Ugis Gruntmanis, M.D.
Internal Medicine Grand Rounds
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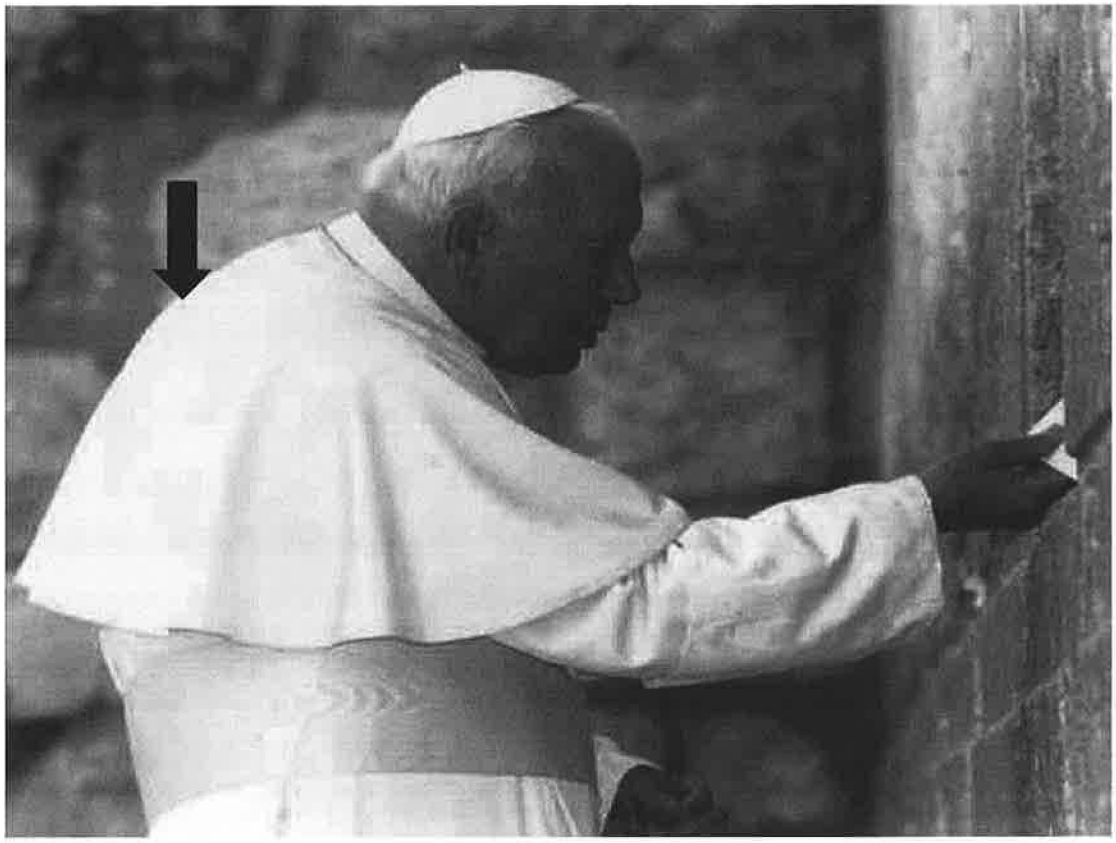
Male Osteoporosis: Deadly, But Ignored



This is to acknowledge that Ugis Gruntmanis, M.D. has disclosed financial interests or other relationship with commercial concerns related directly or indirectly to this program. Dr.Gruntmanis will be discussing off-label uses in this presentation.

Ugis Gruntmanis, M.D.
Assistant Professor of Medicine
Endocrinology Division
UT Southwestern Medical Center
Director, Endocrinology and Osteoporosis Clinics
Dallas VA Medical Center

Interests: Male osteoporosis, role of sex hormones in male osteoporosis and renal osteodistrophy, treatment of male osteoporosis and hypogonadism.

Objectives

1. Learn epidemiology of male osteoporosis.
2. Improve understanding of bone quality and its role in bone fractures.
3. Emphasize the role of simple clinical tools on how to detect patients with highest risk of fracture.
4. Understand the importance of work-up for secondary causes in male osteoporosis.
5. Overview of treatments in male osteoporosis.

