TO EVALUATE THE ASSOCIATION BETWEEN VITAMIN D AND BONE MINERAL DENSITY AMONG POSTMENOPAUSAL WOMEN

- A PROSPECTIVE OBSERVATIONAL STUDY

Dissertation submitted to

THE TAMILNADU
Dr.M.G.R MEDICAL UNIVERSITY

In partial fulfilment of the requirement
for the award of

M.S.DEGREE – BRANCH - II
OBSTETRICS & GYNECOLOGY

GOVT. KILPAUK MEDICAL COLLEGE
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APRIL - 2015

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"PROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE THE ASSOCIATION BETWEEN VITAMIN D AND BONE MINERAL DENSITY AMONG POSTMENOPAUSAL WOMEN"** is the bonafide original work of **Dr.PRIYA DHARSHINI.S** under the guidance of **Dr.TK.SHAANTHY GUNASINGH MD., DGO.,** Professor and head of Department of Obstetrics and Gynaecology, KMCH, Chennai in partial fulfilment of the requirements for MS Obstetrics and Gynaecology branch II examination of the Tamilnadu Dr.MGR Medical university to be held in April 2015 .The period of Postgraduate study and training from June 2012 to April 2015.

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DECLARATION

I solemnly declare that this dissertation "**A PROSPECTIVE OBSERVATIONAL STUDY TO EVALUATE THE ASSOCIATION BETWEEN VITAMIN D AND BONE MINERAL DENSITY"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr.TK.Shaanthy Gunasingh MD., DGO.** Professor, Department of Internal Medicine, Government Royapettah Hospital, Chennai.

This dissertation is submitted to **The Tamil nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.S. (Obstetrics and Gynaecology).**

Place: Chennai

Date: **(Dr.S.PRIYA DHARSHINI)**

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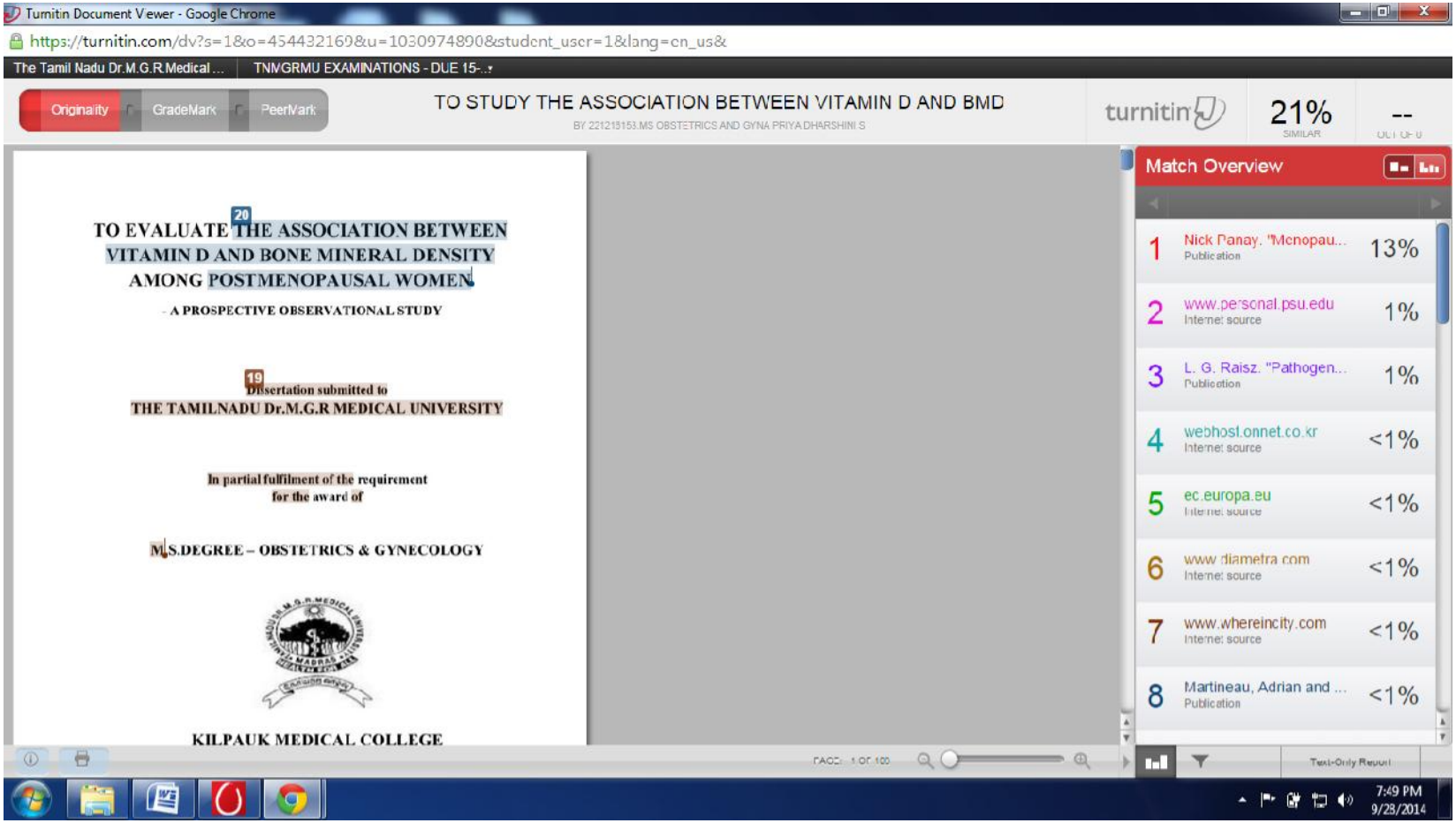
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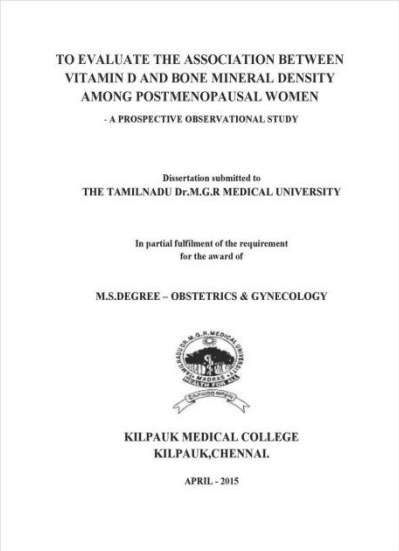

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INDEX

INTRODUCTION

Osteoporosis is a disease characterized by reduced bone mass and strength and the deterioration of the integrity of the structure of bone tissue,resulting in fragile bones and an increased risk of fracture. Osteoporosis is a major public health concern. An estimated 34 million Indians with osteopenia (low bone) are at risk for osteoporosis, and another 10 million have osteoporosis. The prevalence of osteoporosis is expected to increase as the age increases. One in two women of 50 years and older will experience an osteoporotic fracture in their lifetime (NOF, 2008).

Past research has shown that there is a link among non-modifiable risk factors such as age, gender, family history of osteoporosis or related fractures, frame size, race/ethnicity, low sex hormones (estrogen and testosterone) and modifiable lifestyle risk factors such as diet (decreased calcium and vitamin D intakes, increased intake of protein, sodium and caffeine intake), sedentary lifestyle, smoking, alcohol abuse, and few medications (NOF 2008).

Osteoporosis is the most common bone problem in the elderly. It is reduced bone mass with normal ratio of mineral to matrix. It is a major public health problem, affecting four times more than women. The future

risk of fracture from osteoporosis in women will depend on bone mass during menopause and the rate of bone loss after menopause.

The skeleton consists of two bone types.

1) Cortical bone
2) Trabecular bone

Cortical bone is the bone of the peripheral skeleton which constitutes 80% of total bone. Trabecular bone is the bone of the axial skeleton (spinal column, the pelvis, and the proximal femur), constitutes a honeycomb structure filled with red marrow and fat, giving larger surface area per unit volume. Estrogen exposure during adolescence is vital. Late menarche are associated with less bone mass and increased incidence of fractures. Women with amenorrhoea during adolescence have increased prevalence of osteoporosis. Calcium supplementation in prepubertal girls and pubertal girls will have improved bone density.

MENOPAUSE:

Menopause is defined as when permanent cessation of menstruation occurs following the loss of ovarian activity. Menopause is derived from greek words ‘men’ (month) and ‘pausis’ (cessation) . Years before menopause from normal menstrual cycles to stoppage of menses – perimenopausal transition. Climacteric is defined as when

woman passes from reproductive stage through perimenopausal transition and the menopause to the postmenopausal years.

Several months of amenorrhoea together with an FSH level of 40 IU/L or more are indicators that menopause is reached.

With this study aiming at to study the association between vitamin D and BMD,

1) Whether level of vitamin D at which patients are prone for osteoporosis can be ascertained.

2) Whether supplementation with vitamin D can prevent or delay the onset of osteoporosis can be predicted.

REVIEW OF LITERATURE

MENOPAUSE:

Demography

In India, an average of 60 million women are living with age more than 55 years. Most of the women are spending one-third of their lifetime in postmenopausal age group .So it is very important to identify problems that will occur in menopause and to rectify them, so that they can improve their quality of life. An average Indian woman now lives up to 65 years of age, whereas in developed countries a lifespan up to 80 years is possible, with the consequence that a woman spends one-third of her life after menopause and poses health problems.

Age:

The average age of menopause is 47 years (45-50 years). Premature menopause is cessation of menstruation before 40 years.

Menopausal age is not related to menarche, race, socioeconomic status, number of pregnancies and lactation, or taking of oral contraceptives. It is directly related to smoking and genetic disposition. Smoking lead to premature menopause.

Pathophysiology:

Hormone levels:

Table 5-1. Hormone levels in a menopausal woman

E_2	5-25 pg/ml
Oestrone	20-70 pg/ml-more in obese women
FSH	>40 mIU/ml
Androgen	0.3-1.0 ng/ml
Testosterone	0.1-0.5 ng/ml
LH	50-100 mIU/ml
Androstenedione	800 pg/ml

E_2/E_1 ratio maintained over 1 in the premenopausal period is reduced to less than 1 in the menopausal age, causing an oestrogen deficiency state. Oestrogen level of over 40 pg/ml exerts bone and cardiotrophic effect, but the level below 20 pg/ml may predispose to osteoporosis and ischaemic heart disease (Table 5.1). Low level of growth hormone causes ovarian failure.

Risk factors for menopause-related diseases are as follows:

- Early menopause.
- Surgical menopause or radiation.
- Chemotherapy especially alkalytic agents.
- Smoking, caffeine, alcohol.
- Family history of menopausal diseases.

Drugs related such as GnRH, heparin, corticosteroids and clomiphene (anti-oestrogen) when given over a prolonged period (over 6 months) can lead to oestrogen deficiency.

Apart from the atrophy of the genital organs, general disturbances that develop are almost certainly caused by alterations in the endocrine balance maintained during the childbearing period. Fat is deposited around the breasts, hips and abdomen. Although the mammary glandular tissue atrophies, deposition of fat often makes the breasts more pendulous. Whereas glandular tissue constitutes 30% of the breast volume, it is reduced to only 5% after the menopause.

Other symptoms

Almost 60-70% women go through menopausal period without problems. Rest need guidance and treatment. The most common

symptoms of menopause are hot flushes and sweating. Hot flushes are the cycles of vasodilation affecting face and the neck and these persists for 2-5 minutes each. It is more severe during the night, and can disturb sleep. The hot flushes are sometimes preceded by headache. Palpitation and anginal pains may be felt. Mental depression due to disturbed sleep or otherwise, irritability and lack of concentration are noticed. With passage of time, the frequency and severity of flushes diminish over a period of 1-2 years. Hot flushes are caused by noradrenaline, which disturbs the thermoregulatory system. Oestrogen deficiency reduces hypothalamic endorphins, which release more norepinephrine and serotonin. This leads to inappropriate heat loss mechanism.

Some women develop a condition of pseudocyesis, when they fear pregnancy and attribute amenorrhoea and increased abdominal girth to pregnancy.

Cancer phobia may also develop, and the woman starts worrying over her looks.

Neurological

Vasomotor symptoms and paraesthesia take the form of sensations of pins and needles in the extremities.

Libido

Sexual feeling and libido may increase in some, if they feel happy to get rid of menstruation and fear of pregnancy. Many however notice decreased libido after menopause.

The symptoms which develop little later are as follows:

- Urinary such as dysuria, stress incontinence and urge, recurrent infection (urethral syndrome).
- Genital such as dry vagina, dyspareunia, loss of libido.
- Faecal incontinence

Urinary tract

Oestrogen deficiency lead to urethral caruncle, dysuria, with or without infection, urge and stress incontinence. The stress incontinence is caused by poor vascularity and tone of the internal urinary sphincter. These urinary symptoms are together called as 'urethral syndrome'.

Genital

Atropic vagina decreases the vaginal secretion, and dry vagina can cause dyspareunia. Loss of libido will be there. Rarely senile vaginitis can cause vaginal bleeding . Prolapse of genital tract and stress incontinence of urine and faeces are mostly menopausal related.

Late sequelae

Menopausal women with chronic oestrogen deficiency are liable to develop the following:

- Arthritis, osteoporosis and fracture.
- Cardiovascular accidents such as ischaemic heart disease, myocardial infarction, atherosclerosis and hypertension.
- Stroke.
- Skin changes.
- Alzheimer disease.
- Ano-colonic cancer.
- Tooth decay.
- Prolapse genital tract, stress incontinence of urine, faecal incontinence.
- Cataract, glaucoma and macular degeneration.

Locomotor system disorders: Menopausal arthropathy, osteoarthritis, fibrositis and backache may be age related.

Osteoporosis:

It is an incipient slowly progressing skeletal disorder characterized by microarchitectural deterioration of bone mass resulting in increased

fragility and predilection to fracture in the absence of significant trauma. About 15% of elderly women suffer from osteoporosis and almost three times as many suffer from osteopenia (deficient bone mass). Both osteopenia and osteoporosis predispose to fractures. These constitute a significant cause of morbidity such as pain, deformity and impaired respiratory and other bodily functions. Hip fractures are often associated with a high rate of mortality.

Cardiovascular disease

Oestrogen is cardioprotective by maintaining a high level of high density lipoprotein (HDL) and lowering the low density lipoprotein (LDL) and triglycerides. Oestrogen deficiency therefore can cause atherosclerosis, ischaemic heart disease and myocardial infarction. Obese women with hypertension and previous thromboembolic episodes are liable to cardiovascular accidents. Oestrogen prevents atherosclerosis through its antioxidant property.

Stroke

The incidence of stroke also increases in menopausal women.

Skin

Collagen content is reduced, causing skin to wrinkle. The 'feminine forever' thought applies to oestrogen cream to delay the age-related skin

changes. However, it is observed that after a few months, the skin actually thins out, and oestrogen cream may be beneficial temporarily and only in the initial phase of treatment.

Alzheimer disease

Lately it is reported that Alzheimer disease is precipitated by oestrogen deficiency at menopause, and hormonal therapy is beneficial in preventing or delaying its onset.

- Tooth decay.
- Keratoconjunctivitis, cataract, glaucoma and macular degeneration.

Ano-colonic cancer and teeth decay are known to increase after menopause.

Endocrine system

Mild virilization as seen in the form of hirsutism is probably adrenal in origin, as also is obesity, especially the deposit of fat around the hips. Hypothyroidism with low BMR, high cholesterol level, dryness of skin, brittleness of hair and lack of concentration are noticed in a few menopausal women.

Pyometra

Years after menopause, a woman may develop senile pyometra caused by cervical stenosis, and needs drainage by cervical dilatation under general anaesthesia.

Management

The clinician should adopt a holistic approach towards management of health problems of menopausal women and selectively prescribe hormone therapy according to the requirement. Minimal required dose avoids risks while conferring the beneficial effects

Counselling

The woman often develops pregnancy and cancer phobia. It is the duty of the gynaecologist to convince her, after thorough examination and investigations that all is well with her. It is a good practice to document baseline recordings of pelvic ultrasound, which includes the ovarian size and the endometrial thickness, mammography and as well as E_2 and FSH levels, when HRT is considered. Regular counselling may be required until the woman is well settled in menopause.

The advice on contraceptives is necessary. Until menopause is well established and amenorrhoea has lasted for 12 months, couple is advised

to use barrier method. Hormonal pills may not be safe from the point of view of thromboembolism. Progestogen pills or depot injections may be the alternative, but they cause irregular bleeding and depression.

Diet should include at least 1.2 g of calcium, Vit A, C, E and 400 mg of Vit D Soya beans are good. Weight bearing exercises (walking and aerobic) delay onset of osteoporosis.

Mild tranquillizers

These relieve woman's anxiety, sleeplessness and depression. Anti-depressants such as sulpiride may be needed.

Hormone replacement therapy

Not all women require hormone replacement therapy (HRT). Besides, HRT does not suit all, and it may cause complication and be harmful. However, it is logical to prescribe HRT and not withhold it when one needs it in the minimal effective dose for the shortest needed duration under supervision while on therapy.

Initially, every menopausal woman was advised to go on HRT as soon as menopause set in to be taken for several years. Newer researches and their observations reveal that a few women need prophylactic and

therapeutic HRT, but 70-85% of women remain healthy and need only good nutrition and healthy life style.

Who needs HRT?

- Symptomatic woman who suffers from oestrogen deficiency (therapeutic).
- High-risk cases for menopausal complications such as cardiovascular disease, osteoporosis, stroke, Alzheimer disease, colonic cancer (prophylactic).
- Premature menopause, spontaneous or following surgery (hysterectomy, tubectomy). The surgical procedures disturb and compromise the blood supply to the ovaries. Menopause caused by radiotherapy and chemotherapy for cancer, especially alkylating agents (prophylactic).
- Gonadal dysgenesis in adolescents (therapeutic).

MENOPAUSE-THERAPEUTIC OPTIONS:

HRT

OESTROGEN

Dosage

There is general agreement now that patients should be started on the minimum effective dose of oestradiol, increasing the dose only if needed to alleviate symptoms. Although there is no direct evidence that higher doses of exogenous oestrogen are associated with increased risk of breast cancer or heart disease there is a link with venous thromboembolic risk. Importantly, lower doses of oestrogen are less likely to produce breast tenderness and bleeding problems which will reduce continuance of therapy.

- The minimum dosages of currently available systemic oestrogen are as follows:
- 0.3–0.625 mg oral conjugated equine oestrogens
- 1mg of oral micronized oestradiol or oestradiol valerate
- 25–50 mcg transdermal oestradiol
- 25–50 mg of implanted oestradiol
- 150 mcg transnasal oestradiol
- 50 mcg oestradiol silicone ring

Data suggest that the benefits of a 2 mg dose of oestradiol for symptoms and bone protection can be maintained by a 1 mg dose and similarly the benefits of a 50 mg oestradiol implant are maintained by a 25 mg implant [13]. Studies are currently ongoing to facilitate the licensing of a 0.5 mg oestradiol containing preparation which appears to adequately relieve symptoms. Exceptions to this ‘low dose rule’ are women who suffer premature ovarian failure who need higher doses of oestrogen to reproduce the physiological hormone levels which would have been present if the ovaries had not failed early. The optimum route of administration or dosage in this groupof young women has yet to be determined.

