoid hypercalcemia. Substitution resulted in an increase in vitamin D plasma levels from +/- 29.6 nmol/L to +/- 81.4 nmol/L ($p < 0.0001$), after +/- 14 days. However, vitamin D level remained below the desired threshold of 75 nmol/L in 29%. Therefore it was decided to increase the treatment period from 3 days to 7 days in the next 54 patients with a hip fracture in a prospective phase III (December 2016-March 2017). This time rapid substitution resulted in an increase from +/-31.4 nmol/L to +/-131.1 nmol/L ($p < 0.0001$), after +/-

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16 days, and 100% of treated patients achieved plasma levels above the desired threshold of 75 nmol/L.

Results: Virtually all patients with a hip fracture have low vitamin D plasma levels ; substitution with 50,000 IU oral cholecalciferol daily for 7 days increases vitamin D plasma levels rapidly, safely and consistently.

Conclusions: The study confirms that the vast majority of patients with hip fracture are vitamin D deficient and require supplements. The current target for 25-hydroxyvitamin D serum concentration in secondary fracture prevention is 75 nmol/L. The current study also demonstrates that, in patients with a normal corrected calcium level (< 2.60 mmol/L),rapid high dose substitution with 50,000 IU of vitamin D3 can normalize circulating serum vitamin D levels quickly and safely.

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Introduction:-

Hip fractures are a major cause of morbidity and mortality in the elderly, and are associated with chronic pain, reduced mobility, disability, and an increasing degree of dependence (24). These low-energy injuries are costly to treat and have a significant physical and social impact. An estimated worldwide incidence of hip fractures in the year 2000 was 1.6 million (23). This number is projected to rise up to 2.6 million by 2025, and to more than 4.5 million by 2050 (17). Most hip fractures in the elderly can be related to the development of osteoporosis, a progressive, systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (28). It has been shown that identification and management of patients at risk can significantly reduce the risk of a further fracture through modification of life style, adequate treatment of osteoporosis, and a falls prevention program (13,27). In the last decades, the development of effective therapies (e.g. bisphosphonates, RANK ligand inhibitors, selective estrogen receptor modulators (SERMs) and strontium ranelate) has extended the spectrum of osteoporosis treatment. Most current osteoporosis guidelines assume that patients who receive treatment for secondary prevention of osteoporotic fragility fractures have an adequate calcium intake and are vitamin D replete. Adequate levels of calcium and vitamin D are needed to ensure optimum effects of the treatments for osteoporosis and are recommended in the data sheets of all the commonly used drugs. Vitamin D status is best evaluated by measuring the circulating 25-hydroxyvitamin D concentration in the serum. Although controversy surrounds the definition of low vitamin D status, there is general acceptance that the optimal circulating 25-hydroxyvitamin D level should be 75 nmol/L or above (3). A threshold for optimal 25-hydroxyvitamin D and hip Bone Mineral Density (BMD) has been established from 13,432 individuals of NHANES III (Third National Health and Nutrition Examination Survey), including both younger (20-49 years) and older (≥ 50 years) individuals with different ethnic racial background (7). This study shows that high serum 25-hydroxyvitamin D levels are associated with higher BMD throughout the reference range of 22.5-94 nmol/L in all subgroups. In younger whites and younger Mexican Americans, higher 25-hydroxyvitamin D was associated with higher BMD even beyond 100 nmol/L. A meta-analysis (9) of 12 double-blind RCTs for non-vertebral fractures (n = 42,279) and eight RCTs for hip fractures (n = 40,886) found that the efficacy of vitamin D in preventing fractures is dose dependent and increases significantly with a higher achieved level of 25-hydroxyvitamin D in the treatment group, starting at 75 nmol/L (6,9). However, serum 25-hydroxyvitamin D levels above 220 nmol/L have been associated with hypercalcemia and other signs of toxicity (15,34). Bone remodeling is a balance between bone formation by osteoblasts and bone resorption by osteoclasts and mononuclear cells. It involves several hormones . Indeed, low calcium levels increase parathyroid hormone (PTH) production by the parathyroid glands. This stimulates calcium release from the bones and increases the reabsorption of calcium in the distal renal tubule cells. PTH also stimulates the renal production of biologically active vitamin D, which in turn increases calcium absorption from the gut. All these actions increase the calcium level in plasma. High calcium levels on the other hand stimulate the thyroid gland to produce and release calcitonin, which inhibits bone resorption by blocking PTH receptors on the osteoclasts, decreases calcium reabsorption in the kidney, and decreases calcium

