OSTEOPOROSIS IN CHRONIC SPINAL CORD INJURY

AND

THE EFFECT OF ZOLEDRONIC ACID

Dissertation submitted to the Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirements for the M.D. in Physical Medicine and Rehabilitation, March 2010

CERTIFICATE

This is to certify that this thesis entitled **"Osteoporosis in chronic spinal cord injury and the effect of zoledronic acid"** is the bonafide work of Dr. Shiela Mary Varghese and was conducted at the Department of Physical Medicine and Rehabilitation, Christian Medical College, Vellore.

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CONTENTS

LIST OF ABBREVIATIONS

SCI	-	Spinal cord injury
BMD	-	Bone mineral density
BMC	-	Bone mineral content
SPA	-	Single photon absorptiometry
DPA	-	Dual photon absorptiometry
QCT	-	Computed tomography
SXA	-	Single energy x-ray absorptiometry
DEXA/DXA	-	Dual energy x-ray absorptiometry
VDR	-	Vitamin D receptor
SERM	-	Selective estrogen receptor modulator
ONJ	-	Osteonecrosis of jaw
PTH	-	Parathyroid hormone

INTRODUCTION

INTRODUCTION

Spinal cord injury (SCI) is a traumatic insult to the spinal cord that can result in alterations of normal motor, sensory, and autonomic function. It is one of the most catastrophic injuries because of its multi-system involvement. Patients with chronic SCI experience musculoskeletal effects of non-weight bearing throughout their lives. Osteoporosis is one of the complications of spinal cord injury. Osteoporosis is defined as a disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk(1-3) . Osteoporosis is now widely recognized as a public health problem since this disease, which increases bone fragility and thereby the risk of fractures, is associated with high mortality, morbidity and medical expenses throughout the world (1).

Osteoporosis has been shown to have a prevalence of 70-80% in paraplegics in studies world wide(4), though its prevalence in traumatic spinal cord injury(SCI) in Indian patients has not been studied. The decline in bone density has been detected as early as 6 weeks post SCI and has been shown to steadily progress over the next 12-16 weeks before stabilizing. It is a major cause of skeletal fragility and fractures in these patients. The complications of fracture and their treatment cause considerable financial and social burden.

(DEXA) Dual Energy X-ray Absorptiometry, to determine bone density is the gold standard in diagnosing osteoporosis. DEXA is, by far, the most widely used technique for bone measurements since it is considered to be cheap, accessible, easy to use, and able to provide an accurate estimation of bone mineral density in adults(5).

DXA uses two x-ray beams with differing energy levels, which are aimed at the patient's bones. When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each beam by bone. However, the radiation dose is approximately 1/10th that of a standard chest X-ray. DEXA provides a means to assess bone density and predict fracture risk in chronic SCI patients and can help in planning preventive measures and rehabilitation.

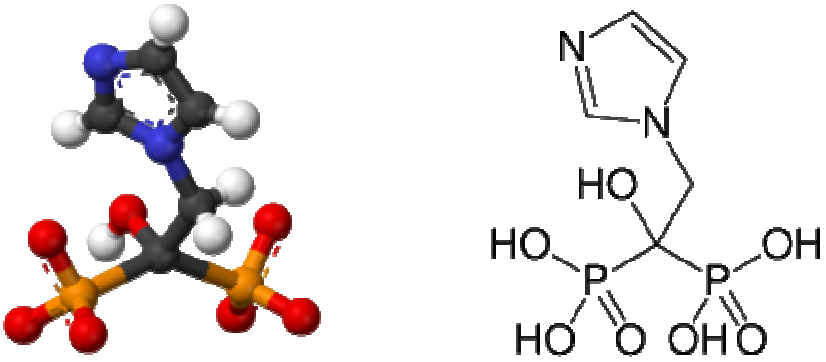
Among the antiresorptive drugs, the predictive value of preclinical studies has been particularly well documented with the bisphosphonates(1). Bisphosphonates are stable analogs of pyrophosphates, chelating agents originally used by industry to prevent calcium carbonate precipitation in plumbing(6). Owing to their chemical composition, bisphosphonates have a high binding affinity with the bone. They are primary agents in the current pharmacological arsenal against osteoclast mediated bone loss due to post menopausal osteoporosis, Paget`s disease of bone, malignancies with metastatis to bone, multiple myeloma or hypercalcemia of malignancy. In addition to currently approved uses, bisphosphonates are commonly prescribed for prevention and treatment of a variety of other skeletal conditions such as low bone density and osteogenesis imperfecta. Several types of bisphosphonates are being used at present.

Etidronate, Clondronate, Tiludronate, Pamidronate and Alendronate have been administered to individuals following acute and chronic spinal cord injury, in order to prevent bone loss. Varying results have been obtained with different bisphosphonates.

Although the exact mechanism of the bisphosphonate-mediated osteoclast inhibition has not been completely elucidated, there is evidence that these substances could block dissolution of hydroxyapatite, inhibit differentiation of bone marrow precursors into osteoclasts, inhibit osteoclast function by interfering with the mevalonate pathway of cholesterol biosynthesis, and induce apoptosis of osteoclasts (6).

Zoledronic acid (1-hydroxy-2-imidazole-1-yl-1-phosphono-ethyl phosphonic acid), is a newer and more potent bisphosphonate, belonging to a new class of highly potent nitrogen containing bisphosphonates.

(Figure 1) Chemical structure of Zoledronic acid



It has been approved by the US FDA for use in hypercalcemia of malignancies and for treatment of postmenopausal osteoporosis. When given every year by intravenous infusion, the drug increases bone mineral density and reduces fracture risk in women with postmenopausal osteoporosis. It also reduces subsequent fractures in patients who have had an osteoporosis-related fracture, and increases survival in those who have sustained a low impact hip fracture. In postmenopausal women, zoledronic acid produces an effect on bone turnover and bone density as great as those achieved with daily oral administration of other bisphosphonates, with proven efficacy against fractures with only an annual infusion.

It is also used to prevent skeletal fractures in patients with cancers, such as multiple myeloma and prostate cancer. Zoledronate has been approved as a once yearly 4 mg infusion for treatment of osteoporosis and it has shown significant benefits versus placebo with a reduced number of vertebral fractures and improved markers of bone density.

JUSTIFICATION OF THE STUDY

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Comprehensive care and early rehabilitation has improved the quality of life of people following spinal cord injury. However osteoporosis among this group of individuals often predisposes them to the risk of secondary fractures and related complications. These are the cause of considerable financial and social burden.

The sites and severity of skeletal bone loss can now be more accurately determined with use of densitometry. Bone loss has been reported to occur in the lower extremities mostly and DEXA scan provides a means to predict fracture risk in chronic SCI patients. This can help in planning fracture preventive measures during their rehabilitation.

Although various groups of bisphosphonates have been studied in the past for osteoporosis treatment and prophylaxis among SCI patients, the results have shown only a modest potential benefit and the compliance poor for the forms requiring regular oral intake. Zoledronic acid, a newer and more potent bisphosphonate with potential for single dose yearly intravenous infusion has been shown to be beneficial in osteoporosis in postmenopausal women and in liver transplant patients. However its benefit in osteoporotic chronic spinal cord injured patients needs to be studied. If found beneficial it has the potential to ensure better compliance and fracture prophylaxis in our subset of chronic spinal cord injured patients due to the advantage of yearly dose administration.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

Introduction

Osteoporosis is a disease that occurs commonly in the rehabilitation patient population in its primary and secondary forms(7). Osteoporosis is a disease of the skeletal system characterized by low bone mass and deterioration of bone tissue leading to an increased risk of bone fractures (1, 2, 8). Osteoporosis due to immobilization is an important and increasingly prevalent clinical condition in the aged and disabled populations(9). Persons with traumatic spinal cord injury (SCI) undergo transition immediately from a normal ambulatory lifestyle to a state of markedly impaired mobility(8). The osteoporosis that accompanies SCI predisposes to fracture after minor trauma. Bone mineral loss occurs throughout the entire skeleton, except the skull(10). Most bone loss occurs rapidly and below the pelvis. Homeostasis is reached by 16 months at two thirds of original bone mass, near fracture threshold(10).

Conceptual Definition of Osteoporosis

Various definitions of osteoporosis have been offered to describe the outcome of events (fragility fractures), the process giving rise to porous bones, or the resultant diminution in bone mass. The following definition is now generally accepted '*a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk*'(1, 3)

The World Health Organization (WHO) defines osteoporosis as a spinal or hip bone mineral density (BMD) of 2.5 standard deviations or more below the mean for healthy, young persons (t-score of −2.5 or below) as measured by dual energy x-ray

absorptiometry (DEXA). Osteopenia is defned as a spinal or hip BMD between 1 and 2.5 standard deviations below the mean (11).

Thus, the decrease in bone mass with changes in micro-architecture and consequent increased fragility represents the disease, whereas low-energy fractures represent a complication of the disease that will occur when the force applied to a bone, such as that resulting from falling, exceeds its load-bearing capacity(1). Thus, the osteporotic fracture depends upon several internal and external factors that are not directly related to the osteoporotic process.

CLASSIFICATION OF OSTEOPOROSIS(7)

Osteoporosis can be classified according to localization in the skeleton and according to etiology. Localized osteoporosis affects part of the skeleton; generalized osteoporosis affects, to a greater or lesser extent, different parts of the whole skeleton. Both types of osteoporosis can further be classified into primary and secondary osteoporosis.

A. Primary osteoporosis: basic etiology unknown, no associated disease
    1. Postmenopausal osteoporosis: elderly women
    2. Senile osteoporosis: elderly men

B. Secondary osteoporosis: secondary to inherited or acquired abnormalities/diseases or to physiologic aberrations
    1. Hyper parathyroidism
    2. Cushing's disease
    3. Multiple myeloma
    4. Hyperthyroidism (endogenous and iatrogenic)
    5. Idiopathic hypercalciuria

a. Due to renal calcium leak

b. Due to renal phosphate leak

6. Malabsorption (including partial gastrectomy)

7. 25 – OH vitamin D deficiency

    a. Due to chronic liver disease

    b. Due to chronic anticonvulsant therapy (phenytoin, barbiturates)

8. 1, 25$(OH)_2$ vitamin D deficiency due to lack of renal synthesis

    a. Due to chronic renal failure

9. Adult hypophosphatasia

10. Osteogenesis imperfecta tarda

11. Male hypogonadism (Klinefelter's syndrome)

12. Female hypogonadism (Turner's syndrome)

13. Conditions consistent with hypoestrogenism secondary to anorexia and/or exercise

    a. Anorexia nervosa

    b. Exercise-induced amenorrhoea

14. Conditions associated with disuse

    a. Paraplegia/hemiplegia

    b. Immobilization

    c. Prolonged bed rest

15. Alcoholism

16. Diabetes mellitus

17. Rheumatoid arthritis

18. Chronic obstructive pulmonary disease

19. Systemic mastocytosis

20. Conditions associated with the use of medications

    a. Corticosteroids b. Heparin

    c. Anticonvulsants d. Excess thyroid hormone

21. Malignancy

ETIOLOGY AND RISK FACTORS FOR OSTEOPOROSIS

Risk of developing an osteoporosis related fracture is dependent on an individual`s peak bone mass and strength of bone achieved in one's lifetime and the subsequent rate of bone loss. Multiple etiologic factors may act independently or in combination in an individual patient to produce diminished bone mass.

RISK FACTORS FOR OSTEOPOROTIC FRACTURES(7)

Personal history of low-impact fracture

Current low bone mineral density

History of fracture in a first-degree relative

Caucasian race

Advanced age

Female sex

Dementia

Recurrent falls

Inadequate physical activity

Poor health/frailty

Current smoker

Low body weight

Estrogen deficiency

Corticosteroid use

Testosterone deficiency

Vitamin D deficiency

Low life time calcium intake

Alcoholism

Impaired eye sight despite correction

PATHOGENESIS(12)

The pathogenesis of osteoporosis is complex. In childhood and adolescent period, rate of bone formation exceeds resorption, resulting in continued skeletal growth and denser, longer and heavier bones. This process slows down in adulthood, and peak bone mass is attained at about 30 years of age. After this, resorption begins to exceed formation. Normal bone loss averages 0.7 per cent per year. It gets accelerated at the time of menopause to 2-5 percent per year, which may continue for up to 10 years. Since cancellous bone is metabolically much more active than cortical bone, in periods of accelerated bone loss cancellous bone loss is 3-fold greater. Osteoporotic fractures therefore commonly occur in vertebrae. Peak bone mass is primarily determined by genes but may be modified to a considerable extent by factors such as physical activity, calcium, vitamin D nutrition, smoking, alcohol, concurrent illness and medications – glucocorticoids and antiepileptics. The level of peak bone mass achieved at puberty is a major determinant of bone mass in later life and hence an important factor in the ultimate development of osteoporosis.

Cellular abnormalities

Conclusive evidence of cellular abnormalities contributing to the pathogenesis of osteoporosis is lacking. It may be that failure of osteoblast (the cell responsible for bone formation), due to either decreased cell number or decreased cell activity, may accompany advancing age but is not specific for osteoporosis(7).

DIAGNOSIS OF OSTEOPOROSIS

The first clinical indication of osteoporosis, either primary or secondary, will usually be a fracture. An absolute diagnosis of osteoporosis is usually made when an atraumatic fracture occurs in the presence of low bone mass (most typically of the spine, femur, and/or distal radius). However it is obviously of value from the standpoint of patient management to evaluate the patient at risk for fracture before a fracture occurs, as well as to determine the cause of the fracture in patients in whom a fracture has occurred. Because the amount of bone mass present is the principal determinant of fracture, a non-invasive technique for quantifying bone mass would consequently be of value not only in the diagnosis of osteoporosis, but also in following a response to therapy.

Methods for measuring bone mass

Bone mass measurements and biochemical markers of bone turnover are key methods to diagnose osteoporosis, predict future fracture, and monitor therapeutic regimens.

Biochemical markers of bone turnover

Markers for bone formation:

Serum

i. Osteocalcin

ii Bone-specific alkaline phosphatase.

Markers for bone resorption:

Plasma

i. Tartrate-resistant acid phosphatase.

ii. Free pyridinoline and deoxypyridinoline and Type I collagen N and C-telopeptides breakdown products.

Urine

i. Urinary pyridinoline and deoxypyridinoline (collagen cross links) and type I collagen N and C-telopeptides breakdown products.

ii. Fasting urinary calcium and hydroxyproline.

iii. Urinary hydroxylysine glycosides.

Roberts et al (13) demonstrated a dramatic rise in bone resorption markers, beginning within the first week of injury and peaking around weeks 10–16. Depending on the resorption marker examined, the peak was as high as 10 times the upper limit of normal. Values had not returned to baseline at 6 months, indicating ongoing loss of bone. Contrasting with the large rise in resorption markers, the change in markers of bone formation was modest and barely exceeded the reference range.

Quantitating bone mass

Most commonly used techniques

1. Single- and dual- photon absorptiometry (SPA and DPA respectively)
2. Quantitated computed Tomography. (QCT)
3. Single or dual-energy x-ray absorptiometry. (DXA)
4. Peripheral quantitated computed tomography. (pQCT)

Attenuation or absorption of ionizing radiation by bone is the basic principle used in the majority of the noninvasive techniques (with the exception of ultrasound). A generally linear relationship exists between bone mass and radiation attenuation: the greater the amount of bone present, the greater the attenuation of ionizing radiation, and subsequently the less radiation quantitated in a detector(7).

DXA is the clinical ‘‘gold standard’’ for diagnosing osteoporosis(14). DXA allows the measurement of bone mineral density in the axial and peripheral skeleton. Bone density measurements can be obtained within 30 seconds to 2 minutes with a radiation exposure of approximately 10 m rad (one-sixth the exposure of a chest x-ray) with 99% precision and approximately 97% accuracy(7). However the DEXA technology for diagnosing osteoporosis by measuring bone density became available in India only in 1997(12).