Route of administration

If we adhere to the principle that we should try to reproduce the most physiological state possible with a 2:1 oestradiol: oestrone ratio then we should avoid the oral route altogether. Oral oestradiol preparations are partially metabolized to oestrone by hepatic first pass metabolism and therefore do not fully restore this ratio. There are twice weekly or once weekly changed transdermal systems containing either oestradiol alone or both oestradiol and progestogen. The combined patches are available in either sequential or continuous regimens. The hormone is adsorbed onto the adhesive matrix which avoids the skin reactions caused by the old alcohol reservoir patches.

Oestradiol can also be used transnasally in a ‘pulsed’ fashion which is thought to maintain the benefits while minimizing the side effects of chronically elevated oestrogen, for example, breast tenderness. It is also available as a low-volume daily transdermal gel or even as a silicone vaginal ring delivering oestradiol systemically for 3 months. The nasal, gel and ring preparations are oestrogen alone and should be combined with progestogen in women with a uterus .

Recently developed vaginalHRT regimens have managed to avoid the problem of endometrial stimulation. Creams using oestriol do not produce endometrial hyperplasia and the 17β oestradiol vaginal tablet and silicone vaginal ring also provide effective relief of local symptoms without any significant endometrial effects. These preparations can be used without progestogenic opposition but are only licensed for 3 months use in the UK and 1 year in Europe.

Options for local vaginal oestrogen are as follows:

• 0.01% Oestriol cream and pessaries

• 0.1% Oestriol cream

• 25 mcg/24 h Oestradiol vaginal tablets

• 7.5 mcg/24 h Oestradiol releasing silicone ring

• Premarin cream – this preparation can potentially cause endometrial hyperplasia and should not be used without progestogenic opposition for more than 3 months.

PROGESTOGEN/PROGESTERONE

Regimens

Oestrogen was originally used unopposed in non hysterectomized women. It was noted that this led to endometrial hyperplasia in up to 30% of cases. Progestogen has therefore been added to oestrogen therapy for the last 30 years to avoid hyperplasia and carcinoma. It is generally accepted that women commencing HRT should start on a sequential regimen, that is, continuous oestrogen with progestogen for 12 to 14 days per month.

Bleeding problems

If bleeding is heavy or erratic the dose of progestogen can be doubled or duration increased to 21 days. Persistent bleeding problems beyond 6 months warrant investigation with ultrasound scan and endometrial biopsy. After 1 year of therapy women can switch to a continuous combined regimen which aims to give a bleed free HRT regimen which will also minimize the risk of endometrial hyperplasia. Alternatively, women can be switched to the tissue selective agent tibolone. With both these regimens there may be some erratic bleeding to begin with but 90% of those that persist with this regimens will eventually be completely bleed free. If starting HRT de novo a bleed free

regimen can be used from the outset if the last menstrual period was over a year ago.

Progestogenic side effects

It is vital that we maximize compliance if patients are to receive the full benefits from hormone replacement therapy (HRT). One of the main factors for reduced compliance is that of progestogen intolerance. Progestogens have a variety of effects apart from the one for which their use was intended, that of secretory transformation of the endometrium. Symptoms of fluid retention are produced by the sodium retaining effect of the renin-aldosterone system which is triggered by stimulation of the mineralocorticoid receptor. Androgenic side effects such as acne and hirsuitism are a problem of the testosterone derived progestogens due to stimulation of the androgen receptors. Mood swings and PMS-like side effects result from stimulation of the central nervous system progesterone receptors.

Minimizing progestogen intolerance

The dose can be halved and duration of progestogen can be reduced to 7–10 days. However, this may result in bleeding problems and hyperplasia in a few cases (5–10%) so there should be a low threshold for performing ultrasound scans and endometrial sampling in these women.

Natural progesterone has less side effects due to progesterone receptor specificity but is only available in a vaginal form in the UK (200–400 mg pessaries or 4–8% progesterone gel) though micronized oral progesterone is available in France. The levonorgestrel intrauterine system, recently granted a 4 year license in the UK for progestogenic opposition, also minimizes systemic progestogenic side effects by releasing the progestogen directly into the endometrium with low systemic levels. However, in severely progestogen intolerant women, even the low systemic levels of the 20 mcg levonorgestrel intrauterine system can still produce side effects.Asmaller, lower dose, 10 mcg system is in phase III clinical trial stage of development and should be ideal for the severely progestogen intolerant woman [16]. A new progestogen, drospirenone, a 7 that even non-hysterectomized women should be treated with oestrogen-only containing preparations. According to the MWS data, after 10 years of oestrogen and progestogen HRT there would be an extra 19 per 1000 cases of breast cancer and no cases of endometrial cancer; after 10 years of oestrogen alone in non-hystectomized women, there would be an extra 5 cases per 1000 of breast cancer and 10 cases per 1000 of endometrial cancer (total 15:1000). From this simplistic point of view, it would seem reasonable that all women (even with a uterus) should receive oestrogen alone. However, this does not take into account

the excess cases of endometrial hyperplasia and bleeding problems. This would generate excessive investigations such as endometrial sampling, hysteroscopies and even hysterectomies which would not be without their own morbidity and mortality.

Current advice remains that progestogenic opposition should still be used. However, it is imperative that we continue to seek improved ways of administering the progestogens which are important in protecting the endometrium to avoid progestogenic side effects andminimize effects on breast tissue, for example, vaginal and intrauterine progestogens and natural progesterone. However, there is a lack of data as to the risk of breast cancer in women using oestrogen with a levonorgestrel intrauterine system.

TESTOSTERONE

Preparations/regimens

Unfortunately, only 100 mg/6 months implanted testosterone pellets are licensed for use in women; 25 mg pellets exist but must be ordered on a named patient basis. The realization that there is currently an unfilled market for female androgen replacement has led to the development of the 300 mcg per day testosterone transdermal system to treat ‘hypoactive sexual desire disorder’. While the license for this

product is awaited it is necessary to continue improvising if one wishes to use preparations other than implants.

One option is to use testosterone gel which comes in 50 mg, 5 ml sachets at a dose of 0.5–1.0 ml/day. If the free androgen index is kept within the physiological range there are rarely any side effects such as hirsuitism. Levels should be checked at baseline and repeated at 4–6 weeks.

Research so far has suggested at worst a neutral effect on the cardiovascular system, for example, arterial compliance and lipid effects. Alternatives to this include scaled down dosages of testosterone injections and oral preparations though many avoid the latter route because of hepatic concerns.

THE HRT CONTROVERSY

Over the last few years, health professionals and their patients have been inundated with information regarding the potential benefits and risks of hormone replacement therapy. Information is available from a variety of sources; some are more reliable than others. The popular press subeditors, responsible for the headlines, often sensationalize the risks of HRT. This has left the average health professional in a very difficult

position as to what to advise their patients and has left patients bemused as to where they should turn to obtain reliable advice.

Osteoporosis

HRT is the cornerstone in the prophylaxis and treatment of osteoporosis. After menopause, the woman loses on an average 3% BMD every year causing osteopenia and eventually osteoporosis and fracture of the vertebra, femur and of the wrist. The trabeculated bone is most affected. The morbidity arising from fracture is considerable. The benefit of HRT is proved beyond doubt in preventing or delaying bone resorption. This allows an optimal benefit of HRT (around the age of 60). Natural oestrogen, progestogen, tibolone and raloxifene are beneficial in osteoporosis, if it occurs early in menopause. Osteoporosis occurring late in menopause benefits from bisphosphonates, as primary treatment.

Since the prolonged therapy beyond 8-10 years is not beneficial but perhaps harmful, most gynaecologists now follow up the woman for osteopenia and prescribe HRT when osteopenia occurs.

Oestrogen delays or protects against osteoporosis by 50% in all skeletal bones, and not restricted to trabecular bones of spine, wrist and upper hip bones.

Osteoporosis is classified into primary and secondary. Primary Osteoporosis otherwise known as idiopathic osteoporosis is seen in postmenopausal womenpredominantly. It can also occur in men who have underlying defects in bone formation. Secondary causes are associated with endocrine disorders like diabetes mellitus, hypothyroidism, cushing' s syndrome, hypogonadism and obesity. Other inflammatory diseases like anorexia nervosa, rheumatoid arthritis chronic renal and liver disease will predispose to the development of osteoporosis.

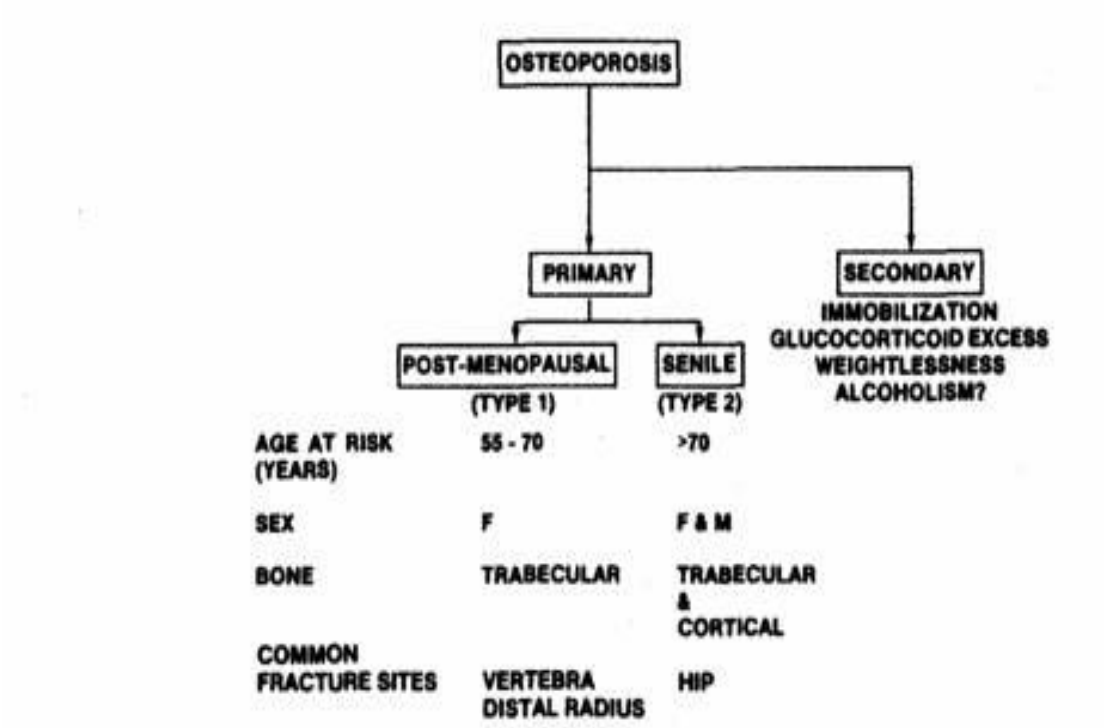


FIG. 1. Classification of osteoporosis.

DEMOGRAPHY:

The age of onset of osteoporosis is usually more than 50 years, mostly in postmenopausal women. Male to female ratio is 1:2.66. Indians are prone to the development of osteoporosis, because of the increasing incidence of vitamin D deficiency in Indian subcontinent.

Precipitation and Absorption of Calcium and Phosphate in Bone-Equilibrium with the Extracellular Fluids

The concentrations of calcium and phosphate ions in extracellular fluid are considerably greater than those required to cause precipitation of hydroxyapatite. However, inhibitors are present in almost all tissues of the body, as well as in plasma, to prevent such precipitation; one such inhibitor is pyrophosphate. Therefore, hydroxyapatite crystals fail to precipitate in normal tissues except in bone despite the state of supersaturation of the ions.

Mechanism of Bone Calcification

The initial calcium salts to be deposited are not hydroxyapatite crystals but amorphous compounds (noncrystalline), a mixture of salts such as $CaHPO_4 \cdot 2H_2O$, $Ca_3(PO_4)_2 \cdot 3H_2O$, and others. Then by a process of substitution and addition of atoms, or reabsorption and reprecipitation, these salts are converted into the hydroxyapatite crystals over a period of

weeks or months. A few percent may remain permanently in the amorphous form. This is important because these amorphous salts can be absorbed rapidly when there is need for extra calcium in the extracellular fluid.

The mechanism that causes calcium salts to be deposited in osteoid is not fully understood. The osteoblasts supposedly also secrete a substance into the osteoid to neutralize an inhibitor (believed to be pyrophosphate) that normally prevents hydroxyapatite crystallization.

Although calcium salts almost never precipitate in normal tissues besides bone, under abnormal conditions, they do precipitate. For instance, they precipitate in arterial walls in arteriosclerosis and cause the arteries to become bonelike tubes. Likewise, calcium salts frequently deposit in degenerating tissues or in old blood clots. Presumably, in these instances, the inhibitor factors that normally prevent deposition of calcium salts disappear from the tissues, thereby allowing precipitation.

Calcium Exchange Between Bone and Extracellular Fluid

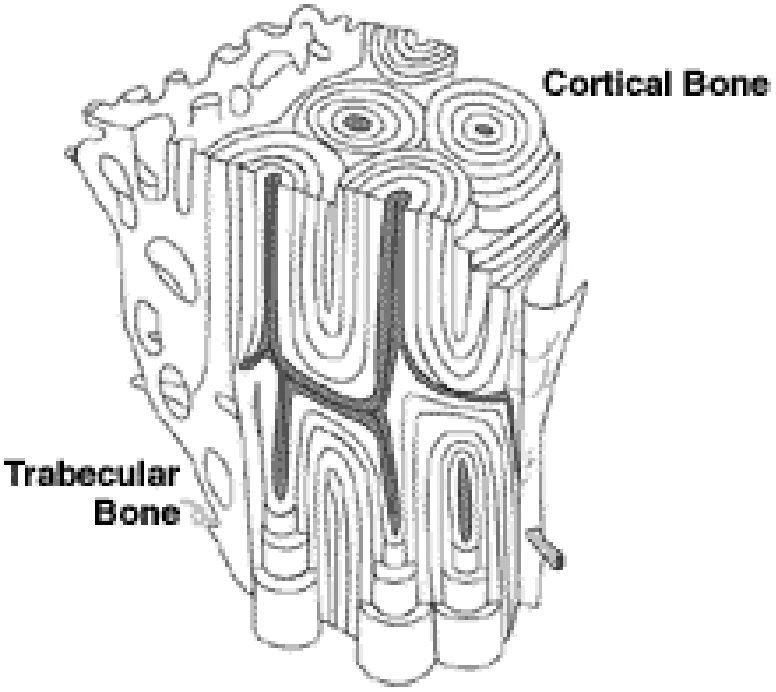
If soluble calcium salts are injected intravenously, the calcium ion concentration may increase immediately to high levels. However, within 30 to 60 minutes, the calcium ion concentration returns to normal.

However, most of the exchangeable calcium is in the bone. It normally amounts to about 0.4 to 1 percent of the total bone calcium. This calcium is deposited in the bones in a form of readily mobilizable salt such as $CaHPO_4$ and other amorphous calcium salts.

PATHOPHYSIOLOGY OF OSTEOPOROSIS:

Osteoporosis has a complex pathogenesis. During the period of growth the bone formation exceeds bone resorption till adolescence.After the period of 30 years, the bone resorption exceeds bone formation[1]. The bone loss as compared to premenopausal bone loss increases to 2-3 percent per year after menopause[1].The cancellous bone is more metabolically active, so it bears the major brunt of the disease. The bone makeover is linked with polymorphisms in the gene for vitamin D receptor (VDR)[2]. Also polymorphisms in gene coding for estrogen receptor α (ERα) is associated with accelerated postmenopausal bone loss in women[3].The basis pathogenic mechanism in osteoporosis is excess skeletal tissue fragility Which is mainly due to:

1) During childhood and puberty, production of skeleton with decreased mass and endurance[4].
2) Enhanced bone resorption which lead on to decreased bone mass and distorted architectural pattern of bone[4].
3) Deficient bone formation response[4].

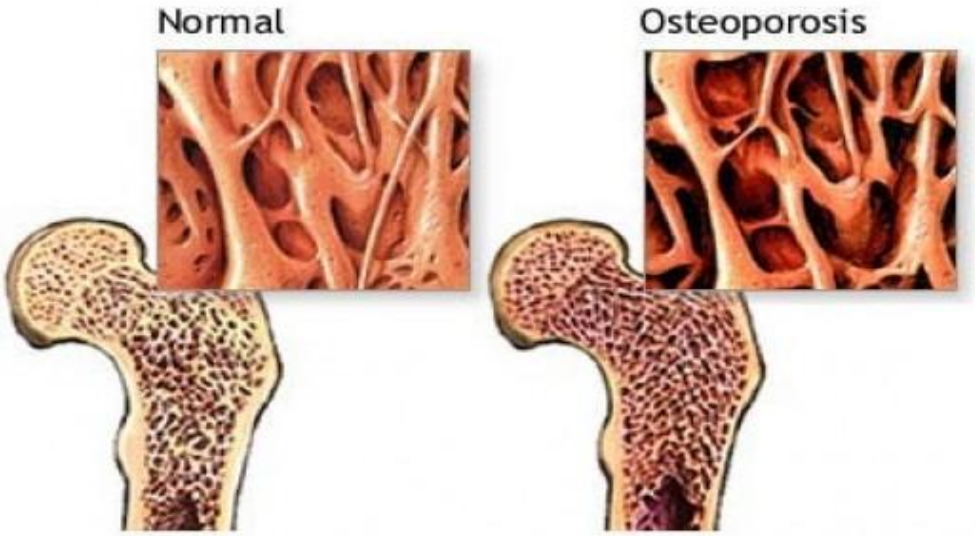


Cross section of bone (enlarged)

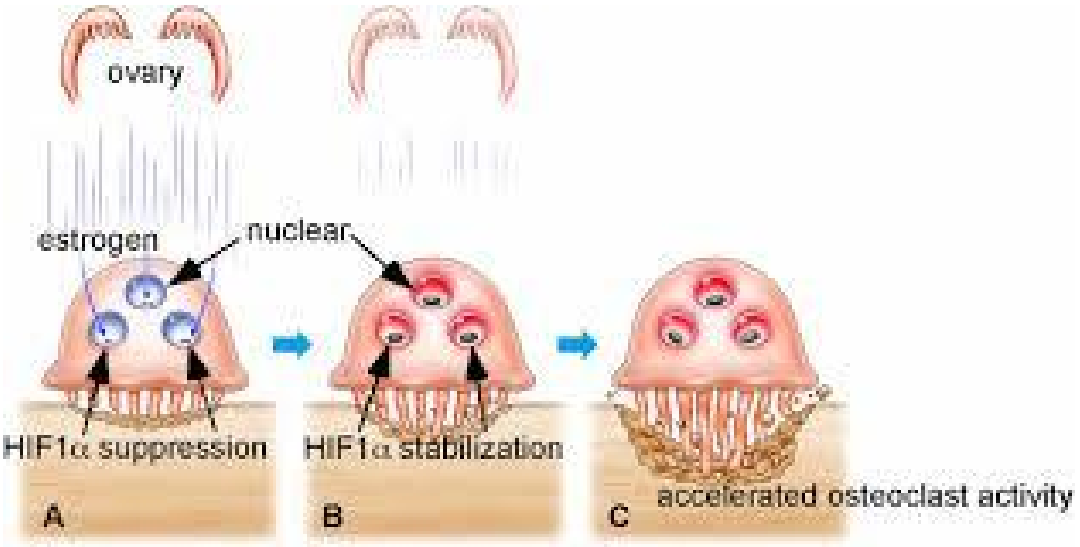
MECHANISM OF BONE REMODELLING

Remodeling involves two processes.