absorption from the gut. Thus reducing plasma calcium levels. Vitamin D deficiency may be characterized bio-chemically by the presence of secondary hyperparathyroidism, which can also contribute to the bone loss in osteopenic patients. Secondary hyperparathyroidism is a physiological response to hypocalcaemia associated with vitamin D deficiency, and treatment with vitamin D will normalize the elevated PTH levels without significantly elevating the serum calcium level. It is important to distinguish secondary hyperparathyroidism from primary hyperparathyroidism due to a parathyroid adenoma, hyperplasia, or malignancy, in which excessive PTH secretion leads to bone resorption and high calcium levels in the plasma. In primary hyperparathyroidism substitution with vitamin D will not normalize PTH levels, and a potentially dangerous hypercalcemia may ensue. In the general population, particularly in the elderly, vitamin D levels are commonly reduced as a result of low dietary intake, decreased sun exposure, decreased intrinsic vitamin D production, and decreased vitamin D receptor activity. There is some evidence that vitamin D deficiency is also becoming widespread in younger patients (33). Other authors have also measured vitamin D levels in patients with a hip fracture, and demonstrated that levels are consistently low. In this study, we noted the levels of circulating 25-hydroxyvitamin D in a consecutive series of 381 patients sustaining a hip fracture (phase I, retrospective), and evaluated the effect of rapid substitution therapy with high dose oral vitamin D3 (cholecalciferol) (phase II : 3 days, and phase III : 7 days, both prospective). From these data, guidelines were developed for the management of low vitamin D levels in patients with a hip fracture.

Materials And Methods:-

Phase I (retrospective) : circulating 25-hydroxy-vitamin D and serum calcium levels were recorded from the files of 381 consecutive patients admitted with 387 hip fractures between May 2015 and November 2016 at Government hospital for Bone and Joint surgery, Barzulla, Kashmir, India. All patients were included. Vitamin D analysis was performed on serum using a direct competitive chemiluminescence immunoassay. Levels above 75 nmol/L were defined as sufficient, between 25-75 nmol/L as insufficient, and below 25 nmol/L as deficient. Calcium and corrected calcium (= calcium level based on the serum albumin level) analyses were also performed, using spectrophotometry. Phase II and phase III (both prospective) focused on rapid substitution therapy, respectively during 3 and 7 days. Inclusion criteria : all patients presenting with a hip fracture, with corrected calcium below 2.60 mmol/L (to avoid hypercalcemia), who agreed with a written informed consent. Exclusion criteria : patients with corrected calcium above 2.60 mmol/L, because treatment could potentially lead to dangerously high calcium levels ; they were assessed biochemically for primary hyperparathyroidism. Prior intake of a low dose of vitamin D and a calcium supplement was not an exclusion criterion. Patients with cognitive impairment resulting in non-compliance with therapy, and patients with a significantly reduced life expectancy (ASA grade 5) or significant renal impairment (GFR < 30 mL/min/1.73m2) were also excluded. Clinical side effects of hypercalcemia and hypervitaminosis D, such as nausea, vomiting, constipation, thirst and polyuria were recorded. Phase II (prospective) : rapid substitution therapy with 50,000 IU oral vitamin D3 (cholecalciferol) daily for 3 days was started in 14 consecutive patients with a hip fracture (November 2016). Phase III (prospective) : rapid substitution therapy with 50,000 IU oral vitamin D3 (cholecalciferol) daily for 7 days was started in 54 consecutive patients with a hip fracture, between November 2016 and March 2017. Initially 60 patients had been considered, but 6 were excluded (2 non-compliant, 2 absent repeat sample, 2 initial corrected calcium above 2.60 mmol/L).Both patient groups (phase II and phase III) had similar demographic characteristics, and did not differ in terms of age-related comorbidities, drug intake or dwelling status. Repeat vitamin D and calcium measurements were performed between 7 and 42 days after the start of substitution therapy. After completion of the study all patients were recommended to take a low dose vitamin D and calcium supplement for life : calcium carbonate (1500 mg) and vitamin D3 (400 IU).