(Figure 2) DEXA scan of left hip (Report from Department of Endocrinology, CMC, Vellore)

L = 1.141, dB = 52.2
103 x 99
NECK: 48 x 15

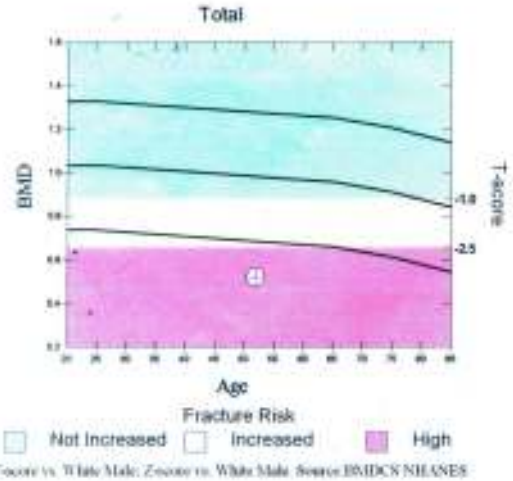
Scan Information:

Scan Date: 05 May 2009 ID: A0505090D
Scan Type: f Left Hip
Analysis: 05 May 2009 09:53 Version 12.7.3.1:7
Hip
Operator: PK
Model: Discovery W (S/N 70471)
Comment:

DXA Results Summary:

Region	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T-score	Z-score	AM (%)
Neck	4.93	2.40	0.486	-3.3	-2.5	59
Troch	11.14	5.00	0.449	-2.6	-2.3	61
Inter	16.86	9.76	0.579	-3.4	-3.2	58
Total	**32.93**	**17.16**	**0.521**	**-3.4**	**-3.0**	**53**
Ward's	1.15	0.50	0.433	-2.5	-1.2	73

Total BMD CV 1.0%, ACF = 1.025, BCF = 0.999, TH = 4.950
WHO Classification: Osteoporosis
Fracture Risk: High

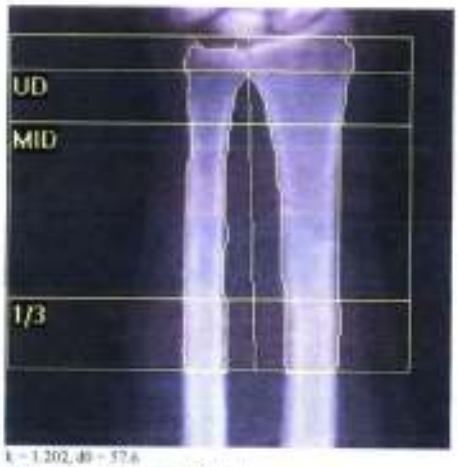


T-score vs. White Male; Z-score vs. White Male. Source: BMDCS NHANES

Physician's Comment:

HOLOGIC

(Figure 3) DEXA scan of left forearm (Report from Department of Endocrinology, CMC, Vellore)



L = 1.202, d0 = 57.6
228 x 96. Forearm Length: 26.0 cm

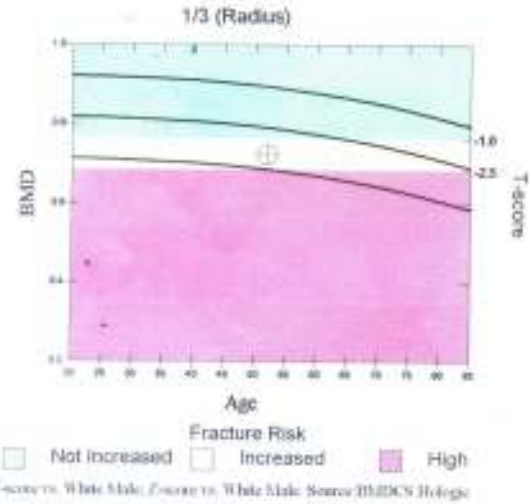
Scan Information:

Scan Date: 05 May 2009 ID: A0505090C
Scan Type: a L.Forearm
Analysis: 05 May 2009 09:47 Version 12.7.3.1:7
Left Forearm
Operator: PK
Model: Discovery W (S/N 70471)
Comment:

DXA Results Summary:

Radius	Area (cm^2)	BMC (g)	BMD (g/cm^2)	T - score	Z - score	AM (%)
UD	3.32	1.35	0.408	-2.3	-1.7	80
MID	7.34	4.36	0.594	-2.1	-1.7	86
1/3	2.79	2.01	0.723	-1.8	-1.3	92
Total	**13.44**	**7.73**	**0.575**	**-2.2**	**-1.7**	**87**

Total BMD CV: 1.0%, ACF = 1.025, BCF = 0.999
WHO Classification: Osteopenia
Fracture Risk: Increased



Reference: White Male; Z-score vs. White Male; Source: BMDCS Hologic

Physician's Comment:

HOLOGIC

Interpretation of BMD analysis report

The measurements, which are carried out to three decimal places, are given in grams per square centimeter. They are used to determine the T score and the Z score. The T score assesses the risk of fracture. It compares the subject's BMD with the predicted mean peak BMD (in an average 30 year old of the same sex) and expresses the difference in standard deviation (SD). In other words, the T score shows how the subject's BMD compares with the ideal level. A patient who's BMD is 1 SD below that of an average 30-year-old has a T score of –1. The Z score determines whether the subject's bone loss is out of proportion with what is expected. It compares the subject with the mean for age matched, sex-matched, and ethnic-matched controls and expresses the difference in SD. Thus, a 70-year-old woman with a Z score of –1 is 1 SD below the BMD of the average 70-year-old woman, but her T score is –3 because she is 3 SD below the BMD of the average 30-year-old woman. The T score is useful in assessing a patient's risk of fracture and deciding whether to recommend pharmacological therapy. In general, almost all patients whose BMD is in the osteoporotic range should be considered for such therapy. Many patients with values in the osteopenic range, particularly those in the lower end of the range or with several risk factors for fracture, should also be considered for pharmacological therapy.

In a meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures, Marshal et al concluded that bone mineral density can identify people who are at increased risk of developing a fracture, but it cannot with any certainty identify individuals who will develop a future fracture(15). It was also found that most measuring sites (proximal radius, distal radius, hip lumbar spine, calcaneus, and all sites) had virtually the same predictive ability for a decrease of 1 SD in bone density. There were

two exceptions to this general observation. Measurement at the spine seemed to have a better predictive ability for spine fractures (relative risk 2.3 (95% confidence interval 1.9 to 2.8)), while measurement at the hip was better for predicting hip fractures [relative risk 2.6 (2.0 to 3.5)](15).

VITAMIN D

VITAMIN D is essential for maintaining calcium and phosphorus homeostasis, and optimizing bone health(16). It is widespread in nature and photosynthesized in most plants and animals exposed to sunlight(17). Its major role in vertebrate animals and humans is to increase the absorption of calcium and phosphate for the mineralization of the skeleton(18).

Inadequate intake of calcium and vitamin D leads to reduced calcium absorption, increased serum parathyroid hormone concentrations, and bone loss (19). Dawson-Hughes et al (19) in their study concluded that calcium and vitamin D supplementation leads to a moderate reduction in bone loss and may substantially reduce the risk of nonvertebral fractures among men and women 65 years of age or older who live in the community. Bischoff-Ferrari et al (20) in their meta-analysis concluded that oral vitamin D supplementation in the range of 700 to 800 IU/d should reduce the risk of hip or any non-vertebral fracture by approximately 25%. The role of additional calcium supplementation together with 700 to 800 IU/d vitamin D could not be clearly defined, but dietary calcium intakes of more than 700 mg/d may be necessary for nonvertebral fracture prevention(20). In a meta-analysis of randomized controlled trials, Bischoff-Ferrari(20) described 2 physiological explanations for the beneficial effect of vitamin D on fracture risk in older persons. First, the well-described decrease in bone loss in older persons (19); and second, vitamin D appears to have a beneficial effect on muscle

strength, reduction in fall (21) and balance(22) mediated through highly specific receptors in muscle tissue.

Physiology of vitamin D and bone mineralization

Vitamin D3, or cholecalciferol, is synthesized in the skin(18). Its precursor, 7-dehydrocholesterol, is converted by the UV light of the sun (UVB 290–315 nm) into previtamin D3, which is slowly isomerized to vitamin D3(18). Vitamin D binding protein (DBP) binds vitamin D and its metabolites and transports them in the bloodstream. Some nutrients also contain vitamin D3, e.g., fatty fish, eggs, and dairy products. Vitamin D2, or ergocalciferol, originates from irradiation of ergosterol, a major plant sterol, and has been added to dairy products and multivitamin preparations. Vitamin D2 is also transported in the circulation by DBP, and its metabolism is similar to that of vitamin D3(18). Vitamin D is hydroxylated in the liver into 25-hydroxy vitamin D [25(OH) D], which is the major circulating metabolite. Further hydroxylation into 1, 25-dihydroxy vitamin D [1, 25-$(OH)_2$ D] occurs primarily in the kidney. The hydroxylation in the kidney is stimulated by PTH and suppressed by phosphate. While 25(OH) D has limited biological activity, 1, 25-$(OH)_2$ D is the most active metabolite stimulating the absorption of calcium and phosphate from the gut. The production of 1, 25-$(OH)_2$ D is under tight feedback control, directly by serum calcium and phosphate and indirectly by calcium via a decrease of serum PTH.

The free serum 1, 25-$(OH)_2$ D concentration is very low, as it is more than 99% bound to DBP and albumin. The active metabolite 1, 25-$(OH)_2$ D acts through the vitamin D receptor (VDR), a specific nuclear receptor, related to the T4 and steroid hormone receptors. The VDR is present in the intestine where 1, 25-$(OH)_2$ D, after binding to the VDR, stimulates the synthesis of several proteins in the intestinal cells, which participate

in the transport of calcium from the intestinal lumen into the bloodstream. The VDR is also present in many other organs such as bone, muscle, pancreas, and pituitary. The active metabolite 1, 25-$(OH)_2$ D influences muscle function and stimulates cell differentiation and immunological function in general. The action of 1, 25-$(OH)_2$ D on bone is not well understood. It stimulates the osteoblasts to produce osteocalcin and alkaline phosphatase. On the other hand, 1, 25-$(OH)_2$ D stimulates bone resorption in vitro. The effects of 1,25-$(OH)_2$D on bone mineralization appear to be indirect by stimulating the calcium and phosphate supply, mainly by absorption from the gut(18).

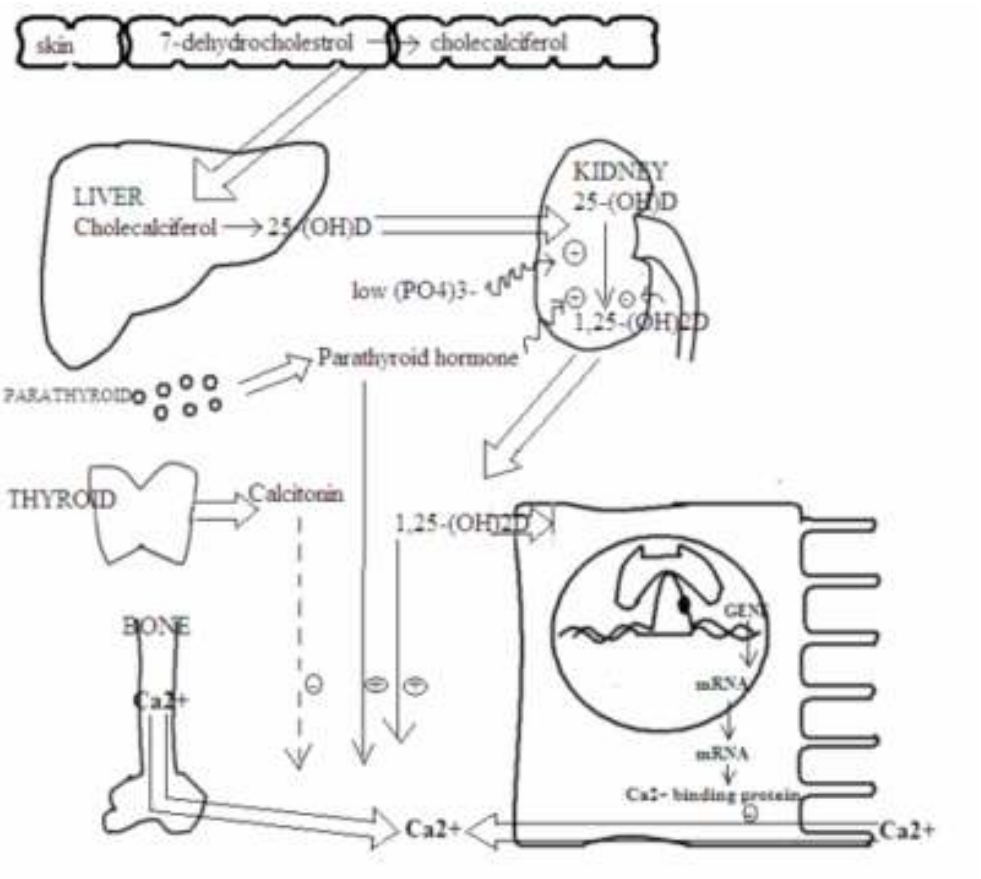
The bone remodeling sequence by which new osteons are formed starts with osteoclasts resorbing existing bone. Thereafter, osteoblasts appear and construct the new un-mineralized bone matrix, the osteoid. Subsequently, the osteoid is mineralized. The mineralization of the osteoid occurs in two phases. During primary mineralization, about half of the bone mineral accumulates within a few days, increasing the density to 1.4 g/ cm^3. The secondary mineralization proceeds more slowly during 6 months or more and increases the density to 1.9 g/cm^3(18). When mineralization is normal, the mineral content of an osteon depends on its age. Young, low-density bone is more prevalent when bone turnover is high. Older, completely mineralized high-density bone is associated with low bone turnover.

Consequences of Vitamin D Deficiency - Secondary hyperparathyroidism and high bone turnover

A low serum 25(OH) D concentration is the hallmark of vitamin D deficiency(18). The 1,25-dihydroxy vitamin D assay should never be used for detecting vitamin D deficiency because levels will be normal or even elevated as a result of secondary hyperparathyroidism (23). The low serum 25(OH) D concentration leads to a decrease of

serum 1, 25-$(OH)_2$ D and calcium absorption. The lower serum calcium concentration causes an increase of PTH secretion, which stimulates the production of 1, 25-$(OH)_2$ D. By this mechanism serum 1, 25-$(OH)_2$ D is kept at (nearly) normal levels at the expense of a higher serum PTH concentration, which is referred to as "secondary hyperparathyroidism." It implicates that serum PTH is relatively high for the associated serum calcium concentration, although it may still be within normal reference limits(18).

(Figure 4) Metabolism of vitamin D and the biologic actions of 1,25-dihydroxycholecalciferol



Vitamin D3 supplementation causes a decrease of the serum PTH concentration, a decrease of bone turnover, and an increase of bone mineral density(18). Recent

recommendations suggest that in the absence of sun exposure, adults should ingest 1000 IU of vitamin D3 per day. The ideal healthy blood level of 25-hydroxyvitamin D should be 30 to 60 ng/mL. Vitamin D intoxication occurs when 25-hydroxyvitamin D levels are greater than 150 ng/mL(24).

Adami et al in 2008 concluded that optimal vitamin D repletion seems to be necessary to maximize the response to anti-resorbers in terms of both BMD changes and anti-fracture efficacy(25). They also found that the adjusted incidence of clinical fracture is 77% higher in vitamin D depleted women(25). Shinchuk(16) et al found that Vitamin D deficiency, osteopenia and osteoporosis are highly prevalent in both men and women admitted for subacute rehabilitation after an acute hospitalization. Bone remodeling activity was elevated with a disproportional increase in bone resorption. It was suggested that this, could be due to vitamin D deficiency that should be corrected before antiresorptive therapy is considered(16).

Proposal for staging of vitamin D deficiency (18)- Lips et al

Mild Vitamin D deficiency (Vitamin D insufficiency) - 10-20 ng/ml

Moderate Vitamin D deficiency - 5-10 ng/ml

Severe Vitamin D deficiency - <5 ng/ml

Untreated, Vitamin D deficiency will lead to development of osteopenia and osteoporosis defined by World Health Organization (WHO) as bone mass 1 and 2.5 standard deviations (SDs) below the sex-controlled young adults, respectively(16).

MANAGEMENT OF OSTEOPOROSIS

Because osteoporosis results in fractures due to minimal trauma, rapidly effective therapy is required to reduce fracture risk(26). Treatment of osteoporosis includes pharmacological and non-pharmacological methods.

NON-PHARMACOLOGICAL TREATMENT

The avoidance of lifestyles known to result in bone loss, including cigarette smoking, excessive alcohol intake, lack of exercise, and so forth, should be addressed along with recommendations for nutritional and pharmacologic therapy(7). Morse et al reported that increased alcohol consumption after SCI may exacerbate sublesional bone loss(27).

Fall prevention

A multifactorial approach that addresses vision deficits, balance and gait abnormalities, cognitive impairment, and dizziness is the cornerstone of fall prevention. Improving lighting, removing loose rugs, and adding grab bars near bathtubs, toilets, and stairways can enhance safety(28).