1. Maintenance of skeletal strength by repairing microdamage to bone.
2. Maintenance of blood calcium levels by constant supply of calcium[5].


Normal
Osteoporosis

REGULATION OF OSTEOCLASTIC FUNCTION:



Initial step in remodeling is the interaction between osteoblastic and osteoclastic cell lines. Macrophage colony stimulating factor combines with its receptor, c-fms, to activate proliferation and differentiation of haematopoeitic progenitors, which expresses RANK as preosteoclasts. Osteoclast are stimulated by RANK/RANKL interaction, and this is inhibited by osteoprotegerin(OPG). The COX2 activity is stimulated by bone resorping factors which in turn produce prostaglandins and amplify the responses to RANKL and OPG. In proinflammatory states osteoclastogenesis increased by production of M-CSF and RANKL along with PTH – related protein ,cystokines and prostaglandins. These osteoclasts needs interplay with osteoblastic cell line. In resorption phase with osteoclasts holding center stage, which is of shorter duration followed by reversal phase[4] .

ROLE OF ESTROGEN:

Estrogen deficiency will lead to bone loss, as evidenced by increased prevalence of osteoporosis in post menopausal age groups. Bone remodeling process is accelerated at menopause as evidenced by studies[6].

MECHANISM:

The amount of estrogen required to inhibit the resorption is less than one fourth that is needed for the growth of breast tissue and uterus[8]. Estrogen is required for epiphyscal closure in men and women. In addition, the lower estrogen levels are the most important cause of osteoporosis in older men than low androgen levels[9].

Estrogen has skeletal and extra skeletal activities, in skeletal action it has direct and indirect action. Direct action is mediated via estrogen receptors in osteoclasts and osteoblasts. The indirect effects are mediated via its action on estrogen receptors on stromal cells. Estrogen deficiency will lead to increased expression of RANKL on bone marrow stromal cells, which is important for bone resorption[16]. Estrogen itself stimulates Osteoprotergerin(OPG) production in osteoblasts and antagonizes resorptive effects on bone[17]. The extraskeletal manifestations are increased renal calcium excretion and inhibition of calcium absorption from gut, these effects may lead to secondary hyperparathyroidism, in addition estrogen has suppressive action on parathyroid hormone levels[18].

Estrogen exerts its action via two receptors ERα and ERβ. The ERα is most important for its action[4]. Estrogen induces osteoclast apoptosis via TGF-β production[10]. It also reduces the amount of reactive oxygen species[11]. The osteo immunology behind estrogen deficiency is the increased production of IL-7, this in turn activates T cells. T cells in turn expresses TNF-α and INF γ and leads to over expression of MHC(major histocompatibility complex) class 11 molecules on the surface of bone marrow stromal cell which further leads to more production of T cells and production of RANNKL and TNF-α, both are pro osteoclastogenic.

Role of vitamin D, calcium and parathyroid hormone:

Calcium deficiency that results from either decreased intake or deficient absorption from intestine secondarily due to disease per se or due to aging along with vitamin D deficiency leads to secondary hyperparathyroidism[14]. Vitamin D3 is needed not only for absorption of calcium from the small intestine but also for its negative influences on paratharmone[12]. Various trials had proved that vitamin D supplementation along with calcium in elderly people will results in increased bone mass along with reversibility of falls.

Secondary hyperparathyroidism is commonly seen in patients with vitamin D insufficiency which is defined less than 30 ng/ml, hence forth the target vitamin D levels should be mor than this level[19]. There is a seasonal decrease in vitamin D levels along with elevated levels of parathyroid hormone. There is also increased risk of cardiovascular mortality in people with secondary hyperparathyroidism, the mechanism behind this is unknown[20].

Genetis in osteoporosis:

The signal transduction pathways and transcription factors necessary for osteoblastic activity had shown several novel pathways to decipher and to understand the pathophysiology of osteoporosis[4]. The second fiddle played by the Wnt signaling pathway in controlling osteoblast activation is of great interest to researchers, and it was recently identified it plays an important role in determining bone mass and strength[4].

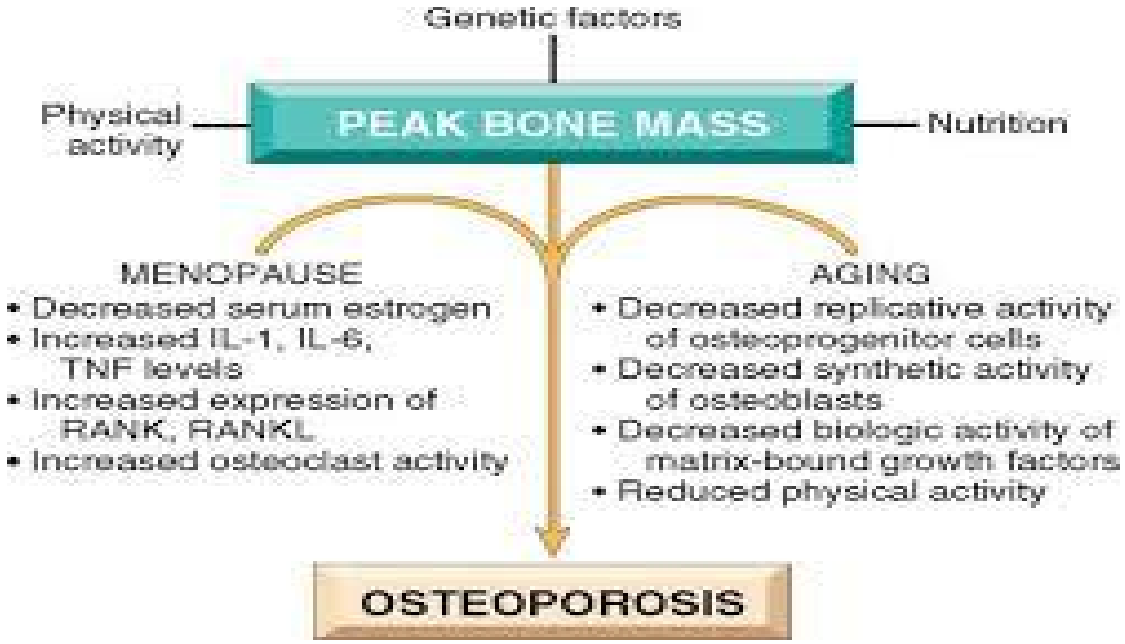
The wnt signaling pathway is a network of messenger system that transfer the information from the cell surface to the nuclear DNA.

LDL Receptor related protein 5(LRP5) communicates with the frizzled receptor to transfer the message through Wnt ligands. Any mutation of LRP5 that leads to activation of wnt pathway at a constant

rate will culminate in an increased bone mineral density[25]. Deletion of LRP5 gene will result in osteoporosis along with abnormality in the eye movements. Loss of function mutations in the gene coding for LRP5 is seen in few of the patients with idiopathic juvenile osteoporosis.

The Wnt signaling pathway is crucial to responsiveness of the effects on mechanical loading on bone[27]. Wnt singaling can affect the peak bone mass[28].

Role of inflammatory mediators:



The chemokines such as interleukin-1(IL-1) and prostaglandin E2 (PGE2) can affect bone remodeling process[32]. Prostagladins have both agonistic and antagonistic effectson bone. However, the most important action of PGE2- the most abundant prostaglandin synthesized in skeletal tissue, is to enhance bone resorption and subsequently bone formation[33]. The fact that these chemokines may play an important role in the evolution of osteoporosisis proved by experimental models of skeletal loss after gonadectomy[34]. The genetic polymorphisms of interleukins 1,6 and tumor necrosis factor α and their receptors can affect the osseous mass in humans[4].

PGE2 is synthesized in bone cells mainly by the effect of inducible cyclooxygenase 2(COX2). Cyclooxygenase is stimulated by the factors that may also induce resorption of bone and may augments the riposte[35]. Treatment with Cyclooxygenase blockers decreases the response to mechanical effects of weight bearing and fluid shear stress. Prostaglandins have pivotal role to play in response to weight loading, and this effect is augmented by estrogen[36].

In addition to endothelial cells, NO synthesized in bone cells is an important cofactor for the growth response of bone to weight bearing[4]. NO inhibits bone resorption, possibly by increasing OPG production there by having opposing action to PGE2[37]. This may be the possible

reason for the enhanced Bone Mineral Density that is seen in patients on nitrates.

NO pathway activators[4]. Leukotrines the products of lipooxygenase cascade can also influence the bone remodeling by enhancing bone resorption and blocking the bone formation process[38].

Methods to assess Bone Mineral Density:

Currently there are various methods available to qualitatively assess the mineral contents of the bone. All of them are noninvasive with low radiation hazard.

These tests include:

1) Dual-energy X-ray absorptiometry(DXA or DEXA)
2) Quantitative computer tomography(QCT)
3) Qualitative ultrasound(QUS)

Though ultrasound had proved cost effective, DEXA still remains the most commonly used. It is a sensitive assay to assess the bone mineral density.

DUAL ENTERGY X RAY ABSORPTIOMETRY:

Dual-energy X-ray absorptiometry is the best technique that is currently available to measure bone density (BMD). The physics behind the genesis of dual energy X ray is that, X rays are generated in Coolidge

tube by tiny negatively charged particles called electrons which exists from a wire filament when heated. When X ray particles are passed through the human body there is attenuation in the intensity of the beam. Now to measure the BMD, X ray beam is passed through the bone and the attenuation is measured and expressed in gram/cm^2 which accounts for mineral density of bone. Likewise in dual energy X ray abosorptiometry, attenuation is measured between high and low energies. Previously used in this technology are radioactive gadolinium 153 because of potential hazards associated with its use the photons are replaced by X ray tube[70]. Typically this technique involves scintillation detector mounted on C arm. The purpose of this arrangement is to expose the patient in a pencil beam of x rays in a rectilinear fashion.

Measurements of the variable from the DEXA scan:

The values are scored by T-score and Z-score. Each of this score ranges from negativity to positivity. A Negative score indicates decreased BMD and a Positive score indication higher. In addition it measures fat content in grams,lean mass, regional fat content and bone mineral content.

Importance of T-score:

For the measure of osteoporosis the relevant variable is **T score.**A T score may show how much a bone mass may deviate from the average bone mass of a healthy adult. It refers to the bone mineral density of that particular site compared with young normal reference mean population. In simplistic terms it is the comparison of bone mineral density of patients with that of a normal 30 year old of same sex and ethnicity. This value is compared with that of postmenopausal women and men over fifty years of age to evaluate the risk of osteoporosis[71]. One standard deviation refers to 10-20% difference in bone mass. For example if the patient's bone is less dense its SD-2 or -3 indicating the patient's bone is 20 to 30% less dense than average 30 year old.

WHO – WORLD HEALTH ORGANISATION published following criteria for the diagnosis of osteoporosis:

WHO CRITERIA:

T score	**DIAGNOSIS**
>-1.0	ADEQUATE BMD
-1.0 TO -2.5	OSTEOPENIA
< -2.5	OSTEOPOROSIS

< -2.5 WITH FRACTURES	SEVERE OSTEOPOROSIS

Importance of Z score:

A Z-score compares the patient's bone density to the average for same age and gender. For example a 60 year female patients BMD is compared with that of average BMD of 60 year old females.In simplistic terms it is comparison of age matched normal. It refers to the number of times in standard deviation in which patients BMD differs from that of their age,sex and ethnicity. For evaluation of osteoporosis T score is considered more significant than Z score.

Z SCORE	**DIAGNOSIS**
>-1.5	ADEQUATE BMD
-1.5 TO -2.5	OSTEOPENIA
< -2.5	OSTEOPOROSIS

Radiation dose in DEXA imaging:

Albabese et al had compared various modalities of radiological investigations and the radiation dose associated with it. It has been found that the average DEXA scanner exposes the patient to radiation dose of 0.3 micro Sievert units this is hardly any radiation dosage when compared

with chest X ray, which acarries a radiation dosage of 50 micro sievert units. Similarly Njeh et al had proved the radiation dose was negligible when compared with environmental exposure.

Comparison of available radiological investigation's in respect to their radiation dosage. **NOTE:** New generation pencil beam DEXA has an exposure rate of 0.3-0.4 micro Sieverts.

OBESITY A NEW RISK FACTOR FOR OSTEOPOROSIS:

In the era of evidence based medicine,what holds true today may not hold for tomorrow. This is very much applicable for obesity. The old concept that obesity is a protective factor for the development of osteoporosis is no longer holds true. Recent studies had clearly proved that obesity is not protective and in fact it is detrimental for the development of osteoporosis[41,85-87].

The primary action of skeletal framework is to offer a tough core to back up,preserve, and promote the activities of soft tissues. Ribs, skull and pelvis safe guard their contents. The ribs will be essential for thoracic movements, like wise femur and tibia are important for ambulation. Therefore it is credible from maturation point of view, that the skeletal framework's endurance would be closely related to soft tissue mass. If all humans had the similar sized skeleton irrespective of their body weight,

few maybe at disadvantage of having bones that were inefficient to perform the task, and few might be having a heavier frame of skeleton than it need to be.

Body weight is a composition of lean mass and fat mass[41]. It should be emphasized that, the simple correlation between lean body mass and mineral content of bone tends to overestimate the relationship BMD and muscle mass[42]. Muscle mass and bone mineral content are conspicuously depends on height, but the bone density is an independent variable that does not depend on height. Simply, longer legs in taller individuals have larger muscle mass to cover them. Hence larger mass imparts a greater mechanical loading on the bone Emerging studies are now concentrating on new variable called percentage fat mass. Bakker etal[63]found that fat free mass had correlated positively with lumbar bone mineral content over 10 year follow up period in young subjects. Because fat free mass [FFM] can be accounted as a proxy for skeletal muscle mass. Observation from bakker et al indicate that the importance of muscle contractions to increase bone strength in the study population[63].

Review of existing concepts about obesity and bone mass:

It has been proved form the vast available epidemiological data that the excess body weight will result in a high bone mass,so reduction in the weight may lead to bone loss[44,45,46]. The physiology reasons have been

advocated. It is an accepted hypothesis that heavier the body mass bigger will be the impact of shear stress on bone and that bone mass increases proportionately to accommodate the load. In postmenopausal women the major source of estrogen is adipocytes. Estrogen by blocking the activity of osteoclasts inhibits the resotption process. The argument being any increased adiposity will increase the body mass index in postmenopausal women. This effect may translate into decreased osteoclast mediated resorption with resultant increase in bone mineral density[47].

Obesity leads to insulin resistance and increased insulin levels causes an increased synthesis of androgens as well as estrogen and decreased production of sex hormone binding globulins by liver which in turn causes increased levels of free sex steroids and stimulation of osteoblastic activity by sex steroids, Recent developments in science had questioned this concept.

The relationship is far more complex as thought between these variables. The discovery of appetite hormone leptin and its role in energy metabolism had thrown light on its influences bone metabolism[51]. Ducy et al had reported that leptin receptor and leptin deficient mice had showed increased bone formation. Leptin-defecient and wild-type mice had showed bone loss when leptin was injected to cerebral ventricles[51].

LEPTIN-ROLE IN OSTEOPOSOSIS:

Leptin meaning thin is a 16-kDa protein,called as satiety hormone plays a very crucial role in regulating energy intake and expenditure including gappetite/hunger and metabolism. It is an adipose tissue derived hormone. The leptin gene is located on chromosome 7 in humans[52].

Human leptin has 167 amino acids. It is synthesized primariy from white adipocytes, and the amount of leptin circulating in plasma is directly proportional to the total body fat content. The other sources of leptin are from brown adipose tissue, skeletal muscle, fundic glands, syncytiotrophoblasts of placenta,ovaries, mammary cells, pituitaty, liver and bone marrow[53].

The fact obesity and osteoporosis are interrelated disease can be explained by the fact that both adipocyte and osteoblast arises from common mesenchymal cells[55].

Mesenchymal cell upon its differentiation is committed for pre-osteoblasts and pre-adipocyte. But upon stimulation by the cytokine called Peroxisome Proliferator Activated Receptor(PPAR-γ) the mesenchymal stem cell is more committed towards the differentiation in to adipocyte. Hence further, adipocyte expresses its hormones like estrogen, leptin, adiponectin and resistin[55].

SIGNS AND SYMPTOMS OF OSTEOPOROSIS:

Osteoporosis has no symptoms. osteoporotic fractures are otherwise known as fragility fractures. It is most commonly occur in vertebral column, ribs, hip, wrist.

TYPES:

1) Vertebral collapse (compression fractures)
2) Spinal cord compression (cauda equine syndrome)
3) Colle's fracture
4) Tooth loss

SYMPTOMS:

1) Asymptomatic
2) Symptoms of vertebral collapse
3) Sudden back pain, often radicular pain(due to nerve root compression)
4) Multiple vertebral fractures – lead to stooped posture, loss of height, chronic pain which make patients bedridden.

Osteoporosis and its effects on Orthodontic tooth movement[11]

Postmenopausal Osteoporosis	- Alveolar bone loss - Increased orthodontic tooth movement - Periodontal disease - Increased relapse and decreased stability
Senile Osteoporosis	- Increased relapse - Orthodontic movement is decreased
Corticosteroid-Induced Osteoporosis	- Increased relapse - Inhibits bone resorption - Increases orthodontic tooth movement
Estrogen supplementation	- Delayed Orthodontic tooth movement
Bisphosphonate therapy (oral)	- Decreased orthodontic tooth movement - Susceptibility to Osteonecrosis

COMPLICATIONS:

1) Deep vein thrombosis
2) Pulmonary embolism

(hip fractures requiring surgery)

Fracture risk calculated based upon

1) BMD
2) Age
3) Smoking
4) Alcohol
5) Weight
6) Gender

Fracture risk calculators – FRAX, Dubbo

RISK FACTORS:

1) Aging – risk of fracture doubles every 7-8 years after age 50
2) Previous history of a fragility fracture

3) Family H/O fragility fracture in close relatives

4) Smoking

5) Being thin and small framed

6) Family H/O osteoporosis

7) Amenorrhoea (hypoestrogenism)

8) Lifelong deficient calcium and vitamin D intake

9) Use of bone-losing medications

10) Sedentary life style

11) Excessive alcohol intake

12) Rheumatoid arthritis.

A complete evaluation is necessary for a patient presenting with fracture. All osteoporotic fractures are associated with increased risk of mortality that persists for 5-10 years after fracture. Women with fractures often have depression. Both are interlinked. It should be identified and treated appropriately to improve the quality of life.

TREATMENT FOR OSTEOPENIA:

Preventive drug therapy is recommended for osteopenia in the presence of one or more risk factors for osteoporosis, or progressive bone loss, or 10 year hip fracture probability of > 3% , 10 year probability > 20% for any osteoporotic fracture.

Treatment Osteoporosis:

The perimenopausal transition is a good opportunity to initiate a discussion about risk factors for osteoporosis and consideration of indications for a BMD test. A low Z-score increases the suspicion of a secondary disease. Height loss >2.5–3.8 cm (>1–1.5 in.) is an indication for radiography or vertebral fracture assessment by DXA to rule out asymptomatic vertebral fractures, as is the presence of significant kyphosis or back pain, particularly if it began after menopause. For patients who present with fractures, it is important to ensure that the fractures are not caused by an underlying malignancy. Usually this is clear on routine radiography, but on occasion, CT, MRI, or radionuclide scans may be necessary.