Results:-

Phase I : over an 18 month period 381 patients were admitted with 387 hip fractures (95 men, 286 women) (mean age 83 years, range 34-97 years). Serum 25-hydroxyvitamin D analysis was per-formed in all patients. Only 27 patients had a sufficient (> 75 nmol/L) circulating vitamin D level (mean 91.2 nmol/L, SD 20.0 nmol/L, range 75.6-171 nmol/L), and of these 22 were taking vitamin D supplements. The remainder, 354 patients, had abnormally low vitamin D levels, with a mean value of 26.4 nmol/L (SD = 17.9 nmol/L, range < 10-74.4 nmol/L) : 155 patients (44%) were vitamin D insufficient with a level between 25 and 75 nmol/L, 199 patients (56%) were vitamin D deficient with a level below 25 nmol/L. Of these patients, 43 had a low vitamin D level despite taking low dose vitamin D (400 or 800 IU) and calcium supplements with a mean level of 57.8 nmol/L (SD = 10.3 nmol/L, range 32.5-74.4 nmol/L). Phase II : 14 patients received 50,000 IU of cholecalciferol orally for 3 days. No patients had been excluded. Mean age was 83 years (range, 65-95 years). Compliance with treatment was 100%. A paired t-test was performed to determine if supplementation was effective. The mean serum 25-hydroxyvitamin D level before

substitution was 29.6 nmol/L, the mean calcium level 2.12 mmol/L, and the corrected calcium level 2.43 mmol/L. Repeat measurements after a mean of 14 days (range, 7-23 days) demonstrated a significant increase in circulating 25-hydroxyvitamin D levels to +/-81.4 nmol/L ($p < 0.0001$). This represents a near threefold increase in circulating vitamin D. However 29% of these patients failed to increase their vitamin D levels above the desired threshold of 75 nmol/L. Mean calcium and corrected calcium values also increased significantly ($p < 0.0001$), but in nearly all cases remained within their normal limits of 2.2-2.6 mmol/L. No clinical or biochemical side effects or complications were noted. Phase III : 60 patients were initially eligible to receive 50,000 IU oral cholecalciferol for 7 days, but 6 were excluded (2 non-compliant, 2 absent repeat sample, 2 initial corrected calcium above 2.60 mmol/L). Hence 54 patients were included. Mean age was 83 years (range, 40-100 years). A paired t-test was performed to determine if supplementation was effective. The mean 25-hydroxyvitamin D level before substitution was 31.4 nmol/L, the mean calcium level was 2.19 mmol/L, and the mean corrected calcium level 2.47 mmol/L. Repeat measurements after a mean of 16 days (range, 7-42 days) demonstrated a significant increase in circulating 25-hydroxyvitamin D levels to +/ 131.1 nmol/L ($p < 0.0001$). This represents a fourfold increase in circulating vitamin D. All patients achieved levels above the desired threshold of 75 nmol/L. Calcium levels increased significantly ($p < 0.0001$), as well as the corrected calcium levels ($p = 0.0002$). No clinical or biochemical side effects or complications were noted.

Table:- Vitamin D, calcium and corrected calcium before and after substitution with 50,000 IU oral cholecalciferol (vitamin D3) for 3 days (phase II : group 1) and 7 days (phase III : group 2)

Group 1	3 Days	
	Before substitution	After substitution
Vitamin D (nmol/L)	29.6 (SD = 15.8, range <10-56.8)	81.4 (SD = 17.0, range 47.4-108.0, $p < 0.0001$)
Calcium (mmol/L)	2.12 (SD = 0.13, range 1.91-2.39)	2.30 (SD = 0.12, range 2.12-2.54, $p < 0.0001$)
Corrected calcium (mmol/L)	2.43 (SD = 0.04, range 2.33-2.47)	2.55 (SD = 0.10, range 2.38-2.73, $p < 0.0001$)

Group 2	7 Days	
	Before substitution	After substitution
Vitamin D (nmol/L)	31.4 (SD = 24.2, range <10-113.0)	131.1 (SD = 30.7, range 85.6-243.0, $p < 0.0001$)
Calcium (mmol/L)	2.19 (SD = 0.13, range 1.94-2.50)	2.33 (SD = 0.17, range 1.84-2.78, $p < 0.0001$)
Corrected calcium (mmol/L)	2.47 (SD = 0.09, range 2.21-2.60)	2.54 (SD = 0.12, range 2.18-2.81, $p < 0.0002$)