NUTRITIONAL ADJUNCTS

Calcium

It is a mainstay of osteoporosis prevention and treatment. Recommended minimum calcium intake is 1000 to 1500 mg/day in all perimenopausal and postmenopausal women and for men is 800 to 1500mg. Calcium is generally safe (in the absence of a history of previous kidney stones, or of idiopathic hypercalciuria), comparatively inexpensive, and logistically simple to ingest. A predisposition for kidney stones and nephrolithiasis may

be seen. A urinary calcium excretion of up to 250 mg per 24 hours is acceptable in individual without a history of kidney stones(7).

Vitamin D

400 to 800 IU per day of vitamin D is recommended. This will help to increase calcium absorption at the gut level, and use of active form of vitamin D analogs as calcitriol may result in increased risk for kidney stones or for hypercalciuria, nephrolithiasis, or even nephrocalcinosis(7).

Protein

Along with calcium and vitamin D supplementation, protein supplementation has been shown to favorably affect outcomes in patients who have sustained hip fractures. The RDA for protein is 44 g/day for women and 56 g/day for men(7).

PHARMACOLOGICAL TREATMENT OF BONE MASS DEFICIENCY

The treatment of osteoporosis and osteopenia is directed at preservation or improvement of bone mass at the specific target sites. Because bone mass is the principal, although not the only, determinant of fracture, such preservation or improvement of bone mass is associated with a reduced risk of fracture. The axial and appendicular sites exhibit varying proportions of cortical (compact) and trabecular (cancellous) bone. Trabecular bone is metabolically more active than cortical bone(7). Trabecular bone appears to be preferentially altered in osteoporosis and is the type of bone most affected by medications used in the treatment of osteoporosis.

A number of U.S. Food and Drug Administration (FDA) approved therapeutic agents are available to decrease bone resorption (anti-bone resorbers). There are also a number of therapeutic modalities that increase bone formation (positive bone formers)(7).

Antiresorptive Agents

Among the antiresorptive drugs, the predictive value of preclinical studies has been particularly well documented with the bisphosphonates.

Bisphosphonates are primary agents in the current pharmacological arsenal against osteoclast-mediated bone loss due to osteoporosis, Paget`s disease of bone, malignancies metastatic to bone, multiple myeloma, and hypercalcemia of malignancy(29). Structurally, bisphosphonates are chemically stable derivatives of inorganic pyrophosphate (PPi), a naturally occurring compound in which 2 phosphate groups are linked by esterification(29). It is the most commonly used treatment for established osteoporosis, inhibits osteoclast-mediated bone resorption and reduces the risk of vertebral fracture. Maimoun et al cited that bisphosphonates reduce bone loss in both the early and chronic phases of SCI, even though the demineralization process cannot be stopped(30).

The various bisphosphonates available are etidronate, tiludronate, alendronate, risedronate, palmidronate, zoledronate and ibandronate. Of these, once-a-week formulations are available for alendronate and risedronate. Ibandronate is available as once a month oral formulation. Newer bisphosphonates such as tiludronate, pamidronate, and alendronate are respectively 10, 100, and 1000 times more potent than etidronate(30). Oral bisphosponates have limitations related to long-term compliance, gastrointestinal intolerance, and poor and variable absorption from the gastrointestinal tract(31). Because

food and certain minerals reduce the absorption of bisphosphonates, they should be taken at least 30 minutes before the first food, drink (other than water), or medication of the day(26). Tablets should be swallowed with 6 to 8 oz of water. To reduce the risk of gastroesophageal irritation, patients should remain upright for at least 30 minutes after dosing(26).

Intermittent intravenous administration of bisphosphonates might address some of these problems and has been shown to be effective in the treatment of malignant hypercalcemia and Paget's disease and to reduce the rate of skeletal complications in patients with breast carcinoma or multiple myeloma(31). An intravenously administered bisphosphonate may have a potential advantage over oral preparations in that oral preparations require that the patient maintain upright posture, which may not be possible for weeks in SCI patients with osteoporois and pressure ulcers, which may prevent the patient from being seated upright.

Intravenous bisphosphonates available in market are palmidronate, zoledronate and ibandronate. Reid et al stated that intermittent intravenous administration of the potent bisphosphonate - zoledronic acid results in changes in biochemical markers of bone turnover and in bone mineral density that are similar to those observed with daily oral bisphosphonate therapy(31). Black et al demonstrated that during a 3-year period, an annual infusion of 5 mg of zoledronic acid significantly reduced the risk of fracture at all key osteoporotic fracture sites, including the two primary end points, vertebral and hip fractures(32).

Intravenous bisphosphonates have been shown to be potent inhibitors of bone resorption in a wide variety of conditions associated with increased osteoclastic function.

Because of their multifactorial pharmacological effects on inhibition of the osteoclast, bisphosphonates may be hypothesized to be efficacious in reducing or preventing the osteoporosis associated with immobilization. Bisphosphonate therapy has also reduced the increased urinary calcium excretion in able-bodied individuals restricted to bed rest.

Zoledronic acid (1-hydroxy-2-imidazole-1-yl-1-phosphono-ethyl phosphonic acid), a newer and more potent bisphosphonate, belongs to a new class of highly potent nitrogen containing bisphosphonates. Zoledronic acid is approved by the FDA for the treatment, but not the prevention, of osteoporosis(33). A single administration of Zoledronic acid has been found to ameliorate bone loss and maintain parameters of bone strength at the three proximal femur sites for 6 month and at the femur intertrochanteric and shaft sites for 12 months(34). Because it has high potency, only small doses are required for the inhibition of bone resorption, and long dosing intervals may be used(31). Prolonged suppression is not the result of the persistence of the drug in the circulation, given that by 24 hours after administration, drug levels are less than 1 percent of the post administration peak and 40 percent of the dose has been excreted in the urine(31). The balance of the dose is presumably bound to bone and is slowly released back into the circulation, giving rise to a 167-hour terminal half-life in plasma.

Reid et al found that Zoledronic acid was generally well tolerated, and the rate of retention of subjects in the study was high(31). He also stated that the adverse events that were more common in women receiving zoledronic acid were those that have occurred previously in patients receiving intravenous aminobisphosphonates and were transient. In the zoledronic acid groups, most adverse events were instances of musculoskeletal pain, nausea, or fever, most of which were rated as mild(31). Infrequent doses may increase tolerance of these side effects. Crawford et al found that despite a total of 20 mg

of zoledronic acid being administered over 12 months to patients with major co-morbid conditions, there was no increase in adverse events other than temporary, induced secondary hypoparathyroidism and hypocalcemia(35). However since late 2003, an increasing number of reports suggest a possible association between the use of bisphosphonates and avascular necrosis of the jaws. The risk of ONJ associated with oral bisphosphonate therapy for osteoporosis seems to be low, estimated between 1 in 10,000 and <1 in 100,000 patient-treatment years(36). The risk of ONJ in patients with cancer treated with high doses of intravenous bisphosphonates is clearly higher, in the range of 1-10 per 100 patients (depending on duration of therapy). MacLean et al in his systematic review found multiple published cases of osteonecrosis of the jaw in patients with cancer who received large doses of bisphosphonates intravenously.

Reid et al also cited that intermittent intravenous administration of the potent bisphosphonate zoledronic acid results in changes in biochemical markers of bone turnover and in bone mineral density that are similar to those observed with daily oral bisphosphonate therapy(31).

Estrogen

Estrogen is also approved by the FDA for preventing osteoporotic fractures in postmenopausal women(33). The evidence suggests that estrogen reduces the risk for vertebral and hip fracture; however, the effect of estrogen on nonvertebral fracture risk is less clear.

Selective estrogen receptor modulators (SERM)

Selective estrogen receptor modulators (SERMs) have been developed to provide beneficial effects similar to those obtained with estrogen, but without the adverse effects(7). The common SERMs used are tamoxifen, raloxifen or droloxifen. Raloxifene (evista), a selective estrogen receptor modulator, is approved for the treatment of postmenopausal osteoporosis(11). Raloxifene has estrogen agonist activity on the bones and lipids, and an estrogen antagonist effect on the breast and uterus. Raloxifene is effective for reducing the incidence of vertebral fractures, but effectiveness at the hip has not been shown.

Raloxifene is commonly associated with increased vasomotor symptoms. Although raloxifene increases the risk of venous thromboembolism, it is indicated to decrease the risk of invasive breast cancer in postmenopausal women with osteoporosis(11). It may be best used in postmenopausal women with osteoporosis who are unable to tolerate bisphosphonates, have no vasomotor symptoms or history of venous thromboembolism, and have a high breast cancer risk score(11).

Salmon Calcitonin

Both intranasal and injectable forms of salmon calcitonin (Miacalcin) are approved for the treatment of postmenopausal osteoporosis. Calcitonin inhibits bone resorption and is recommended for use in women with osteoporosis who are at least five years past menopause and cannot take other agents(26).

Adherence to osteoporosis treatment

The term *adherence* comprises both compliance and persistence to treatment. *Compliance* refers to how the medication is taken or quality of intake. *Persistence* is defined as the time from initiation to discontinuation of treatment(37). In one of the

largest survey to date that has been carried on treatment adherence to osteoporosis treatment, Rossini et al(37) found that the mean discontinuation rate was 19%, over a mean period of follow up of 14 months. The study population consisted of 9851 postmenopausal women who had been referred to the osteoporosis centres at least 1 year after having been prescribed one of the drugs registered in Italy for postmenopausal osteoporosis therapy at the time the study was initiated (2002). The most frequent reasons for discontinuation were drug related side effects, insufficient motivation to treatment, and apprehension regarding side effects(37). Treatment compliance is particularly poor for Calcium and Vitamin D and this emphasizes the need for new ways to supplement at least vitamin D.

Anabolic agents (Positive bone formers)

Parathyroid hormone

Parathyroid hormone, or fragments of the intact peptide molecule, may be of value in osteoporosis when administered parenterally. Such a usage is based on a presumed anabolic effect of parathyroid hormone when administered as a fragment, and it may be of value in established osteoporosis in terms of stimulating bone formation. The FDA approved the use of parathyroid hormone for the treatment of osteoporosis in 2002(7).

Recombinant human parathyroid hormone (Teriparatide)

Teriparatide (Forteo), is a recombinant human parathyroid hormone (rhPTH[1-34]), with potent bone anabolic activity(11). It is approved for the treatment of postmenopausal women with severe bone loss, men with osteoporosis who have a high risk of fractures, and persons who have not improved on bisphosphonate therapy(11). In a dosage of 20 mcg per day given subcutaneously for up to two years, teriparatide

decreases vertebral and nonvertebral fractures(38). Because the long-term effects of teriparatide are not known, this agent is approved for a maximum of two years of use in patients with severe osteoporosis who are at high risk for fractures(26). Adverse effects may include orthostatic hypotension, transient hypercalcemia, nausea, arthralgia, and leg cramps. Increased risk of osteosarcoma is seen in rats exposed to high doses(11). Consequently, teriparatide is contraindicated in patients with risk of osteosarcoma, such as those with Paget`s disease, previous skeletal radiation, or unexplained elevation of alkaline phosphatase level(11).

Fluoride

Fluoride as sodium salt has been introduced in the therapy of human osteoporosis without any well documented preclinical assessment of the relationship between bone mass and strength(1). Sodium fluoride must be viewed as an experimental therapy with some concerns regarding its overall usage in osteoporosis.

Experimental therapies

1. Anabolic Steroids

These currently experimental agents may actually have a beneficial effect on bone mass; their side effects include liver toxicity, masculinisation, and an increased cholesterol level(7).

2. Testosterone

This may be of value in the treatment of osteoporosis in elderly men, particularly those with hypogonadism. Prostate and cholesterol status should always be checked when using testosterone(7).

OSTEOPOROSIS IN SPINAL CORD INJURY

Osteoporosis is a known consequence of spinal cord injury (SCI) and occurs in almost every SCI patient(39). The significance of osteoporosis after SCI is that it results in skeletal fragility and an increased risk of fractures. Complications from fractures lead to an increase not only in the associated morbidity and mortality, but also in the health care costs that they generate. These fractures predispose to exuberant callus that may cause pressure sores or may mimic infection or thrombosis. Fractures are often complicated by profuse diaphoresis and an increase in spasticity(13). The porous nature of the bones means that surgical fixation is often difficult; conservative treatment with plaster casts can result in pressure sores. Vestergaard et al (40) found that low-energy fractures were much more prominent in patients (19.0% of all fractures) than in controls (1.4%, $P < 0.001$). The fracture rate did not differ before the injury but increased after the injury to a constant level from the third year and forward. Fractures of the lower extremities were more prominent in patients than controls while fractures of the forearms and clavicles were absent among patients. Fractures were more frequent in female patients and in male patients with a family history of fracture.

The pattern of bone loss seen in SCI patients is different from that in osteoporosis, which occurs as a result of other etiologies such as endocrine diseases, nutritional disorders and drug-related factors(39).

Mechanism of bone loss in SCI

The effect of mechanical loading on bone tissue is an increase in bone formation on the periosteal bone surfaces, thus improving bone strength and reducing bone turnover and bone porosity(2). Consequently, mechanical loading can improve both bone size and shape and strengthen the bone tissue by improving tissue density.

Unloading

Kondo et al (41) revealed that sympathetic nervous tone is mediating unloading-induced bone loss via reduction in osteoblastic cell activity as well as enhancement in osteoclastic cell activity. SCI causes unloading and restricted movement of the lower limb joints for substantial periods of time, and substantial muscle atrophy has been seen in SCI patients. Unloading may play an important role in the development of osteoporosis after SCI(42).

Neuronal changes - Denervation

Innervation of bone is reported to have trophic effects on bone metabolism and a growing number of experimental and clinical studies indicate that innervation is important for bone remodelling(2). Similarly, SCI may lead to a significant decrease in innervation density and neuropeptides in the sublesional bones, thus distorting the balance of bone formation and resorption. In addition to the direct role of denervation on bone metabolism, denervation after SCI can cause disordered vasoregulation, thus affecting bone remodelling.

Hormonal changes

Although upper limbs are normally loaded and innervated, bone loss also occurs in the upper extremities in patients with paraplegia. Therefore, systemic hormones such as PTH, vitamin D_3, sex steroids, thyroid hormone and leptin may also be involved in bone loss following SCI(2).

Calcium balance

In general, SCI patients showed negative calcium balance with hypercalciuria after the injury(43). The increased osteoclastic bone resorption is mainly responsible for hypercalciuria following SCI(2). Exercises and ambulation significantly decrease the hypercalciuria and modify the calcium balance in a positive direction(44), indicating that immobilization may be an important factor resulting in this negative calcium balance.

PTH and vitamin D

Secretion of PTH and the increase in circulating $1,25(OH)_2$ vitamin D are subjected to control by negative feedback mechanisms related to serum calcium level(2). In addition, hypercalcaemia after injury may lead to this PTH–vitamin D axis suppression in the acute phase of SCI. PTH suppression in SCI patients is also associated with the degree of neurological impairment. In a cross-sectional study, Mechanick et al (45) investigated serum PTH and $1,25\ (OH)_2$ vitamin D levels in SCI patients, who were tested at a mean of 76·5 days post-injury, and found that patients with complete SCI, when compared to those with incomplete injury, had a greater suppression of the PTH–vitamin D axis. However, a reversal in parathyroid activity from 1 to 9 years after injury has been noted. The parathyroid gland is stimulated to the point where PTH levels are above the reference range. Secondary hyperparathyroidism has always been thought to accelerate the development of SCI-induced osteoporosis(2). Bauman et al (46) showed mild secondary hyperparathyroidism in a subgroup of subjects with chronic SCI.

Effects on gonadal function

Sex steroids play a pivotal role in regulating bone remodelling. Thus, a decrease in the circulating concentrations of these hormones increases osteoclast precursor formation in

the bone marrow and thus increases the number of mature osteoclasts in cancellous bone(47). The inhibitory effect of SCI on the synthesis and secretion of sex steroids therefore contributes to the pathogenesis of SCI-induced osteoporosis. Maimoun et al (48) reported recently that total testosterone and the free androgen index were significantly lower in SCI patients than in able-bodied controls.

A neurological lesion, (such as SCI) with subsequent immobilization, leads to a dramatic reduction in muscle contraction and a redistribution of the gravitational forces applied to the skeleton, to the detriment of the bone segments that normally support body weight(30). Garland et al found significant differences (p less than 0.0001) in bone mass mineral between groups at the arms, pelvis, legs, distal femur, and proximal tibia, with no differences in bone mass of the head or trunk(10). Wilmet et al (49) observed a rapid decrease of BMC in the paralyzed areas, of approximately 4%/month during the first year in areas rich in trabecular bone and of approximately 2%/month in areas containing mainly compact bone. No significant change in BMC was observed in the supra-lesional areas. These data confirm the rapid loss of bone in the paralyzed areas of paraplegic patients, which occurs independently of the presence of spontaneous muscle activity or of passive verticalisation(49). Demirel et al (50)found a significant difference in BMD between upper and lower extremities of paraplegics. BMD of upper and lower extremities were similar in tetraplegics. The BMD values were significantly different when the upper extremity scores of paraplegics and tetraplegics were compared but BMD scores of the lower extremities were similar in the two groups(10, 50). The decrease in BMD was less in the spastic patients when compared to the flaccid group. There was a positive correlation between time from injury and the degree of BMD deficit in the paralyzed areas(50).