Routine Laboratory Evaluation:

There is no established algorithm for the evaluation of women who present with osteoporosis. A low urine calcium (<50 mg/24 h) suggests osteomalacia, malnutrition, or malabsorption; a high urine calcium (>300 mg/24 h) is indicative of hypercalciuria and must be investigated further. Hypercalciuria occurs primarily in three situations: (1) a renal calcium leak, which is more common in males with osteoporosis; (2) absorptive

hypercalciuria, which can be idiopathic or associated with increased $1,25(OH)_2D$ in granulomatous disease; or (3) hematologicmalignancies .

Asymptomatic malabsorption may be heralded by anemia (macrocytic—vitamin B_{12} or folate deficiency; microcytic—iron deficiency) or low serum cholesterol or urinary calcium levels. If these or other features suggest malabsorption, further evaluation is required. Asymptomatic celiac disease with selective malabsorption is being found with increasing frequency; the diagnosis can be made by testing for antigliadin, antiendomysial, or transglutaminase antibodies but may require endoscopic biopsy. A trial of a gluten-free diet can be confirmatory (Chap. 294). When osteoporosis is found associated with symptoms of rash, multiple allergies, diarrhea, or flushing, mastocytosis should be excluded by using 24-h urine histamine collection or serum tryptase.

A bone marrow biopsy may be required to rule out myeloma (in patients with equivocal electrophoretic results) and also can be used to exclude mastocytosis, leukemia, and other marrow infiltrative disorders such as Gaucher's disease.

Treatment: Osteoporosis

Management of Osteoporotic Fractures:

Back-strengthening exercises (paraspinal) may be beneficial. Heat treatments help relax muscles and reduce the muscular component of discomfort. Various physical modalities, such as US and transcutaneous nerve stimulation, may be beneficial in some patients. Pain also occurs in the neck region, not as a result of compression fractures (which almost never occur in the cervical spine as a result of osteoporosis) but because of chronic strain associated with trying to elevate the head in a person with a severe thoracic kyphosis.

Multiple vertebral fractures often are associated with psychological symptoms; this is not always appreciated. The changes in body configuration and back pain can lead to marked loss of self-image and a secondary depression. Altered balance, precipitated by the kyphosis and the anterior movement of the body's center of gravity, leads to a fear of falling, a consequent tendency to remain indoors, and the onset of social isolation. These symptoms sometimes can be alleviated by family support and/or psychotherapy. Medication may be necessary when depressive features are present.

Vitamin D

Vitamin D is really a hormone

Vitamin D regulates calcium absorption. Its deficiency leads to rickets in children and osteomalacia in adults. vitamin D is synthesized in skin from 7-dehydro cholesterol. It is because of this sunlight exposure is important for vitamin D synthesis. Vitamin D is necessary for calcium absorption and hence its deficiency leads to osteoporosis.

Rickets and Osteomalacia:

In children, the proliferation and differentiation of the chondrocytes in the rachitic growth plate are normal, and the expansion of the growth plate is a consequence of impaired apoptosis of the late hypertrophic chondrocytes, an event that precedes replacement of these cells by osteoblasts during endochondral bone formation. Investigations in murine models demonstrate that hypophosphatemia, which in vitamin D deficiency is a consequence of secondary hyperparathyroidism, is a key etiologic factor in the development of the rachitic growth plate.

This hypomineralized matrix is biomechanically inferior to normal bone; as a result, patients with vitamin D deficiency are prone to bowing of weight-bearing extremities and skeletal fractures. Vitamin D and calcium supplementation have been shown to decrease the incidence of

hip fracture among ambulatory nursing home residents in France, suggesting that undermineralization of bone contributes significantly to morbidity in the elderly. Proximal myopathy is a striking feature of severe vitamin D deficiency both in children and in adults. Rapid resolution of the myopathy is observed upon vitamin D treatment.

Though vitamin D deficiency is the most common cause of rickets and osteomalacia, many disorders lead to inadequate mineralization of the growth plate and bone. Calcium deficiency without vitamin D deficiency, the disorders of vitamin D metabolism previously discussed, and hypophosphatemia can all lead to inefficient mineralization. Even in the presence of normal calcium and phosphate levels, chronic acidosis and drugs such as bisphosphonates can lead to osteomalacia. The inorganic calcium/phosphate mineral phase of bone cannot form at low pH, and bisphosphonates bind to and prevent mineral crystal growth. Since alkaline phosphatase is necessary for normal mineral deposition, probably because the enzyme can hydrolyze inhibitors of mineralization such as inorganic pyrophosphate, genetic inactivation of the alkaline phosphatase gene (hereditary hypophosphatasia) also can lead to osteomalacia in the setting of normal calcium and phosphate levels.

Radiologic features of vitamin D deficiency in children include a widened, expanded growth plate that is characteristic of rickets. These findings not only are apparent in the long bones but also are present at the costochondral junction, where the expansion of the growth plate leads to swellings known as the "rachitic rosary." Impairment of intramembranous bone mineralization leads to delayed fusion of the calvarial sutures and a decrease in the radi-opacity of cortical bone in the long bones. If vitamin D deficiency occurs after epiphyseal fusion, the main radiologic finding is a decrease in cortical thickness and relative radiolucency of the skeleton. A specific radiologic feature of osteomalacia, whether associated with phosphate wasting or vitamin D deficiency, is pseudofractures, or Looser's zones. These are radiolucent lines that occur where large arteries are in contact with the underlying skeletal elements; it is thought that the arterial pulsations lead to the radiolucencies. As a result, these pseudofractures are usually a few millimeters wide, are several centimeters long, and are seen particularly in the scapula, the pelvis, and the femoral neck.

Treatment: Vitamin D Deficiency:

Treatment of vitamin D deficiency should be directed at the underlying disorder, if possible, and also should be tailored to the severity of the condition. Vitamin D should always be repleted in conjunction

with calcium supplementation since most of the consequences of vitamin D deficiency are a result of impaired mineral ion homeostasis. In patients in whom 1α-hydroxylation is impaired, metabolites that do not require this activation step are the treatment of choice. If the pathway required for activation of vitamin D is intact, severe vitamin D deficiency can be treated with pharmacologic repletion initially (50,000 IU weekly for 3–12 weeks), followed by maintenance therapy (800 IU daily). Pharmacologic doses may be required for maintenance therapy in patients who are taking medications such as barbiturates or phenytoin, that accelerate metabolism of, or cause resistance to $1,25(OH)_2D$. Calcium supplementation should include 1.5–2 g/d of elemental calcium. Normocalcemia is usually observed within one week of the institution of therapy, although increases in PTH and alkaline phosphatase levels may persist for three to six months. In patients who are vitamin D replete and are taking adequate calcium supplementation, the 24-hour urinary calcium excretion should be in the range of 100–250 mg/ 24 hours. Lower levels suggest problems with adherence to the treatment regimen or with absorption of calcium or vitamin D supplements. Levels >250 mg/24 hours predispose to nephrolithiasis and should lead to a reduction in vitamin D dosage and/or calcium supplementation.

AIM OF THE STUDY

- TO STUDY THE ASSOCIATION BETWEEN VITAMIN D AND BONE MINERAL DENSITY AMONG POSTMENOPAUSAL WOMEN

SAMPLING METHOD

INCLUSION CRITERIA

- Patients attending gynaec OPD KMCH with any one of the following:
    1) Postmenopausal women
    2) Age > 50 years

EXCLUSION CRITERIA

- Diabetic women
- Hypertensive women
- On medication (calcium and vitamin D)
- On medication affecting calcium metabolism
- Those who on hormonal therapy.

Sample size

- **Sample Size for Frequency in a Population-200**

Population size(for finite population correction factor or fpc)(N):	400
Hypothesized % frequency of outcome factor in the population (p):	50%+/-5
Confidence limits as % of 100(absolute +/- %)(d):	5%
Design effect (for cluster surveys-DEFF):	1

Gynaec women attending OP with Age >50 years(Exclusion criteria :

1. Hypertensive
2. Diabetic
3. Drugs affecting calcium metabolism is about 400 per year. The prevalence of osteoporosis women is 50 percentage. Based on these, the sample size is 197 = 200 during the study period.

OBSERVATIONS AND RESULTS

age group * T score Cross tabulation

			Outcome of T scores			
			NORMAL	OSTEOPENIA	OSTEOPOROSIS	Total
age group	<=50		13	12	5	30
		% within age group	43.3%	40.0%	16.7%	100.0%
		% within outcome	37.1%	11.2%	8.6%	15.0%
		% of Total	6.5%	6.0%	2.5%	15.0%
	51-60	Count	21	62	24	107
		% within age group	19.6%	57.9%	22.4%	100.0%
		% within ost	60.0%	57.9%	41.4%	53.5%
		% of Total	10.5%	31.0%	12.0%	53.5%
	61 & Above	Count	1	33	29	63
		% within age group	1.6%	52.4%	46.0%	100.0%
		% within outcome	2.9%	30.8%	50.0%	31.5%
		% of Total	.5%	16.5%	14.5%	31.5%
	Total	Count	35	107	58	200
		% within age group	17.5%	53.5%	29.0%	100.0%
		% within ost	100.0%	100.0%	100.0%	100.0%
		% of Total	17.5%	53.5%	29.0%	100.0%

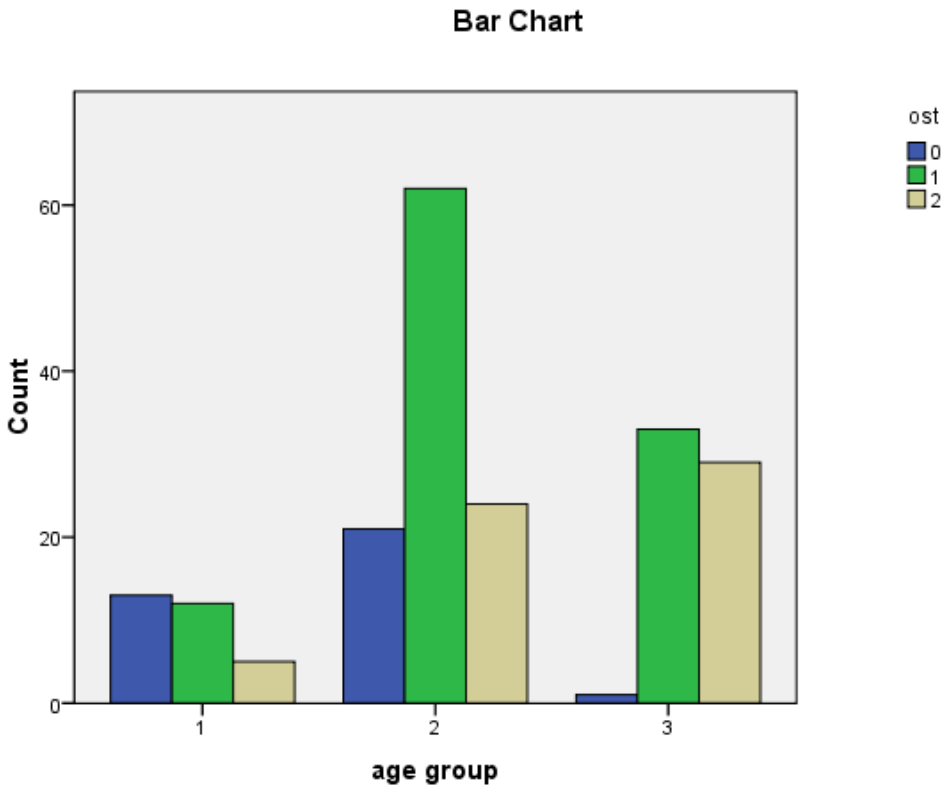
Chi square = 31.732 P= 0.000< 0.001 . There exists a statistical significance between normal, osteopenia and osteoporosis patients with respect to Age Distribution.

In my study out of 200 cases, 17.5% falls under normal BMD, 53.5% osteopenia, 29.0% falls under osteoporosis.

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	31.732[a]	4	.000
Likelihood Ratio	34.038	4	.000
Linear-by-Linear Association	26.090	1	.000
N of Valid Cases	200		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.25.


Bar Chart
ost
0
1
2
Count
60
40
20
0
1
2
3
age group

Descriptives

AGE

					95% Confidence Interval for Mean	
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound
Normal	35	53.34	4.291	.725	51.87	54.82
Osteopenia	107	57.71	5.970	.577	56.57	58.85
Osteoporosis	58	60.47	7.451	.978	58.51	62.42
Total	200	57.75	6.603	.467	56.82	58.67

The mean age for normal BMD is 53 yrs, for osteopenia average age is 57 yrs, and for osteoporosis average age is 60 yrs.

Descriptives

AGE

	Minimum	Maximum
Normal	47	62
Osteopenia	47	76
Osteoporosis	47	78
Total	47	78

ANOVA

AGE

	Sum of Squares	**df**	**Mean Square**	**F**	**P**
Between Groups	1107.660	2	553.830	14.416	0.000
Within Groups	7568.335	197	38.418		
Total	8675.995	199			

Inference: There exists a statistical significance among Normal, Osteopenia and osteoporosis patients with respect to Age. The Post hoc multiple comparison test reveals that all the three groups were significantly different within groups (Normal, Osteopenia & osteoporosis).

0 – normal

1 – osteopenia

2 – osteoporosis

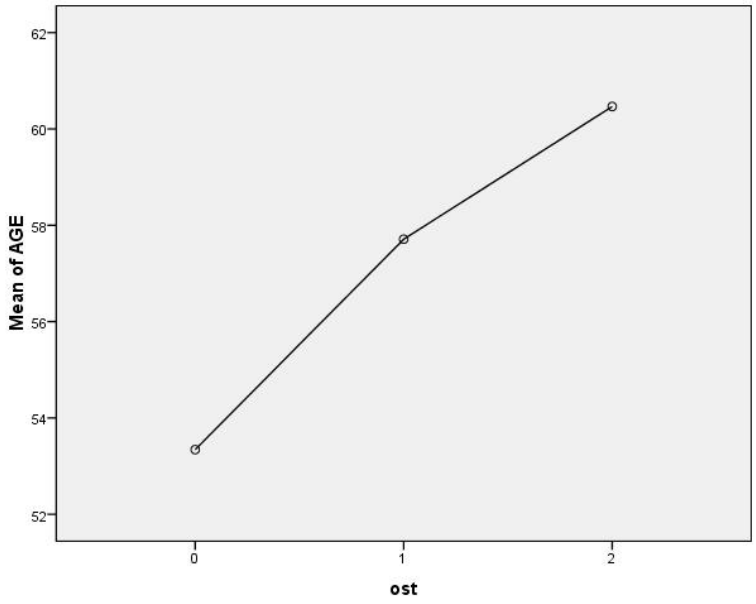
Multiple Comparisons

AGE

(I) ost	(J) ost	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
0	1	-4.367*	1.207	.000	-6.75	-1.99
	2	-7.123*	1.327	.000	-9.74	-4.51
1	0	4.367*	1.207	.000	1.99	6.75
	2	-2.755*	1.011	.007	-4.75	-.76
2	0	7.123*	1.327	.000	4.51	9.74
	1	2.755*	1.011	.007	.76	4.75

*. The mean difference is significant at the 0.05 level.

Means Plots



Descriptives

VIT D

					95% Confidence Interval for Mean	
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound
0	35	30.926	5.7176	.9664	28.962	32.890
1	107	24.722	3.6365	.3516	24.025	25.419
2	58	22.841	23.0492	3.0265	16.781	28.902
Total	200	25.263	13.1266	.9282	23.432	27.093

The mean vitamin D in patients with normal BMD is 30.92, in patients with osteopenia it is 24.72, and in patients with osteoporosis it is 22.84.

Descriptives

VIT D

	Minimum	Maximum
0	17.0	44.0
1	17.0	39.0
2	18.0	195.0
Total	17.0	195.0

ANOVA

VIT D

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	1493.715	2	746.858	4.486	.012
Within Groups	32795.454	197	166.474		
Total	34289.169	199			

Inference: There exists a statistical significance among Normal, Osteopenia and osteoporosis patients with respect to Vitamin D. The Post hoc multiple comparison test reveals that all the Normal patients vitamin D level is significantly differ with the other two groups(Osteopenia &osteoporosis).But , there is no statistical significance between ostopenia and osteoporosis patients vitamin D levels.

Post Hoc Tests

Multiple Comparisons

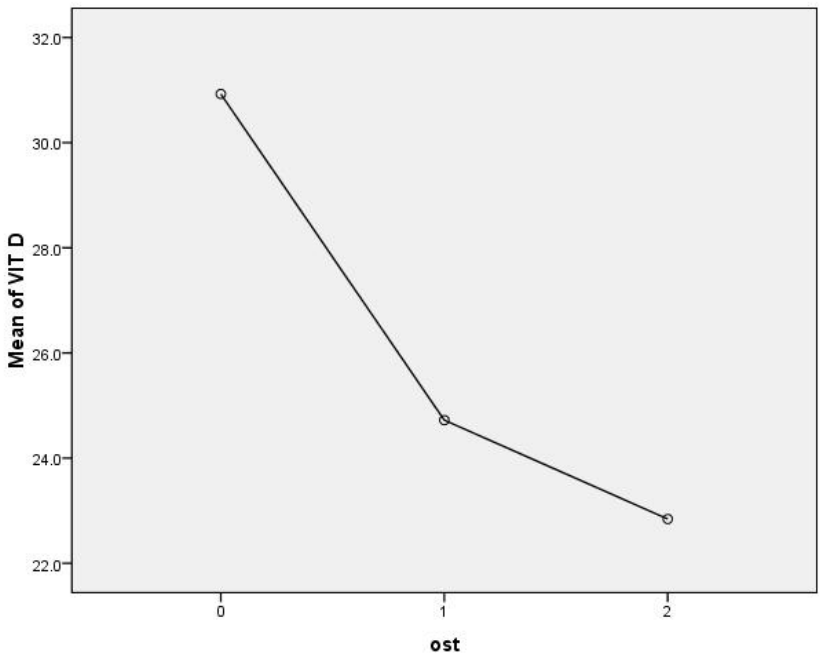
VIT D

LSD

(I) ost	(J) ost	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
0	1	6.2033*	2.5124	.014	1.249	11.158
	2	8.0843*	2.7616	.004	2.638	13.531
1	0	-6.2033*	2.5124	.014	-11.158	-1.249
	2	1.8811	2.1038	.372	-2.268	6.030
2	0	-8.0843*	2.7616	.004	-13.531	-2.638
	1	-1.8811	2.1038	.372	-6.030	2.268

*. The mean difference is significant at the 0.05 level.