Group 1 (phase II ; n = 14) : substitution with 50,000 IU oral vitamin D3 (cholecalciferol) daily for 3 days. Significant increase in circulating 25-hydroxyvitamin D levels and normalizing of calcium levels 14 days (range, 7-23 days) after start of substitution ; 29% of patients do not reach desired threshold of 75 nmol/L.
Group 2 (phase III ; n = 54) : substitution with 50,000 IU oral vitamin D3 (cholecalciferol) daily for 7 days. Significant increase in circulating 25-hydroxyvitamin D levels and normalizing of calcium levels 16 days (range, 7-42 days) after start of substitution. All patients achieve the desired vitamin D threshold of 75 nmol/L.

Discussion:-

Vitamin D is responsible for the absorption of calcium from the intestine, and may have other bone-protective effects independent of those on calcium metabolism (14,32). In addition, vitamin D plays an important role in muscular function : higher levels of vitamin D are associated with increased muscular strength and balance, reducing the risk of falls and subsequent fractures (5,12). In several double blind randomized controlled trials, vitamin D supplementation increased muscle strength and balance, and reduced the risk of falling (4,8,10,29,30). A study by Glerup et al (16) suggests that vitamin D deficiency may cause muscular impairment even before adverse effects on bone occur.

Hip fracture correlated with vitamin D deficiency:-

This study clearly confirms that the vast majority of patients with hip fracture are vitamin D deficient and require supplements. The current target for 25-hydroxyvitamin D serum concentration in secondary fracture prevention is 75 nmol/L. The fact that the majority of the patients taking low dose supplements were also found to be vitamin D

deficient raises the question as to whether the current dose recommended for supplementation is adequate. This question has also been raised by others (2,19). According to studies in younger adults, intakes of as high as 4,000-10,000 IU are safe (18,35). Furthermore, other studies indicate that individuals with a low starting level may need a high dose of vitamin D to achieve desirable vitamin D levels (18,20).

Vitamin D3 preferable to vitamin D2:-

The aim of the current study was to examine the effect of rapid vitamin D substitution with vitamin D3 (cholecalciferol). Pappaionnou et al (26) studied in 2011 the effect of a loading dose of vitamin D2 (ergocalciferol) and found no long-term advantage over daily supplementation (26). However, it has been shown that, although both vitamin D2 and D3 produce similar rises in serum 25-hydroxyvitamin D concentration over 3 days, levels decline much more rapidly in subjects treated with D2 (1). This may possibly reflect lower affinity of vitamin D2 for vitamin D binding protein in the circulation, leading to more rapid clearance. As such, use of supplements containing vitamin D3, rather than vitamin D2, is generally recommended (22). The current study demonstrates that, in patients with a normal corrected calcium level (< 2.60 mmol/L),rapid high dose substitution with 50,000 IU of vitamin D3 can normalize circulating serum vitamin D levels quickly and safely. This is important because all drugs used in the management of osteoporosis require normal vitamin D levels before they are started. However, the authors suspect that the majority of patients started on such treatment do not have their vitamin D levels checked systematically and are almost all deficient. This was certainly the case in the authors' institution before they undertook this study. This means that rapid substitution with high doses vitamin D3 makes sense after hip fractures. Interestingly, also calcium levels increase from an abnormal low value to within the normal range.

Vitamin D protects against falls and non-vertebral fractures:-

In addition, the fact that fall prevention and non-vertebral fracture prevention increased significantly with higher achieved 25-hydroxyvitamin D levels in two meta-analyses (8) of double-blind RCTs, is in itself a good reason to normalize vitamin D as soon as possible after admission with a fracture. Fall prevention was effective with 25-hydroxyvitamin D levels of 60 nmol/L up to 95 nmol/L, while 75-112 nmol/L were required for non-vertebral fracture prevention (9,25). Whether higher levels of vitamin D give even more protection against falls and fracture is not known, but has been postulated (6).