Case History

A 75 year-old male comes to see a physician for erectile dysfunction. He denies history of fractures, family history of fractures, height loss or osteoporosis.
He has smoked one and a half packs of cigarettes a day for the last 30 years. He doesn't exercise and his daily calcium and vitamin D intake consists of "some milk with cereal, slice of cheese and egg a day", roughly ~ 500mg of calcium a day.
On physical exam he is surprised to learn that he has lost 2.5 inches of height (~6cm). His height is 175 cm. He has mild thoracic kyphosis but no point tenderness on palpation and he does not need his arms to stand up. On testicular exam testes are ~20cc each but soft.

What to do? What to recommend?

Introduction

Osteoporosis is currently defined as a systemic skeletal disorder characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (1). Simply, bones break after loads exceed the bone's ability to tolerate the pressures.
Male osteoporosis is a less known entity as compared with osteoporosis in women. In fact, we are still surprised to learn how many men have osteoporosis and how many fractures are caused by it every year.
Each year 1.5 million fractures take place in the U.S. (2). One third of those fractures occur in men. The fact is that one in four men over age 60 will have an osteoporosis related fracture in their remaining lifetime (3,10,11). Hip fractures without a doubt are the most serious consequence of deteriorating bone mass. After hip fracture, 50% of men and women never regain their independence and mobility and more than one quarter of men die within one year (3,9). In addition to personal suffering it is a tremendous cost to society. The estimated national direct cost for osteoporosis related fractures in men and women was $47 million US dollars each day or a total of $17 billion for the year 2001.
From NHANES III data set it is known that 3-6% (2.3 million) of U.S. men have osteoporosis at hip and this number will roughly double by year 2020 (4). 24-47% (11.8 million) men have osteopenia, a stage of the bone disease where bone loss is milder than in osteoporosis (4). In Texas alone, it is estimated that in 2002 there were 140,800 men with osteoporosis and 738,600 men with osteopenia. Recognizing the seriousness of this problem, Surgeon General Dr. Carmona released his report on "Bone Health and Osteoporosis" in 2004 (5).
Despite this very worrisome data, few of those men who have sustained a fracture receive any kind of treatment. In a study by Kiebzak et al. upon discharge only 4.5% of men with hip fractures were put on treatment for osteoporosis, compared with 27% for women (6). Even at year five, discordance between treated patients remained, 27% of men and 71% of women were receiving treatment. In another study by Feldstein et al., only 2.8% of men but 42.4% of women received treatment for osteoporosis, again demonstrating a lack of awareness toward male osteoporosis problem as a whole (7). The good news is that admissions due to hip fractures have decreased steadily from 1996 to 2001. In 1996,

102,541 men with hip fractures were admitted to hospitals as compared with 89,887 in year 2001.
In addition to "expected" or age associated bone loss many other medical conditions can accelerate it (table 1) (8).

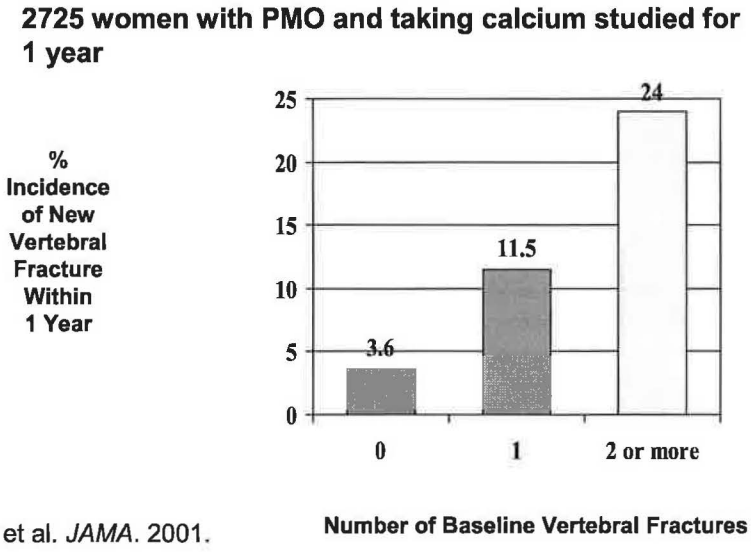
Endocrine disorders	Hyperthyroidism, hypogonadism (primary or secondary), hyperprolactinemia, Cushing's syndrome, type 1 diabetes, eating and nutritional disorders
Gastrointestinal disorders	Malabsorption syndromes, inflammatory bowel disease, gastrectomy, severe liver disease
Bone marrow disorders	Multiple myeloma, lymphoma, leukemia, mastocytosis,hemochromatosis, hemophilia
Genetic syndromes	Hypophosphatasia, osteogenesis imperfecta
Medications	Glucocorticoids, anticonvulsants, heparin, gonadotropin-releasing hormone agonists, lithium, cytotoxic drugs, various chemotherapy agents
Other	Multiple sclerosis, rheumatoid arthritis, COPD, organ transplantation, chronic renal failure, cigarette smoking

