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Original Article

THE STUDY OF RELATIONSHIP BETWEEN UNDERCARBOXILATED OSTEOCALCIN AND ADMINISTRATION OF VITAMIN K_2, VITAMIN D_3 AND CALCIUM IN PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL OSTEOPENIC WOMEN WHO ARE ADOPTING A SEDENTARY LIFE STYLE

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ABSTRACT

The aim of the study was to establish relation between undrcarboxilated osteocalcin and administration of combination of vitamin K2+ vitamin D3+calcium in prevention of osteoporosis in osteopenic postmenopausal women . This study included 60 postmenopausal osteopenic women.They were were administered 1gm calcium,vitamin D3 1mcg and vitamin K2 45mg/day.All the patients were investigate for bone marker under carboxilated osteocalcin, NTelopeptideand bone mineral density. It was observed that patients who were treat with vitamin K2,vitaminD3 and calcium had improvement in bone minerel density and reduction of undercarboxilated osteocalcin and N telopeptide. According the results of this study combination of calcium ,vitamin D3 and vitamin K2 to be effective and protective agent in prevention of osteoporosis in postmenopausal osteopenic women.

Key words: vitamin K_2,vitamin D_3,BMD,uc(OC) ,N telopeptide, osteoporosis, osteopenia.

INTRODUCTION

A sedentary life style reduces the constant forces that bone needs to experience in order to continue its normal process of remodeling(1).Immobilization leads to rapid loss of bone mass.Longterm immobilization can have serious skeletal consequences and may lead to increased fracture liability. Most cases of disuse osteoporosis require a long time for bone to recover its bone mineral density and strength. Hence we have to keep in mind that there are no treatment better than prophylaxis for disuse osteoporosis(2). Osteoporosis, a condition characterized by decrease bone strength is prevalent among postmenopausal women, with underlying condition or major risk factors associated with bone demineralization(10)(2397 harisson,s 17 edition). Osteoporosis is one of the major health problems in elderly and postmenopausal women in modern world Hence WHO operationally define osteoporosis as a bone density that falls - 2.5 standard deviations (SD) below the mean for young healthy adult of same gender. Postmenopausal women who fall at the lower end of the young normal range (T-score of >1SD below the mean between -1

to 2.5 SD) are defined as having low bone mineral density(osteopenia) and are also at increased risk of osteoporosis.Osteoporosis , a multifactorial pathology has been reviewed extensively.Vitamin K2 exerts a powerful influence on bone building, especially in osteoporosis, and has been cited as one of the most frequently prescribed treatment for osteoporosis.Various form of vitamin K are transformed into K2 in the femur.Vitamin K2 has been shown to be the most important inducer of bone mineralization in human osteoblasts(3) .Vitamin K2 in combination with 1-alpha-25-dihydroxyvitamin D_3has also been shown to increase osteocalcin production alpha ,25(OH)2 vitamin D3 induced mineralization in human periosteal osteoblast(4) .Application of K2 result in gamma-carboxylation of 1-alpha-25-dihydroxyvitamin D3- induced osteocalcin, which in turn is able to deposit gamma-carboxyglutamic acid-containing osteocalcin to the extracellular matrix on human osteoblast.In vitro studies using assays from various species demonstrate vitamin K2 inhibits osteoclastogenesis of bone .Undercarboxylation of the bone matrix protein osteocalcin appears to be a sensitive measure of vitamin K status. When defined as elevated concentrations of undercarboxylated osteocalcin(ucOC),vitamin K insufficiency appears to be common in postmenopausal women.High serum ucOC concentration has been associated with skeletal turnover(12) low bone mineral density and increased risk of osteoporotic fractures(13).N Telopeptide, the amino terminal cross-linked peptide of type I collagen is released during bone resorption and has been correlated with BMD T-Score(11) .

METHODS AND MATERIALS

The study began in march 2010 and ended in June 2011.We studied 60 postmenopausal women, with mean age 50 years and normal body mass index having no other concurrent illness. Subjects were recruited from urban areas all subjects were working women whose working hours were 10-12 hr and during work they had to sit at least 9-10 hr. They had bone mineral density between - 2.5 to -1.0 T-score(osteopenia). Patients were included according to their Bone mineral density, and bone marker. Measurement of bone mineral density done by Dual energy x-ray absorptiometry (DEXA) at spine and hip bone, and laboratory studies were performed before starting the treatment , after the 6 month of treatment and after the completion of treatment. Measurement of bone turnover marker done by commercially available specific kit. N-Telopeptide (NTx) bone resorption marker in urine was measured with a commercially available ELISA. Measurment of undercarboxylated osteocalcin in serum was measured by ELISA with IRMA. Sample were collected early morning.

Study design-It was prospective comperative study. All patients were informed about benefit , adverse effect, aim and objective of study and written consent taken from each patient.In this study subjects were recieved calcium 1 gram day + vit D_3 1 mcg/day + vit K_2 45 mg/day.Subjects were aware of their random assignment to receive medication .Compliance with study preparation was evaluated by tablet counts by 1 and 2 weeks.Serum and plasma were obtained at baseline, 6 weeks, 6 month and 1 year.Blood samples were obtained by routine venipuncture between 0800hr and 1100hr after subjects fasted for ≥8 hr.Bone mineral density also done at baseline, 6 weeks, 6 month and 1 year.

