ROLE OF RALOXIFENE IN POST MENOPAUSAL OSTEOPOROSIS

A PROSPECTIVE STUDY

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CERTIFICATE

This is to certify that this dissertation entitled "**ROLE OF RALOXIFENE IN POST MENOPAUSAL OSTEOPOROSIS"** has been done by Dr. R. Shanmuga Priya Postgraduate in MD (Obstetrics and Gynaecology) under my overall supervision and guidance at Govt. Kasturba Gandhi Hospital, Madras Medical College Chennai in partial fulfillment of regulation of Tamilnadu Dr. MGR. Medical University for the award of MD .Degree in Obstetrics and Gynaecology.

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Table of Contents

INTRODUCTION

In 1000 BC life expectancy was only 17 years and by the time of 100 BC in the time of Julius Caesar, it had reached 25 years. In 2000 AD the average life expectancy was 79.7 years for women and 74.3 for men (Centers for Disease Control and Prevention 2004). Osteoporosis the most prevalent and a major global public health problem affecting elderly women 4 times more commonly than men. (National osteoporosis foundation 2003) Because of this demographic change the number of hip fractures increase approximately six fold increasing the morbidity in the postmenopausal group. (Cooper et al) [1]

Osteoporosis is highly prevalent in India, 4 to 6 million people are affected, it is projected that by the year 2030 the proportion of postmenopausal women will be 2nd highest next to china and the burden of osteoporosis in India will also be very high (Gupta et al) [2]

Osteoporosis is characterized by low bone mass and micro architectural deterioration of Bone tissue leading to enhanced bone fragility consequently increased risk of fractures even with little or no trauma. Post menopausal status directly attributes to osteoporosis due to hormonal deficiency and contributes to

significant morbidity, mortality, reduction in quality of life, and increasing health care costs. Various drugs used are as follows:

- *Sex hormones*
- *Bisphosphonates*
- *Calcitonin*
- *Calcium and vitamin D*
- *Tibolone*
- *Teriparatide*
- *Flouride*
- *Statins*
- *Thiazides*
- *SERMS*

Raloxifene is a selective estrogen receptor modulator used in the prevention and management of postmenopausal osteoporosis. To date there has been few prospective trials and several randomized control trials since 1997 comparing Raloxifene with various other standard therapies. This prospective study was undertaken to assess the efficacy of Raloxifene in the treatment of postmenopausal osteoporosis.

REVIEW OF LITERATURE

MENOPAUSE AND OSTEOPOROSIS

MENOPAUSE:

Menopause is defined as the permanent cessation of menstruation resulting from loss of ovarian follicular activity (WHO Scientific group 1983). There should be amenorrhea for at least 6 months in a women aged about 45 -50 years without any associated clinical manifestation other than those connected with low endogenous estrogen.

Usually occurs between 45 and 52. The average age being 48 (McKinley et al) [3].

POST MENOPAUSE:

A woman who has ceased to menstruate for at least 6 months to 1 year after the onset of menopause. Epidemiological studies, have found the mean age of menopause to be around 51 yr in Caucasians and Asians. Boulet et al[4]

Menopause – An overview

The life cycle of a woman can be divided into three sub cycles:

- Reproductive life
- Perimenopausal period (premenopausal symptoms accompanied by amenorrhea lasting up to one year)
- Post menopause (confirmed menopause with no menstruation for at least one year).

Cross-sectional and longitudinal studies have shown the age of menopause to be between 49 and 51 years in Caucasian women; around 49 years in US black and South African women; and 45 years on average in India [41] Boulet et al. Differences may be due to such factors as socioeconomics, nutrition, health status, health habits, marital status and employment status. Health habits, such as nicotine and CO2 intake from smoking, can hasten the onset of menopause by adversely affecting ovarian circulation, reducing hemoglobin and destroying undeveloped ova.

Type of onset of menopause:

Gradual

- Gradual decrease in the amount of flow.
- Interval between the consecutive cycles increases with time.

Abrupt

- Sudden without any warning.

IMPACT OF POST MENOPAUSAL ESTROGEN DEPRIVATION:

- Vasomotor disturbances
- Atrophic changes
- Cognition and Alzheimer's disease
- Cardiovascular disease
- Osteoporosis

Most women experience some effects of estrogen deficiency during menopause. Effects range from short term discomfort to long term changes that have profound effect on women's health.

IMPACT OF MENOPAUSE ON OSTEOPOROSIS:

Bones are comprised of two major ingredients:

I Minerals (including calcium and phosphorous)

II Bone cells (consisting of osteoblasts and osteoclasts).

Large amounts of calcium and other minerals are laid down during teenage years, in preparation for adult growth. In order to stay strong and healthy,bones constantly regenerate themselves. The bone cells work together to reabsorb and then regenerate our bones. Peak bone mass is reached between the ages of 20 and 30.

After the age of 30, bones do not regenerate in the same way. Most women and men lose about 1% of their bone mass throughout a year - this is part of the natural aging process.Since Estrogen keeps the osteoclasts in check, allowing the osteoblasts to build more bone,during menopause women begin to lose much more bone than their male counterparts as much as between 2% and 7% of the bone mass every year making the bones susceptible to fractures. Bugliosi R, et al [5] and Cummings et al [6].

The largest amount of bone loss occurs in the first five years following menopause. Leo Vankrieken [7]. It is important to conserve bone mass to avoid debilitating fractures of the hip, spine, and wrist. Osteoporosis is of particular concern as it is a silent epidemic can seriously affect health and longevity.

OSTEOPOROSIS

A clinical definition of osteoporosis was developed in 2001 by the **NIH Consensus Development Panel on Osteoporosis**. It stated: “Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture”.

The **WHO Working Group** defines osteoporosis according to measurements of bone mineral density (BMD) using dual-energy X-ray absorptiometry (DEXA). Thus osteoporosis is defined as a bone density T scores at or below 2.5 standard deviations (T score) below normal peak values for young adults.

PATHOPHYSIOLOGY OF OSTEOPOROSIS:

A deficiency in estrogen is associated with greater responsiveness of the bone to Parathyroid hormone. Thus, for any given level of Para thyroid hormone there is more calcium removed from the bone raising serum ca which in turn lowers PTH and decreases vitamin D and intestinal absorption of calcium. Osteoporosis develops insidiously. Symptoms typically do not appear until advanced stages of bone resorption have already been reached. Risk of fracture from Osteoporosis

will depend on bone mass at the time of menopause and rate of bone loss following menopause. (Riis BJ et al) [8]

Most of the bone mass in the hip and the vertebral body is accumulated by the age of 18 only a slight gain continues thereafter that ceases around 30 and this declines by 0.7 % every year. For the first 20 years following menopause 50% reduction takes place in trabecular bone and 30% in cortical bone. High rate of bone loss after menopause (the fast looser) is highly predictive of an increased risk of fracture. These fast losers probably reflect the lower endogenous levels of estrogen. (Sabatier et al) [9]

RISK FACTORS FOR OSTEOPOROSIS

- Female sex
- Age > 70 years
- Caucasian or Asian race
- Early onset of menopause
- Longer postmenopausal interval
- Inactivity, especially lack of weight bearing exercise

Osteoporosis can be classified as primary or secondary. Primary osteoporosis is the form seen in older persons and women past menopause in which bone loss is

accelerated over that predicted for age and sex. Secondary osteoporosis results from a variety of identifiable conditions that may include:

- Metabolic bone disease, such as hyperparathyroidism
- Neoplasia, as with multiple myeloma or metastatic carcinoma
- Malnutrition
- Drug therapy, as with corticosteroids
- Prolonged immobilization
- Weightlessness with space travel
- Anorexia nervosa,
- Type I diabetes

Modifiable risk factors that may potentiate osteoporosis include:

- Smoking
- Alcohol abuse
- Excessive caffeine consumption
- Excessive dietary protein consumption
- Lack of dietary calcium
- Lack of sunlight exposure (to generate endogenous vitamin D)

SIGNS AND SYMPTOMS OF OSTEOPOROSIS:

- Back pain
- Decreased height and mobility
- Fractures of the vertebral body, humerus, and upper femur, distal forearm and ribs.
- Pain due to fractures.

DIAGNOSIS

Diagnosis of osteoporosis is made by three methods:

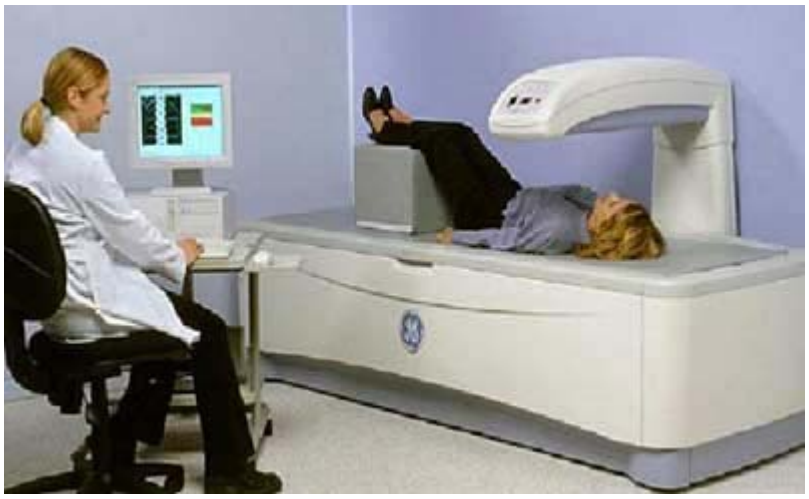
1. Radiographic measurement of bone density
2. Laboratory biochemical markers
3. Bone biopsy with pathologic assessment

Of these three the best is radiographic bone density

BONE MINERAL DENSITY:

Bone mineral density is defined as the amount of calcium and other bone minerals in grams per square centimeter — collectively known as bone mineral content packed into a segment of bone. Mineral content and the density of the bones are directly proportional

Bone mineral density (BMD) test measures the mineral density in the bones using computed tomography (CT scan), or ultrasound.