Table 1

Best predictors of future fracture

Previous fracture is clearly one of the strongest predictors of future fracture. In a pivotal analysis by Lindsey et al., women with osteoporotic range bone mineral density (BMD) had a 3.6% risk of fracture within one year of follow-up. However, women with two vertebral fractures at baseline had a 24% risk of fracture, almost eight times higher than those with low BMD only (figure 1) (12).
This study included 2,725 placebo-treated women from four large trials conducted at 373 study centers across the world. We must remember that most vertebral fractures are non-clinical but morphometric fractures, and 80% of the cases go unrecognized (12) due to a lack of any complaints. With that in mind we have to be more aggressive in identifying those patients with existing fractures. One very simple and practical approach is to measure patients' height and look for thoracic kyphosis. Anecdotally, I divide men with height loss into two groups: one of which is very surprised to learn that they have lost height, and another which assumes it to be part of the normal aging process. Neither of them is correct and do not suspect even remotely that the height loss has direct relationship to osteoporosis related fractures. In a study by Vallarta-Ast et al., 52.5% of men with 2.5 inches of height loss had confirmed vertebral fractures (13). The patients with more than

Existing Vertebral Fracture in Predicts Future Fracture

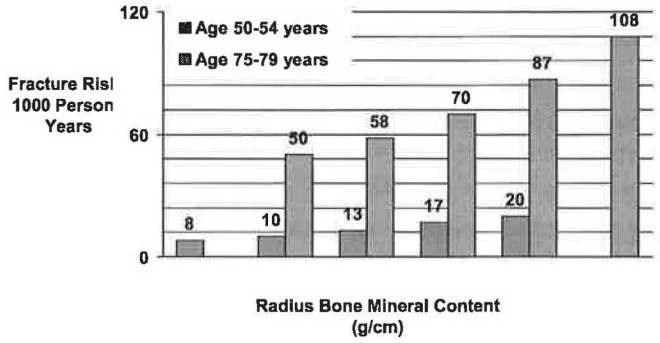


Lindsay et al. *JAMA*. 2001.

Figure 1

2.5 inches height loss need to have spine films to rule out compression fractures, as their presence in many cases may radically change our treatment approach. The second important predictor of fracture is age. This was proven by Hui et al., which compared radius fractures risk between women of different age groups, but similar BMD (14). For the first time she revealed that age is more powerful than BMD in predicting future risk of fracture (figure 2). Such studies have not been done in men.

Fracture Risk Increases With Advancing Age



Hui et al. *J Clin Invest*. 1988.

The same conclusion was drawn by Kanis' group who were analyzing Swedish men and women from the Malmö area (15).
With this information in mind, and knowing that population above 65 will quadruple from year 2000 to 2020, more fractures are a certainty in the future.
However,
a fundamental question remains:

Figure 2

Why are patients with previous fractures and ones who are older but with similar BMD fracturing at higher rates? The higher frequency of falls partially explains it.
Another important factor to look at is how good the BMD test is at analyzing bone quality. The short answer is, not good at all. In fact, it is known that subjects with similar BMD measurements may have different degrees of perturbation of bone microarchitecture when evaluated by histomorphometry (figure 3) (16).