To limit the bone loss resulting from neurological lesions, a logical approach would be to develop rehabilitation techniques that mechanically re-stimulate the bone segments to return, as much as possible, to the pre-lesional physiological and biomechanical conditions(30).

MANAGEMENT OF OSTEOPOROSIS IN SPINAL CORD INJURY

Morse et al (27) cited that, although admission for osteoporotic fractures accounted for only 2.6% of the admissions, these hospitalizations resulted in longer lengths of stay than other admissions, and individuals also required increased levels of assistance for transfers and self-care during immobilization of a fractured limb. Hence prevention of fractures would therefore decrease health care costs and promote independence in this population.

NON-PHARMACOLOGICAL MANAGEMENT

Prevention of falls

Morse et al (27) also found that the most common cause of fracture in chronic spinal cord injury was falls, which may be difficult to prevent. However, based on record review, 20% of the fractures resulting in hospitalization were due to transfer and wheelchair ambulation technique. It may be possible to reduce fracture risk by improving counseling and educating patients regarding limb protection during various self-care activities and reinforce the importance of adequate doorway width for wheelchair clearance(27).

Standing-up and orthotically aided walking

The study by De Bruin et al (51) indicates that early mobilization led to no or insignificant loss of trabecular bone, whereas the immobilized individuals showed a marked decrease when monitored for 25 weeks. In addition, the recent prospective study

by Alekna et al (52) found that standing, particularly after 2 years, gave significantly higher BMD in legs, pelvis and the total body.

Physical exercise

The quality of evidence available for evaluation is poor (53). Miyahara et al (54) found that the earlier the athlete started sports after injury, the higher the BMD of the legs, body trunk and the entire body. Further, a longer period of athletic career after restarting was significantly related to higher leg BMD.

Functional electrical stimulation

Functional electrical stimulation is a method of exercise that has been employed in the SCI population that has demonstrated some success in improving muscle, with less conclusive evidence that it has a positive effect on bone(14). Be Dell et al (55) demonstrated that there was no significant increase in bone density in the hip parameters of chronic SCI patients after functional electrical stimulation induced lower extremity cycling, though a positive trend was observed in the lumbar spine. Giangregorio et al (14) demonstrated that nine months of thrice weekly FES cycle ergometry failed to increase BMD at the femoral neck, distal femur, and proximal tibia in individuals with complete SCI.

Low-intensity pulsed ultrasound

Naruse et al (56) demonstrated that low-intensity, pulsed ultrasound, which has been clinically used to accelerate the healing processes of fractured bone, induces a direct anabolic reaction of osteogenic cells, leading to bone matrix formation. Warden et al (57) applied specific US at the calcaneum for 6 weeks in young subjects with 1–6-month histories of complete SCI. The results showed that low-intensity pulsed US were unable

to protect against SCI-induced calcaneal bone demineralization. Further investigations are needed.

PHARMACOLOGICAL MANAGEMENT

The physiopathological data have shown that bone demineralization in patients with SCI can be principally attributed to an alteration of the bone remodeling process that dramatically favors an increase in bone resorption. Drug treatment thus mostly consists of substances that inhibit osteoclast cell activity(30).

Calcitonin

Calcitonin is a potent inhibitor of bone resorption. Transcutaneous injection or intranasal intake of salmon calcitonin has been reported to limit immobilization hypercalcemia and hypercalciuria, to reduce osteoclast activity, and to preserve trabecular bone volume. However, the optimal dosage and long-term effectiveness of calcitonin treatment remain unclear(30).

Bisphosphonates in osteoporosis after spinal cord injury

Various bisphosphonates such as alendronate, palmidronate, etidronate have been tried in patients with osteopororis after spinal cord injury.

Chappard et al (58) observed an insignificant decrease of bone volume in the placebo group and the patients who received 200 mg/day of tiludronate. In patients receiving 400 mg/day, a slight increase was noted. Eroded surfaces increased in all groups. The number of osteoclasts (identified histochemically by TRAP staining) was found to have increased in the placebo group but decreased in groups receiving tiludronate. Chappard et al

concluded that tiludronate appeared to be effective in reducing bone resorption without impairing bone formation in a manner that preserved bone mass and bone cell coupling.

Pearson et al (59) found that there was significant interaction between etidronate treatment and ambulatory status over time with respect to bone density of the patients after SCI ($p = .0003$). They found that the patients who became ambulatory and received etidronate treatment had a preservation of bone density as compared to all other patients who showed a loss of bone density over time. The loss of bone density occurred in the leg bones, not the spine. They also concluded that cyclical etidronate is a feasible treatment and may prevent osteoporosis associated with SCI in patients who eventually walk.

Nance et al (60) found that after acute SCI, patients treated with intravenous pamidronate had significantly less bone density loss compared with those who did not receive pamidronate ($p<.02$). Also, ambulatory subjects had significantly less bone density loss over the study period ($p<.05$) than nonambulatory subjects. Nance et al concluded that intravenous pamidronate treatment and ambulatory ability in the first 6 months after an acute spinal cord injury prevents bone density loss.

AIMS

&

OBJECTIVES

AIMS AND OBJECTIVES

To study the effect of a single dose of intravenous zoledronic acid in subjects with chronic spinal cord injury on the bone mineral density in the forearm and hip after 1 year of intervention.

MATERIALS

&

METHODS

MATERIALS AND METHODS

STUDY DESIGN: Randomised double blind placebo control study.

The study was approved by the institutional review board and signed informed consent was obtained from each subject prior to enrollment. Patients attending the Physical Medicine and Rehabilitation out patient department, those admitted in the wards and those attending the yearly spinal cord injury follow up Mela were recruited based on inclusion and exclusion criteria after preliminary screening. Those who fulfilled the inclusion criteria, underwent a baseline DEXA scan to detect the prevalence of osteoporosis. In those detected to have osteoporosis of the hip or femur neck, the following investigations were done which included

1) Serum sodium
2) Serum potassium
3) Serum calcium
4) Serum phosphorus
5) Serum creatinine
6) Serum urea
7) 25 OH Vitamin D
8) X-ray of the pelvis with both hip joints

The patients were then enrolled, after proper informed consent into a randomized, double blinded trial to receive either a single dose intravenous infusion of Zoledronic acid (study group) or normal saline (placebo group). These patients were reassessed with DEXA bone densitometry after 1 year to compare and analyse the difference in bone density at the femoral neck and forearm.

INCLUSION CRITERIA:

1) Patients who are more than 12 months post traumatic spinal cord injury.

2) Age group 18- 60 years.

EXCLUSION CRITERIA:

1) Patients with non traumatic spinal cord lesions.

2) Patients with renal failure.

3) Heterotrophic ossification involving both hips.

4) Patients with recent onset grade 4 pressure sores that may hinder DEXA bone densitometry study.

5) Patients already on other medication or treatment regimens for osteoporosis treatment or prophylaxis.

6) Postmenopausal women.

Sample size

A descriptive study with randomised, double blinded analysis was planned. Using the formula:

$$n = \frac{(Z_{a} \times Z_{1-b}) \times 2\,p \times q}{d^2}$$

Here, $(Z_a \times Z_{1-b})$ is a constant coefficient with 'a' being the type 1 error and '1-b' being the power of the study. For a study with 80% power and a type 1 error of less than 5%. The coefficient value usually is around 10.4.

n is the sample size of the study.

p is the prevalance of osteoporosis in the study population and q signifies the non osteoporotic normal population calculated as '1-p'.

d is the approximate percentage difference between the study and control arms.

Comparing with other similar studies worldwide the prevalence of osteoporosis was hypothesized to be 80% in SCI. The approximate percentage difference between the study and control arms from zoledronic acid studies done in transplant patients worldwide was around 50%.

Using the above formula, the sample size in each arm was estimated to be 15, so a total of 30 and considering a 25% loss to follow up due to various reasons a sample size of 40 was arrived upon in consultation with the statisticians.

Randomization

The patients were allocated into treatment and control arms by stratified, blocked, random method. The randomization code was prepared by the statistician and handed over to the in-charge of manufacturing unit in Pharmacy who then distributed the vials (drug/saline) for infusion.

Intervention

The patients in the treatment arm received injection zoledronic acid 4 mg in 100 ml normal saline, while the control arm received plain normal saline, intravenously over 20 minutes. These solutions were prepared in the Pharmacy of the Christian Medical College Hospital, Vellore. Both the physician and the patient were blinded to the treatment allocation. The patients were observed for one day post injection for possible complications from the medication.

Measurements

Total of 73 subjects with spinal cord injury were screened for osteporosis at the hip using DEXA scan- [Delphi W (S/N 70471) version 11.2]. These individuals were recruited during the period from February to July 2008, from the yearly spinal cord injury follow up Mela 2008 and from among those individuals who attended the out patient services of the department of Physical Medicine and Rehabilitation. Out of these 11 people were found to have normal bone mineral density at the hip, 31 osteopenic and another 31 osteoporotic. Twenty eight (28) osteoporotic subjects with chronic SCI (more than 12 months) who gave their informed consent were enrolled into a double-blind, placebo-controlled study for determining the effect of bisphosphonate administration on loss of bone following chronic spinal cord injury. The other 3 patients who did not give consent were excluded.

Repeat DEXA scan [Discovery W (S/N 70471) version 12.7.3.1] was done 1 year post study drug infusion.

(Figure 5) Photograph of the DEXA scan table

DEXA scan measurement procedures

Patients with Spinal Cord Injury, who fulfilled the inclusion criteria were subjected for the first DEXA scan. Standard technical parameters were followed according to DEXA scanning user guide instructions. A hip positioner or foot restraint was used to maintain the leg rotated inwards by 25 degrees and foot was firmly strapped to the device. Cross hair of the laser light was centered 3 inches below the level of the Greater trochanter & slightly medial to the shaft of femur. The regions to be scanned (hip and forearm) were graphically displayed, and the operator adjusted the final cut lines for each division.

Quality control was done using phantoms to ensure reproducibility and accuracy of BMD measurement. Measurements were made at base line and at 1 year follow up.

(Figure 6) Position for DEXA forearm and femur

Statistical analysis

Statistical analysis was performed using SPSS (statistical package for social sciences) version 16 with the help of a Clinical Epidemiologist. Two-tailed paired t tests ($P<0.05$) were performed on BMD data for the placebo and zoledronic acid group, to test for significant differences within group before and after intervention. Since the sample size was small and some of the data showed a skewed distribution (did not follow a normal distribution curve), it was decided in consultation with the statistician, to use non-parametric tests for analysis.

RESULTS

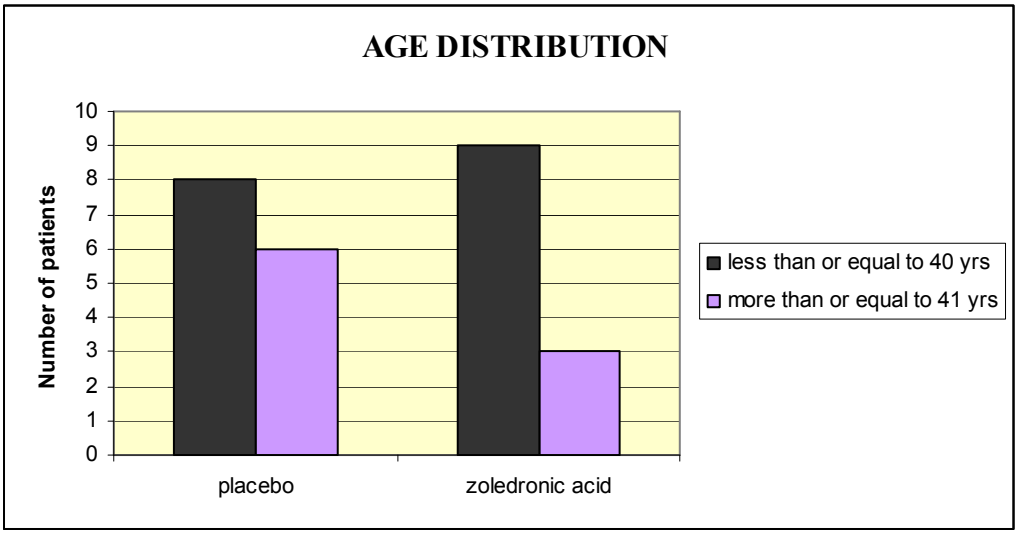
RESULTS

PATIENT DEMOGRAPHY

Age distribution

In the placebo group the mean age of all the patients was 38.35 years (range from 24 to 58 years). In the zoledronic acid group the mean age of all the patients was 37.91 years (range from 30 to 56 years). There was no statistically significant difference between the two groups with respect to age, (p value = 0.777).

Figure 7



Gender distribution

In the placebo group there were 14 males and no females. In the zoledronic acid group there were 9 males and 3 females.

Figure 8

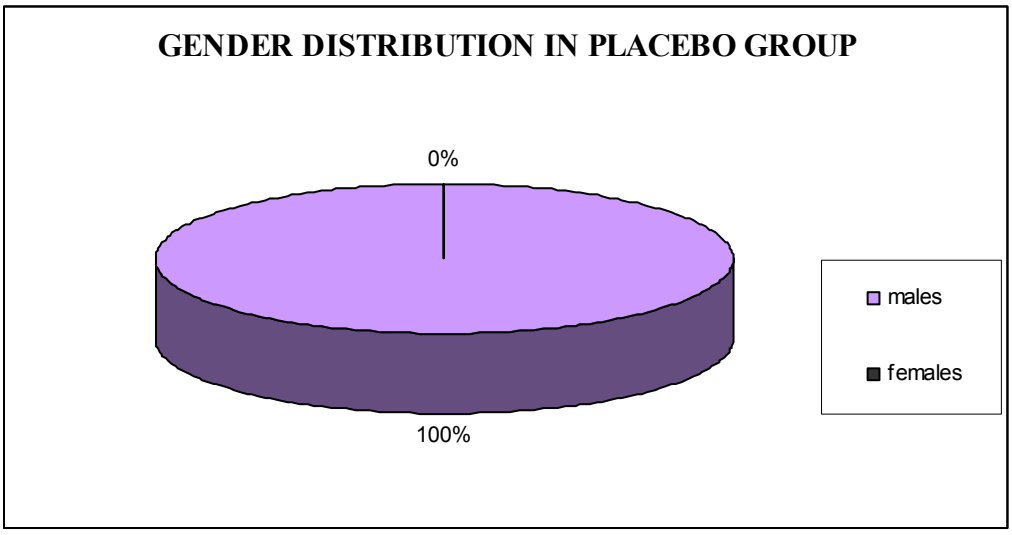
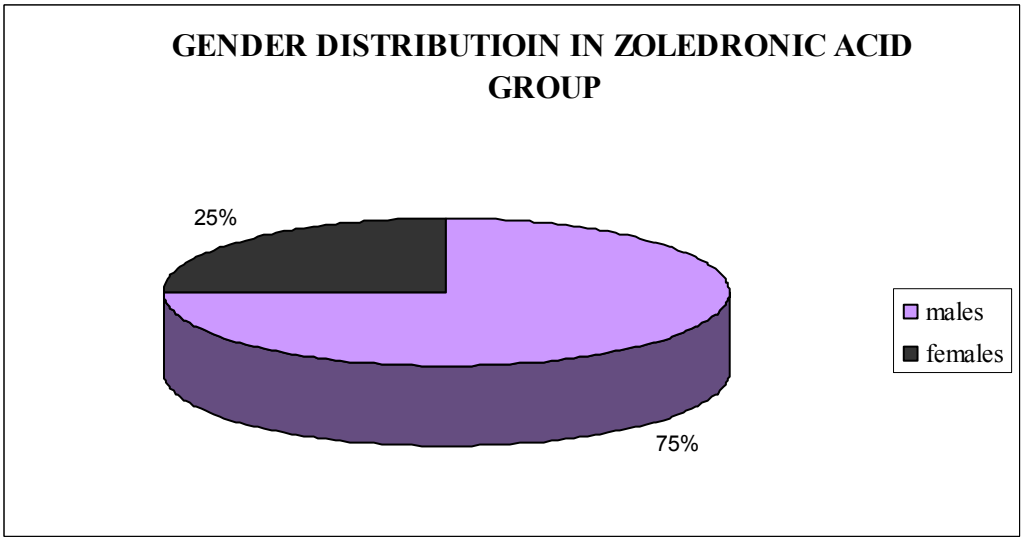


Figure 9

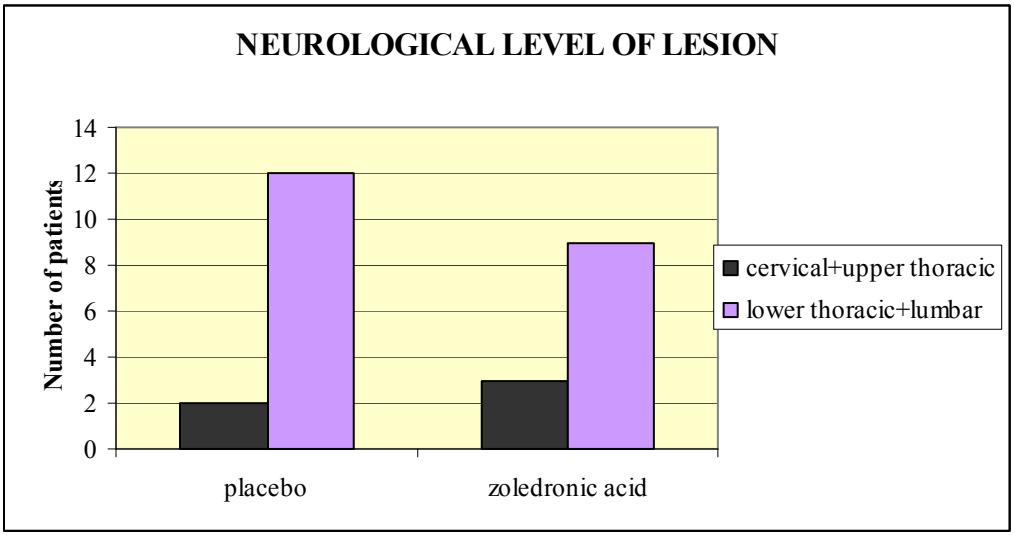


Neurological level

In the placebo group there were 2 patients with a high lesion (cervical and upper thoracic) and 12 patients with a low level lesion (lower thoracic and lumbar).