Means Plots



Descriptives

Z SCORE

					95% Confidence Interval for Mean	
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound
0	35	.094	1.3958	.2359	-.385	.574
1	106	-1.084	1.1975	.1163	-1.315	-.853
2	58	-1.703	1.2524	.1644	-2.033	-1.374
Total	199	-1.057	1.3797	.0978	-1.250	-.864

Descriptives

Z SCORE

	Minimum	Maximum
0	-2.2	2.0
1	-2.8	1.9
2	-3.7	1.7
Total	-3.7	2.0

ANOVA

Z SCORE

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	70.706	2	35.353	22.630	.000
Within Groups	306.201	196	1.562		
Total	376.907	198			

Post Hoc Tests

Multiple Comparisons

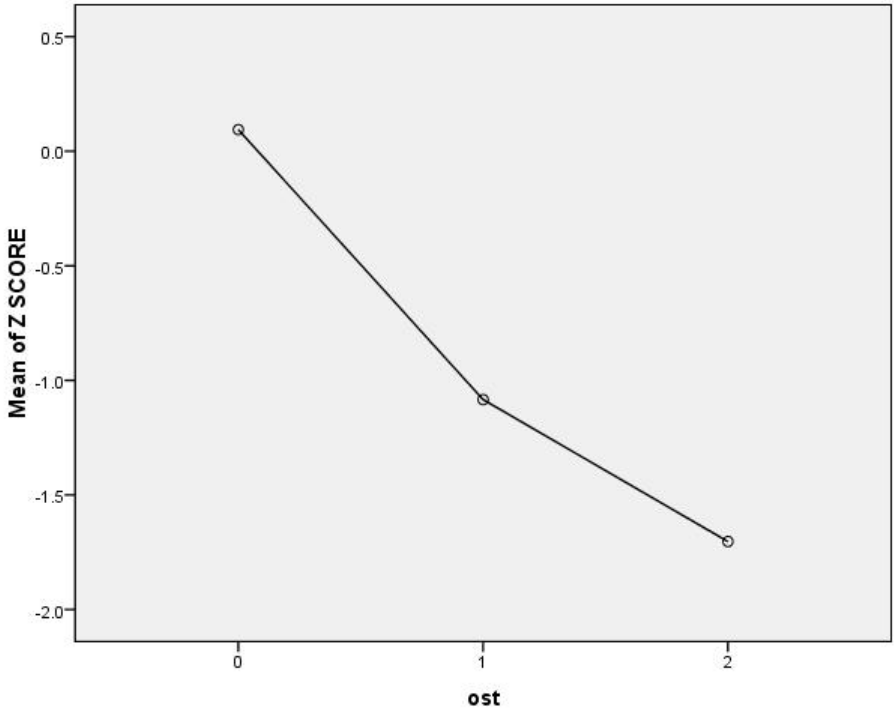
Z SCORE

LSD

(I) ost	(J) ost				95% Confidence Interval	
		Mean Difference (I-J)	Std. Error	Sig.	Lower Bound	Upper Bound
0	1	1.1782*	.2437	.000	.698	1.659
	2	1.7977*	.2675	.000	1.270	2.325
1	0	-1.1782*	.2437	.000	-1.659	-.698
	2	.6195*	.2041	.003	.217	1.022
2	0	-1.7977*	.2675	.000	-2.325	-1.270
	1	-.6195*	.2041	.003	-1.022	-.217

*. The mean difference is significant at the 0.05 level.

Means Plots



Descriptives

BMI

					95% Confidence Interval for Mean	
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound
0	35	25.963	4.6924	.7932	24.351	27.575
1	107	25.708	5.3213	.5144	24.688	26.728
2	58	26.239	4.0939	.5375	25.162	27.315
Total	200	25.907	4.8682	.3442	25.228	26.586

The mean BMI in all patients is around 25. There is no significant difference among all three groups.

Descriptives

BMI

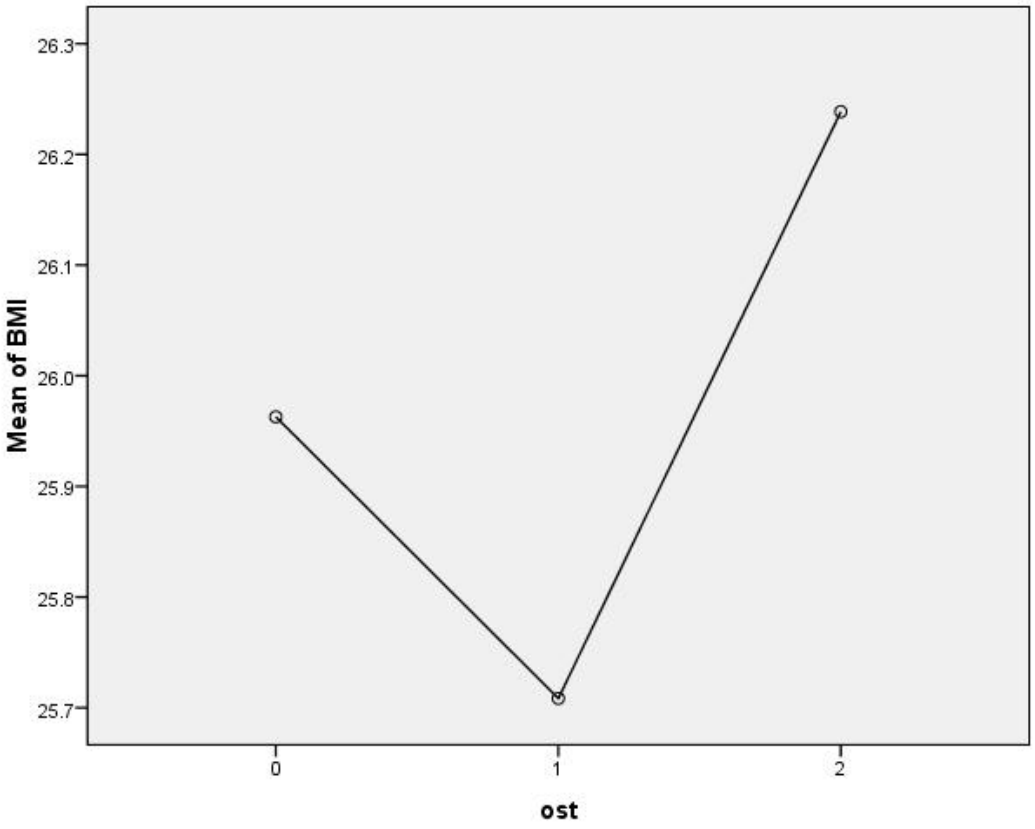
	Minimum	Maximum
0	19.2	40.5
1	16.4	50.0
2	17.5	38.2
Total	16.4	50.0

ANOVA

BMI

	Sum of Squares	**df**	**Mean Square**	**F**	**Sig.**
Between Groups	10.707	2	5.354	.224	.799
Within Groups	4705.483	197	23.886		
Total	4716.191	199			

Means Plots



Descriptives

BMD

					95% Confidence Interval for Mean	
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound
0	35	1.04006	.221818	.037494	.96386	1.11625
1	107	1.01753	.225557	.021805	.97430	1.06076
2	58	1.08991	.231045	.030338	1.02916	1.15066
Total	200	1.04246	.227570	.016092	1.01073	1.07420

Descriptives

BMD

	Minimum	Maximum
0	.801	1.908
1	.452	1.867
2	.714	1.946
Total	.452	1.946

ANOVA

BMD

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.197	2	.099	1.923	.149
Within Groups	10.109	197	.051		
Total	10.306	199			

Post Hoc Tests

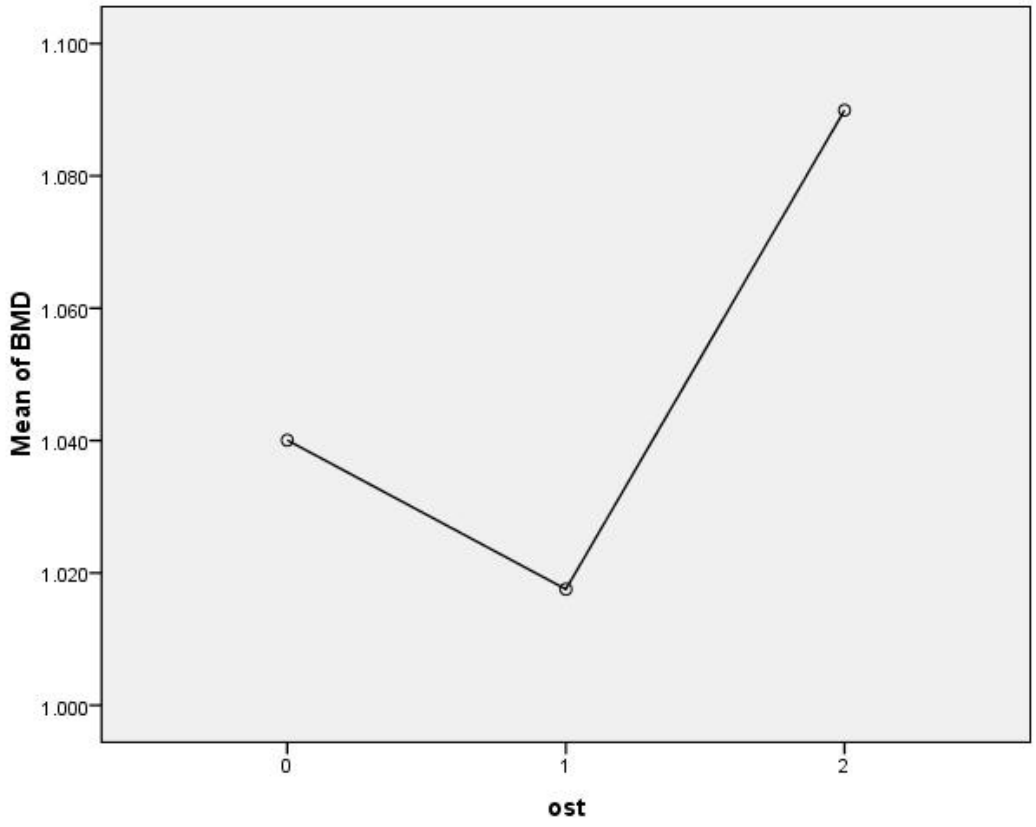
Multiple Comparisons

BMD

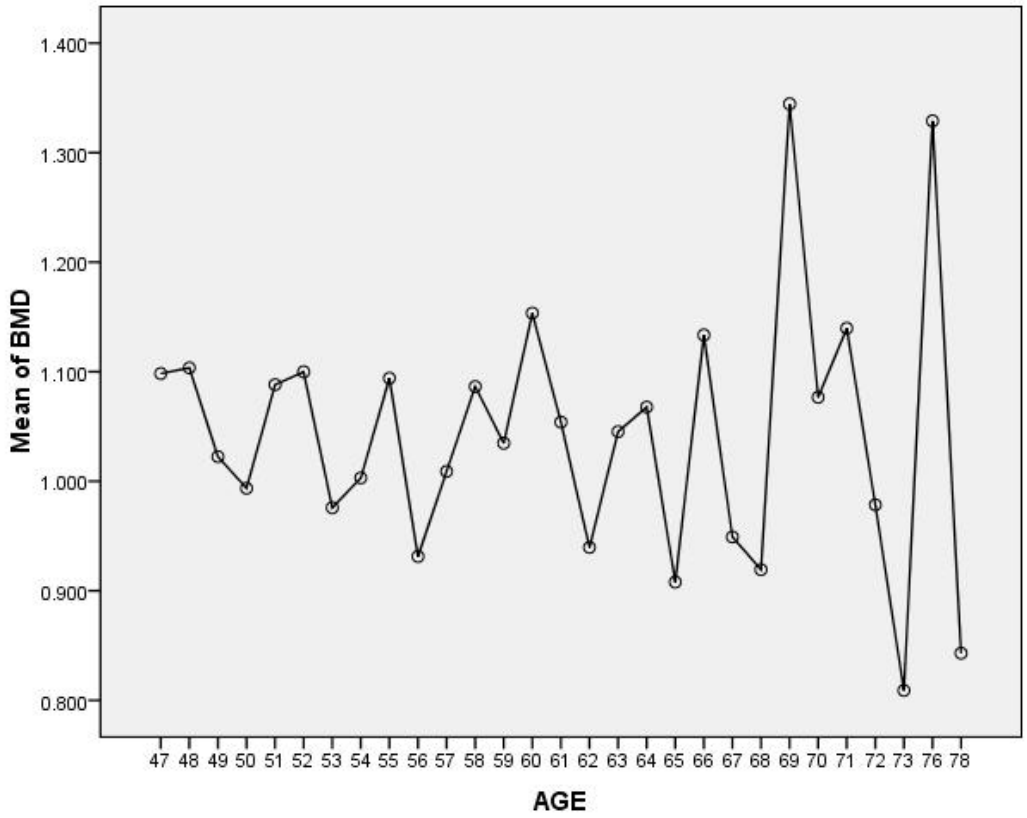
LSD

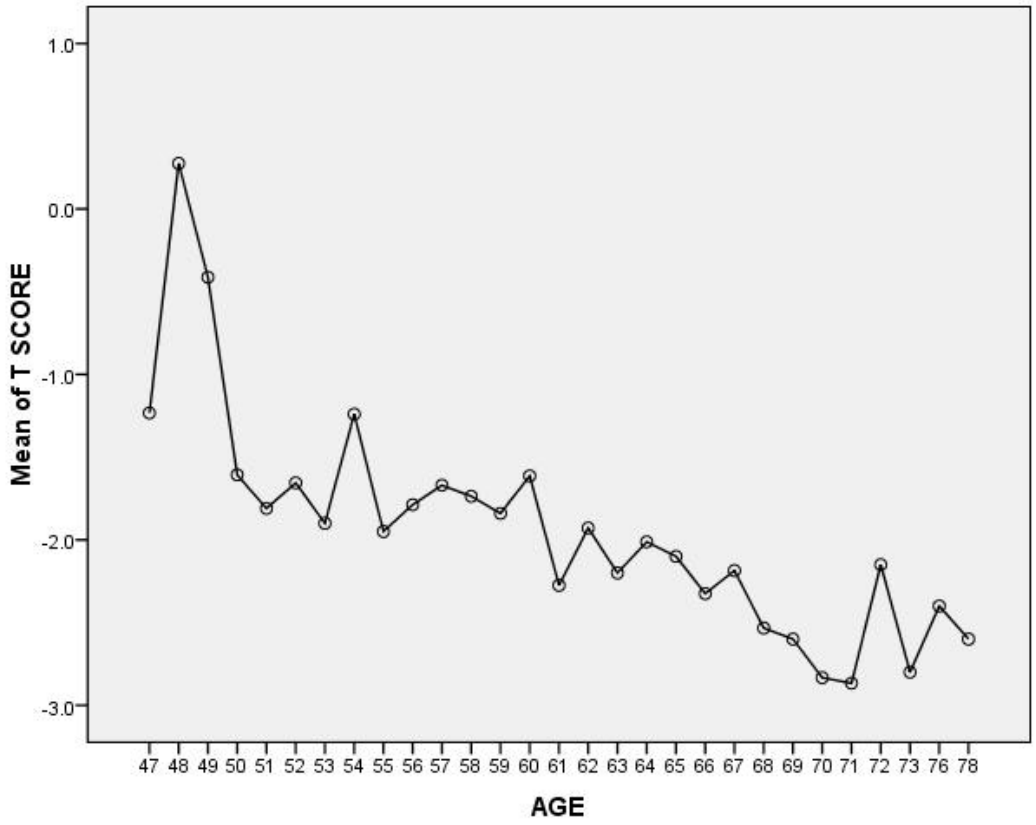
					95% Confidence Interval	
(I) ost	(J) ost	Mean Difference (I-J)	Std. Error	Sig.	Lower Bound	Upper Bound
0	1	.022524	.044109	.610	-.06446	.10951
	2	-.049857	.048485	.305	-.14547	.04576
1	0	-.022524	.044109	.610	-.10951	.06446
	2	-.072381	.036936	.051	-.14522	.00046
2	0	.049857	.048485	.305	-.04576	.14547
	1	.072381	.036936	.051	-.00046	.14522