. 

Bone mass increases in both sexes through the growth stage. After puberty, men develop approximately twice as much bone mass as women, both achieve peak bone mass in the third decade of life. During this time, bone formation and resorption are at equilibrium. Depending on an individual's bone mass at age 25, there is a greater or lesser risk for osteoporosis over time.

Although bone mass declines with age in both men and women, decreases in the production of estrogen at menopause trigger a more rapid rate of bone mass loss in some women. On average, women have less bone mass than men and, after menopause, they lose bone mass at a more rapid rate. Ross et al [10]

The rate of decline in BMD at menopause differs widely among women, exceeding 5 percent per year in some. Such individuals have been called "rapid bone losers." Riggs et al [11]. Since women reach disproportionately low bone mass levels, osteoporosis is predominantly a disease of post menopausal women.

METHODS TO ASSESS BONE MINERAL DENSITY:

Standard X rays: They do not provide an early assessment of fracture risk 30% to 40% of the bone must be lost before radiological changes become apparent**.**

Ultrasonography: This method is effective rapid, painless, and does not use potentially harmful radiation like X-rays and low cost for bone mass assessment. (Gregg et al) [12].

Ultra sound measurements of calcaneum have been reported to be as accurate as femoral neck measurements by DEXA in predicting hip fractures (Nejh CF et al [43]**).** Ultrasound is generally used as an initial screening test. If results from an ultrasound test indicate that bone density is low, DEXA is recommended to confirm the results. One disadvantage of ultrasound is it cannot measure the density of the bones most likely to fracture (the hip and spine) from osteoporosis. Also, ultrasound has limited usefulness (compared to DEXA) for monitoring and comparing the effect of medications used to treat osteoporosis

Single Photon absorptiometry: It uses 125 I as a source of energy more recently by minature X ray tubes. Bone density of radius and calcaneum are measured and

are relatively inexpensive, these measurements correlate with vertebral bone density and predict future fracture risk (Johnston et al [13]).

Dual photon absorptiometry (DPA). DPA uses a radioactive substance to produce radiation. It can measure BMD in hip and spine. DPA also uses very low doses of radiation but has a slower scan time than the other methods.

Quantitative computed tomography (QCT). Quantitative computed tomography (QCT) is a type of CT scan that measures the density of a bone in the spine. A form of QCT called peripheral QCT (pQCT) measures the density of bones in limbs, such as wrist. QCT is not usually recommended because it is expensive, uses higher radiation doses, and is less accurate than DEXA, P-DEXA, or DPA.

Peripheral dual-energy X-ray absorptiometry (P-DEXA). P-DEXA is a modification of the DEXA technique. It measures the density of bones in limbs, such as wrist—it cannot measure the density of the bones most likely to fracture (the hip and spine). If hip or spinal bone density is measured, peripheral measurement is not needed. P-DEXA machines are portable units that can be used in a doctor's office. P-DEXA also uses very low doses of radiation, and the results are faster than conventional DEXA measurements. P-DEXA has limited

usefulness (compared to DEXA) for monitoring the effect of medication used to treat osteoporosis.

QUANTITATIVE COMPUTED TOMOGRAPHY DUAL-ENERGY X-RAY ABSORPTIOMETRY (DEXA).

Dual-energy x-ray absorptiometry (DXA) is considered the gold standard because it is the most extensively validated test against fracture outcomes DEXA uses two different X-ray beams to estimate bone density in spine and hip. .It provides good precision for osteoporotic fractures and the radiation dose is much less than for a standard chest X ray. Scans by Dexa can measure total body calcium lean body mass and fat mass.

DEXA can measure as little as 2% of bone loss per year. It is fast and uses very low doses of radiation but is more expensive than ultrasound testing. The lumbar region from L1 to L4 is specifically very sensitive to the osteoporotic changes due to estrogen deficiency.

Patient Name:	MRS.GRACY	Current Height:	148 cm
Social Security No:		Current Weight:	48 kg
Patient ID:	8617		
Postal Code:		DOB:	1/1/52
Sex:	F	Menopause Age:	
Ethnicity:	I	Age:	54

Referring Physician: DR.S P

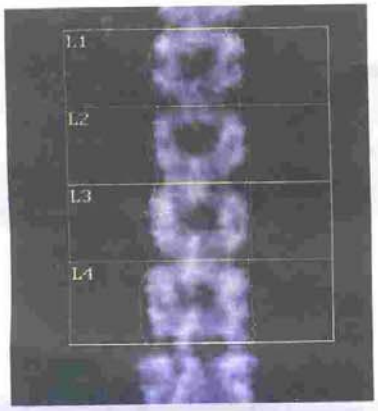


Image not for diagnostic use
Total BMD CV 1.0%

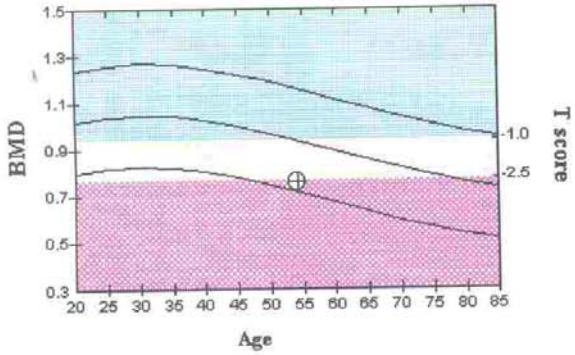
DXA Scan Information:

Scan:	8/7/06 - A0807060A
Scan Mode:	Fast Performance
Analysis:	8/7/06 15:57 - Ver 8.26
Operator:	S.P
Model:	Hologic QDR-4000 (S/N 55504)
Comment:	post menopause

Results Summary:

Total BMD:	**0.758 g/cm²**		
Peak reference:	**72%**	T score:	**-2.6**
Age matched:	**81%**	Z score:	**-1.6**

Region	Area [cm²]	BMC [g]	BMD [g/cm²]	T score	%PR	Z score	%AM
L1	9.00	5.70	0.633	-2.7	68%	-1.8	77%
L2	9.58	6.61	0.690	-3.1	67%	-2.1	75%
L3	10.69	8.48	0.793	-2.6	73%	-1.6	82%
L4	12.68	11.02	0.869	-2.2	78%	-1.2	87%
Total:	41.94	31.80	0.758	-2.6	72%	-1.6	81%



Reference Curve: TK 4 November 91
Age and Sex Matched

Fracture Risk	WHO Classification*
Not Increased	Normal
Increased	Osteopenia
High	Osteoporosis

* WHO 1994

HOLOGIC
V2.0 8/7/06

T Score --- Standard deviations between patient and average peak young adult bone mass. The more negative, the greater the risk of fracture.

Z Score --- Standard deviations between patient and average bone mass for same age and weight. A Z score lower than -2.0 (2.5 % of normal population of same age) requires diagnostic evaluation for causes other than post menopausal bone mass.

DEFINITION BASED ON BONE MINERAL DENSITY (Kanis et al) [14]

NORMAL --- 0 TO -1 S.D from the reference standard (84% of the population)

OSTEOPENIA --- -1 TO -2.5 S.D

OSTEOPOROSIS --- T score less than - 2.5

The clinical relevance of bone density measurement in post menopausal women is estimated by using T score. For younger women is estimated by Z score.

World Health Organization's definitions of osteoporosis based on bone mineral density T-scores.

Bone mineral density	
	T-score
Normal:	2.5 to 1 below the young adult reference range (2.5 to –1)
Low bone mass (osteopenia):	1 to 2.5 SDs below the young adult reference range (–1 to –2.5)
Osteoporosis:	2.5 or more SDs below the young adult reference range (–2.5 or less)
Severe osteoporosis:	2.5 or more SDs below the young adult reference range (–2.5 or less) and the presence of one or more bone fractures

Every change of 1 SD means a twofold increase in the risk of fracture at that site. Decision for clinical treatment is based on lowest T score at particular site rather than the highest average score as this is associated with increased fracture risk

Low BMD values may be caused by other disorders, such as hyperthyroidism, hyperparathyroidism, multiple myeloma, Cushing's syndrome, ankylosing spondylitis, rickets, premature menopause, or a vitamin D deficiency.

Factors that interfere with the accuracy of the results:

- Correct positioning, which is important for an accurate bone mineral density (BMD) measurement.
- Previous bone fracture. This can cause falsely high BMD values.
- Metal objects, such as buttons, buckles, jewelry, or metal implants from hip replacement surgery or hip fracture.
- Barium tests within 14 days of the BMD test.

The DEXA machine sends a thin, invisible beam of low-dose x-rays with two distinct energy peaks through the bones being examined. One peak is absorbed mainly by soft tissue and the other by bone. The soft tissue amount can be subtracted from the total and what remains is a patient's bone mineral density.