In the zoledronic acid group there were 3 patients with a high lesion and 9 patients with a low level lesion. There was no statistically significant difference between the two groups with respect to the level of lesion. (p value 0.498)

Figure 10



Duration of injury

In the placebo group the mean duration of injury was 10.92 years (range from 3 to 25 years).

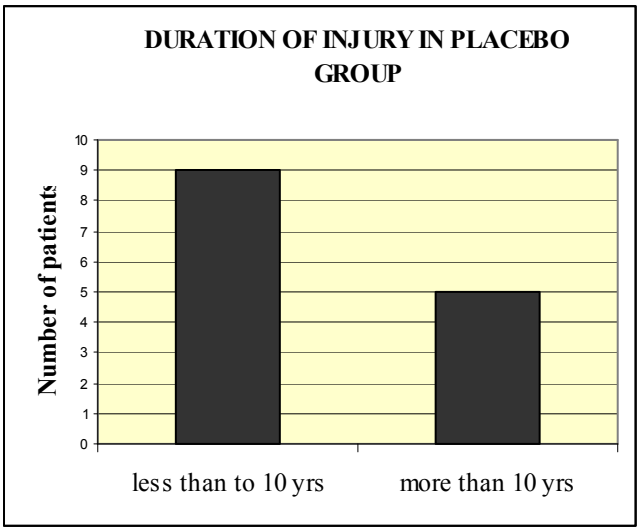


Figure 11

In the zoledronic acid group the mean duration of injury was 13.33 years (range from 2 to 22 years).

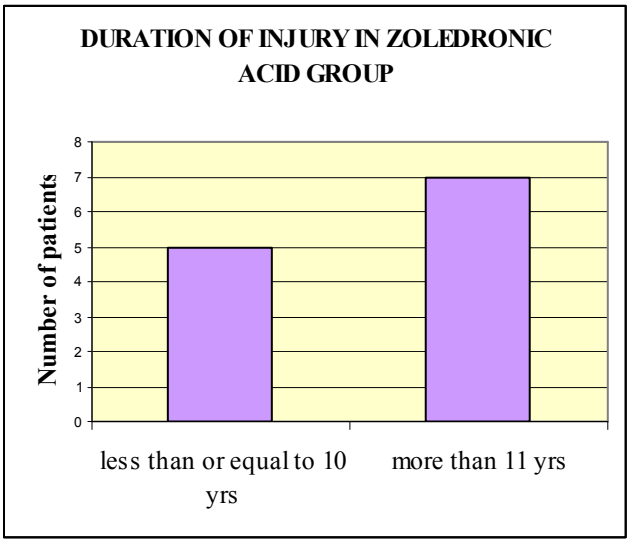


Figure 12

There was no statistically significant difference between the two groups with respect to the duration of injury (p value 0.279).

Vocation

The total number of patients in the placebo group and zoledronic acid group were divided into two depending upon the nature of their vocation (outdoor and indoor). In the placebo group 8 patients were involved in indoor vocation while 6 patients were involved in outdoor vocation. In the zoledronic acid group 7 patients were involved in indoor vocation while 5 patients were involved in outdoor vocation.

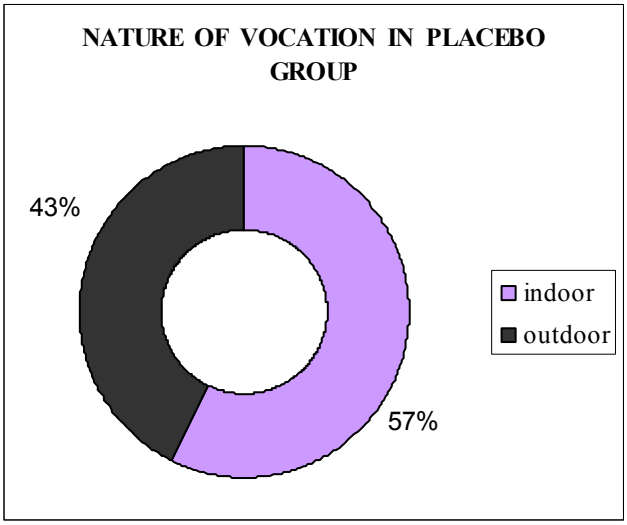


Figure 13

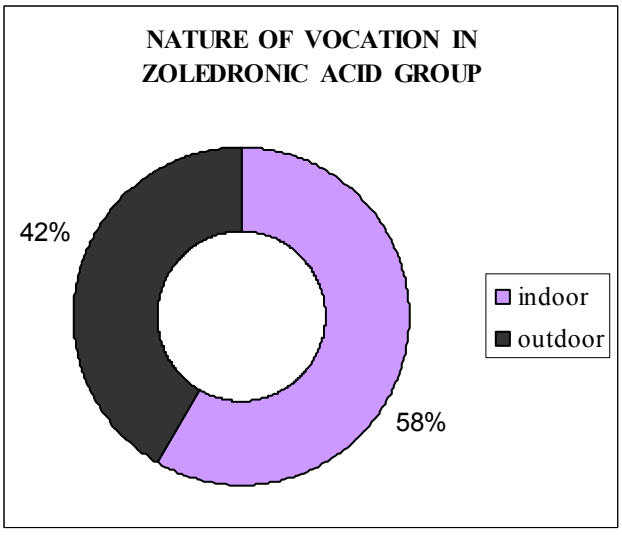


Figure 14

There was no statistically significant difference between the two groups with respect to the nature of vocation (p value 0.952).

Sun exposure

The total number of patients in the placebo group and zoledronic acid group were divided into two depending upon the amount of sun exposure per week as those receiving less than 1 hour of sun exposure per week and those receiving more than 1 hour of sun exposure per week. There was no statistically significant difference between the two groups with respect to amount of sun exposure (p value 0.952)

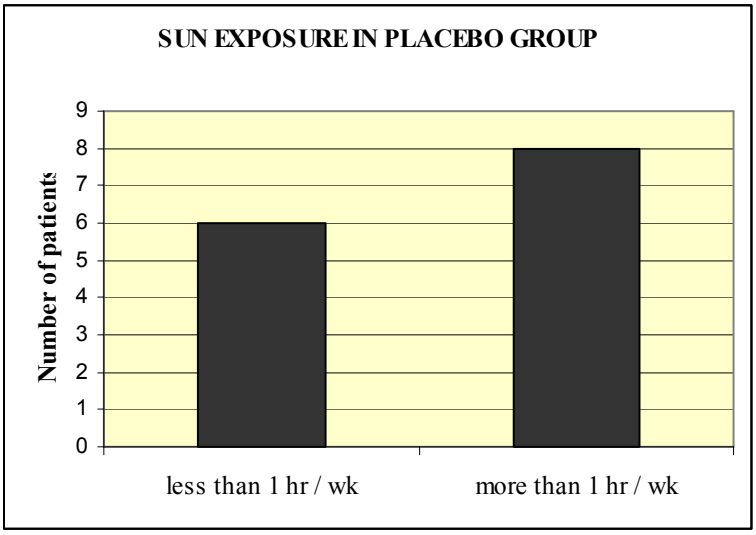


Figure 15

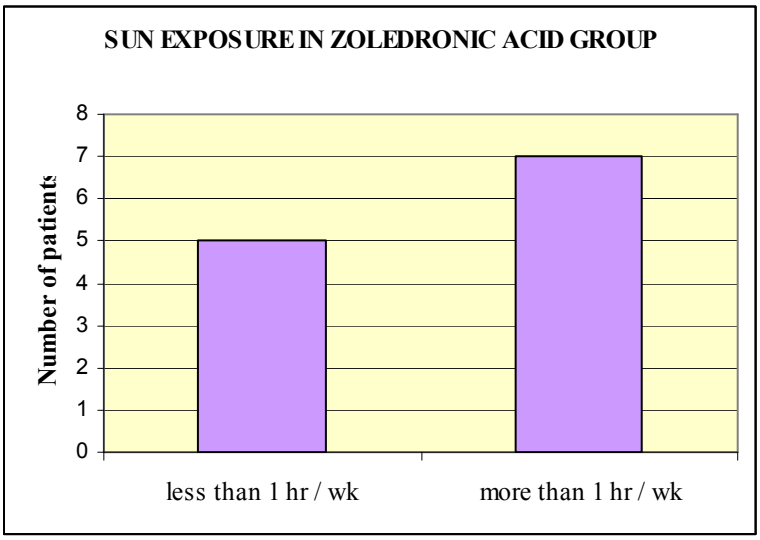


Figure 16

Vitamin D

There was no statistically significant difference between the zoledronic acid and the placebo group with respect to the level of vitamin D (p value 0.757).

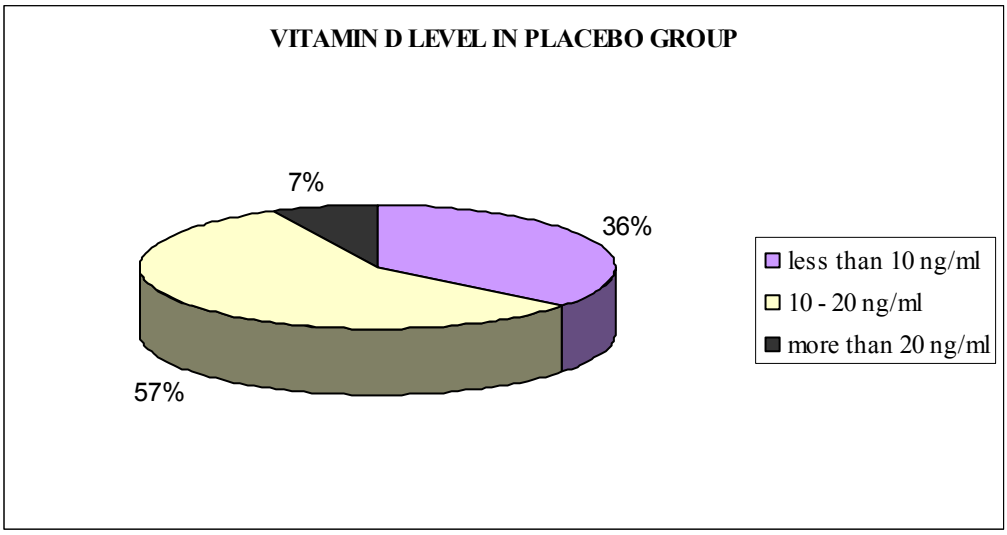


Figure 17

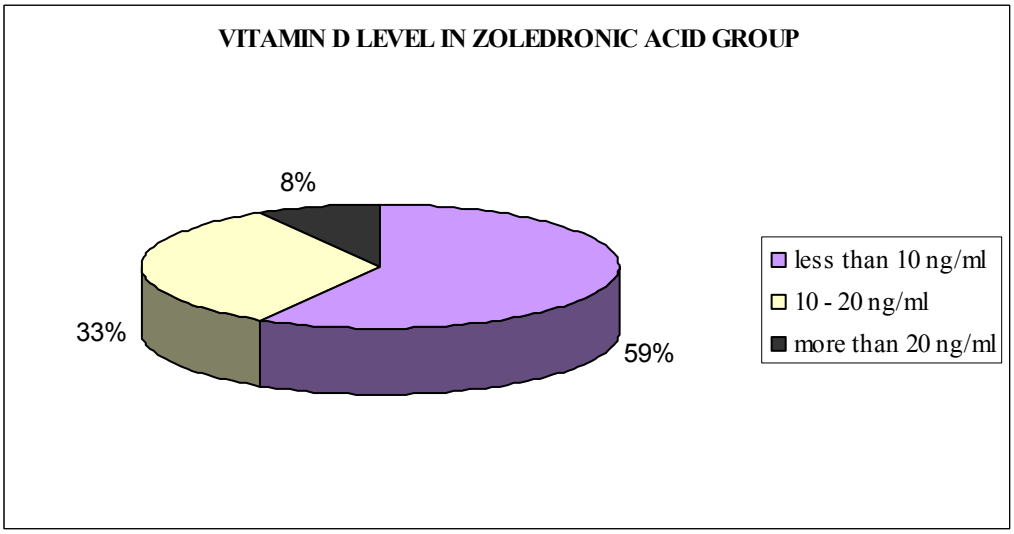


Figure 18

Mobility

In the placebo group, out of 14, half the patients were ambulant and half non ambulant. In the zoledronic acid group 8 out of 12 patients were ambulant while 4 were non ambulant. There was no statistically significant difference between the two groups with respect to the mobility (p value 0.400)

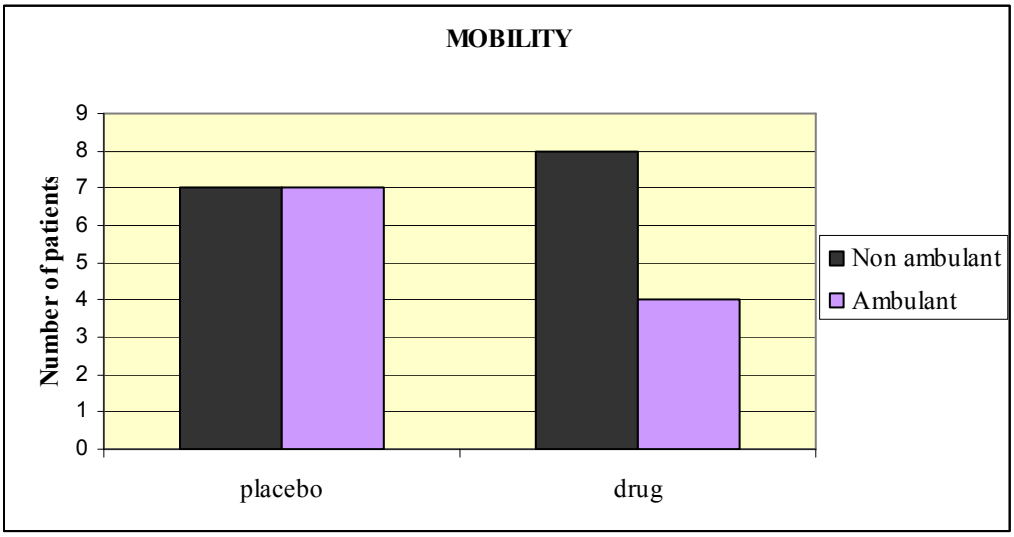


Figure 19

Adverse events

Five out of the 28 subjects had flu-like syndromes, including bone pain, fever, fatigue, and rigors. One participant reported of myalgia for almost 2-3 months following the infusion. Another individual had post injection conjunctival redness. It was later found on opening the randomization code that all the subjects with adverse effects were in the zoledronic acid group.