Limitations:-

Phase II and III : patients were not randomized, but were treated sequentially. Both phase II and phase III groups were relatively small (14 and 54 patients), but the dramatic rise in vitamin D levels($p < 0.0001$) makes the likelihood of the effects being fortuitous improbable. More research is needed to establish if the effect of a short course of high dose oral vitamin D3 substitution is maintained if followed by long term low dose therapy or if an occasional booster is required. Of more concern is the possibility that a patient with primary hyperparathyroidism might get high dose vitamin D supplementation causing severe hypercalcemia and the complications thereof. For this reason only patients with uncompromised renal function (GFR > 30 mL/min/1.73 m2) and a calcemic < 2.60 mmol/L received such a large dose. Patients who do not fit these criteria should be treated with much more caution. An algorithm for the management of all patients is shown. The authors' current practice for patients who present with a corrected calcium of 2.60-2.80 mmol/L is to measure the PTH level and renal function, and start a weekly dose of 50,000 units vitamin D3 and regular calcium monitoring. In the majority of cases initial high PTH levels are due to secondary hyperparathyroidism and at six weeks their repeat PTH level and calcium levels will have returned to normal. They can then receive additional vitamin D supplementation as required before remaining on a lifelong low dose vitamin D3 and calcium regime. Patients who present with corrected calcium of > 2.80 mmol/L and patients with corrected calcium between 2.60-2.80 mmol/L, whose PTH does not fall after a week of rapid vitamin D substitution, are referred to an endocrinologist for further investigation.

Conclusion:-

The benefits of maintaining adequate vitamin D levels in hip fracture patients have been established and the very low cost of the treatment makes it highly cost effective. The very low levels of vitamin D in this patient group took us by surprise, and further studies to evaluate levels in younger populations are clearly indicated. There have been recent reports of the re-emergence of vitamin D deficient related rickets in children in the, and it has been postulated that the national obsession with preventing sunburn because of the risk of skin cancer in later life, coupled with less time spent outdoors by the majority of the population, has had the unintended consequence of creating an entire population which is vitamin D deficient (21). The authors believe that the management of many other types of

osteoporotic fractures faces similar challenges with regard to vitamin D supplementation, although this needs to be explored. Investigating this should be a major public health priority, particularly because treatment would be easy and inexpensive.