The effective radiation dose from this procedure is about 0.01 mSv, despite its effectiveness as a method of measuring bone density, DEXA is of limited use in people with a spinal deformity or those who have had previous spinal surgery. The presence of vertebral compression fractures or osteoarthritis may interfere with the accuracy of the test

DRUGS USED IN OSTEOPOROSIS:

HORMONES: Treatment with conjugated estrogens effectively reduces the osteoporotic fractures but long term estrogen use is necessary to reduce the risk after 75 years.

BISPHOSPHONATES: Bisphosphonates enhance the osteoclast apoptosis and inhibit bone resorption, bind to bone mineral and exert their actions .they are taken half an hour prior to food.

CALCITONIN: It helps in reducing bone resorption; recombinant salmon calcitonin is more potent. In a randomized 5 year trial calcitonin treatment was less effective than estrogen, bisphosphonates and Raloxifene (Chesnut et al) [15].

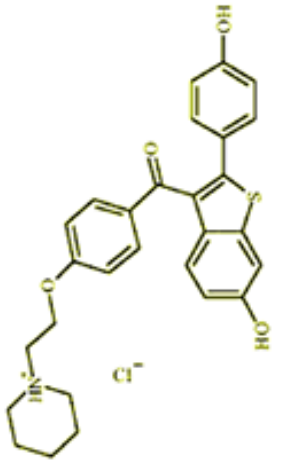
FLOURIDE: It is a potent stimulator of bone formation. Slow release sodium fluoride with calcium reduces the vertebral fracture risk. Treatment is recommended no longer than 4 years due to toxic accumulation of the drug [16]. Pak et al

TIBOLONE: It is structurally related to 19-nor testerone progestins. Prevents bone loss effectively as estrogens. Its ultimate effect on fractures and bone mineral density awaits more clinical trials. Studd et al [17]

TERIPARATIDE: It is a recombinant human amino acid fragment of parathyroid hormone. Given once daily subcutaneous dose improves the bone density (cosman et al). Because of the expense and difficulty in self administration used only in severe osteoporosis.

GROWTH HORMONE: Growth hormone improves the bone density significantly .its expense and the high incidence of unpleasant side effects makes it a poor option**.** (Holloway et al)

RALOXIFENE



SERMS are group of drugs that activate the estrogen receptors, but have different effects on different tissues. Raloxifene is the first of a benzothiophene series of anti-estrogens to be labeled a SERM. (Droloxifine, idoxifene and toremifene are similar SERM agents, but they are still considered experimental.).

It has been studied in placebo-controlled trials with durations up to 8 years.

In December 1997, the U.S. Food and Drug Administration (FDA) labeled Raloxifene for the prevention of osteoporosis.

CHEMISTRY:

Raloxifene hydrochloride (HCl) has the empirical formula $C_{28}H_{27}NO_4S$•HCl, which corresponds to a molecular weight of 510.05 g/mol. Raloxifene HCl is an off-white to pale-yellow solid that is very slightly soluble in water.

Systematic (IUPAC) name [6-hydroxy-2-(4-hydroxyphenyl) - benzothiophen-3-yl] - [4-[2-(1-piperidyl) ethoxy] phenyl] –methanone. $\mathbf{C_{28}H_{27}NO_4S}$

MECHANISM OF ACTION:

SERMs are capable of inducing conformational changes in the estrogen receptor which are of two kinds; they mediate specific pharmacologic activity involving multiple molecular pathways that may result in gene expression of ligand-, tissue- and/or gene-specific receptors. (Mitlak et al) [18] through their unique agonist or antagonist properties.

Raloxifene has the ability to bind to and activate the estrogen receptor alpha more than beta while exhibiting tissue-specific effects distinct from estradiol. (Yang et al) [19]. Some of these will act like estrogen; others will inhibit the actions of

estrogen. (Stabilize bone mass, improve lipid profile, reduce hot flashes) but do not act like estrogen in undesirable ways (cause breast cancer, stimulate the endometrium).

ROUTE OF ADMINISTRATION: Oral.

PHARMACOKINETICS [25]

Raloxifene is rapidly absorbed after oral administration, and its absolute bioavailability is 2 percent. The drug can be administered without regard to foods, consumption of high-fat meals may increase its systemic bioavailability Raloxifene undergoes extensive systemic biotransformation, but it is not metabolised by the cytochrome P450 pathway.

Raloxifene has a plasma elimination half-life of 27 hours. This has attributed to the drug's reversible systemic metabolism and significant enterohepatic cycling. **[20]**

Although Raloxifene and its metabolites are highly bound to plasma proteins (more than 95 percent), Raloxifene does not interact with the binding of other

highly protein-bound drugs. Raloxifene is eliminated primarily in the feces and only negligible amounts appear in the urine.

INDICATION

In the treatment and prevention of osteoporosis in postmenopausal women.

CONTRAINDICATION

- Lactating women or women who are or may become pregnant
- Active or past history of venous thromboembolic events (deep vein thrombosis,
- pulmonary embolism, and retinal vein thrombosis)
- Hypersensitive to Raloxifene.

ADVERSE REACTIONS

Common adverse events to be drug-related are hot flashes (Weerapan et al) [21] and leg cramps.

Raloxifene may infrequently cause serious thrombosis. (Miltak et al) [18]

Effects on Bone

Raloxifene decreased bone turnover markers to levels similar to those found in pre-menopausal women. It increases the mean bone mineral density in the spines, hip and femoral neck.

Effects on Lipids

Raloxifene produces a reduction in total and low-density lipoprotein cholesterol concentrations, but high-density lipoprotein cholesterol and triglyceride concentrations do not increase.(Weerapa et al) [21] and Yang et al [19]

Effects on the Uterus

Raloxifene lacks proliferative effects on endometrial tissue. It has minimal effects on the uterus and causes no significant changes in the histological appearance of the endometrium. (Huster et al) [22]. It neither affects the endometrial thickness nor the uterine volume) Boss et al [23].

VARIOUS STUDIES ON RALOXIFENE

The introduction of Raloxifene for the treatment of postmenopausal osteoporosis has decreased the fracture rates and improved the well being in the postmenopausal group (MORE STUDY)

An estimate of 61 million people in India are reported to be affected by osteoporosis (Joshi VR et al) [24]

The **MORE study** by Ettinger et al [25] shows that three years of Raloxifene treatment preserves bone density, reduces bone turnover, and reduces the rate of vertebral fracture in postmenopausal women with osteoporosis. (CORE). [26]

The **FDA** labeling of Raloxifene for the prevention of osteoporosis in postmenopausal women was originally based on the results of three large randomized, placebo-controlled trials conducted over a 24-month period. (Mitlak et al) [18].

A study conduced by **Pierre Delmas et al** [27] on effects of Raloxifene on Bone Mineral Density, Serum Cholesterol Concentrations, and Uterine Endometrium in Postmenopausal Women, concluded that Raloxifene increases the bone mineral

density, and decreases the total and low density lipoproteins and no effects on uterine endometrium.

A double blinded randomized parallel trial comparing Raloxifene with HRT by **Brian W. Walsh et al** [28] concluded that Raloxifene favorably alters biochemical markers of cardiovascular risk by decreasing LDL-C, fibrinogen, and lipoprotein (a), and by increasing HDL_2-C without raising triglycerides.

A randomized, double-blind, placebo-controlled trial with Raloxifene by **Annie W. C. Kung et al** [29] in postmenopausal Asian women concluded to have beneficial effects in terms of bone mineral density and lipid profile.

A phase II clinical trial conducted by **J. Eng-Wong et al** [30] on Effect of Raloxifene on bone mineral density in pre-menopausal women at increased risk of breast cancer revealed a decrease in the bone mineral density.

Three-year data from 2 double-blind, randomized, placebo-controlled trial by **Johnston CC Jr et al** [31] on Long-term effects of Raloxifene on bone mineral density, bone turnover, and serum lipid levels in early postmenopausal women concluded that Raloxifene preserves BMD at important skeletal sites, lowers

serum low-density lipoprotein cholesterol levels, and has a tolerability profile comparable to placebo. These results indicate a favorable benefit-risk profile of Raloxifene for long-term use in healthy postmenopausal women.

Three-Year Data From 2 Double-blind, Randomized, Placebo-Controlled Trials by **C. Conrad Johnston, et al** [32] on Long-term Effects of Raloxifene on Bone Mineral Density, Bone Turnover, and Serum Lipid Levels in Early Postmenopausal Women shows that Raloxifene preserves BMD in important skeletal sites and has good tolerability profile comparable to placebo.

Effects of Raloxifene on Markers of Bone Turnover in Older Women Living in Long-Term Care Facilities, a clinical intervention by **Helga Hansdóttir et al,** [33] were that Raloxifene reduces bone turnover in elderly women living in long-term care facilities. The effect of Raloxifene on bone turnover was comparable with that seen in younger postmenopausal women.

Draper et al [34] studied the effects of Raloxifene on biochemical markers of bone turnover. In this randomized, double-blind, multicenter trial, authors concluded that Raloxifene appears to exert an estrogen-like positive effect on the markers of bone turnover.