Two of the participants did not follow up after 1 year for the repeat DEXA scan. One of them developed fracture of the left tibia while attempting to transfer to a chair about 10 months after the study drug infusion. On opening the randomization code, it was found that this subject had received placebo.

The mean and standard deviation values of the BMD at the hip, femur neck, forearm and distal radius, prior to and after intervention for both drug and placebo group are mentioned in **table 1**.

	BMD Total hip				BMD Femoral Neck				BMD Total forearm				BMD Distal third of radius			
	Pre		Post		Pre		Post		Pre		Post		Pre		Post	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Zoledronic acid group	0.583	0.066	0.563	0.079	0.576	0.064	0.552	0.074	0.588	0.065	0.623	0.080	0.717	0.066	0.760	0.072
P value	0.082				* 0.044				* 0.002				* 0.004			
Placebo group	0.607	0.073	0.491	0.169	0.548	0.111	0.480	0.163	0.589	0.036	0.612	0.036	0.713	0.031	0.747	0.028
P value	* 0.017				*0.002				*0.004				*0.004			

Table 1

Non parametric test - Wilcoxon signed ranks test was used to look for statistically significant difference between bone mineral density at total hip, femoral neck, total forearm and distal third of radius, post intervention in both the zoledronic acid group and the placebo group.

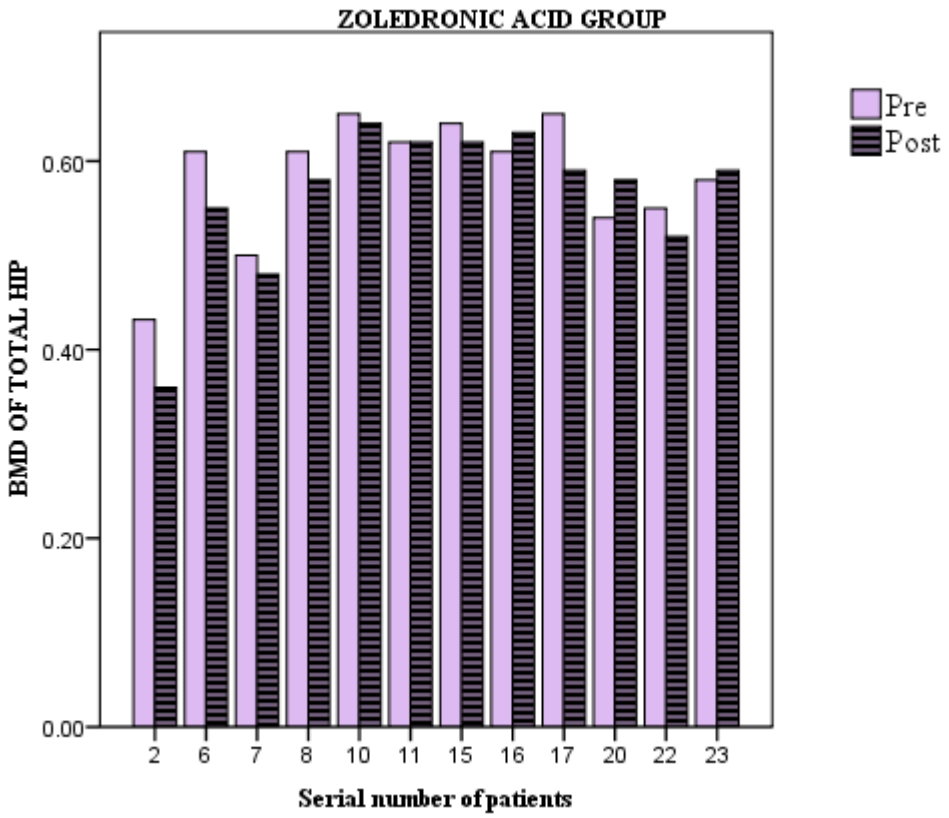


Figure 20

Fig 20 illustrates the pre and post intervention BMD values of total hip in the zoledronic acid group.

There was a statistically significant reduction in bone mineral density at the total hip in the placebo group (p = 0.017) while the reduction in bone mineral density in the subjects who received zoledronic acid (p = 0.082)was not statistically significant.

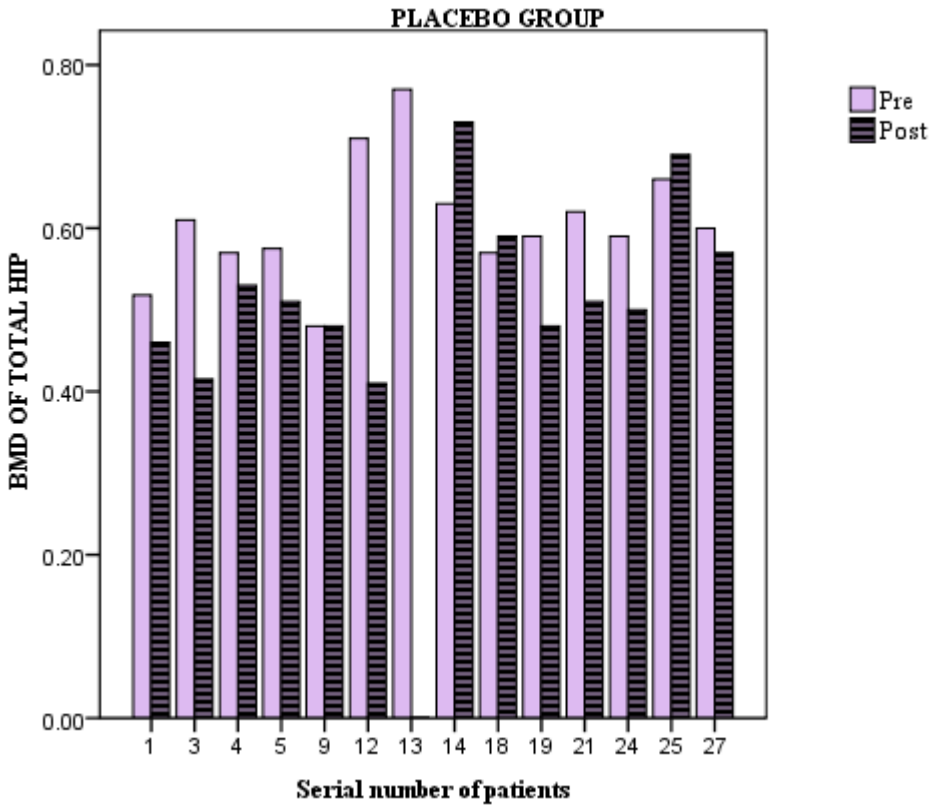


Figure 21

Figure 21 illustrates the pre and post intervention BMD value of total hip in the placebo group.

In one subject the post intervention DEXA scan could not be measured at the hip due to technical difficulties. The updated version of the software could not detect total hip value, as an osteotomy had been performed at the hip.

There was a statistically significant drop in the bone mineral density post intervention at the femoral neck in both the zoledronic acid group (p value = 0.044) and the placebo group (p value = 0.002). The drop in the bone mineral density, post intervention was greater in the placebo group as compared to the zoledronic acid group.

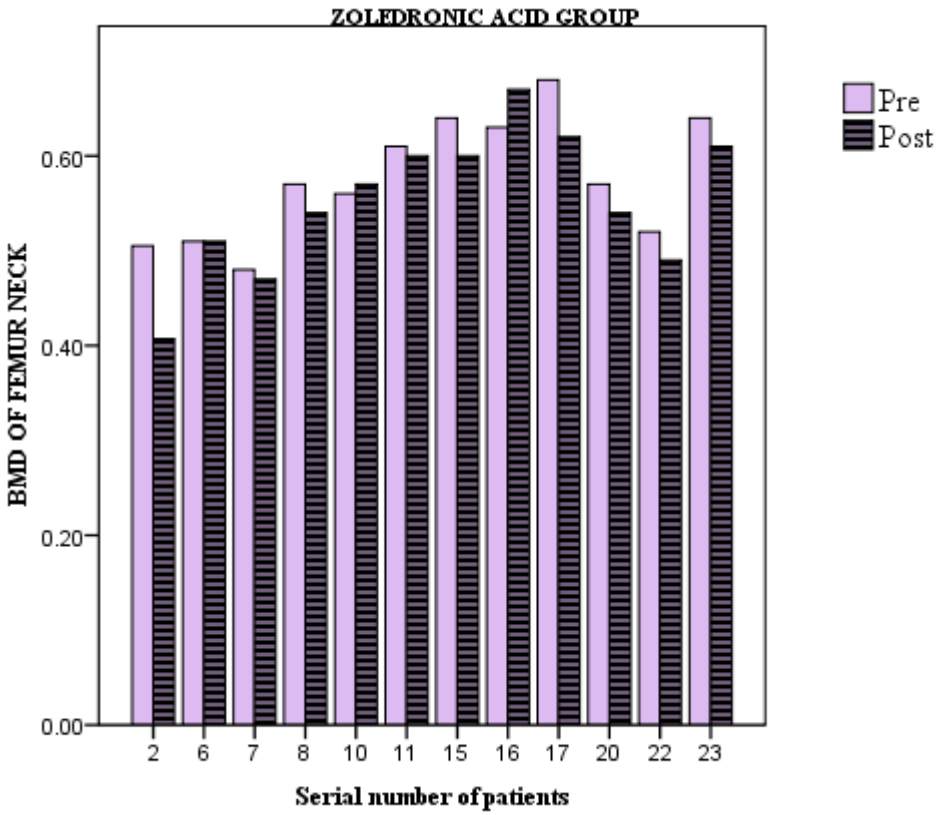


Figure 22

Figure 22 illustrates the BMD of femoral neck in zoledronic acid group, pre and post intervention.

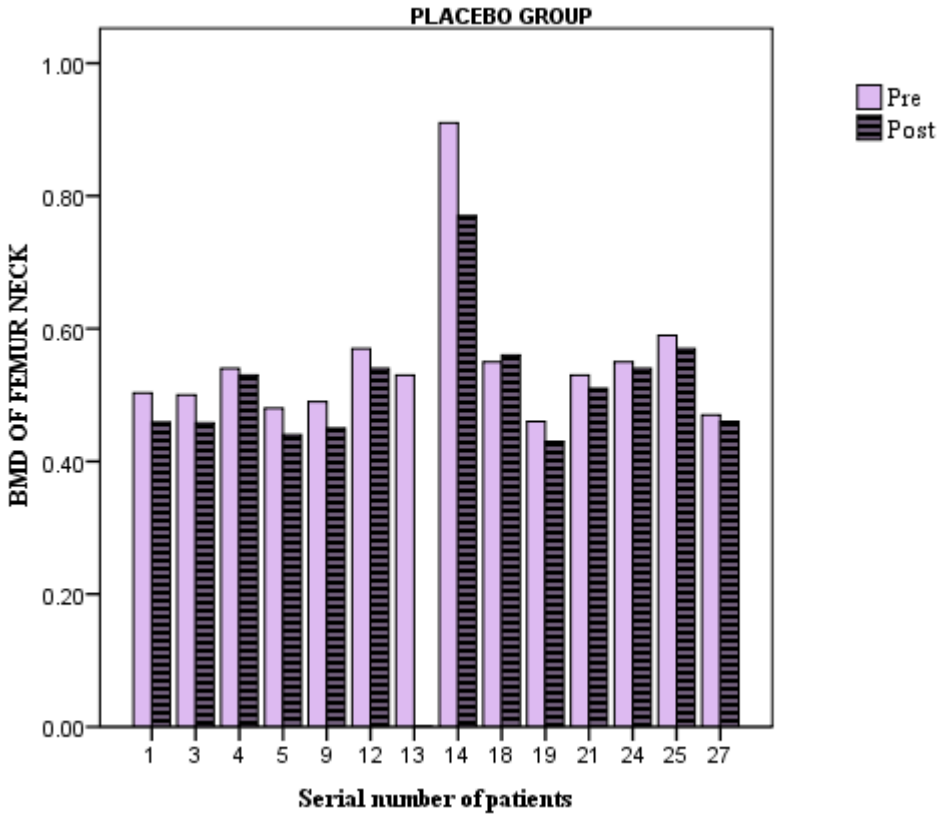


Figure 23

Figure 23 represents the pre and post intervention BMD of femoral neck in the placebo group.

Bone mineral density scores of total forearm showed a statistically significant improvement post intervention in both the zoledronic acid (p value = 0.002) and placebo group (p value = 0.004). The improvement in the bone mineral density post intervention was more in the zoledronic acid group as compared to the placebo group.

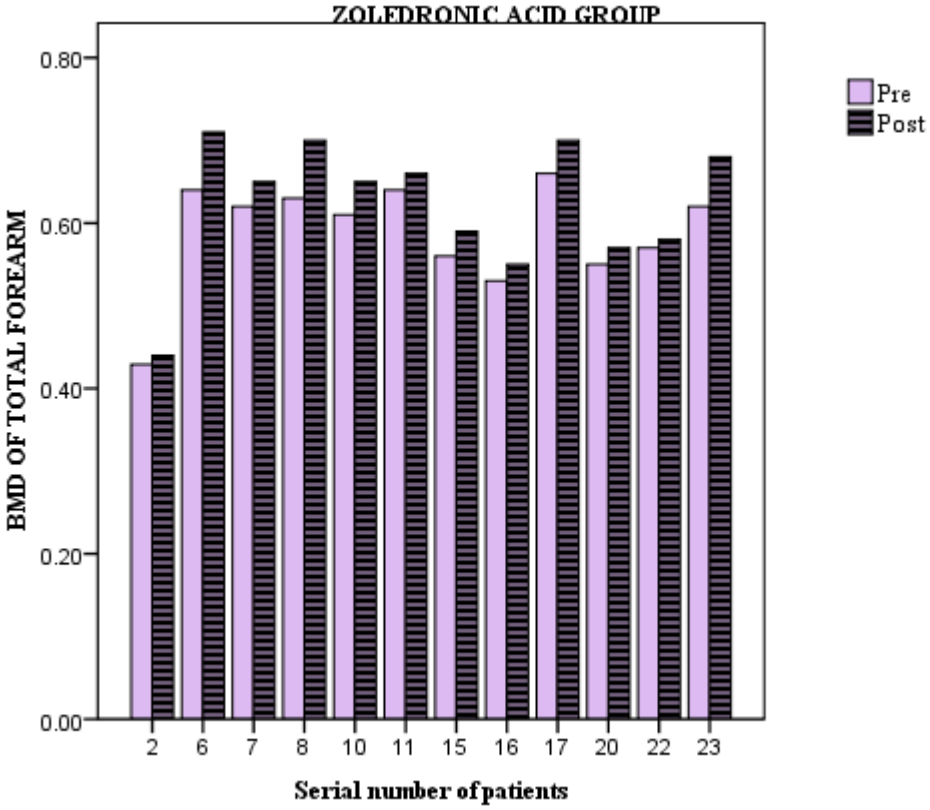


Figure 24

Figure 24 illustrates the BMD of total forearm, pre and post intervention in the zoledronic acid group.

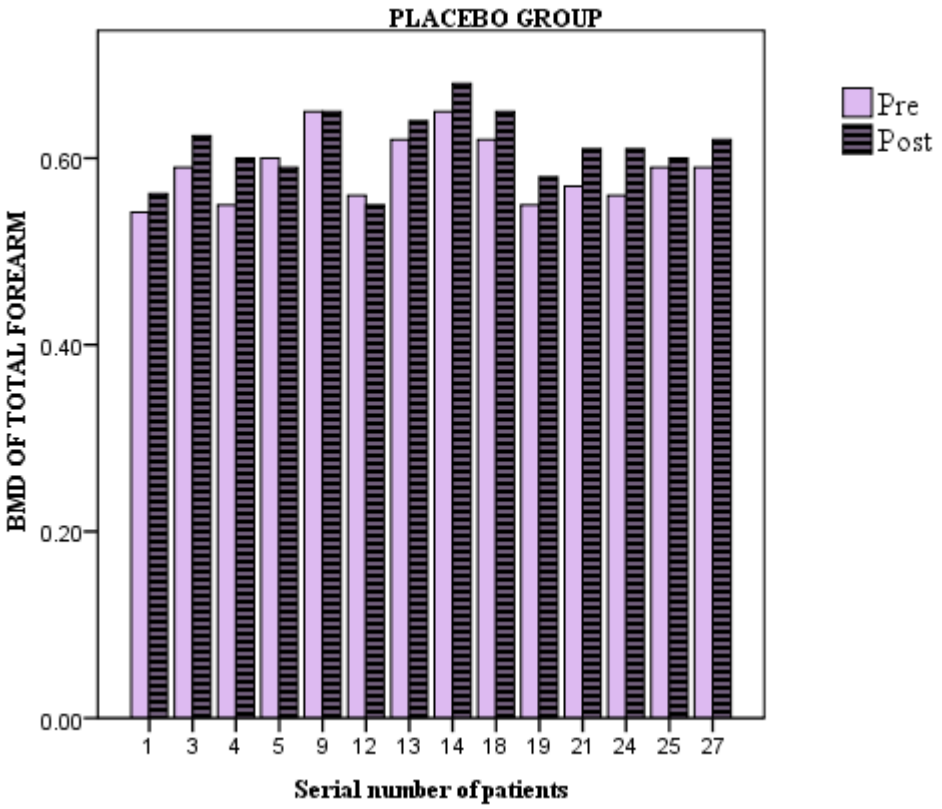


Figure 25

Figure 25 represents the BMD of total forearm, pre and post intervention in the placebo group.