Statistical analysis –For analysis of baseline characteristics ,we included data

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from all subjects For analyses involving changes over time ,we analyzed data separately by treatment group.Descriptive statistics are presented as the mean ± SD unless otherwise noted. Study groups were defined by treatment and age.Baseline comparisons of variables were performed by using Student *t* test .Change over time in serum % of BMD, N-Telopeptide, undercarboxylated osteocalcin was evaluated by repeated-measures analysis of variance(ANOVA) with full interaction. **Result**-Baseline characteristic were measured mean age was 50.56 years ±50.56,Body mass index was 21.7 kg/body weight ±1.99.Bone mineral density was-1.61±0.268,N telopeptide(NTx) was 21.10±0.832nm/l BEC(nanomoles per L of bone collagen equivalents) and Uc(OC)8.64±0.462ng/ml respectively. After the treatment 6of 1gm calcium /day+1 mcg Vitamin D_3/day + Vitamin K_2 45 mg/day the improvement in BMD was 9.74%, 35.44% and 47.65% of base line at 6 week,6 month and 1 year respectively. Serum NTx was reduced 7.04%,11.37% and 14.84% of baseline at 6 week,6 month and 1 year respectively.Undercarboxilated osteocalcin was reduced 13.42%, 26.61% and 34.20% of baseline at 6 week,6 month and 1 year respectively.

One way ANOVA Table(variation between baseline and after the treatment)

Group	Base line Mean ±SD	6 weeks Mean ±SD	6 Month Mean± SD	1 Years Mean ±SD	F-Value	P-Value
BMD	-1.61±0.268	-1.45±0.616	-1.04±0.772	-0.84±0.390	12.662	<0.0001*
NTx	21.10±0.832	19.62±2.025	18.70±0.909	17.97±0.898	34.0190	<0.0001*
Uc(OC)	8.64±0.462	7.48±0.519	6.34±0.456	5.69±0.387	242.066	<0.0001*

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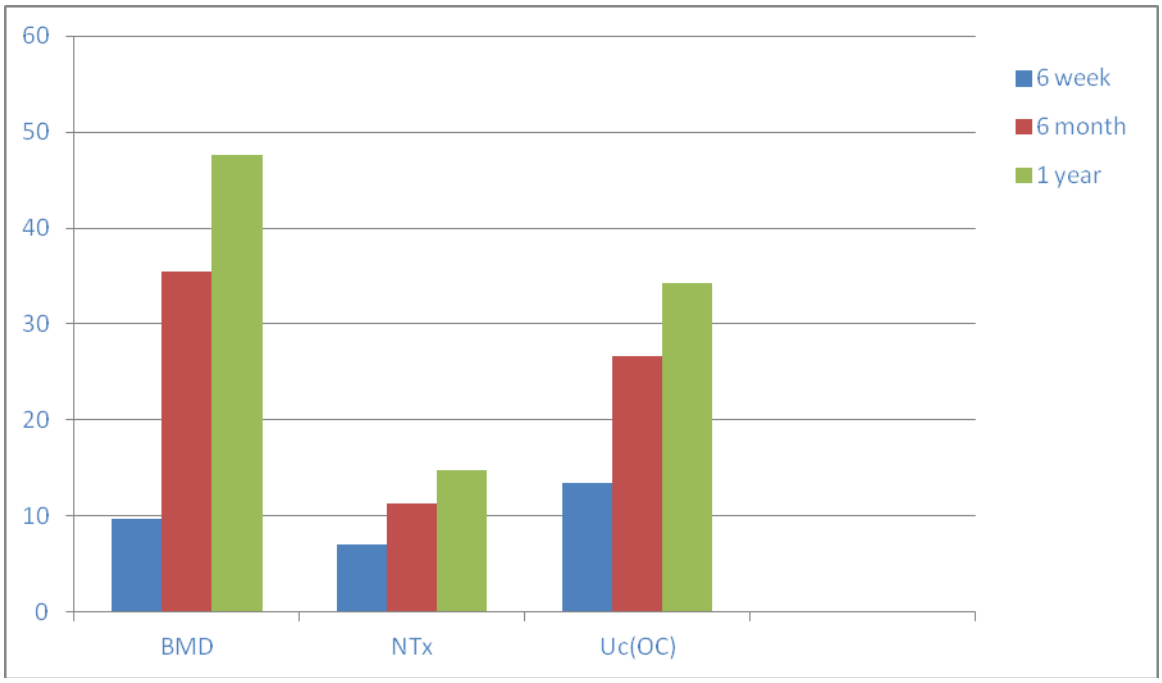
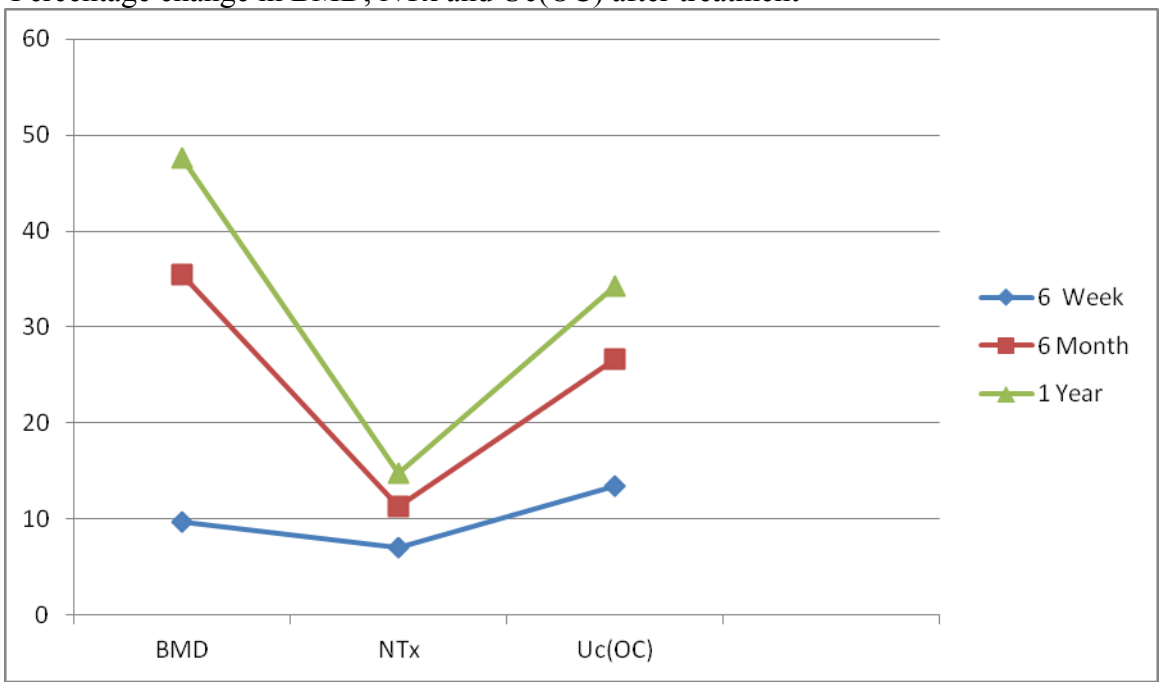