A comparative study by **Christoph A Meier et al** [35] comparing Raloxifene with alendronate (bisphosphonate) shows, Although alendronate has been proven effective in preventing vertebral fractures in women with established osteoporosis, it is cumbersome to ingest (the drug needs to be taken on an empty stomach, and requires remaining in an upright position for 30min) and lacks the cardio protective effects of estrogen. The benefits of Raloxifene (lipid lowering, antiestrogenic action on breast and uterus) beyond its action on bone resorption are very useful.

Meta-Analysis of Raloxifene by **Ann Cranney et al** [36] for the Prevention and Treatment of Postmenopausal Osteoporosis, data shows an increase in bone density, and the effect increases over 2 yr. The data suggest a positive impact of Raloxifene on vertebral fractures with little effect of Raloxifene on no vertebral fractures.

A comparative study by **Robert S. Weinstein** [37] on the Effects of Raloxifene, hormone replacement therapy, and placebo on bone turnover in postmenopausal women supports the hypothesis that Raloxifene preserves bone mass by reducing the elevated bone turnover found in postmenopausal women receiving placebo, by mechanisms similar to those operative in postmenopausal women receiving HRT.

A study conducted on Clinical effects of Raloxifene hydrochloride in women by **Khovidhunkit W et al** [38] Raloxifene has been shown to have beneficial effects in selected organs in postmenopausal women. Although estrogen remains the drug of choice for hormonal therapy in most postmenopausal women, Raloxifene may be an alternative in certain groups of women at risk for osteoporosis.

Liu Jian et al [39] in a randomized controlled study with Chinese population determined a positive effect of Raloxifene on bone mineral density of the hip and a decrease in the biochemical markers of bone metabolism. A decrease in total cholesterol and LDL with no change in HDL and triglycerides.

H mori et al [40] in a study on effects of Raloxifene in Japanese population revealed an increase in lumbar BMD and favourable effects in the biochemical markers of bone turn over and lipid profile. There were no reported thromboembolic events.

Sambrook PN et al [41] in a study on combination therapy of Alendronate and Raloxifene in post menopausal osteoporosis proved to have additive effects on bone mineral density than either treatment alone.

A study conducted by **L J Black et al** [42] on the effects of Raloxifene suggests that it prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats.

AIM OF THE STUDY

The aim of this study was to determine the efficacy of Raloxifene in postmenopausal women by comparing the pretreatment and post treatment bone mineral density levels.

SUBJECT AND METHODS

This was a prospective randomised placebo control study conducted at Govt. Kasthurba Gandhi Hospital, Chennai at the department of Obstetrics and Gynecology. This study comprised of study subject (n=50) postmenopausal women attending gynaec op for other problems from September 2004 to September 2006. The study was approved by the hospital ethical committee. The BMD studies were done at SMS Medica-Chennai osteoporosis detection centre, Nungambakkam Chennai.

INCLUSION CRITERIA:

- Women who attained spontaneous menopause
- The duration of menopause being minimum of two years.
- Not on any drugs like hormone replacement, Vit D, Ca supplementation.
- No history of any vertebral compression fractures
- No history any spinal deformity or spinal surgery.
- No history of osteoarthritis

EXCLUSION CRITERIA:

- Patients with menopausal symptoms.
- Patients with history of postmenopausal bleeding
- Patients on chronic medication.
- Patients who had hysterectomy or premature menopause.
- Patients having active rheumatoid arthritis, gastrointestinal, liver, metabolic, and Neoplastic or endocrinological disease.
- History of recurrent vascular thrombosis
- Family history of any breast or genital malignancies.
- Hyperparathyroidism, Pagets disease, Renal osteodystrophy
- History of treatment with bisphosphonates, sodiumflouride, calcitonin, estroprogestins,
- anabolic steroids, cortcosteroids, Calcium or vitamin D supplementation
- Smokers or alcoholics

METHODS:

The women so selected based on the inclusion and exclusion criteria were explained about the study and consent was obtained. Detailed menstrual, obstetric, drug intake history was taken. Each subject underwent general physical,

systemic abdominal examination. They were randomly assigned to the study and control groups and were subjected to DEXA scan. On the day of scan subjects were asked to eat normally. To avoid calcium supplements for at least 24 hours before the scan.

They were requested to wear loose, comfortable clothing, avoiding garments that have zippers, belts or buttons made of metal and were asked to remove jewelry, eye glasses and any metal objects or clothing that might interfere with the images.

Following DEXA, those assigned to the study group were given 60 mg Raloxifene orally for one year. For the randomly assigned matched control group, similarly shaped inert capsules were given for the same duration.

PROCEDURE:

Scan mode—fast performance

Model—Hologic QDR-4000(S/N 55504)

To assess the spine, the patient's legs are supported on a padded box to flatten the pelvis and lumbar spine.

The detector is slowly passed over the area, generating images on a computer monitor. The patient was asked to hold her breath for a few seconds while the picture is taken to reduce the possibility of a blurred image.

All the women were reviewed monthly to detect any adverse effects, and their adherence to the treatment protocol. The same patients were subjected to DEXA scan at the same site after one year. The patients, who failed to turn up for any visit, were personally traced to their residence and hence there were no drop outs in the study.

The results were recorded in a predesigned proforma and the data were statistically analyzed.

RESULTS

This study, conducted at government Kasturba Gandhi Hospital for Women and Children, Chennai during the period September 2004 to September 2006 compares the efficacy of Raloxifene in post menopausal osteoporosis with that of a placebo. The findings from both the group of patients were correlated in terms of bone mineral density.

50 patients were included in the study and the outcomes were analyzed using various parameters. The results were subjected to statistical analysis using chi-square test, ANOVA, frequency and percentage analysis, T-test, one way tests and group correlations. Many crosstabs were formed from the results to understand various relationships in the results between the control and the placebo group.

Total number of patients selected: 50

Bone mineral density was measured by Dexascan before treatment for 50 patients.

Bone mineral density was measured by Dexascan after treatment for 50 patients

Group I – Study group n= 25

Group II –Control group n= 25

Characteristics of the group.

Table I – Age Distribution n=50

S.No	Age in years	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	46-50	6	24	3	12	9	18
2	50 to 59	13	52	18	72	31	62
3	60and above	6	24	4	16	10	20
	Total	25	100	25	100	50	100

- Majority of patients belong to the age group 50 to 60 years (62%) and the youngest was 46 years and the oldest one 70 years old.
- 18 % of the patients were less than 50 years.
- 20 % of the patients were more than 60 years.

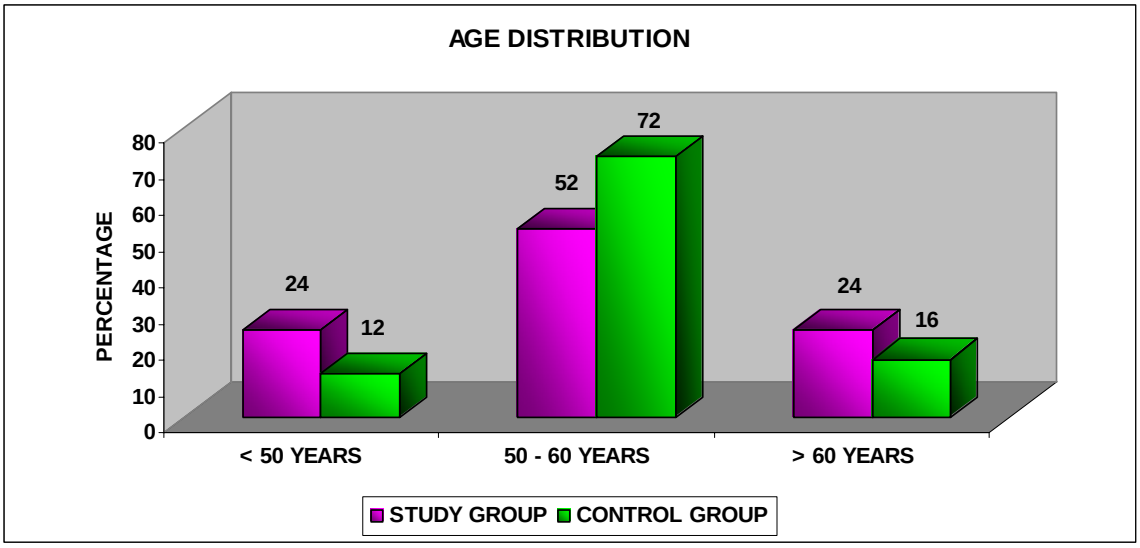


Table II – Distribution of Parity n=50

S.No	Parity	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	1	1	4	1	4	2	4
2	2	11	44	10	40	21	42
3	3	5	20	7	28	12	24
4	4	5	20	5	20	10	20
5	5	3	12	2	8	5	10
	Total	25	100	25	100	50	100

- Majority belonged to the parity class 2 (42%). Primipara were the least in the study.

- 24 % belonged to parity 3 and 20 % to parity 4
- Though there is no established relationship between parity and postmenopausal osteoporosis, this is an observation during the study.

Table III – Socio Economic Status n=50

S.No	Socio-Economic Status	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	IV	5	20	5	20	10	20
2	V	20	80	20	80	40	80
	Total	25	100	25	100	50	100

- 20% of the women were from class IV socioeconomic group
- 80% the majority lot belonged to class V socioeconomic group.
- Most of the women were from the economically weaker sections of the society as our hospital caters essentially to the BPL population.