There was statistically significant improvement in the bone mineral density at distal radius in the zoledronic acid group (p value = 0.004) as well as the placebo group (p value = 0.004). The improvement was similar in both the groups.

Figure 26 BMD of distal third of radius pre and post intervention in the zoledronic acid group

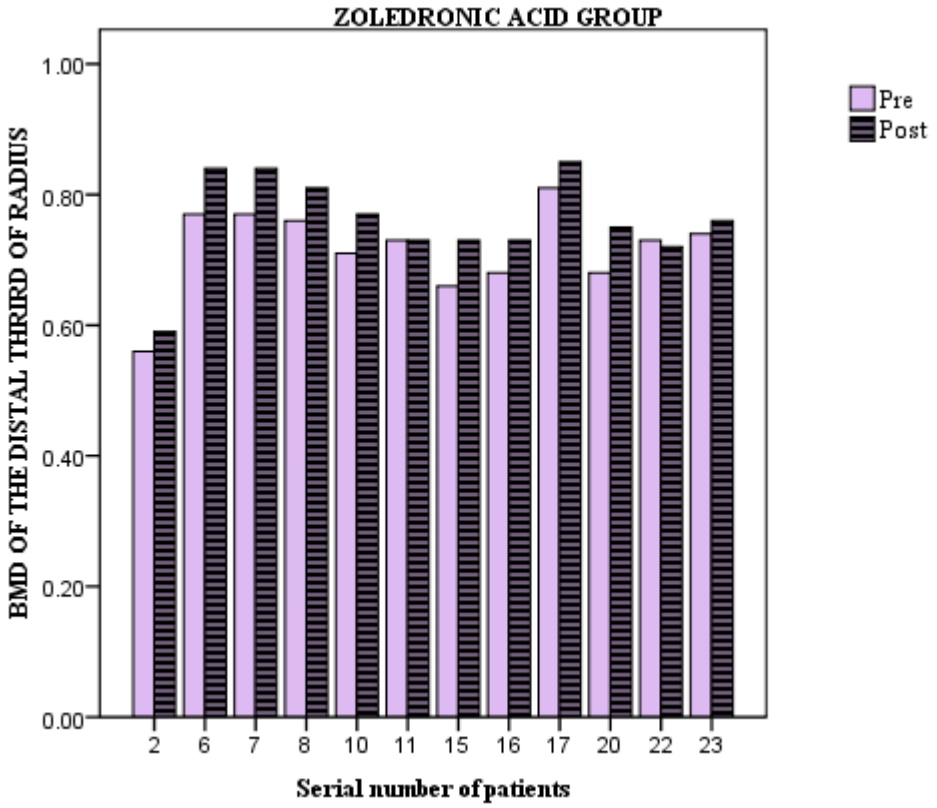


Figure 26

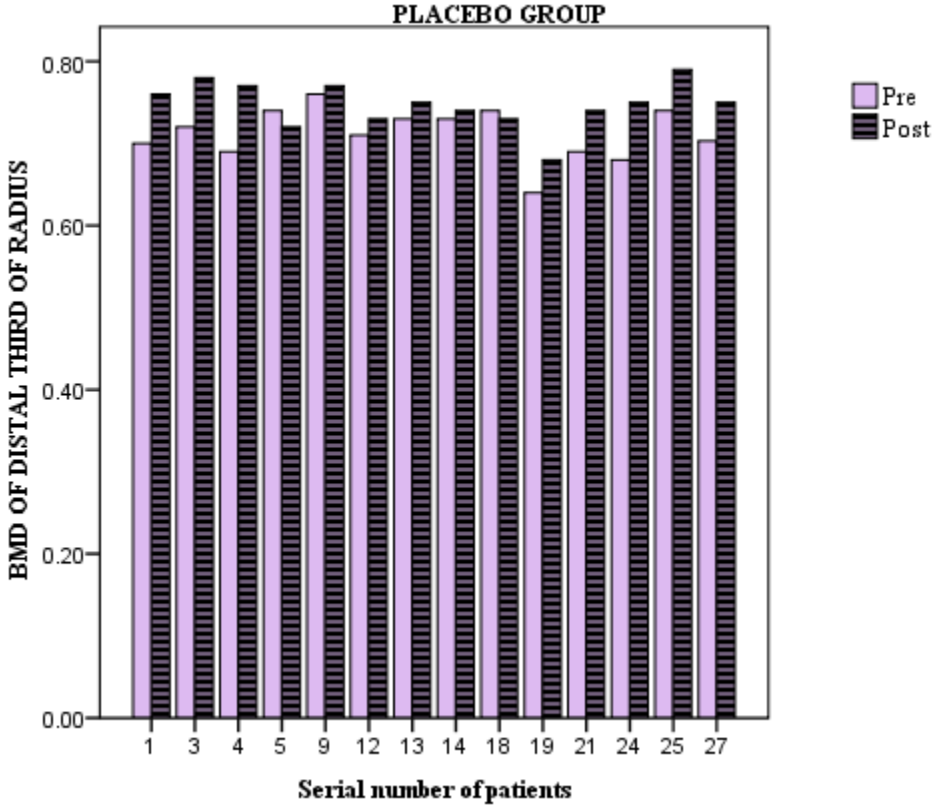


Figure 27

. **Figure 27** represents the BMD of distal third of radius pre and post intervention in the placebo group.

Mann Whitney test was applied to look for statistically significant difference in percentage change in bone mineral density at the hip, femur neck or distal radius between the zoledronic acid and the placebo group.

Percentage change in bone mineral density was calculated using the formula –

$$\frac{(\text{BMD post intervention} - \text{Baseline BMD}) * 100}{\text{Baseline BMD}}$$

There was no statistically significant difference in percentage change in bone mineral density at the hip (p value = 0.227), femur neck (p value = 0.471) or distal radius (p value = 0.758) between the zoledronic acid and the placebo group.

Correlation between BMD and Vitamin D value

The Spearman`s correlation coefficient comparing the percentage change in BMD of femur neck and and Vitamin D level in the 12 patients of the zoledronic acid group was 0.039 (p=0.905) showing there was no correlation between these two.

The Spearman`s correlation coefficient comparing the percentage change in BMD of femur neck and and Vitamin D level in the 14 patients of the placebo group was 0.037 (p=0.899) showing there was no correlation between these two.

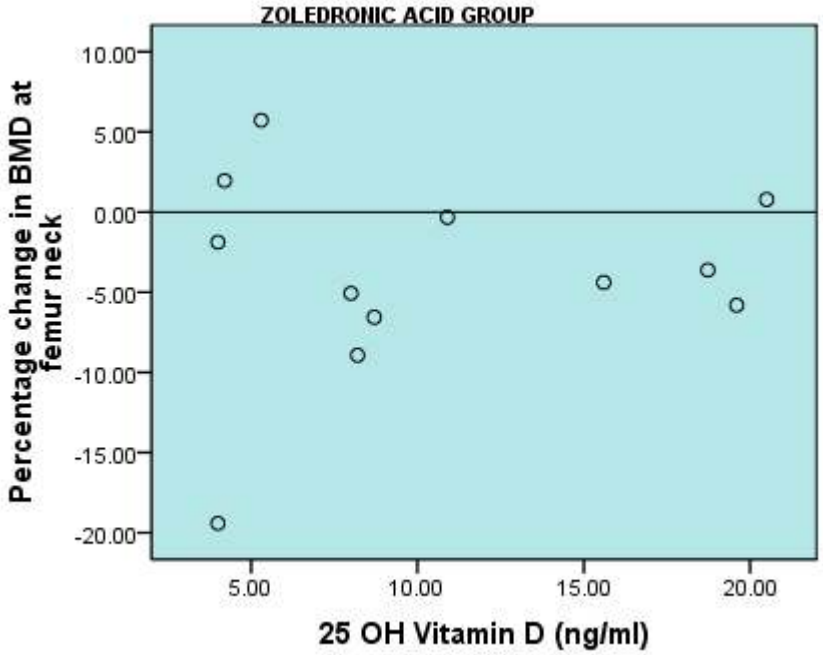


Figure 28

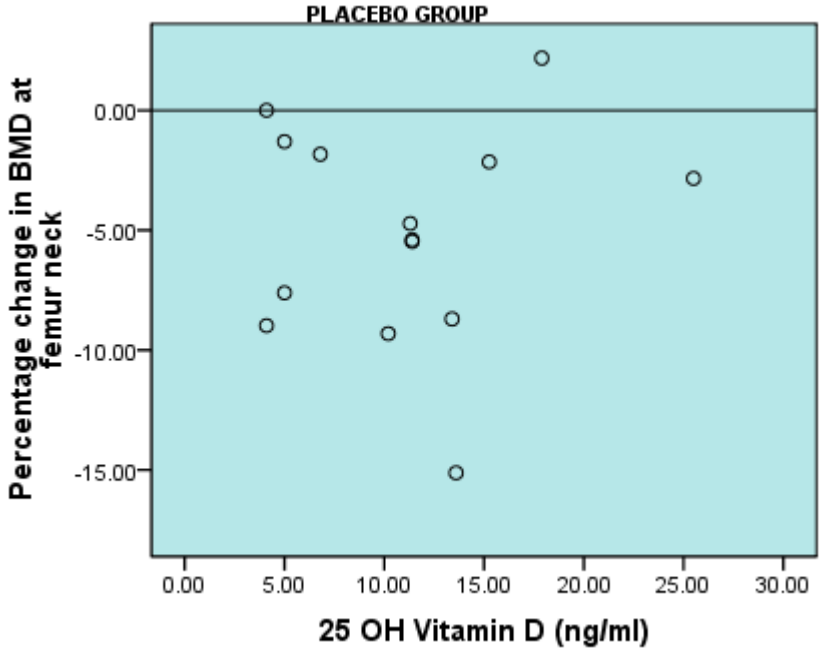


Figure 29

Figure 28 & **29** represent percentage change in BMD at femur neck in relation to the serum vitamin D level in the zoledronic acid group and placebo group respectively.

Figure 30 & 31 represent percentage change in BMD at distal radius in relation to the serum vitamin D level in the zoledronic acid group and placebo group respectively.

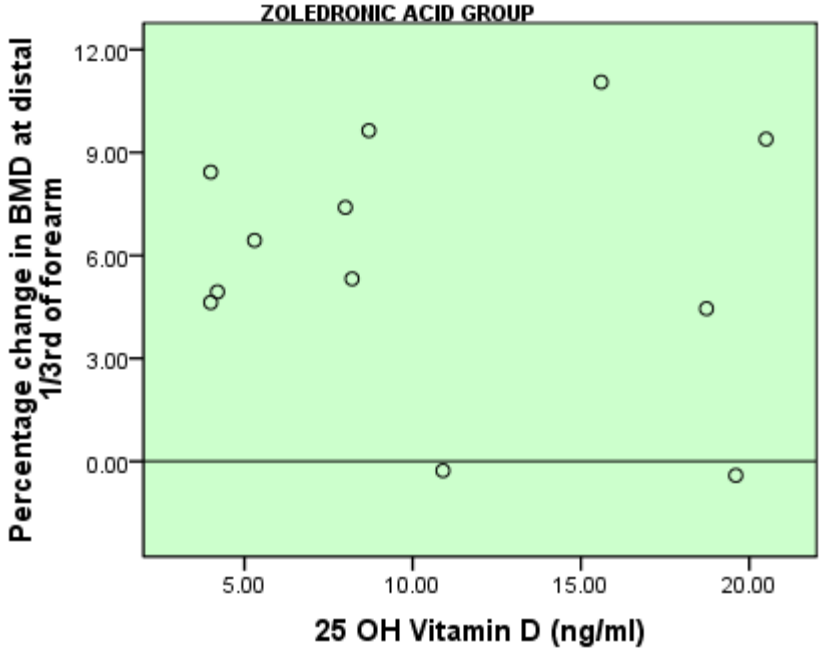


Figure 30

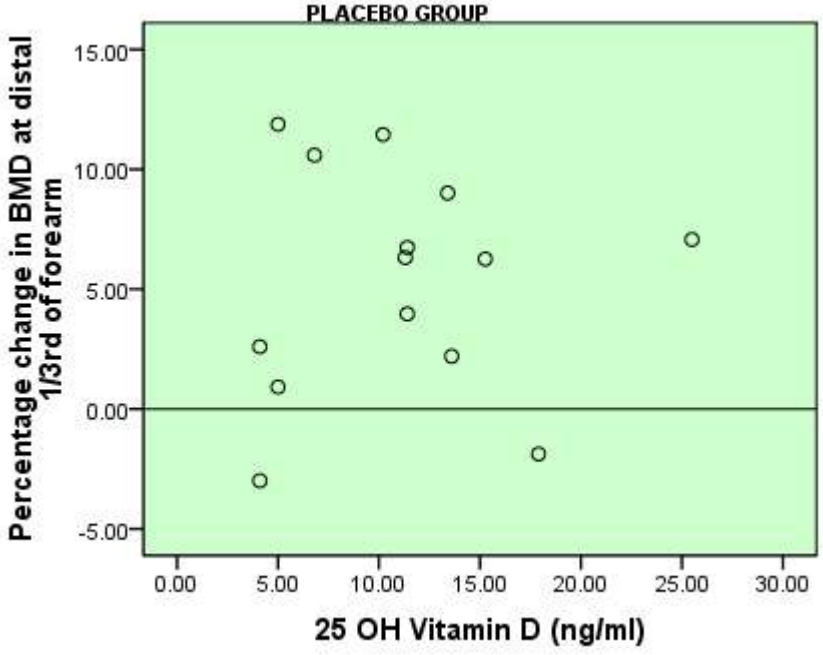


Figure 31

The Spearman`s correlation coefficient comparing the percentage change in BMD of distal radius and Vitamin D level in the 12 patients of the zoledronic acid group was -0.046 (p=0.888) showing there was no correlation between these two.

The Spearman`s correlation coefficient comparing the percentage change in BMD of distal radius and Vitamin D level in the 14 patients of the placebo group was 0.029 (p=0.923) showing there was no correlation between these two.

DISCUSSION

DISCUSSION

Bone is constantly remodeling, with an increase in bone resorption, typically followed within 30 to 45 days by the process of bone formation. With normal bone remodeling, there is no net change in the amount of bone mass present(7) in young adults. In most forms of osteoporosis, however, a perturbation of bone remodeling occurs. Bone resorption increases over the normal levels, and bone formation does not compensate for this increase, with a net loss of bone mass overall(7). In any condition that causes immobilization, loss of bone occurs and is correlated to the severity of unloading. Osteoporosis is a well recognized complication of SCI(13). Nearly all patients who sustain SCI will experience a significant loss of BMD in their paralyzed extremities, resulting in a greatly increased risk for fracture(61). The incidence of lower extremity fractures in SCI patients was found to be ranging from 1 to 34% (40, 62). With each 0.1 g/cm^2 and each unit of t-value decrement of BMD at the femoral neck the risk of fracture increases by a factor of 2.2 and 2.8 times, respectively(4).

In an attempt to prevent osteoporosis, a common complication in the SCI population, we used a single IV dose of zoledronic acid and compared it with placebo.

DEXA is the most widely used technique to examine BMD because of its high accuracy and low radiation exposure(63). In our study 73 patients with SCI, underwent BMD scanning to diagnose osteoporosis.

We identified certain physical barriers during this study (which were also described by Morse et al (64) in their study), which interfered with dual energy x-ray absorptiometry in individuals with spinal cord injury. These barriers represent a significant limitation to widespread DXA scanning in the disabled, particularly, in the SCI population. The scan table height was too great for standard independent transfers from a wheelchair. To

overcome the physical barrier of the tabletop height, 3 persons were required to assist with lifting subjects from the wheelchair to the scanner table. The average positioning and scan time for subjects with more complete and higher SCI levels was between 30 to 45 minutes. This is considerably longer in duration than the average positioning and scan time (20 minutes) for DXA exams in the general population. This extra time was needed to assist patients during transfer to the tabletop and during repositioning of paralyzed limbs for the scanning of the various skeletal sites. Positioning the lower limbs for scanning was especially difficult in patients who had spasticity.