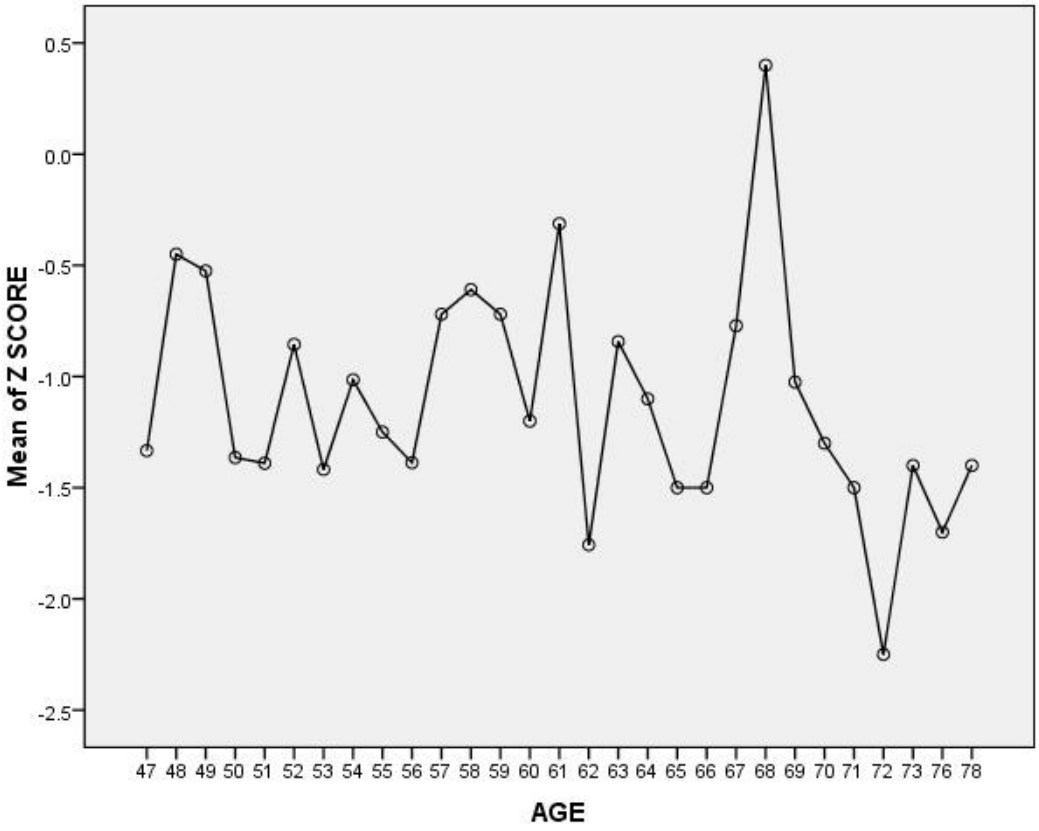
Means Plots

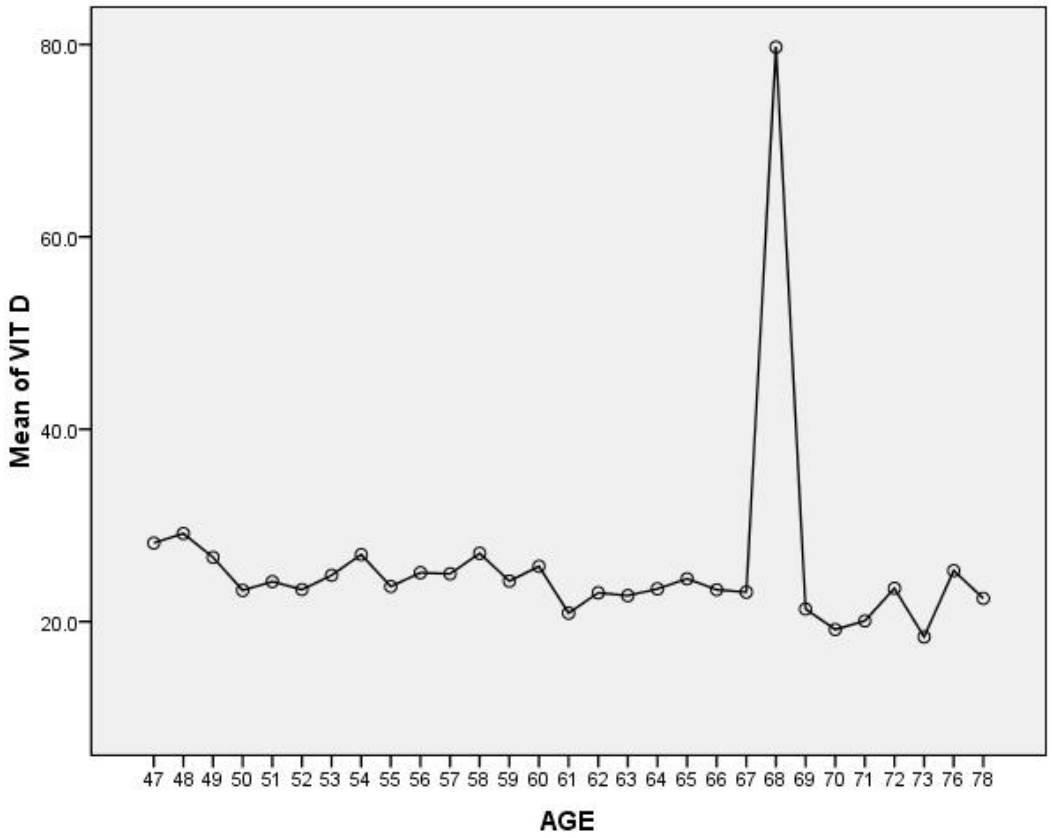


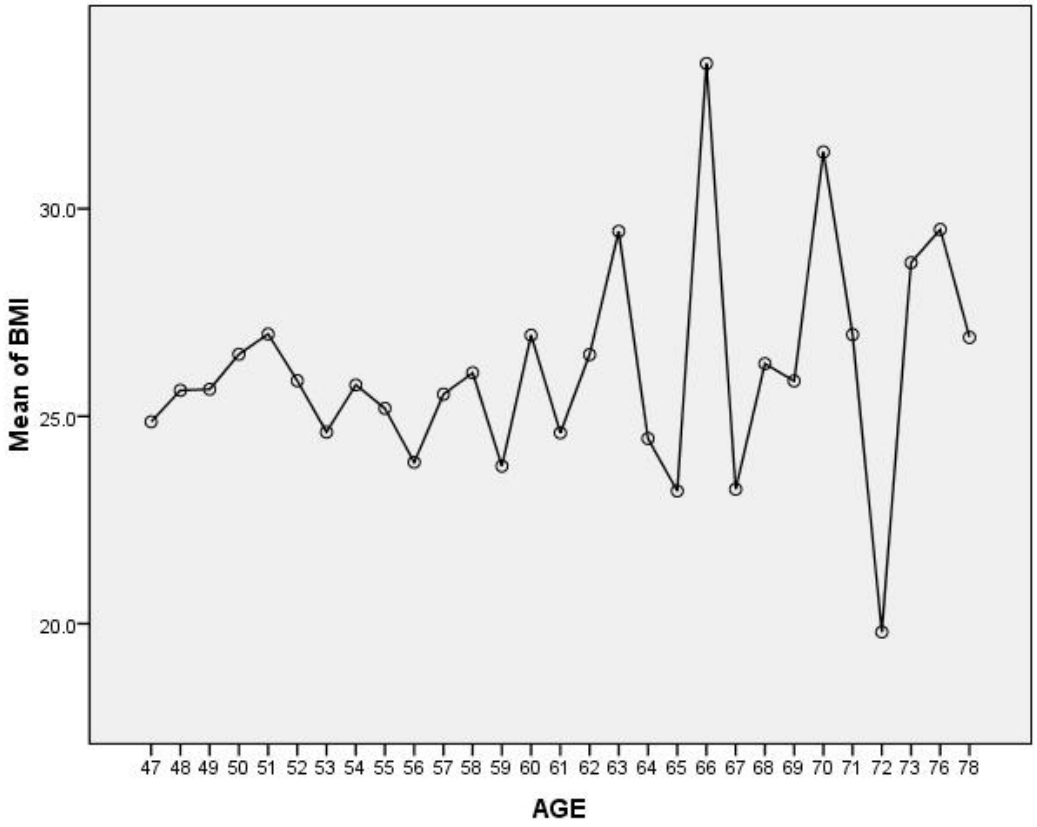
Means Plots


Mean of BMD
1.400
1.300
1.200
1.100
1.000
0.900
0.800
47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 76 78
AGE


Mean of T SCORE
1.0
0.0
-1.0
-2.0
-3.0
47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 76 78
AGE


Mean of Z SCORE
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 76 78
AGE


80.0
60.0
40.0
20.0
Mean of VIT D
47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 76 78
AGE


Mean of BMI
30.0
25.0
20.0
47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 76 78
AGE

Age vs. BMD and others.

Descriptives

						95% Confidence Interval for Mean	
		N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound
BMD	<=50	30	1.02643	.217793	.039763	.94511	1.10776
	50-60	107	1.04952	.231907	.022419	1.00507	1.09397
	>=60	63	1.03811	.227725	.028691	.98076	1.09546
	Total	200	1.04247	.227570	.016092	1.01073	1.07420
T SCORE	<=50	30	-1.000	1.5006	.2740	-1.560	-.440
	50-60	107	-1.662	1.0220	.0988	-1.858	-1.466
	>=60	63	-2.276	.6596	.0831	-2.442	-2.110
	Total	200	-1.756	1.0939	.0774	-1.909	-1.603
Z SCORE	<=50	29	-1.003	1.7973	.3338	-1.687	-.320
	50-60	107	-1.066	1.3172	.1273	-1.319	-.814
	>=60	63	-1.067	1.2854	.1619	-1.390	-.743
	Total	199	-1.057	1.3797	.0978	-1.250	-.864
VIT D	<=50	30	25.437	6.0023	1.0959	23.195	27.678
	50-60	107	25.308	5.3739	.5195	24.278	26.338
	>=60	63	25.102	22.0631	2.7797	19.545	30.658
	Total	200	25.263	13.1266	.9282	23.432	27.093
BMI	<=50	30	25.990	4.1236	.7529	24.450	27.530
	50-60	107	25.665	4.6011	.4448	24.783	26.547
	>=60	63	26.278	5.6281	.7091	24.860	27.695
	Total	200	25.907	4.8682	.3442	25.228	26.586

Descriptives

		Minimum	Maximum
BMD	1	.452	1.412
	2	.709	1.908
	3	.714	1.946
	Total	.452	1.946
T SCORE	1	-3.0	2.6
	2	-3.2	2.6
	3	-3.3	.5
	Total	-3.3	2.6
Z SCORE	1	-3.7	2.0
	2	-3.5	2.0
	3	-2.7	1.9
	Total	-3.7	2.0
VIT D	1	17.0	40.0
	2	17.0	44.0
	3	18.0	195.0
	Total	17.0	195.0
BMI	1	17.1	35.1
	2	17.2	45.0
	3	16.4	50.0
	Total	16.4	50.0

ANOVA

		Sum of Squares	Df	Mean Square	F	Sig.
BMD	Between Groups	.014	2	.007	.136	.873
	Within Groups	10.292	197	.052		
	Total	10.306	199			
T SCORE	Between Groups	35.146	2	17.573	17.054	.000
	Within Groups	202.987	197	1.030		
	Total	238.133	199			
Z SCORE	Between Groups	.098	2	.049	.026	.975
	Within Groups	376.809	196	1.922		
	Total	376.907	198			
VIT D	Between Groups	2.767	2	1.383	.008	.992
	Within Groups	34286.402	197	174.043		
	Total	34289.169	199			
BMI	Between Groups	15.141	2	7.571	.317	.729
	Within Groups	4701.049	197	23.863		
	Total	4716.191	199			

Post Hoc Tests

Multiple Comparisons

LSD

Dependent Variable	(I) age group	(J) age group	Mean Difference (I-J)	Std. Error	Sig.
BMD	1	2	-.023090	.047219	.625
		3	-.011678	.050701	.818
	2	1	.023090	.047219	.625
		3	.011412	.036297	.754
	3	1	.011678	.050701	.818
		2	-.011412	.036297	.754
T SCORE	1	2	.6617*	.2097	.002
		3	1.2762*	.2252	.000
	2	1	-.6617*	.2097	.002
		3	.6145*	.1612	.000
	3	1	-1.2762*	.2252	.000
		2	-.6145*	.1612	.000
Z SCORE	1	2	.0629	.2903	.829
		3	.0632	.3111	.839
	2	1	-.0629	.2903	.829

		3	.0003	.2202	.999
	3	1	-.0632	.3111	.839
		2	-.0003	.2202	.999
VIT D	1	2	.1283	2.7254	.963
		3	.3351	2.9264	.909
	2	1	-.1283	2.7254	.963
		3	.2068	2.0950	.921
	3	1	-.3351	2.9264	.909
		2	-.2068	2.0950	.921
BMI	1	2	.3251	1.0092	.748
		3	-.2878	1.0836	.791
	2	1	-.3251	1.0092	.748
		3	-.6129	.7758	.430
	3	1	.2878	1.0836	.791
		2	.6129	.7758	.430

*. The mean difference is significant at the 0.05 level.

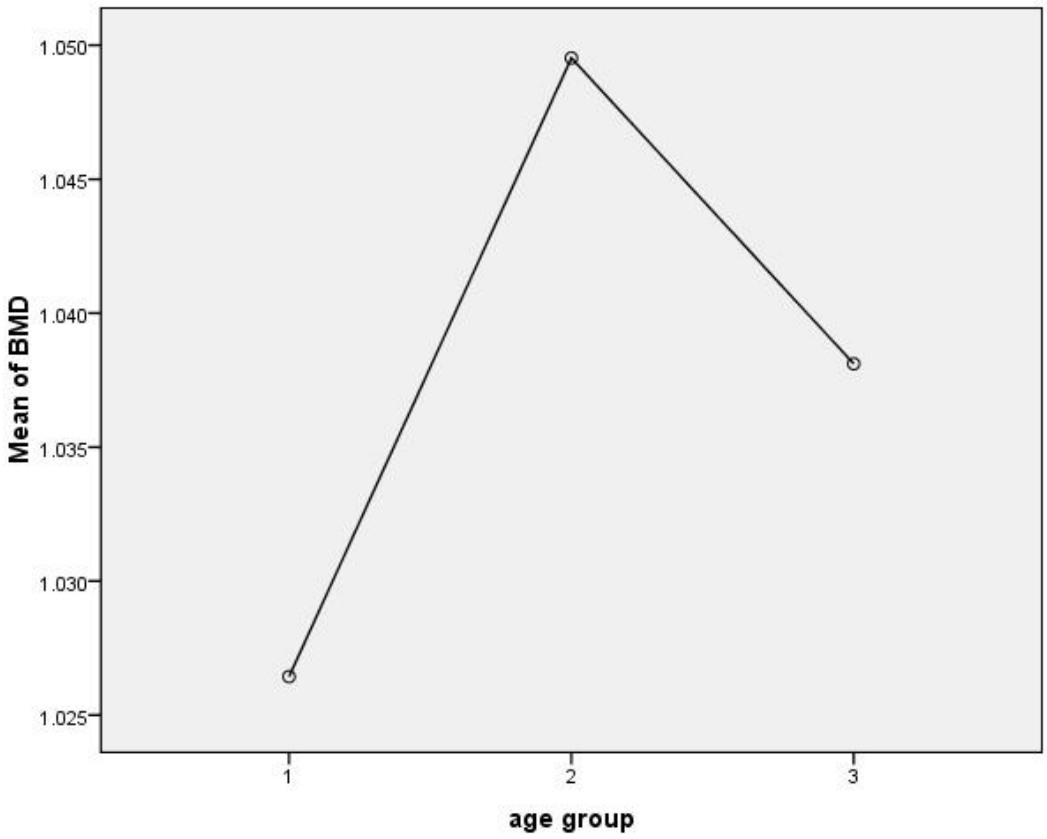
Multiple Comparisons

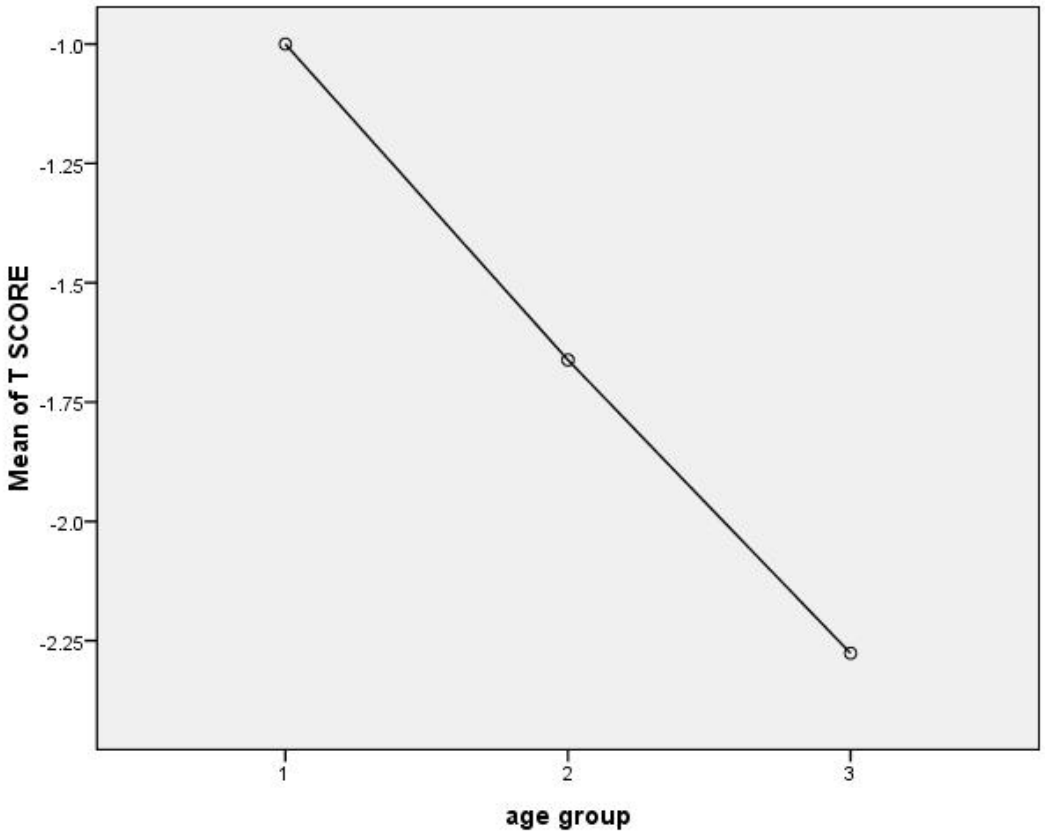
LSD

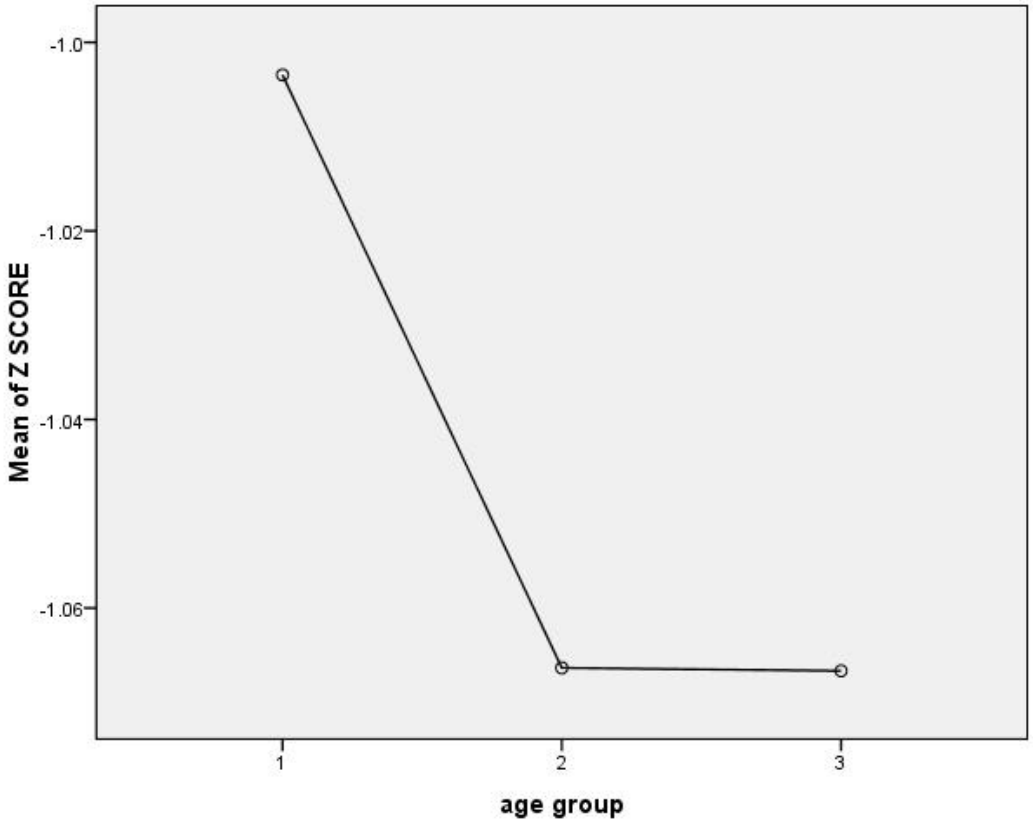
Dependent Variable	(I) age group	(J) age group	95% Confidence Interval	
			Lower Bound	Upper Bound
BMD	1	2	-.11621	.07003
		3	-.11166	.08831
	2	1	-.07003	.11621
		3	-.06017	.08299
	3	1	-.08831	.11166
		2	-.08299	.06017
T SCORE	1	2	.248	1.075
		3	.832	1.720
	2	1	-1.075	-.248
		3	.297	.932
	3	1	-1.720	-.832
		2	-.932	-.297
Z SCORE	1	2	-.510	.635
		3	-.550	.677
	2	1	-.635	.510