Table IV – BODY MASS INDEX n=50

S.No	BMI	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	Normal	17	68	10	40	27	54
2	Overweight	4	16	7	28	11	22
3	Obese	4	16	8	32	12	24
	Total	25	100	25	100	50	100

- Using WHO standards for BMI, more than half the study sample belonged to the normal limits of BMI (54%)
- 22% of the cases belonged to the overweight category
- 24% of the cases belonged to the obese category.

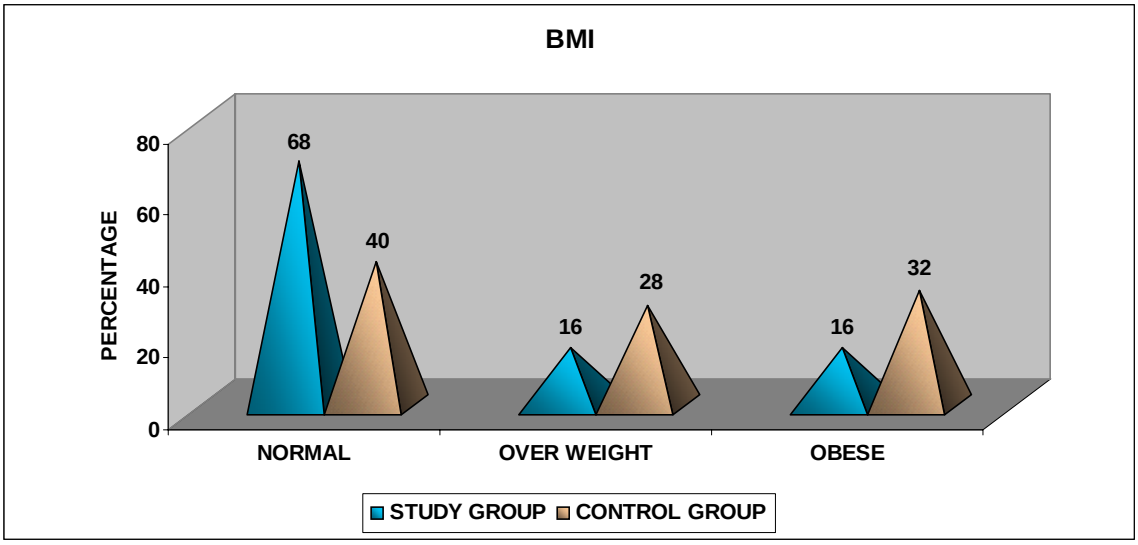


Table V – Years since menopause n=50

S.No	Years since menopause	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	2 to 5 years	12	48	13	52	25	50
2	6 to 10 years	3	12	5	20	8	16
3	11 to 15 years	8	32	4	16	12	24
3	> 15 years	2	8	3	12	5	10
	Total	25	100	25	100	50	100

- 50% of the cases belonged to a shorter duration of menopause of 2 to 5 years.
- 24 % of the cases belonged to a menopause duration of 11 to 15 years
- 16% of the cases belonged to a duration of 6 to10 years
- Only 10% belonged to more than 15 years duration.

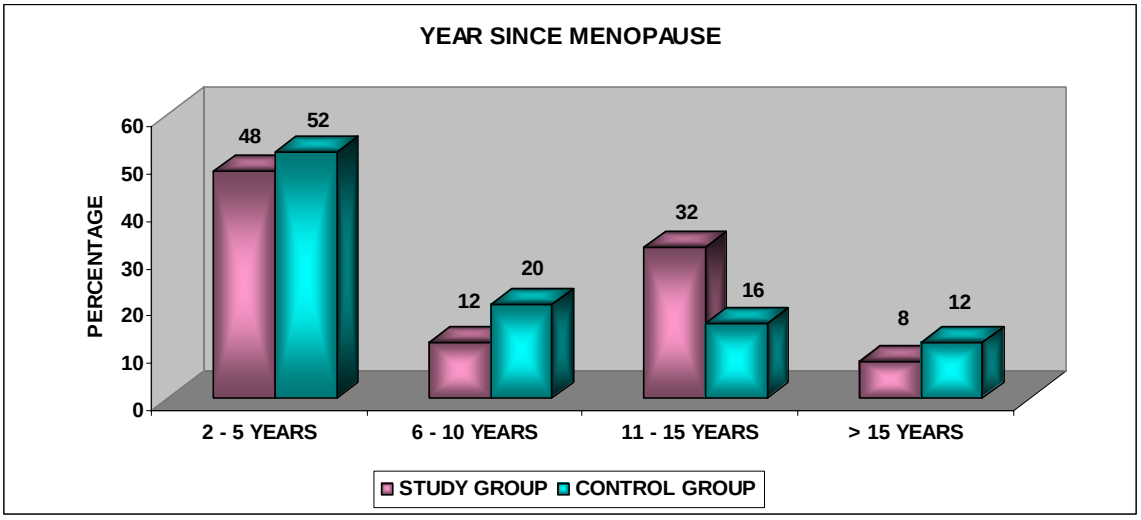


Table VI – Type of menopause n=50

S.No	Type of menopause	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	Abrupt	12	48	14	56	26	52
2	Gradual	13	52	11	44	24	48
	Total	25	100	25	100	50	100

- The Abrupt and Gradual types of menopause are almost equally distributed in the sample
- 52 % of the cases belonged to the abrupt variety.
- 48 % of the cases belonged to the gradual variety.

Table VII – Adverse Effects n=50

S.No	Adverse Effects	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	Hot Flashes	1	4	--	--	1	4
2	Influenza Syndrome	--	--	--	--	--	--
3	Leg Cramps	1	4	--	--	1	4
4	Peripheral edema	--	--	--	--	--	--
5	Thrombosis/phlebitis	--	--	--	--	--	--
6	No adverse effects	23	92	25	100	48	92
	Total	25	100	25	100	50	100

- Majority of the patients did not have any complaints except for hot flushes and leg cramps which did not affect the continuation of the drug. There was no episodes of influenza like syndrome, peripheral edema and thrombosis.

- Through out the study Raloxifene did not cause any vaginal bleeding nor breast tenderness.
- There was no adverse effects reported in the placebo group

Table VIII: T value for study and control group

S.No	T value	Group I		Group II		Total	
		No. of cases	%	No. of cases	%	No. of cases	%
1	-2.5 to -2.9	12	48	14	56	26	52
2	-3 to -3.5	13	52	11	44	24	48
		25	100	25	100	50	100

52 % of the patients had T value between -2.5 to-2.9

48 % of the patients had T value between -3 to -3.5

Similar ranges of T value were equally distributed in the study and control group.

Table IX – Study Group-Lumbar spine BMD (pre and post-treatment) n=50

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	< 50	6	.64800	7.1878E-02	2.93E-02	.57257	.72343	.565	.747
	50 - 60	13	.66085	8.2970E-02	2.30E-02	.61071	.71098	.533	.793
	> 60	6	.65400	6.8399E-02	2.79E-02	.58222	.72578	.569	.774
	Total	25	.65612	7.4315E-02	1.49E-02	.62544	.68680	.533	.793
BMD - Post Treatment	< 50	6	.65000	7.2139E-02	2.95E-02	.57430	.72570	.567	.749
	50 - 60	13	.66323	8.2472E-02	2.29E-02	.61339	.71307	.536	.795
	> 60	6	.65617	6.8590E-02	2.80E-02	.58419	.72815	.570	.776
	Total	25	.65836	7.4139E-02	1.48E-02	.62776	.68896	.536	.795

There is a significant increase in the bone mineral density in the study group comparing the pre BMD and the post BMD levels in the lumbar spine which is statistically significant.($p<0.05$)

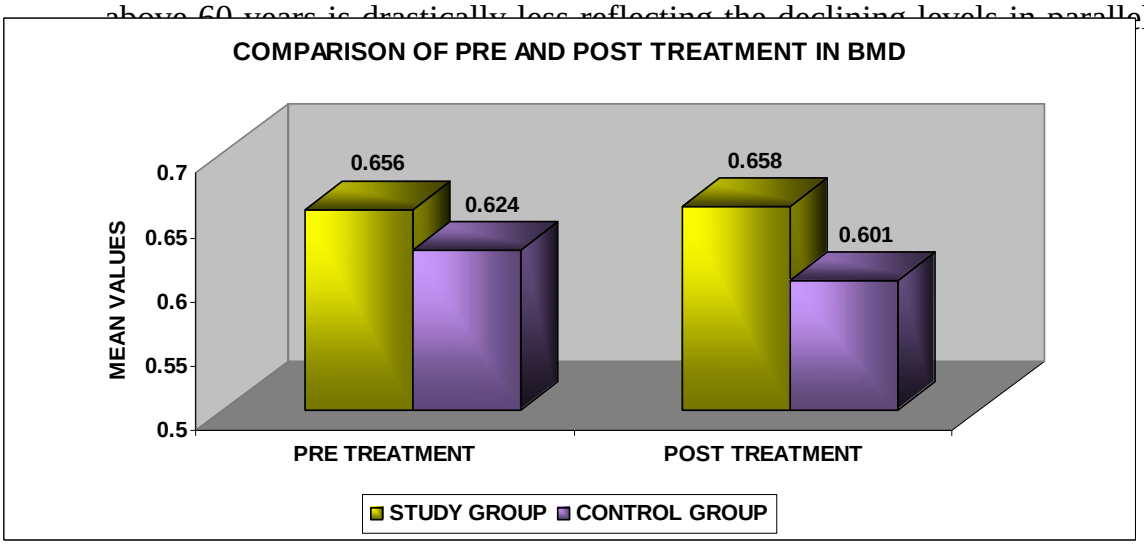
The increase is about 3.6 % which is comparable with the randomized clinical trials conducted by Ettinger et al(11) in a three year randomized control study of 6828 women, shows that compared to placebo Raloxifene increased the bone mineral density by 2.6% ,Pierre Delmas et al (37) and Annie W. C.Kung et al (42).