References:-

1. **Armas LA, Hollis BW, Heaney RP.** Vitamin D2 is much less effective than vitamin D3 in humans. J Clin Endocrinol Metab 2004 ; 89 : 5387-5391.
2. **Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF.** Vitamin D and its major metabolites : serum levels after graded oral dosing in healthy men. Osteoporos Int 1998 ; 8 : 222-230.
3. **Binkley N, Ramamurthy R, Krueger D.** Low vitamin D status : definition, prevalence, consequences, and correction. Endocrinol Metab Clin North Am 2010 ; 39 : 287-301.
4. **Bischoff HA, Stähelin HB, Dick W et al.** Effects of vitamin D and calcium supplementation on falls : a randomized controlled trial. J Bone Miner Res 2003 ; 18 : 343-351.
5. **Bischoff HA, Stähelin HB, Tyndall A, Theiler R.** Relationship between muscle strength and vitamin D metabolites : are there therapeutic possibilities in the elderly ? Z Rheumatol 2000 ; 59 (Suppl.1) : 39-41.
6. **Bischoff-Ferrari H.** Vitamin D : what is an adequate vitamin D level and how much supplementation is necessary ? Best Pract Res Clin Rheumatol 2009 ; 23 : 789-795.
7. **Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson Hughes B.** Positive association between 25-hydroxy vitamin D levels and bone mineral density : a population-based study of younger and older adults. Am J Med 2004 ; 116 : 634-639.
8. **Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B.** Effect of cholecalciferol plus calcium on falling in ambulatory older men and women : a 3-year randomized controlled trial. Arch Intern Med 2006 ; 166 : 424-430.
9. **Bischoff-Ferrari HA, Willett WC, Wong JB et al.** Prevention of nonvertebral fractures with oral vitamin D and dose dependency : a meta-analysis of randomized controlled trials. Arch Intern Med 2009 ; 169 : 551-561.
10. **Broe KE, Chen TC, Weinberg J et al.** A higher dose of vitamin D reduces the risk of falls in nursing home residents : a randomized, multiple-dose study. J Am Geriatr Soc 2007 ; 55 : 234-239.
11. **Dixon T, Mitchell P, Beringer T et al.** An overview of the prevalence of 25-hydroxy-vitamin D inadequacy amongst elderly patients with or without fragility fracture in the United Kingdom. Curr Med Res Opin 2006 ; 22 : 405-415.
12. **Faulkner KA, Cauley JA, Zmuda JM et al.** Higher 1,25-dihydroxyvitamin D3 concentrations associated with lower fall rates in older community-dwelling women. Osteoporos Int 2006 ; 17 : 1318-1328.
13. **Fisher AA, Davis MW, Rubenach SE et al.** Outcomes for older patients with hip fractures : the impact of orthopedic and geriatric medicine cocare. J Orthop Trauma 2006 ; 20 : 172-178.
14. **Frolik CA, Deluca HF.** 1,25-dihydroxycholecalciferol : the metabolite of vitamin D responsible for increased intestinal calcium transport. Arch Biochem Biophys 1971 ; 147 : 143-147.
15. **Gertner JM, Domenech M.** 25-Hydroxyvitamin D levels in patients treated with high-dosage ergo- and cholecalciferol. J Clin Pathol 1977 ; 30 : 144-150.
16. **Glerup H, Mikkelsen K, Poulsen L et al.** Hypovitaminosis D myopathy without biochemical signs of osteomalaecic bone involvement. Calcif Tissue Int 2000 ; 66 : 419-424.
17. **Gullberg B, Johnell O, Kanis JA.** World-wide projections for hip fracture. Osteoporos Int 1997 ; 7 : 407-413.
18. **Heaney RP.** The Vitamin D requirement in health and disease. J Steroid Biochem Mol Biol 2005 ; 97 : 13-19.
19. **Heaney RP.** Barriers to optimizing vitamin D3 intake for the elderly. J Nutr 2006 ; 136 : 1123-1125.
20. **Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ.** Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003 ; 77 : 204-210.
21. **Holick MF, Chen TC.** Vitamin D deficiency : a worldwide problem with health consequences. Am J Clin Nutr 2008 : 87 : 1080S-1086S.
22. **Houghton LA, Vieth R.** The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr 2006 ; 84 : 694-697.
23. **Johnell O, Kanis JA**. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis Int 2006 ; 17 : 1726-1733.
24. **Keene GS, Parker MJ, Pryor GA.** Mortality and morbidity after hip fractures. BMJ 1993 ; 307 : 1248-1250.
25. **Moniz C, Dew T, Dixon T.** Prevalence of vitamin D inadequacy in osteoporotic hip fracture patients in London. Curr Med Res Opin 2005 ; 21 : 1891-1894.
26. **Papaioannou A, Kennedy C, Giangregorio L et al.** A randomized controlled trial of vitamin D dosing strategies after acute hip fracture : no advantage of loading doses over daily supplementation. BMC Musculoskeletal Disord 2011 ; 12 : 135.

27. **Parker MJ, Pryor GA, Myles J.** 11-year results in 2,846 patients of the Peterborough Hip Fracture Project : reduced morbidity, mortality and hospital stay. Acta Orthop Scand 2000 ; 71 : 34-38.
28. **Peppone LJ, Hebl S, Purnell JQ et al.** The efficacy of calcitriol therapy in the management of bone loss and fractures : a qualitative review. Osteoporos Int 2010 ; 21 : 1133-1149.
29. **Pfeifer M, Begerow B, Minne HW et al.** Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000 ; 15 : 1113-1118.
30. **Pfeifer M, Begerow B, Minne HW et al.** Effects of a long term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int 2009 ; 20 : 315-322.
31. **Prentice A.** Vitamin D deficiency : a global perspective. Nutr Rev 2008 ; 66 (10 Suppl 2) : S153-S164.
32. **Richy F, Ethgen O, Bruyere O, Reginster JY.** Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis : a meta-analysis of their effects on bone mineral density and fracture rate. Osteoporos Int 2004 ; 15 : 301-310.
33. **Tangpricha V, Pearce EN, Chen TC, Holick MF.**Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002 ; 112 : 659-662.
34. **Vieth R.** Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999 ; 69 : 842-856.Efficacy and safety of vitamin D3 intake exceeding the lowest observed adverse effect level. Am J Clin Nutr 2001 ; 73 : 288-294.