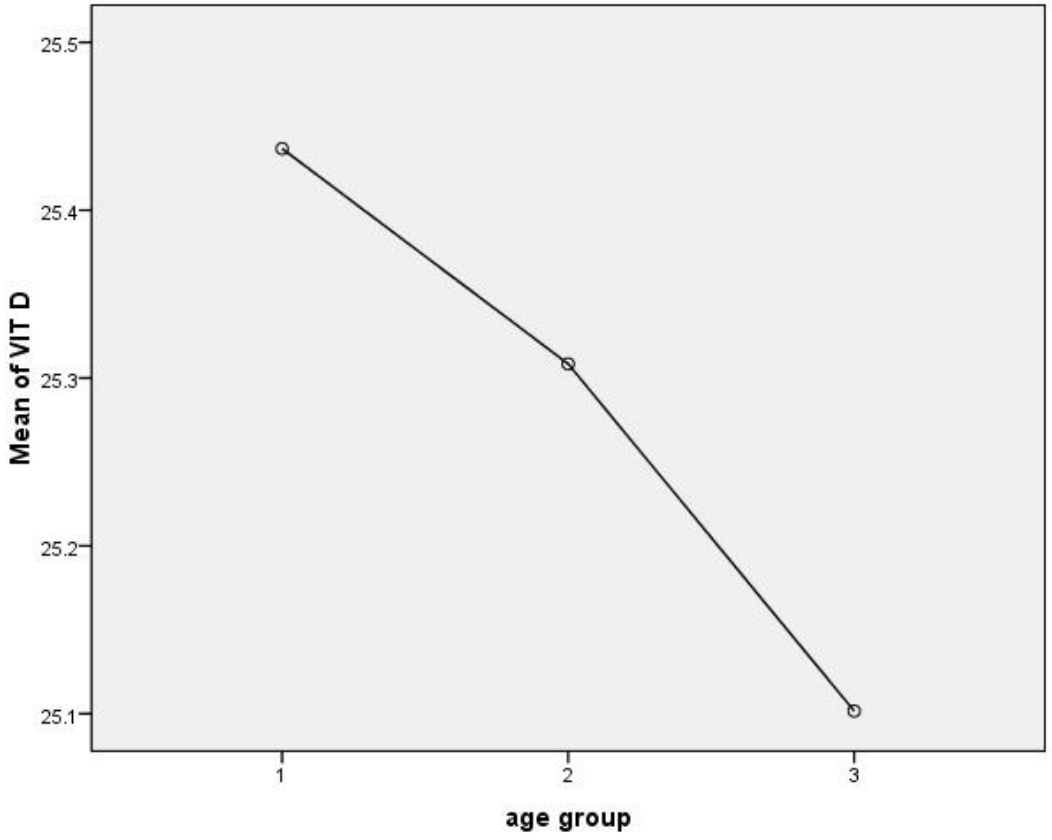
		3	-.434	.435
	3	1	-.677	.550
		2	-.435	.434
VIT D	1	2	-5.247	5.503
		3	-5.436	6.106
	2	1	-5.503	5.247
		3	-3.925	4.338
	3	1	-6.106	5.436
		2	-4.338	3.925
BMI	1	2	-1.665	2.315
		3	-2.425	1.849
	2	1	-2.315	1.665
		3	-2.143	.917
	3	1	-1.849	2.425
		2	-.917	2.143

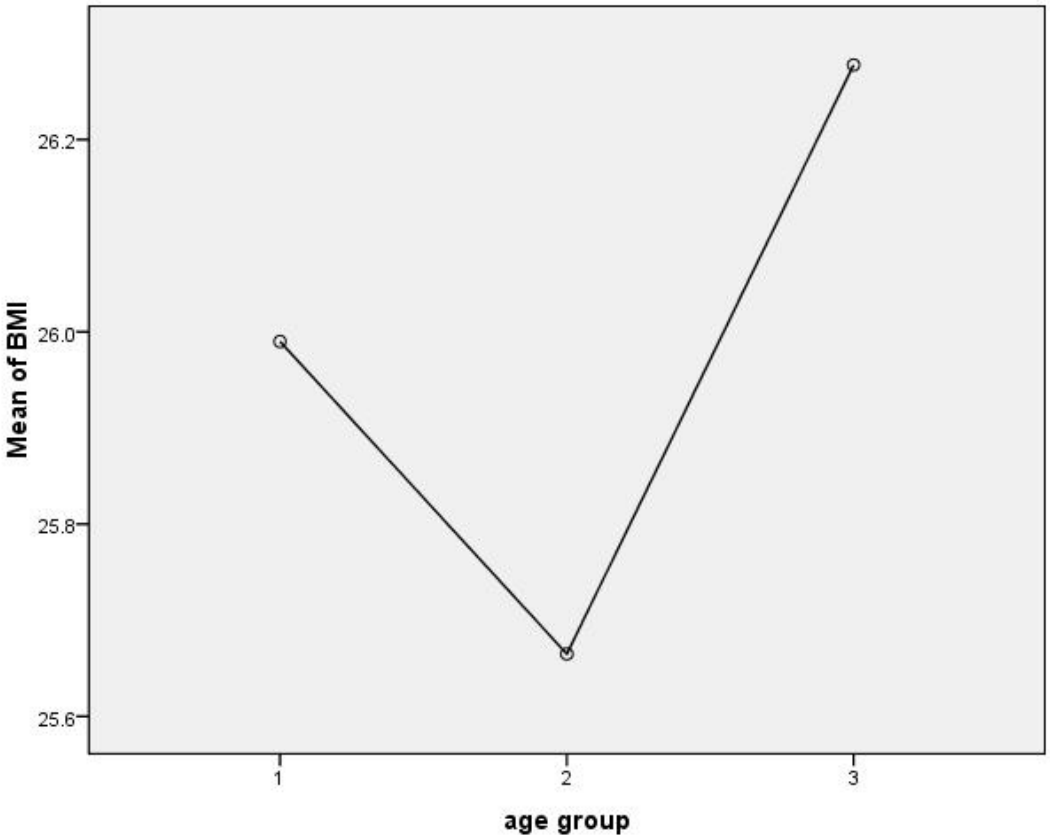
Means Plots

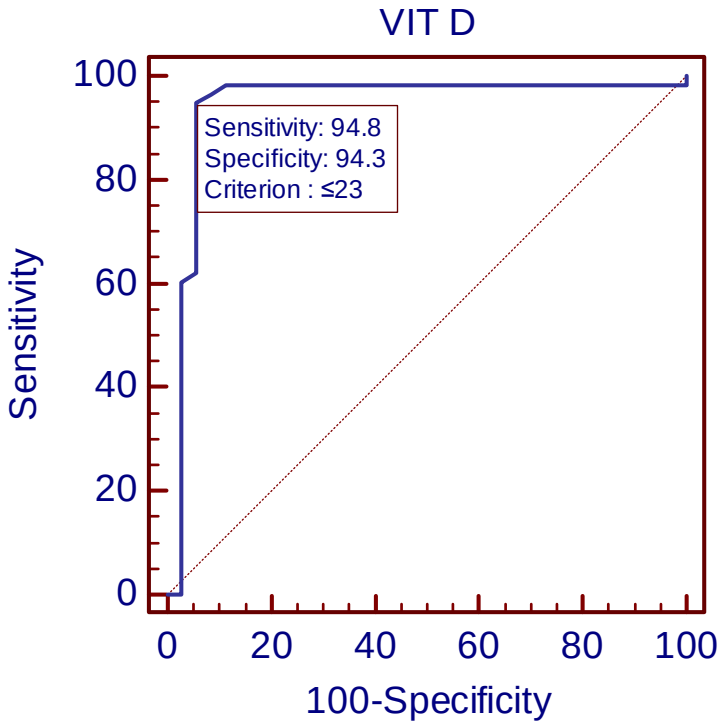



-1.0
-1.25
-1.5
-1.75
-2.0
-2.25
Mean of T SCORE
1
2
3
age group


-1.0
-1.02
-1.04
-1.06
Mean of Z SCORE
1
2
3
age group


25.5
25.4
25.3
25.2
25.1
Mean of VIT D
1
2
3
age group


Mean of BMI
26.2
26.0
25.8
25.6
1
2
3
age group


VIT D
Sensitivity: 94.8
Specificity: 94.3
Criterion : ≤23
Sensitivity
100-Specificity
0
20
40
60
80
100

ROC curve

Variable	VIT_D VIT D
Classification variable	Ost

Sample size		93
Positive group :	osteoporosis = 1	58
Negative group :	normal = 0	35

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.943103
Standard Error[a]	0.0341
95% Confidence interval[b]	0.874824 to 0.980509
z statistic	13.012
Significance level P (Area=0.5)	<0.0001

[a] DeLong et al., 1988

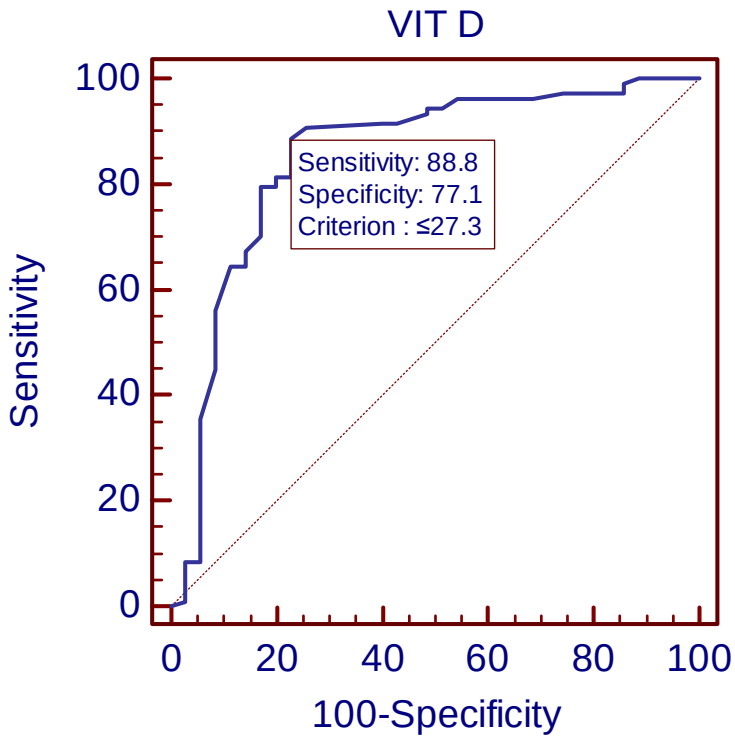
[b] Binomial exact

Youden index

Youden index J	0.8911
Associated criterion	≤23

Criterion values and coordinates of the ROC curve [Hide]

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<17	0.00	0.0 - 6.2	100.00	90.0 - 100.0		1.00
≤17	0.00	0.0 - 6.2	97.14	85.1 - 99.9	0.00	1.03
≤19.6	60.34	46.6 - 73.0	97.14	85.1 - 99.9	21.12	0.41
≤19.9	62.07	48.4 - 74.5	94.29	80.8 - 99.3	10.86	0.40
≤23	94.83	85.6 - 98.9	94.29	80.8 - 99.3	16.59	0.055
≤24	96.55	88.1 - 99.6	91.43	76.9 - 98.2	11.26	0.038
≤25	98.28	90.8 - 100.0	88.57	73.3 - 96.8	8.60	0.019
≤44	98.28	90.8 - 100.0	0.00	0.0 - 10.0	0.98	
≤195	100.00	93.8 - 100.0	0.00	0.0 - 10.0	1.00	


VIT D
Sensitivity: 88.8
Specificity: 77.1
Criterion : ≤27.3
Sensitivity
100-Specificity
0
20
40
60
80
100

ROC curve

Variable	VIT_D VIT D
Classification variable	Ost

Sample size		142
Positive group :	osteopenia = 1	107
Negative group :	normal = 0	35

Disease prevalence (%)	unknown

Area under the ROC curve (AUC)

Area under the ROC curve (AUC)	0.850868
Standard Error[a]	0.0437
95% Confidence interval[b]	0.781450 to 0.905046
z statistic	8.026
Significance level P (Area=0.5)	<0.0001

[a] DeLong et al., 1988

[b] Binomial exact

Youden index

Youden index J	0.6593
Associated criterion	≤27.3

Criterion values and coordinates of the ROC curve [Hide]

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
<17	0.00	0.0 - 3.4	100.00	90.0 - 100.0		1.00
≤17	0.93	0.02 - 5.1	97.14	85.1 - 99.9	0.33	1.02
≤19	8.41	3.9 - 15.4	97.14	85.1 - 99.9	2.94	0.94
≤19.9	8.41	3.9 - 15.4	94.29	80.8 - 99.3	1.47	0.97
≤23.9	35.51	26.5 - 45.4	94.29	80.8 - 99.3	6.21	0.68
≤24	44.86	35.2 - 54.8	91.43	76.9 - 98.2	5.23	0.60
≤24.9	56.07	46.1 - 65.7	91.43	76.9 - 98.2	6.54	0.48
≤25	64.49	54.6 - 73.5	88.57	73.3 - 96.8	5.64	0.40
≤25.2	64.49	54.6 - 73.5	85.71	69.7 - 95.2	4.51	0.41
≤25.7	67.29	57.5 - 76.0	85.71	69.7 - 95.2	4.71	0.38
≤25.8	70.09	60.5 - 78.6	82.86	66.4 - 93.4	4.09	0.36
≤26.2	79.44	70.5 - 86.6	82.86	66.4 - 93.4	4.63	0.25
≤26.3	79.44	70.5 - 86.6	80.00	63.1 - 91.6	3.97	0.26
≤26.5	81.31	72.6 - 88.2	80.00	63.1 - 91.6	4.07	0.23
≤26.8	81.31	72.6 - 88.2	77.14	59.9 - 89.6	3.56	0.24
≤27.3	88.79	81.2 - 94.1	77.14	59.9 - 89.6	3.88	0.15
≤28	90.65	83.5 - 95.4	74.29	56.7 - 87.5	3.53	0.13
≤29	91.59	84.6 - 96.1	60.00	42.1 - 76.1	2.29	0.14
≤29.5	91.59	84.6 - 96.1	57.14	39.4 - 73.7	2.14	0.15
≤30	93.46	87.0 - 97.3	51.43	34.0 - 68.6	1.92	0.13
≤30.3	94.39	88.2 - 97.9	51.43	34.0 - 68.6	1.94	0.11
≤30.6	94.39	88.2 - 97.9	48.57	31.4 - 66.0	1.84	0.12
≤31	96.26	90.7 - 99.0	45.71	28.8 - 63.4	1.77	0.082
≤32	96.26	90.7 - 99.0	31.43	16.9 - 49.3	1.40	0.12
≤33	97.20	92.0 - 99.4	25.71	12.5 - 43.3	1.31	0.11
≤36	97.20	92.0 - 99.4	14.29	4.8 - 30.3	1.13	0.20
≤37	99.07	94.9 - 100.0	14.29	4.8 - 30.3	1.16	0.065
≤39	100.00	96.6 - 100.0	11.43	3.2 - 26.7	1.13	0.00
≤44	100.00	96.6 - 100.0	0.00	0.0 - 10.0	1.00	

DISCUSSION

In my study , findings showed a mean vitamin D levels of 30.926 ng/ml, in patients with adequate bone mineral density. Where as in patients with osteopenia, mean vitamin D levels were 24.722 ng/ml and in patients with osteoporosis, mean levels were 22.841ng/ml. This observation is statistically significant [$P < 0.05$].The fact that even though these patients are osteoporotic they had slightly higher vitamin D levels when compared to osteopenic group is probably related to insufficient number in the osteoporotic group.

So from my study, we predicted a cut-off value of vitamin D to diagnose osteopenia and osteoporosis. For diagnosing osteopenia, by keeping vitamin D level of <= 27.3 as cut-off, sensitivity is 88.8% and specificity is 77.1%. Whereas for osteoporosis ,by keeping vitamin D level of <= 23 as cut-off, sensitivity is 94.8% and specifity is 94.3%.

So we can diagnose both osteopenia and osteoporosis by measuring vitamin D levels, which is cheaper with no adverse effects. Vitamin D is less costlier, and no adverse effects like radiation as in DEXA imaging which is most commonly used to diagnose osteoporosis.

A study by Daniele et al studied the effect of calcium and vitamin D on BMD and bone mineral content in peri & post menopausal women. It is a double blinded randomized control study. The results showed a positive effect of calcium and vitamin D supplementation on bone mineral density and bone mineral content in both peri & postmenopausal women. This is in accordance with our study.

A study by lucy cooper et al , a double blinded placebo controlled study which compares the effect of calcium Vs calcium and vitamin D in postmenopausal women. Results were vitamin D and calcium did not confer benefits on BMD than with calcium supplementation alone.

A study by Francisco et al showed positive association between vitamin D and BMD in postmenopausal women. There is high prevalence of hypovitaminosis D in postmenopausal women which is in accordance with our study.

A study by labronite et al showed no independent association between vitamin D and BMD in healthy postmenopausal women which is in contrast to our study which showed a significant association between vitamin D and BMD.

LIMITATIONS OF THE STUDY

- The sample size was small and further studies with larger number of people have to be done to verify the results.

- Since the study was done in ethnic asian population further studies are needed in large population involving same and different ethnic group to verify the reproducibility of the results.

- Environmental influence on bone health has not been taken in to consideration, as factors like nutrition may affect the bone health adversely.

IMPLICATIONS FOR THE FUTURE:

- Supplementation of vitamin D may be needed for those patients who are insufficient, even though they are asymptomatic.

CONCLUSION

In our study,

- There exists a positive association between vitamin D and bone mineral density.
- Obesity doesn't show any significant relation with bone mineral density.
- As age increases, bone mineral density decreases. Inverse relationship exists between age and bone mineral density.

DISCLOSURE:

The investigator had not received any form of support or grant from any institution or pharmaceutical company.