Table X – Control Group BMD pre and post-treatment n=50

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	< 50	3	.62667	5.9652E-02	3.44E-02	.47848	.77485	.560	.675
	50 - 60	18	.62650	7.5556E-02	1.78E-02	.58893	.66407	.522	.768
	> 60	4	.61475	.11538	5.77E-02	.43115	.79835	.508	.719
	Total	25	.62464	7.7613E-02	1.55E-02	.59260	.65668	.508	.768
BMD - Post Treatment	< 50	3	.61700	6.1539E-02	3.55E-02	.46413	.76987	.550	.671
	50 - 60	18	.62306	.10762	2.54E-02	.56954	.67657	.460	.920
	> 60	4	.49325	8.3192E-02	4.16E-02	.36087	.62563	.380	.580
	Total	25	.60156	.10824	2.16E-02	.55688	.64624	.380	.920

- The pretreatment BMD levels in both study and control group were almost in the similar range whereas, the post treatment BMD levels among the study and control groups varied significantly.
- The pre treatment BMD levels in the study as well as the control group above 60 years is drastically less reflecting the declining levels in parallel



STATISTICAL CALCULATIONS

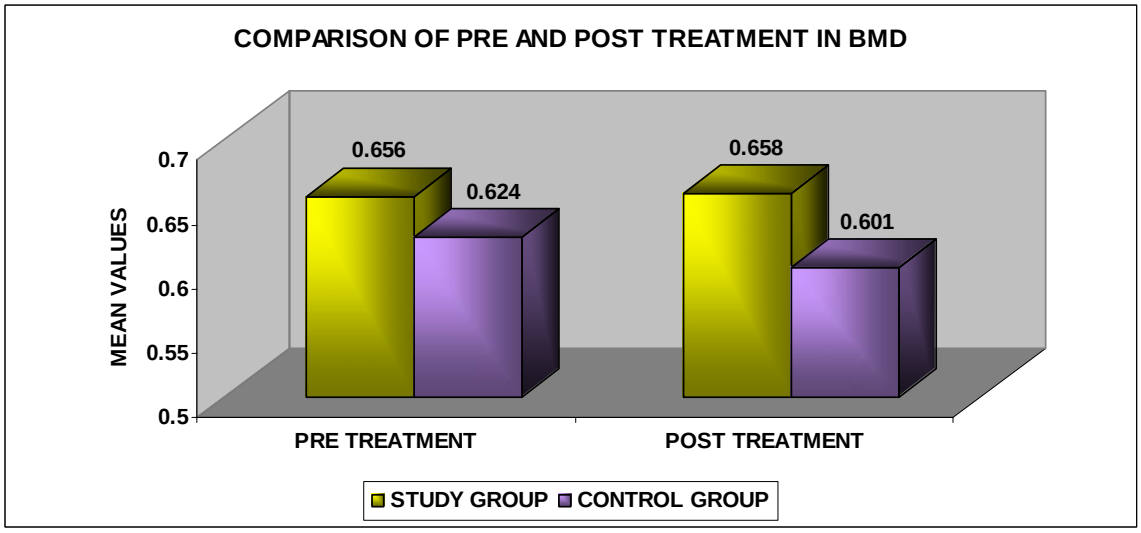
Study Group Oneway - Comparison between pretreatment and post treatment BMD

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	< 50	6	.64800	7.1878E-02	2.93E-02	.57257	.72343	.565	.747
	50 - 60	13	.66085	8.2970E-02	2.30E-02	.61071	.71098	.533	.793
	> 60	6	.65400	6.8399E-02	2.79E-02	.58222	.72578	.569	.774
	Total	25	.65612	7.4315E-02	1.49E-02	.62544	.68680	.533	.793
BMD - Post Treatment	< 50	6	.65000	7.2139E-02	2.95E-02	.57430	.72570	.567	.749
	50 - 60	13	.66323	8.2472E-02	2.29E-02	.61339	.71307	.536	.795
	> 60	6	.65617	6.8590E-02	2.80E-02	.58419	.72815	.570	.776
	Total	25	.65836	7.4139E-02	1.48E-02	.62776	.68896	.536	.795

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
BMD - Pre Treatment	Between Groups	7.129E-04	2	3.565E-04	.059	.942
	Within Groups	.132	22	5.992E-03		
	Total	.133	24			
BMD - Post Treatment	Between Groups	7.566E-04	2	3.783E-04	.063	.939
	Within Groups	.131	22	5.962E-03		
	Total	.132	24			



Control Group Oneway - Comparison between pretreatment and post treatment BMD

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	< 50	3	.62667	5.9652E-02	3.44E-02	.47848	.77485	.560	.675
	50 - 60	18	.62650	7.5556E-02	1.78E-02	.58893	.66407	.522	.768
	> 60	4	.61475	.11538	5.77E-02	.43115	.79835	.508	.719
	Total	25	.62464	7.7613E-02	1.55E-02	.59260	.65668	.508	.768
BMD - Post Treatment	< 50	3	.61700	6.1539E-02	3.55E-02	.46413	.76987	.550	.671
	50 - 60	18	.62306	.10762	2.54E-02	.56954	.67657	.460	.920
	> 60	4	.49325	8.3192E-02	4.16E-02	.36087	.62563	.380	.580
	Total	25	.60156	.10824	2.16E-02	.55688	.64624	.380	.920

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
BMD - Pre Treatment	Between Groups	4.658E-04	2	2.329E-04	.036	.965
	Within Groups	.144	22	6.550E-03		
	Total	.145	24			
BMD - Post Treatment	Between Groups	5.596E-02	2	2.798E-02	2.733	.087
	Within Groups	.225	22	1.024E-02		
	Total	.281	24			

- There is no significant difference between the study group and control group in the pre treatment BMD levels at $P > 0.05$
- The mean value of the study group is more than the control group but statistically not significant.
- There is a significant difference between study group and control group post treatment BMD levels at $P < 0.05$
- There is a significant difference between pretreatment and post treatment BMD in study group at $P<0.001$
- Gradual decrease in comparing the pretreatment and post treatment BMD levels in the control group which is not statistically significant at $P>0.05$

Table XI

Study Group T-Test Correlation between socioeconomic status and BMD

Group Statistics

	Socio Economic status	N	Mean	Std. Deviation	Std. Error Mean
BMD - Pre Treatment	IV	5	.65925	.10031	4.49E-02
	V	20	.64360	6.9328E-02	1.55E-02
BMD - Post Treatment	IV	5	.66150	.10074	4.51E-02
	V	20	.64580	6.8953E-02	1.54E-02

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BMD - Pre Treatment	Equal variances assumed	1.904	.181	-.414	23	.683	-1.565E-02	3.7816E-02	-9.4E-02	6.26E-02
	Equal variances not assumed			-.330	4.997	.755	-1.565E-02	4.7461E-02	-.13767	.10637
BMD - Post Treatmer	Equal variances assumed	2.072	.163	-.416	23	.681	-1.570E-02	3.7725E-02	-9.4E-02	6.23E-02
	Equal variances not assumed			-.330	4.977	.755	-1.570E-02	4.7619E-02	-.13828	.10688

Control Group T-Test- Test Correlation between socioeconomic status and BMD

Group Statistics

	Socio Economic status	N	Mean	Std. Deviation	Std. Error Mean
BMD - Pre Treatment	IV	5	.63470	7.4584E-02	3.34E-02
	V	20	.58440	7.6845E-02	1.72E-02
BMD - Post Treatment	IV	5	.60275	.20027	8.96E-02
	V	20	.59680	7.9675E-02	1.78E-02

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BMD - Pre Treatment	Equal variances assumed	.068	.796	-1.316	23	.201	-5.030E-02	3.8228E-02	-.12938	2.88E-02
	Equal variances not assumed			-1.341	6.311	.226	-5.030E-02	3.7521E-02	-.14102	4.04E-02
BMD - Post Treatment	Equal variances assumed	4.752	.040	-.108	23	.915	-5.950E-03	5.5270E-02	-.12028	.10838
	Equal variances not assumed			-.065	4.321	.951	-5.950E-03	9.1317E-02	-.25222	.24032

- The BMD values of the patients belonging to class IV socioeconomic status were better than those belonging to class V, an observation made during the study reflecting the nutritional values influencing osteoporosis. But was not statistically significant.