Percentage change in BMD, NTx and Uc(OC) after treatment



Difference between each other and difference between baseline & other

Discussion-:In this study administration of vitamin K2 +vitamin D3+calcium increase bone mineral density and reduced % ucOC in all women. Dietary intake provide inadequate vitamin K at the age of menopause due to ↑requirements and ↓ absorption and synthesis allow maximal osteocalcin carboxilation .Accumulating evidence suggest that vitamin K insufficiency contribute to development of osteoporosis. However much of this

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evidence is based on submaximal osteocalcin γ carboxilation ie. Elevated ucOC was associated with low bone mass.(13)This observation in our study is to some extent congruent with the recent finding that vitamin K depletion led to increased bone turnover as measured by serum undercarboxylated osteocalcin, urinary NTx concentration and bone mineral density(14).These markers were subsequently normalized by vitamin K administration on the basis of our observation we speculated that vitamin K insufficiency impairs the function of the calcium(3).In our study finding are supported by evidence that intake of vitamin K can lower serum concentration of uc(OC) and the uc(OC) is positively associated with risk of osteoporosis.Vergnaud et al. reported a significantly elevated odd ratio of 1.9 in women the highest quartile of percentage of uc(OC) after adjustment for bone mineral density(16,17).In our study we observed a significant interaction between Vitamin D and Vitamin K intake. Evidence that Viatamin D stimulate the gama carboxylation of gama carboxyglutamyl – containing proteins(5).promotes osteocalcin synthesis(5,6).and decreased uc(OC)(7)suggested that vitamin D may be a necessary component of the vitamin K dependent carboxylation process in bone.Theoreticaly this finding can be explain by the effect of two vitamins on calcium homeostasis vitamin D acts as an inducer of bone resorption and thus higher intake may result in increased turnover and increased urinary calcium execration.Conversaly results of some studies in animal(8) and humans(9) indicate that vitamin K decrease urinary calcium execration. Thus despite high dietary intake of vitamin D there may be an increased risk of hip fracture when vitamin K intake are low . A sedentary life style reduces the constant forces that bone needs to experience in order to continue its normal process of remodeling(15) .Studies shows that both man and women engage in regular exercise have much lower risk of osteoporosis and fracture(ebeling 2004,englund 2011).Krall and Dawson – hughes using a validated questionnaire, studied participation in outdoor walking and other leisure time physical activity in 239 postmenopausal women. They found significantly increased whole body,leg and trunk BMD in women who walked more than 7.5 miles per weeks compared with womens who walked less than one miles per weeks.

Conclusion-: It was concluded that vitamin k provided protective effects in diminishing bone loss. Combined administration of vitamin k,vitamin D and calcium is more effective then vitamin D and calcium and have a significant reduction of undercarboxilated osteocalcin and improvement in bone mineral density.

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