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QUESTIONNAIRE

- NAME / AGE / OCCUPATION / ADDRESS / IP /OP NO
- HISTORY

  Duration of menopause

  Low backache

  H/O steroid intake

  Anti epilectic medications

  H/O small and large joint pain

  H/O chronic cough

  H/O tremors

  H/O Chronic diarrhea

  H/O Jaundice

- PAST HISTORY

  Hypertension, diabetes mellitus, thyroid illness, H/O fractures and site, past malignancy, dyslipidaemia, CAD, CVA

- PERSONAL HISTORY

  Dietary intake

- DRUG HISTORY

  Calcium, vitamin D supplementation, oral hypoglycaemic agents, antihypertensives, antianginals, other drugs affecting calcium metabolism

- GENERAL EXAMINATION

  BP, PR

  Height, Weight, BMI

- SYSTEM EXAMINATION

  CVS/RS/Abdomen/CNS

- LOCAL EXAMINATION

- PER SPECULUM EXAMINATION

- PER VAGINAL EXAMINATION

- INVESTIGATIONS

  CBC WITH ESR

  25 (OH) VITAMIN D LEVELS

  BMD-**DEXA**

  - T-SCORE LUMBAR SPINE
  - Z-SCORE LUMBAR SPINE
  - BONE MINERAL DENSITY

COMMENTS

MASTER CHART

Sl. No.	NAME	AGE	WEIGHT	HEIGHT	BMI	T SCORE	Z SCORE	PENIA	POROSIS	VIT D	BMD
144	MARIYAMMAL	71	58	144	29.5	-3.3	-1.6	NO	NO	18	0.999
164	BACKIYA	53	65	150	28.8	-3.2	-3	NO	NO	18.5	0.83
143	VALARMATHI	60	59	163	23	-3.1	-2	NO	NO	19.3	0.909
84	PUSHPAM	52	58	162	22.1	-3	-3.5	NO	NO	19.2	1.452
95	MABOOBEE	62	57	140	29	-3	-2	NO	NO	19	0.813
102	SUMATHY	60	64	149	29	-3	-1.8	NO	NO	18.6	1.295
116	ANGAMMA	70	81	155	33	-3	-1.8	NO	NO	18.8	0.937
128	DEVI	50	50	154	21	-3	-3.7	NO	NO	19	1.027
130	SAROJA	63	66	167	23.7	-3	-1.9	NO	NO	19	0.924
179	BACKIYAM	69	66	143	33	-3	-1.7	NO	NO	18.2	1.1
94	BHUVANA	64	60	152	25.9	-2.9	-1.4	NO	NO	18.5	1.205
101	LEELAVATHY	68	67	148	30.5	-2.9	-2	NO	NO	195	0.714
127	CHOKKI	70	58	156	22.9	-2.9	-0.6	NO	NO	18.2	1.381
129	RAMA	50	65	155	27	-2.9	-2.7	NO	NO	19	1.085
135	PARIMALAM	69	59	154	24.8	-2.9	1.7	NO	NO	20	1.085
142	RANI	61	52	159	20.6	-2.9	-2.1	NO	NO	20.8	0.901
162	KOMALAVALLI	58	68	149	30.6	-2.9	-2.6	NO	NO	20.4	1.42
178	RAKKAMMA	67	68	170	23.5	-2.9	-2	NO	NO	18	1.26
192	JOTHIBAI	63	69	143	33.8	-2.9	-1.8	NO	NO	19.9	0.732
11	MANORANJITHAM	60	49	150	21.7	-2.8	-2.9	NO	NO	20.2	1.34
20	UMAYUN NISHA	72	55	154	23.2	-2.8	-2.6	NO	NO	20	1.023
25	FARITHABANU	56	56	156	23.04	-2.8	-2.5	NO	NO	20	1.11
60	VASANTHA	50	63	168	22.3	-2.8	-2.3	NO	NO	19.2	0.9
64	SRIDEVI	53	59	163	22.2	-2.8	-0.5	NO	NO	19.4	1.208
92	JOTHI	51	64	151	28	-2.8	-2.7	NO	NO	19.3	1.457

97	MUTHU	67	56	156	23	-2.8	1	NO	NO	19.2	0.888
115	KARPAGAM	73	79	166	28.7	-2.8	-1.4	NO	NO	18.4	0.809
125	MAHALAKSHMI	52	45	160	17.5	-2.8	-2.5	NO	NO	18.3	0.924
152	ARASI	51	59	139	30.5	-2.8	-1.3	NO	NO	18.6	1.278
165	VIJAYALAKSHMI	54	69	145	32.8	-2.8	-3.1	NO	NO	18.3	0.86
180	ESAKKIYAMMAL	71	57	152	24.6	-2.8	-0.3	NO	NO	18.3	1.308
45	GOMATHI	65	58	157	23.5	-2.7	-2.7	NO	NO	19.4	0.964
59	SAROJA	61	69	148	31.5	-2.7	1	NO	NO	19.2	0.923
80	KAMALAM	47	62	159	24.6	-2.7	-2.9	NO	NO	19.5	1.412
89	RASATHI	55	50	144	24.1	-2.7	-1.9	NO	NO	19.3	0.937
126	NAGAMMAL	55	54	147	25	-2.7	-2.2	NO	NO	19.6	1.35
134	MALAR	63	58	150	25.7	-2.7	1.2	NO	NO	19.3	1.023
138	PADMINI	57	57	151	25	-2.7	1	NO	NO	19	1.156
151	KALAISELVI	68	57	142	28.5	-2.7	1.5	NO	NO	19.3	1.223
167	JEYAM	66	74	147	34.2	-2.7	-1.3	NO	NO	19.3	0.91
171	SUGUMARI	62	58	157	23.5	-2.7	-2.6	NO	NO	19.3	1.178
186	ASHA	61	55	155	22.9	-2.7	-0.4	NO	NO	19.4	1.312
198	RUPAVATHY	51	59	158	23.6	-2.7	-2.5	NO	NO	19.4	1.204
10	LALITHA	64	61	160	23.8	-2.6	-2.6	NO	NO	20	1.232
43	ARPUTHAM	54	80	147	27	-2.6	-2.9	NO	NO	20	1.245
48	KURUVAMMA	69	54	148	24.6	-2.6	-1.8	NO	NO	21	1.946
77	BHAVANI	60	51	154	21.5	-2.6	-2	NO	NO	21	1.35
90	SEETHA	56	60	158	25	-2.6	-2.1	NO	NO	22	1.014
93	KATHAYI	53	68	144	32.8	-2.6	-2.2	NO	NO	25	1.035
107	GANDHIMATHI	56	54	146	25.3	-2.6	-1.6	NO	NO	20.5	0.893
117	MAHADEVI	70	75	140	38.2	-2.6	-1.5	NO	NO	20.5	0.912
133	NEELA	67	64	149	28.8	-2.6	-1.7	NO	NO	21.3	0.866
136	PODUMPONNU	49	60	150	26.6	-2.6	-3.3	NO	NO	21.5	1.094
139	SENGAMALAM	55	56	152	24.2	-2.6	-1.9	NO	NO	23	1.145
145	SEMBA	78	62	154	26.9	-2.6	-1.4	NO	NO	22.4	0.843

146	VANI	55	66	158	26.5	-2.6	-2.3	NO	NO	23	0.812
157	NAGAVALLI	62	68	158	27.3	-2.6	-1.9	NO	NO	24	0.853
197	DEVIBALA	58	53	155	22	-2.6	-0.2	NO	NO	21	1.209
27	LALITHA	71	66	157	26.8	-2.5	-2.6	YES	NO	23.9	1.112
46	THILAGAVATHY	57	57	145	27.1	-2.5	-2.8	YES	NO	23	0.934
61	KUMARI	58	66	142	33	-2.5	-2	YES	NO	23.5	0.947
106	SANTHA	67	53	160	20.7	-2.5	-1.2	YES	NO	24	0.823
148	SUDHA	58	70	156	28.8	-2.5	-0.6	YES	NO	24.2	0.891
158	SUMATHY	65	61	157	24.7	-2.5	-2	YES	NO	24.1	0.956
159	GEETHA	57	60	148	27.3	-2.5	-0.1	YES	NO	23.7	1.067
163	MALA	50	63	148	28.7	-2.5	-2.7	YES	NO	22	1.278
182	PAVALAM	59	47	156	19.3	-2.5	-2.2	YES	NO	24	0.94
183	CHELLAMMA	53	51	154	21.5	-2.5	-2.4	YES	NO	20	0.832
7	THAYAMMA	76	62	145	29.5	-2.4	-1.7	YES	NO	25.3	1.329
96	SIPPI	66	58	149	26.1	-2.4	-1	YES	NO	26.9	0.836
124	SIGAPPI	61	47	154	19.8	-2.4	-1.6	YES	NO	20	0.985
172	PEYARACHI	54	57	155	23.7	-2.4	-2.1	YES	NO	19	1.294
173	FATHIMA	57	59	160	23	-2.4	-1.8	YES	NO	21	1.29
14	KUMARI	52	89	140	45	-2.3	0.7	YES	NO	25	0.907
35	KARUPPAYI	62	60	153	25.6	-2.3	-2.1	YES	NO	23.1	0.824
44	SENGAMALAM	66	69	148	31.5	-2.3	-1.7	YES	NO	24	1.321
105	RADHA	64	57	154	24	-2.3	-2	YES	NO	24.4	0.905
121	KANDHARI	51	50	156	19.7	-2.3	-0.3	YES	NO	22	0.792
33	MARIYAL	50	72	155	30	-2.2	-2.3	YES	NO	22.8	1.385
53	SABURNISHA	61	50	157	20.3	-2.2	1	YES	NO	18.4	0.83
103	NAVAMANI	62	66	146	30.9	-2.2	-1.3	YES	NO	21	1.11
122	VARALAKSHMI	54	52	149	23.4	-2.2	-2	YES	NO	24.9	0.863

123	MUTHAMMA	60	50	160	19.5	-2.2	-2.8	YES	NO	24.6	0.853
181	SUBBULAKSHMI	54	60	144	28.9	-2.2	-2.2	YES	NO	23.6	0.945
49	GENGAMMA	60	65	141	32.8	-2.1	-1.3	YES	NO	26	1.867
104	SAMPOORNAM	64	58	156	23.8	-2.1	-0.5	YES	NO	26.4	0.902
147	SARALA	57	60	154	25.3	-2.1	1.3	YES	NO	27.3	0.845
174	ARPUTHARANI	52	50	158	20	-2.1	-1.2	YES	NO	22.8	1.479
23	ETTAMMAL	57	51	159	20.2	-2	-1.6	YES	NO	18	0.809
24	GOWRI	50	45	162	17.1	-2	-1.5	YES	NO	20	0.911
32	JAMEELA	54	44	157	17.8	-2	-1	YES	NO	20	1.234
54	MARY	68	50	159	19.8	-2	1.7	YES	NO	24.9	0.821
78	CHITRA	63	59	152	25.8	-2	-1.5	YES	NO	24.6	1.385
120	VELAYI	59	51	154	21.5	-2	-0.1	YES	NO	26	0.709
193	MYTHILI	53	52	158	20.8	-2	-1.4	YES	NO	25	0.882
21	SHEELA	66	90	146	42.2	-1.9	-2	YES	NO	23	1.467
38	POONGAVANAM	69	53	159	21	-1.9	-2.3	YES	NO	26	1.247
39	THAVAMANI	61	59	158	23.6	-1.9	-2.4	YES	NO	26.2	0.88
50	NOORJAHAN	58	66	144	33	-1.9	1.2	YES	NO	22	1.221
66	SUSEELA	63	100	143	50	-1.9	1.3	YES	NO	23	0.81
76	SULOCHANA	67	45	158	18	-1.9	-1.4	YES	NO	23.9	1.051
141	SUBATHRA	65	53	159	21	-1.9	-1.8	YES	NO	24	0.856
176	MEENAL	55	65	157	26.4	-1.9	-0.3	YES	NO	25	1.43
200	BALAMANI	50	76	147	35.1	-1.9		YES	NO	22	0.452
79	MAYA	49	68	157	27.6	-1.8	-2.4	YES	NO	23	1.328
82	MARUTHAYI	58	54	158	21.6	-1.8	-1.5	YES	NO	24.4	0.916
112	SARASWATHY	64	63	146	29.5	-1.8	-1.2	YES	NO	23.9	1.287
132	MALLIGA	54	66	160	25.7	-1.8	-1.6	YES	NO	23.7	0.831

140	AMMAN	56	54	156	22.2	-1.8	-2.4	YES	NO	26	0.843
161	MALARVIZHI	59	65	154	27.4	-1.8	1.3	YES	NO	24	1.476
166	SELVI	60	70	158	28.1	-1.8	1.2	YES	NO	25.6	0.952
168	LATHA	47	75	159	29.7	-1.8	-2.5	YES	NO	25	0.929
175	KURUVAMMA	50	64	153	27.3	-1.8	-1.8	YES	NO	24	1.406
177	ESWARI	61	63	155	26.2	-1.8	0.6	YES	NO	19	1.205
36	MANGAMMA	63	53	157	21.5	-1.7	-2.2	YES	NO	28	1.209
65	MANJULA	58	43	158	17.2	-1.7	-0.6	YES	NO	33	0.799
98	AMMA	54	54	147	25	-1.7	-0.3	YES	NO	31	0.914
113	POONGAVANAM	53	53	148	24.2	-1.7	-1.5	YES	NO	29	0.836
119	BANNARIAMMAN	54	62	149	27.9	-1.7	-1.7	YES	NO	25	0.774
153	KRISHNAVENI	51	53	145	25.2	-1.7	-1.6	YES	NO	24.5	1.286
184	AMALAMARY	54	58	153	24.7	-1.7	1.3	YES	NO	24	0.77
12	MARY	60	59	152	25.5	-1.6	-1.6	YES	NO	25.8	0.842
62	SHANTHI	64	54	158	21.6	-1.6	-1.2	YES	NO	26	0.879
131	SHANTHI	51	62	157	25.2	-1.6	-1.5	YES	NO	26.5	0.861
137	KASTHOORI	48	52	156	21.3	-1.6	-2.1	YES	NO	23	1.12
150	MEENAMBAL	64	55	159	21.8	-1.6	-0.4	YES	NO	23	1.256
155	MANGAMMA	54	74	146	32.1	-1.6	-1.4	YES	NO	19	0.867
160	SUSEELA	51	67	149	30.1	-1.6	1	YES	NO	31	1.012
185	VASUKI	61	69	147	31.9	-1.6	1.4	YES	NO	24	1.396
191	ANGAMMA	55	64	157	26	-1.6	1.4	YES	NO	25	1.084
199	NARAYANI	49	70	153	29.9	-1.6	-2.1	YES	NO	23	1.222
6	ALAMELU	72	40	156	16.4	-1.5	-1.9	YES	NO	26.9	0.934

28	MEENATCHI	57	65	152	28.1	-1.5	-1.7	YES	NO	27	0.976
57	MANGALAM	56	59	159	23.4	-1.5	0.7	YES	NO	26.1	0.81
88	RAMAYI	56	54	155	22.5	-1.5	-1.4	YES	NO	27	0.77
99	KOLANJI	59	57	158	22.8	-1.5	-0.5	YES	NO	30	0.951
111	LAKSMIAMMAL	60	65	147	30.9	-1.5	-0.5	YES	NO	26	1.129
114	MOOKAYI	67	55	157	22.3	-1.5	-2	YES	NO	37	0.881
118	AZHAGI	53	63	158	25.3	-1.5	-2	YES	NO	39	0.934
30	MUNIYAMMAL	59	56	144	28	-1.4	-2.1	YES	NO	17	1.098
41	KURUVAMMA	60	63	148	28.7	-1.4	-2.1	YES	NO	27	1.237
63	AMUDHA	60	50	148	22.8	-1.4	-1.8	YES	NO	30	0.904
108	RUKKU	54	55	157	22.3	-1.4	-0.7	YES	NO	26	1.187
170	BUVANAMMA	50	69	151	30.2	-1.4	-0.9	YES	NO	24	0.815
195	SAVITHRI	52	50	152	21.6	-1.4	-1.2	YES	NO	23.6	0.985
17	SUBBAMMA	55	64	158	25.7	-1.3	-1.2	YES	NO	24.7	1.093
29	VASUKI	54	54	155	22.5	-1.3	-2.6	YES	NO	25.7	0.854
42	VISALATCHI	50	64	146	30	-1.3	-2.1	YES	NO	24	1.011
47	MANGALAM	53	51	149	22.9	-1.3	-2.1	YES	NO	18.6	1.115
55	RAMANI	65	51	147	23.6	-1.3	0.5	YES	NO	30.3	0.856
85	MANGALAM	50	71	158	28.5	-1.3	-2	YES	NO	24.6	0.825
87	VIJAYA	52	54	155	22.5	-1.3	1.4	YES	NO	25	0.851
149	MOHANA	52	82	157	33.3	-1.3	-0.2	YES	NO	26	0.799
196	MYNAA	54	65	148	29.6	-1.3	-0.4	YES	NO	27	0.907
3	KUPPU	63	64	158	25.7	-1.2	-1	YES	NO	25	1.234
9	HABEEBNISHA	62	57	157	23.1	-1.2	-1.4	YES	NO	24.5	0.834
18	KUMUDHA	51	69	159	27.3	-1.2	-2	YES	NO	23.8	0.9
22	CHINNATHAyI	53	57	160	22.2	-1.2	-1.2	YES	NO	25.8	0.849
26	USHARANI	52	67	155	27.9	-1.2	-1.3	YES	NO	19	1.204
56	SAGUNTHALA	64	63	158	25.3	-1.2	0.5	YES	NO	25	0.876
100	RANI	58	62	154	26.1	-1.2	-1.1	YES	NO	28	0.994
15	VENI	56	65	153	27.7	-1.2	-0.5	YES	NO	27	0.804

6											
37	VADIVU	58	53	162	20.2	-1.1	-1.2	YES	NO	37	1.42
67	NAGALAKSHMI	67	62	153	26.4	-1.1	1.9	YES	NO	18	0.875
109	KAMALA	53	62	159	24.6	-1.1	-0.8	YES	NO	25.8	1.157
13	KAMATCHI	51	78	145	37.1	-1	-1.4	NO	YES	25.2	1.098
16	ARAYI	54	52	145	24.7	-1	0.4	NO	YES	26.3	1.402
51	KANAGAVALLI	53	62	156	25.5	-1	1.5	NO	YES	26.8	1.056
86	NAGARATHINAM	54	46	154	19.4	-1	1.5	NO	YES	25.8	0.842
154	TAMILSELVI	49	50	157	19.2	-1	-2.2	NO	YES	24	0.834
194	REVATHY	57	58	150	25.7	-1	-1.6	NO		25	0.843
68	KALYANI	60	63	150	28	-0.9	2	NO	YES	28	0.812
187	AMUDHA	60	90	149	40.5	-0.9	0.6	NO	YES	29	0.96
190	JAMUNA	54	58	147	26.8	-0.9	1.4	NO	YES	36	1.398
69	INDRA	50	68	158	27.3	-0.8	0.1	NO	YES	17	0.822
8	MARTHAL	60	65	148	29.6	-0.7	-1	NO	YES	29	1.908
31	KANAGA	58	52	149	23.4	-0.5	1	NO	YES	33	1.222
75	JAKKAMMA	57	56	147	25.9	-0.5	-1.5	NO	YES	34	1.065
169	PORKODI	49	76	154	32	-0.5	1.2	NO	YES	33	0.958
15	MYNAA	50	58	150	25.7	-0.4	0.3	NO	YES	30	1.256
40	KAMALAM	50	57	150	25.3	-0.4	1.6	NO	YES	29	0.885
58	PADMINI	58	68	149	30.6	-0.4	0.9	NO	YES	31.5	0.912
83	BOOMA	51	50	147	23.1	-0.4	-1.6	NO	YES	31.2	0.994
74	JEEVA	56	57	161	22	-0.3	-1.3	NO	YES	32	1.207
73	RANJITHAM	55	56	154	23.6	-0.2	-1.6	NO	YES	29.5	0.902
91	RANI	48	64	158	25.7	-0.1	-2	NO	YES	29	1.205
19	KAYARKANNI	49	59	155	24.5	0.4	1	NO	YES	29	1
34	SUBHA	48	64	156	26.3	0.5	1.3	NO	YES	30.6	0.991
81	SARASWATHY	62	64	157	26	0.5	-1	NO	YES	30	0.965
110	KOKILA	57	64	152	27.7	0.5	1.6	NO	YES	31.6	1.105

189	AMBIKA	52	57	158	22.8	0.5	0.1	NO	YES	31	1.298
188	THEIVANAI	50	54	157	21.9	0.6	0.9	NO	YES	32	0.846
5	KOKILA	47	50	157	20.3	0.8	1.4	NO	YES	40	0.954
72	SAVITHRI	54	59	154	24.8	1	0.4	NO	YES	41	0.965
52	VALLI	54	52	156	21.3	1.2	-1.8	NO	YES	44	0.987
70	WAHEEDA	49	54	158	21.6	1.2	1.6	NO	YES	19.9	0.801
2	MUTHAMMAL	60	54	154	22.7	1.8	-2	NO	YES	36	0.945
4	SAVITHRI	48	65	149	29.2	2.3	1	NO	YES	34	1.098
1	MADHAVI	54	74	146	34.7	2.6	-1.5	NO	YES	39	0.923
71	SUGUMARI	49	58	156	23.8	2.6	2	NO	YES	40	0.943

INSTITUTIONAL ETHICAL COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10

Ref.No.134/ME-1/Ethics/2014 Dt:06.02.2014

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on prospective observational study to evaluate the association between vitamin D and bone mineral density among postmenopausal women" - For Project work submitted by Dr.Priyadharshini, MS (O&G), PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

26/3/14.

CHAIRMAN,
Ethical Committee
Govt.Kilpauk Medical College,Chennai

GOVT. KILPAUK MEDICAL COLLEGE
26 MAR 2014
Kilpauk, Chennai-10.