Table XII
Study Group Oneway-Correlation between Parity and BMD

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	1	1	.62400	.	.	.	.	.624	.624
	2	11	.65018	6.5701E-02	1.98E-02	.60604	.69432	.565	.774
	3	5	.67680	8.1232E-02	3.63E-02	.57594	.77766	.542	.747
	4	5	.67340	.10276	4.60E-02	.54580	.80100	.569	.793
	5	3	.62533	8.0152E-02	4.63E-02	.42622	.82444	.533	.677
	Total	25	.65612	7.4315E-02	1.49E-02	.62544	.68680	.533	.793
BMD - Post Treatment	1	1	.62800	.	.	.	.	.628	.628
	2	11	.65236	6.5852E-02	1.99E-02	.60812	.69660	.567	.776
	3	5	.67940	8.0721E-02	3.61E-02	.57917	.77963	.546	.749
	4	5	.67500	.10257	4.59E-02	.54764	.80236	.570	.795
	5	3	.62767	7.9576E-02	4.59E-02	.42999	.82534	.536	.679
	Total	25	.65836	7.4139E-02	1.48E-02	.62776	.68896	.536	.795

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
BMD - Pre Treatment	Between Groups	7.894E-03	4	1.974E-03	.317	.863
	Within Groups	.125	20	6.233E-03		
	Total	.133	24			
BMD - Post Treatment	Between Groups	7.741E-03	4	1.935E-03	.312	.867
	Within Groups	.124	20	6.209E-03		
	Total	.132	24			

Control Group Oneway- Correlation between Parity and BMD

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	1	1	.58400	.	.	.	.	.584	.584
	2	10	.64500	8.5028E-02	2.69E-02	.56857	.69023	.508	.768
	3	7	.61086	8.2372E-02	3.11E-02	.53468	.68704	.522	.719
	4	5	.63440	5.7138E-02	2.56E-02	.56345	.70535	.585	.714
	5	2	.62940	.14566	.10300	-.66374	1.95374	.542	.748
	Total	25	.62464	7.7613E-02	1.55E-02	.59260	.65668	.508	.768
BMD - Post Treatment	1	1	.56400	.	.	.	.	.564	.564
	2	10	.63520	.12646	4.00E-02	.55474	.73566	.501	.920
	3	7	.52314	8.4531E-02	3.19E-02	.44496	.60132	.380	.630
	4	5	.62120	5.1222E-02	2.29E-02	.55760	.68480	.566	.680
	5	2	.62750	.13081	9.25E-02	-.54782	1.80282	.535	.720
	Total	25	.60156	.10824	2.16E-02	.55688	.64624	.380	.920

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
BMD - Pre Treatment	Between Groups	4.513E-03	4	1.128E-03	.161	.956
	Within Groups	.140	20	7.003E-03		
	Total	.145	24			
BMD - Post Treatment	Between Groups	6.677E-02	4	1.669E-02	1.557	.224
	Within Groups	.214	20	1.072E-02		
	Total	.281	24			

There is a decrease in the BMD values as the parity increases from 2 there is no statistical significance as a large sample size is required to provide a relation.

Table XIII
Study Group Oneway-correlation between BMI and BMD

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	Normal	17	.64676	7.1862E-02	1.74E-02	.60982	.68371	.533	.774
	Over weight	4	.63050	6.4470E-02	3.22E-02	.52791	.73309	.574	.720
	Obese	4	.72150	7.3569E-02	3.68E-02	.60444	.83856	.623	.793
	Total	25	.65612	7.4315E-02	1.49E-02	.62544	.68680	.533	.793
BMD - Post Treatment	Normal	17	.64894	7.1714E-02	1.74E-02	.61207	.68581	.536	.776
	Over weight	4	.63350	6.4923E-02	3.25E-02	.53019	.73681	.577	.724
	Obese	4	.72325	7.3405E-02	3.67E-02	.60645	.84005	.625	.795
	Total	25	.65836	7.4139E-02	1.48E-02	.62776	.68896	.536	.795

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
BMD - Pre Treatment	Between Groups	2.121E-02	2	1.061E-02	2.096	.147
	Within Groups	.111	22	5.061E-03		
	Total	.133	24			
BMD - Post Treatment	Between Groups	2.082E-02	2	1.041E-02	2.062	.151
	Within Groups	.111	22	5.050E-03		
	Total	.132	24			

Control Group Oneway- correlation between BMI and BMD

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BMD - Pre Treatment	Normal	10	.61530	7.6639E-02	2.42E-02	.56048	.67012	.522	.768
	Over weight	7	.63929	9.4782E-02	3.58E-02	.55163	.72694	.522	.748
	Obese	8	.62350	7.1136E-02	2.52E-02	.56403	.68297	.508	.710
	Total	25	.62464	7.7613E-02	1.55E-02	.59260	.65668	.508	.768
BMD - Post Treatment	Normal	10	.59000	9.9387E-02	3.14E-02	.51890	.66110	.380	.760
	Over weight	7	.60043	9.2675E-02	3.50E-02	.51472	.68614	.512	.740
	Obese	8	.61700	.14015	4.96E-02	.49983	.73417	.460	.920
	Total	25	.60156	.10824	2.16E-02	.55688	.64624	.380	.920

ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
BMD - Pre Treatment	Between Groups	2.384E-03	2	1.192E-03	.184	.833
	Within Groups	.142	22	6.463E-03		
	Total	.145	24			
BMD - Post Treatment	Between Groups	3.252E-03	2	1.626E-03	.129	.880
	Within Groups	.278	22	1.263E-02		
	Total	.281	24			

There is no significant difference between the study and control group at P>0.05

Table XIV

Study Group T-Test correlation between type of menopause and BMD

Group Statistics

	Type of Menopause	N	Mean	Std. Deviation	Std. Error Mean
BMD - Pre Treatment	Gradual	12	.64375	7.4845E-02	2.16E-02
	Abrupt	13	.66754	7.4941E-02	2.08E-02
BMD - Post Treatment	Gradual	12	.64592	7.4813E-02	2.16E-02
	Abrupt	13	.66985	7.4599E-02	2.07E-02

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BMD - Pre Treatment	Equal variances assumed	.117	.735	-.793	23	.436	-2.379E-02	2.9982E-02	-8.6E-02	3.82E-02
	Equal variances not assumed			-.793	22.845	.436	-2.379E-02	2.9980E-02	-8.6E-02	3.83E-02
BMD - Post Treatment	Equal variances assumed	.105	.749	-.800	23	.432	-2.393E-02	2.9904E-02	-8.6E-02	3.79E-02
	Equal variances not assumed			-.800	22.829	.432	-2.393E-02	2.9908E-02	-8.6E-02	3.80E-02

Control Group T-Test correlation between type of menopause and BMD

Group Statistics

	Type of Menopause	N	Mean	Std. Deviation	Std. Error Mean
BMD - Pre Treatment	Gradual	14	.64479	8.6137E-02	2.30E-02
	Abrupt	11	.59900	5.9331E-02	1.79E-02
BMD - Post Treatment	Gradual	14	.59336	.10731	2.87E-02
	Abrupt	11	.61200	.11373	3.43E-02

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
BMD - Pre Treatment	Equal variances assumed	4.720	.040	1.502	23	.147	4.5786E-02	3.0484E-02	-1.7E-02	.10885
	Equal variances not assumed			1.570	22.686	.130	4.5786E-02	2.9155E-02	-1.5E-02	.10614
BMD - Post Treatment	Equal variances assumed	.115	.738	-.420	23	.678	-1.864E-02	4.4379E-02	-.11045	7.32E-02
	Equal variances not assumed			-.417	20.985	.681	-1.864E-02	4.4703E-02	-.11161	7.43E-02

There is no significant association between the type of menopause and BMD in the study and control group.

Table XV

Study Group Correlations between years since menopause and BMD

Descriptive Statistics

	Mean	Std. Deviation	N
Years Since Menopause	7.92	5.53	25
BMD - Pre Treatment	.65612	7.4315E-02	25
BMD - Post Treatment	.65836	7.4139E-02	25

Correlations

		Years Since Menopause	BMD - Pre Treatment	BMD - Post Treatment
Years Since Menopause	Pearson Correlation	1.000	.026	.029
	Sig. (2-tailed)	.	.901	.891
	N	25	25	25
BMD - Pre Treatment	Pearson Correlation	.026	1.000	1.000**
	Sig. (2-tailed)	.901	.	.000
	N	25	25	25
BMD - Post Treatment	Pearson Correlation	.029	1.000**	1.000
	Sig. (2-tailed)	.891	.000	.
	N	25	25	25

**. Correlation is significant at the 0.01 level (2-tailed).

Control Group Correlations between years since menopause and BMD

Descriptive Statistics

	Mean	Std. Deviation	N
Years Since Menopause	7.36	5.30	25
BMD - Pre Treatment	.62464	7.7613E-02	25
BMD - Post Treatment	.60156	.10824	25

Correlations

		Years Since Menopause	BMD - Pre Treatment	BMD - Post Treatment
Years Since Menopause	Pearson Correlation	1.000	.173	-.346
	Sig. (2-tailed)	.	.407	.090
	N	25	25	25
BMD - Pre Treatment	Pearson Correlation	.173	1.000	.728**
	Sig. (2-tailed)	.407	.	.000
	N	25	25	25
BMD - Post Treatment	Pearson Correlation	-.346	.728**	1.000
	Sig. (2-tailed)	.090	.000	.
	N	25	25	25

**. Correlation is significant at the 0.01 level (2-tailed).

There is a significant correlation between the years since menopause and BMD. As the duration of menopause increases the pre treatment BMD decreases at P <0.01

DISCUSSION:

This prospective, descriptive, comparative study analyzing the role of Raloxifene in post menopausal osteoporosis by giving 60mg tablet once daily for 6 months with Dexascan in assessing the bone mineral density in 50 patients has shown

Table I

- Majority of patients in the study group belonged to the age group 50 to 59 years (62%) and the youngest was 46 years and the oldest one 70 years old.