Of the 73 subjects who underwent DEXA scan, 31 (42.5%) subjects met the WHO criteria for osteoporosis at the hip (T score < minus 2.5). Another 31 subjects (42.5%) were osteopenic (T score <minus 1), and 11 subjects (15%) had normal BMD. This was slightly different from the findings of Lazo et al (4) who, in their study found that (61%) were osteoporotic, (19.5%) osteopenic, and another (19.5%) were normal.

The two study groups (zoledronic acid group and the control group) had similar baseline characteristics with respect to age, duration of injury, neurological level, vitamin D status, mobility, sun exposure and nature of vocation. However, there was difference with respect to gender distribution. In this study there were 23 males and 3 females. All the 3 female participants happened to be in the zoledronic acid group. This male: female ratio suggests that males are affected more commonly than females in traumatic SCI in India. Similar gender distribution with men suffering traumatic spinal cord injury more commonly than women in the ratio of 4:1 was also described by others(7). As the numbers of female participants in the study population is very small, it is not possible to evaluate the difference in osteoporosis with regard to gender in the spinal cord injured population.

Regarding age, Morse et al described that in contrast to the general population where

greater age is a risk factor for osteoporosis, age was not a predictor of fracture hospitalization(27).

Of the 31 subjects with osteoporosis, 26 were included in the randomized controlled study, 3 refused consent and 2 were lost to follow up. Of the 26 subjects, 12 were found to have vitamin D deficiency (<10 ng/ml) while another 12 had vitamin D insufficiency (10-20 ng/ml). Only 2 out of the 26 had normal vitamin D levels. None of these patients were on calcium or Vitamin D supplements. Morse et al (27) in their study on osteoporotic fractures and hospitalization risk in chronic SCI, found that no one was taking any medications for osteoporosis, such as anti-resorptives (bisphosphonates) or calcium/vitamin D, prior to admission. Moreover, no one left the hospital with a prescription for osteoporotic medications, and osteoporosis was not added to anyone's problem list on discharge (27). Bischoff-Ferrari et al (20) in their meta-analysis of randomized control trials on fracture prevention with vitamin D supplementation or without calcium supplementation, reported that for trials using 700 to 800 IU/d oral vitamin D, there is a significant (26%) reduction in risk of sustaining a hip fracture and a significant 23% reduction in risk of sustaining any non vertebral fracture. In contrast, 400 IU/d vitamin D did not appreciably reduce hip or non-vertebral fractures in older persons supplemented with calcium. Some studies show a positive effect of calcium and vitamin D supplementation on BMD in peri and postmenopausal women(65). However there are no data available on the protective efficacy of calcium and vitamin D supplementation in SCI subjects. The risk of hypercalciuria and renal stone disease in SCI subjects may have precluded use of calcium and vitamin D.

In our study we did not find any correlation between the vitamin D levels and the percentage change in BMD at the hip or forearm after intervention. In spite of the lack of correlation between vitamin D status and the percent improvement in BMD at the hip and

forearm in this small series of patients, it is probably necessary to optimize vitamin D status before giving zoledronic acid, as this may afford additional protection. In our series of SCI subjects, all except 2 were vitamin D insufficient or deficient according to Lips criteria. This may have obscured a potential beneficial effect of optimal vitamin D levels (>20 ng/ml). In other words, if we had a large number of patients with optimal vitamin D levels, the BMD changes in response to zoledronate may have been better.

Out of the 28 patients who were initially recruited into the study, one patient had a history of hairline fracture of upper tibia, secondary to fall from a chair during transfer. There were no other patients among the 28 who reported any fracture. This patient had a T12 complete paraplegia. Garland et al.(66) reported motor complete injury to increase both knee osteoporosis and lower extremity fracture rates when compared to motor incomplete injury. Morse et al (27) in their study had findings in agreement with this and stated that individuals with motor complete injury are at greatest risk for fracture hospitalization. The site of fracture sustained by the patient, is one of the most common sites of osteoporotic fracture seen in SCI patients. Morse et al (27) reported that the most common fracture requiring hospitalization in chronic SCI was a tibia/fibula fracture (47.5%), followed by the distal femoral metaphysis (20%) and then the proximal femur (15%). Humerus (5%), metatarsal (5%), and phalanx (7.5%) fractures were less common. Fall from a wheelchair was the most common cause (51%), followed by falls during transfers 14%), and lower extremity getting caught on a doorframe while operating a wheelchair (6%). In our study too the fracture was sustained secondary to a fall during transfer. Frisbie et al reported that the rate of femoral fractures in male SCI patients is greater than that of the general population by factors of 104 and 24 at ages 50 and 70,

respectively(62). The lower relative risk in older age group subjects is due to increased femoral fracture rates at age 70 in the general population.

In our study, we have evaluated the effect of a single dose of zoledronic acid on the bone mineral density at the hip and forearm in chronic SCI subjects. Our study revealed that osteoporosis due to the paralysis and immobility was observed in 42.5% of the chronic SCI individuals and osteopenia in 42.5%. Only 15% of these subjects had normal BMD.

There was a statistically significant reduction in the BMD of total hip at 1 year after placebo, whereas the patients who received zoledronic acid did not show such a statistically significant reduction in total hip BMD.

Considering the femoral neck, even though there was a statistically significant reduction in placebo as well as the zoledronic acid group, the magnitude of decrease in BMD was greater in placebo recipients suggesting a protective effect of zoledronic acid. This observation suggests that administration of zoledronic acid in patients with SCI, can reduce the extent of osteoporosis.

Interestingly the BMD in the forearm demonstrated a statistically significant rise in both the placebo as well as the zoledronic acid group. This could be attributed to the fact that individuals with paraplegia use their upper limbs for mobility with aids like crutches or wheelchair, which exposes the upper limbs to increased mechanical load. The effect of mechanical loading is highlighted by studies which show that BMD of the dominant hand are 5% higher than the non-dominant side(67). However Sergi et al found no significant differences in BMD between the dominant and non-dominant upper limbs in men or women(68), using peripheral quantitative CT. It is not clear whether this is because they used a different technique for BMD measurement.

LIMITATIONS OF THE STUDY

LIMITATIONS OF THE STUDY

- The limitations of this study include a relatively small sample size in each arm of the study. A larger number of patients would have increased the reliability of the conclusions.
- The patients were followed up only once after one year of drug infusion. Continuing follow up yearly after measuring BMD may give us a true picture of the extent of the ongoing bone loss and whether zoledronic acid prevents fractures in these patients.
- The study was not powered to determine fracture prevention.
- Vitamin D was not administered to any of the participants in the study. However, no correlation between percentage change in BMD and vitamin D was observed in this study.

CONCLUSION

CONCLUSION

- The prevalence of osteoporosis and osteopenia in our group of SCI subjects was high at 42.5 % each.
- The reduction in bone mineral density at the hip and femoral neck was partially mitigated in subjects who received a single dose of zoledronic acid.
- The bone mineral density in the forearm showed a statistically significant rise in both the placebo and zoledronic acid group, presumably related to greater mechanical loading of upper limbs in paraplegic subjects.
- A longer duration study with a larger number of subjects is needed to determine if the observed beneficial effect of zoledronic acid on BMD will translate into reduced fracture rates in subjects with chronic SCI.
- The majority of subjects with chronic SCI (92%) are vitamin D deficient or insufficient. The optimum dose of calcium and vitamin D supplementation for these subjects and the potential effect of such supplementation need to be determined. These doses will probably be lower than what is recommended for postmenopausal osteoporosis as chronic SCI subjects are at risk for hypercalciuria and renal stone disease.

RECOMMENDATION FOR FUTURE STUDY

RECOMMENDATION FOR FUTURE STUDY

The short comings of this study could be over come by designing a future study to test the effect of a single 4-mg dose of zoledronic acid,

- given after correction of vitamin D deficiency,
- with vitamin D and calcium supplementation,
- with an adequate sample size, and
- study powered to measure fracture risk in Indian population with spinal cord injury, would provide data to help in management of osteoporosis in SCI.

APPENDIX

APPENDIX

1. Patient information sheet
2. Informed consent document
3. Data sheet

1. PATIENT INFORATION SHEET

You are being requested to participate in a study to see if a drug called Zoledronic acid can help you with increasing the strength of the bones in your paralyzed limbs. The advantage of Zoledronic acid is that it needs to be taken in an injectable form only once yearly and it has been proven to be effective in strengthening bones in patients with weak (osteoporotic) bones due to other conditions like in post menopausal women and in cancer patients with weak bones. However, effect of Zoledronate has not been studied in patients with post injury paralysis. There are other drugs like Alendronate, which can help you do the same but the disadvantage is that, it has to be taken once a week on empty stomach and can cause gastritis. We hope to include about 40 people from this hospital for this study.

Does Zoledronic acid have side effects?

Zoledronic acid has been used by many people world wide to help improve the strength of bones in patients with weak (osteoporotic) bones due to other conditions like in post menopausal women and in cancer patients with weak bones. The majority of the patients have not had side effects. However, some people have experienced side effects like fever, chills and bone and muscle aches. In most of these cases it was mild and temporary and did not require any specific treatment. Some people also had fall in blood calcium and phosphate levels but these did not require treatment. Occasionally nausea, vomiting and swelling or redness at the site of injection may occur. Some people have had rash, itching and chest pain. Some isolated cases have had redness of eyes (conjunctivitis) and fall in blood Magnesium levels. There also have been some reports of impaired kidney function.

If you take part what will you have to do?

If you agree to take part in this study, you will be given either Zoledronic acid mixed with normal saline as an infusion or plain normal saline without Zoledronic acid in it. This is done so that we can be sure that any improvement in the strength of your bones as will be measured by DEXA scan will be actually due to Zoledronic acid and not due to chance (coincidence). Neither you nor your doctor will have any choice in whether you get Zoledronic acid or plain saline as this will be decided by a computer program; this is like tossing a coin and you have an equal chance of getting either Zoledronic acid or saline. Also neither you nor your doctor will know which one you have had till the study is over.

Any other medications, which you are regularly on, and activities, which you routinely do like walking with callipers or using wheelchair/tricycle will be continued during the study. You are expected to come for review exactly 1 year after you receive the injection. If at any time you experience any problems you will be expected to report this to the doctor.

Can you withdraw from the study once it starts?

Your participation in this study is entirely voluntary and you are free to decide to withdraw permission to participate in this study. If you do so, this will not this will not affect your usual treatment at this hospital in any way.

Will you have to pay for the study medications or the tests, which you need to undergo as part of the study?

The blood tests, x-ray examination, DEXA scan as well as Zoledronic acid or plain saline, which you will receive, will be given to you free of cost.

What happens after the study is over?

You may or may not benefit from the study drug, which you are given. Once the study is over and Zoledronic acid is found to be beneficial, those study subjects who had received saline will be given Zoledronic acid free of cost.

Will your personal details be kept confidential?

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without any additional permission, should you decide to participate in this study.

If you have any further questions please ask Dr Shiela Mary Varghese

Telephone no – 0416 2282158 / 9994453379.

Email – drshielavarghese@yahoo.co.in

2. FORMAL INFORMED CONSENT DOCUMENT

Study title: A randomised double blinded case control study of effect of Zoledronic acid on bone mineral density in osteoporotic chronic spinal cord injured patients.

Study Number:

Participant`s name:

Date of birth/Age (in years):

I _____ son/daughter of _____

Confirm that I have read the information sheet provided to me regarding this study and have had the opportunity to ask questions.

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

I also understand that neither I, nor my doctors will have any choice or knowledge of whether I will get the original drug (Zoledronic acid) or the identical looking placebo.

I also understand that during the study the drug or the placebo will be provided free, but after this, if the drug (Zoledronic acid) is found useful and prescribed, I may have to pay for it.

I understand that the study staff and the institutional ethics committee members will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access.

However, I understand that my identity will not be revealed in any information released to third parties or published.

I agree not to restrict the use of any data or results that arise from this study provided, such a use is only for scientific purpose(s).

I voluntarily agree to take part in this study.

Signature (or thumb impression) of the subject/legally acceptable representative):

Date:

Signatory`s name:

Signature of the Investigator:

Date:

Study Investigator`s name:

Signature of the witness:

Date:

Name of the witness:

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ANNEXURE

Sr no:	Hos No:	Sex	Age	Diagnosis	Vocation	Duration of injury	Mobility	Sun exposure	Ca	Alk phos	Vitamin D	BMD Neck 08	BMD Total hip 08	BMD forearm 08	BMD distal radius 08	BMD Neck 09	BMD Total hip 09	BMD forearm 09	BMD distal radius 09
1	132195C	1	1	2	1	1	2	2	8.50	72	1	0.503	0.52	0.54	0.70	0.46	0.46	0.56	0.76
2	129772B	2	1	2	1	2	1	1	8.00	61	1	0.505	0.43	0.43	0.56	0.41	0.36	0.44	0.59
3	019254C	1	1	2	1	1	2	2	8.70	75	1	0.5	0.61	0.59	0.72	0.46	0.42	0.62	0.78
4	887076A	1	2	2	2	2	1	2	9.00	117	1	0.54	0.57	0.55	0.69	0.53	0.53	0.60	0.77
5	123960B	1	2	2	1	2	2	2	8.20	76	1	0.48	0.58	0.60	0.74	0.44	0.51	0.59	0.72
6	043825B	1	2	2	1	2	1	2	8.50	70	2	0.51	0.61	0.64	0.77	0.51	0.55	0.71	0.84
7	426173B	1	2	1	1	2	1	1	8.60	70	1	0.48	0.50	0.62	0.77	0.47	0.48	0.65	0.84
8	905578A	1	2	2	2	2	1	2	8.40	102	1	0.57	0.61	0.63	0.76	0.54	0.58	0.70	0.81
9	167131C	1	1	2	2	1	2	2	9.00	80	1	0.49	0.48	0.65	0.76	0.45	0.48	0.65	0.77
10	584157B	1	1	2	1	1	1	1	8.90	67	1	0.56	0.65	0.61	0.71	0.57	0.64	0.65	0.77
11	058499B	1	1	2	1	2	2	2	8.80	61	1	0.61	0.62	0.64	0.73	0.60	0.62	0.66	0.73
12	365246C	1	2	1	2	1	1	2	9.00	59	1	0.57	0.71	0.56	0.71	0.54	0.41	0.55	0.73
13	200480C	1	1	2	1	1	1	1	8.10	98	1	0.53	0.77	0.62	0.73	0.00	0.00	0.64	0.75
14	416843A	1	2	2	1	2	1	1	8.30	84	1	0.91	0.63	0.65	0.73	0.77	0.73	0.68	0.74
15	818969B	2	1	1	1	1	2	1	9.00	50	1	0.64	0.64	0.56	0.66	0.60	0.62	0.59	0.73
16	109186C	2	1	1	1	1	1	1	8.60	71	1	0.63	0.61	0.53	0.68	0.67	0.63	0.55	0.73
17	849484B	1	1	2	2	1	2	2	8.60	62	1	0.68	0.65	0.66	0.81	0.62	0.59	0.70	0.85
18	378227C	1	1	2	2	1	2	2	9.40	84	2	0.55	0.57	0.62	0.74	0.56	0.59	0.65	0.73
19	230271B	1	2	2	2	2	2	1	9.20	112	1	0.46	0.59	0.55	0.64	0.43	0.48	0.58	0.68
20	636654A	1	2	2	2	2	1	2	9.10	80	2	0.57	0.54	0.55	0.68	0.54	0.58	0.57	0.75
21	850466A	1	2	2	2	2	2	2	8.10	66	2	0.53	0.62	0.57	0.69	0.51	0.51	0.61	0.74
22	673129A	1	2	2	2	2	1	2	8.70	99	2	0.52	0.55	0.57	0.73	0.49	0.52	0.58	0.72
23	960428C	1	1	2	2	1	2	2	9.50	103	2	0.64	0.58	0.62	0.74	0.61	0.59	0.68	0.76
24	972226C	1	1	1	1	1	1	1	9.10	55	1	0.55	0.59	0.56	0.68	0.54	0.50	0.61	0.75
25	175492D	1	1	2	1	1	1	1	9.50	88	1	0.59	0.66	0.59	0.74	0.57	0.69	0.60	0.79
27	230543D	1	1	2	1	1	1	1	9.3	77	2	0.47	0.6	0.59	0.703	0.46	0.57	0.62	0.75