Table II

- Patients were selected irrespective of the parity but majority of the study group belonged to the parity class 2 (44%). Primipara were the least in the study.

Table III

- The majority of the study sample belonged to the socioeconomic class V (80%)

Table IV

- Using WHO standards for BMI, more than half the study sample belonged to the normal limits of BMI (68%)

Table V

In most of the women (48%) the duration of menopause was 2-5 years.

Table VI

- The abrupt and gradual types of menopause are almost equally distributed in the sample. Gradual being 52 % in the study sample.

Table VII

- Majority of the patients did not have any complaints except for hot flushes and leg cramps which did not affect the continuation of the drug. There were no episodes of influenza like syndrome or peripheral edema.

Table VIII

The T values of the study group belonged mostly to the range of -3 to -3.5 in the study group

Table IX & X

- The pretreatment BMD levels in both study and control group were almost in the similar range whereas, the post treatment BMD levels among the study and control groups varied significantly. (p value <0.05).
- There was an improvement of 3.6 % of BMD in the spine.

- There is significant correlation between the duration of menopause and pre treatment BMD at P<0.01 revealing that as duration of menopause increases the BMD decreases.

- There were no dropouts in this study. There is a significant increase in the bone mineral density in the study group comparing the pretreatment BMD and the post treatment BMD levels in the lumbar spine which is statistically significant. (p<0.05)

- The increase is about 3.6 % which is comparable with the randomized clinical trials conducted by Ettinger et al [25]. In a three year randomized control study of 6828 women Raloxifene increased the bone mineral density by 2.6% . Pierre Delmas et al [27] and Annie W. C.Kung et al [29].

Table XI

- The BMD values of the patients in the study group belonging to class IV socioeconomic status were better than those belonging to class V, an observation made during the study reflecting the nutritional values influencing osteoporosis.

- But was not statistically significant at P>0.05

Table XII

- There is a decrease in the BMD values in the study and control group as the parity increases from 2. There is no statistical significance as a large sample size is required to provide a relation.

Table XIII

- There is no significant association between the BMI and BMD in both groups at $P>0.05$

Table XIV

- There is no significant association between the type of menopause and BMD in the study and control group.

Table XV

- There is a significant correlation between the years since menopause and BMD in both the study and control group. As the duration of menopause increases the pre treatment BMD decreases at $P <0.01$ as comparable to the study conducted by Sabatier J P et al [9]

CONCLUSION

- Using Raloxifene in the post menopausal group on an outpatient basis is a relatively safe and simple treatment with no major adverse effects in improving the bone mineral density in the spine and hip joint.
- Raloxifene reduces the incidence of vertebral fractures and reducing the long term morbidity and mortality in postmenopausal women.
- Raloxifene has no risk of endometrial changes and breast cancer, breast tenderness (compared to estrogens) and no major side effect profile. The compliance is good ,
- As the risk of osteoporosis increases with increasing duration of menopause, Raloxifene should be initiated as soon as menopause sets in so that the morbidity in the rapid losers can be prevented.
- In a country where follow up advice is not properly complied with, e Raloxifene can be safely administered and made available in every pharmacy.

So in countries like India where the resources are limited, patients must be made aware of the postmenopausal osteoporosis and treated effectively so health care costs could reduce.

MASTER CHART-STUDY GROUP

S No	NAME	IP NUMBER	AGE	Socio Economic	PARITY	BMI	Years since menopause	Type of menopause	BMD (Pre treatment)	BMD (post treatment)	ADVERSE EFFECTS
1	Rani	5605	52	V	4	27.2	6	Gradual	0.793	0.795	--
2	Muniama	4614	53	V	2	21.5	4	Abrupt	0.690	0.692	--
3	Basheera	4823	60	IV	3	24.6	15	Abrupt	0.720	0.724	--
4	Lakshmi	3478	57	V	3	22.9	11	Abrupt	0.663	0.664	HF[1]
5	Nithya	6726	65	V	4	21.2	12	Abrupt	0.569	0.570	--
6	Rajam	3569	49	V	5	20.8	3	Gradual	0.666	0.668	--
7	Revathy	5472	48	V	2	21.7	4	Abrupt	0.707	0.709	--
8	Nasreen	6120	63	IV	2	21	11	Abrupt	0.774	0.776	--
9	Seetha	5558	54	IV	2	18.7	7	Gradual	0.612	0.614	--
10	Janaki	6769	48	V	1	21.8	3	Abrupt	0.624	0.628	--
11	Ganga	5467	47	V	2	21.4	2	Gradual	0.565	0.567	--
12	Kanaga	2331	52	V	3	21.8	3	Abrupt	0.542	0.546	--
13	Shenbaga	2865	56	V	4	28.2	2	Abrupt	0.758	0.759	--
14	Sathya	5298	62	V	2	32.1	12	Abrupt	0.623	0.625	--
15	Kasthoori	6473	49	V	3	21.4	4	Gradual	0.747	0.749	--
16	sarada	6834	48	IV	2	19.7	2	Gradual	0.579	0.579	--
17	Hema	3668	52	V	2	22.3	2	Abrupt	0.722	0.724	--
18	Kokilavani	4857	59	V	3	26.7	12	Abrupt	0.712	0.714	--
19	Sundari	5125	64	V	4	22	15	Gradual	0.673	0.674	--
20	Kalpana	6648	68	V	2	23.3	20	Gradual	0.633	0.635	--
21	Sindhu	8654	70	V	2	21.7	18	Gradual	0.652	0.657	--
22	Mythili	3445	55	V	4	23.8	3	Abrupt	0.574	0.577	--
23	Rupa	7653	59	IV	5	20.9	12	Gradual	0.533	0.536	--
24	Rangnaygi	7154	57	V	5	21.9	10	Gradual	0.677	0.679	--
25	Vijaya	6990	52	V	4	27.2	6	Gradual	0.793	0.795	--

MASTER CHART-CONTROL GROUP

S No	NAME	IP NUMBER	AGE	Socio Economic	PARITY	BMI	Years since menopause	Type of menopause	T SCORE (Pre treatment)	T SCORE (post treatment)	ADVERSE EFFECTS
26	Kalaivani	4372	59	V	2	23.2	5	Gradual	0.595	0.598	--
27	Vimala	4834	50	V	2	25.4	5	Abrupt	0.633	0.622	--
28	Noor	4370	53	V	1	19.2	7	Abrupt	0.584	0.564	--
29	Kuppamma	7465	55	V	2	23.3	8	Abrupt	0.565	0.560	--
30	Fatima	7635	68	V	3	24.9	22	Gradual	0.719	0.512	--
31	Shankari	2784	55	V	4	24.3	7	Gradual	0.585	0.566	--
32	Dhana	5331	46	V	3	22.2	2	Gradual	0.645	0.630	--
33	Dharani	6352	51	V	2	21.8	4	Gradual	0.768	0.761	--
34	Vindhya	3449	59	V	5	23.2	11	Gradual	0.748	0.721	--
35	Sowmya	7479	58	V	2	24.1	9	Gradual	0.745	0.740	--
36	Pappy	6000	52	V	5	21.1	2	Gradual	0.542	0.535	--
37	Indra	4320	60	V	4	22.1	12	Gradual	0.714	0.680	--
38	Suganya	7832	50	IV	3	24.1	4	Abrupt	0.522	0.517	--
39	Kannagi	7366	54	IV	2	26	4	Abrupt	0.696	0.920	--
40	Sunitha	6583	64	V	2	29.1	14	Abrupt	0.508	0.501	--
41	Hema	5981	48	V	4	31.4	2	Abrupt	0.675	0.671	LC2
42	Komadha	6732	59	V	4	19.8	6	Gradual	0.607	0.601	--
43	Ponnama	6274	52	V	2	26.7	4	Gradual	0.564	0.560	--
44	Leela	8523	50	IV	2	20.8	2	Abrupt	0.622	0.617	--
45	Vinodhini	6007	50	V	2	25.4	5	Abrupt	0.633	0.622	--
46	Akila	4868	65	V	3	25.6	16	Gradual	0.71	0.581	--
47	Amsa	8845	49	IV	2	21.9	3	Abrupt	0.56	0.550	--
48	Sabitha	6219	59	V	3	25.6	11	Gradual	0.569	0.461	--
49	Nagamma	8738	55	V	3	22.4	4	Gradual	0.589	0.583	--
50	Maragadha	4748	70	IV	3	21	16	Gradual	0.522	0.381	--

1 to 25=Study Group; 26 to 50 =Control Group; *HF^1 – Hot Flushes; LC^2 – Leg Cramps; S^3 – Sedentary; A^4 – Active*

PROFORMA:

Name:		Age:	IP No:
Occupation:			
Socioeconomic status:			
Address:			
Menopausal status:			
Menstrual History:			
Type of menopause:			
Yearssince menopause:			
Marital History:			
Age at marriage:			
Obstetric history:			
No. of Children:			
Type of delivery:			
Last child birth:			
Past History:			
Bone disorder history:			
General Examination:	BMI -	Ht -	Wt -
Abdominal examination:			
Speculum examination:			
Per-Vaginal examination:			

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