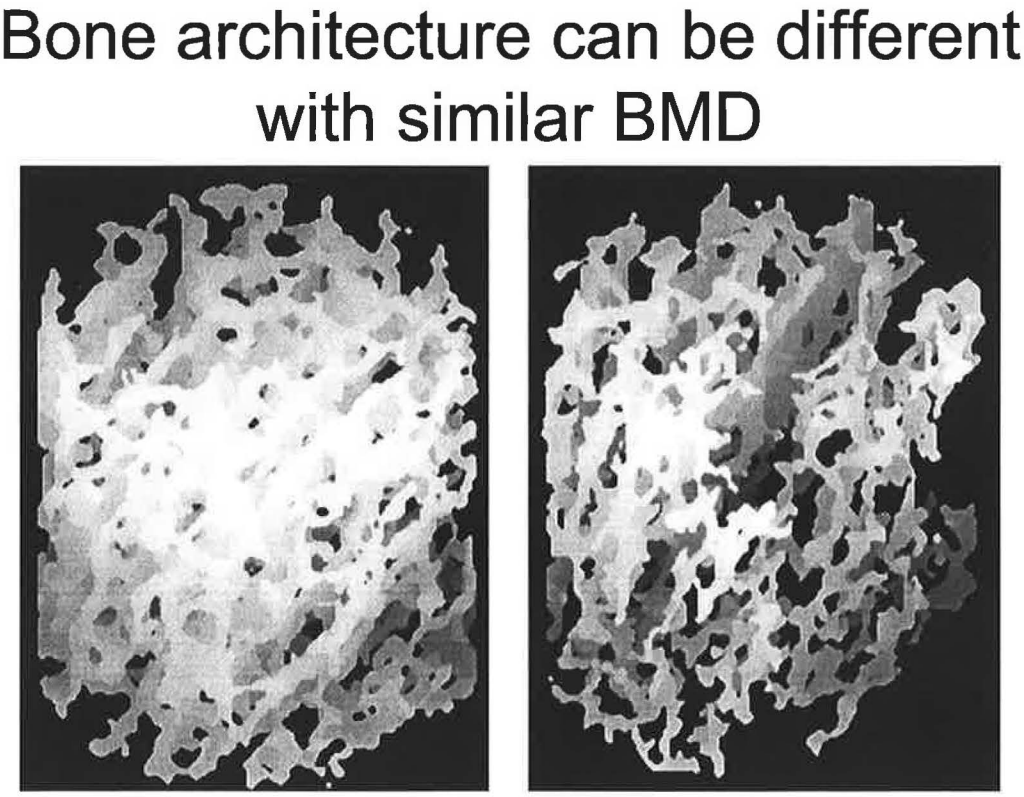


Figure 3

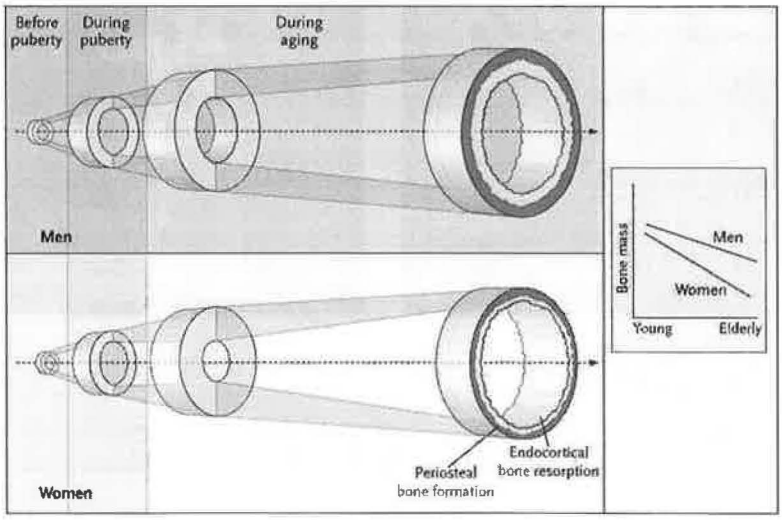
It is also known that some of the therapeutic agents such as raloxifene produce very small change in BMD yet significant decrease in future fracture risk in women. Benito et al. compared 10 hypogonadal men with 10 eugonadal counterparts. They were matched for body mass index, age, race and calcium intake. The results were intriguing. They showed non-statistical difference in BMD between groups, but significant deterioration in trabecular architecture in the group of hypogonadal men (16). If such a difference in trabecular architecture leads to more fractures is still unknown.
The NIH Consensus Development Conference on Osteoporosis in 2000 defined osteoporosis as a "skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture." (1) More so, it was postulated that bone density and bone quality are equally important determinants of bone strength. Bone

quality is determined by bone architecture, turnover, cortical thickness, porosity, damage accumulation, and rate and quality of the mineralization process.
As recently as year 2000, a bone quality term was still illusive for clinicians who were treating patients with osteoporosis. It is partly due to a lack of easy access to techniques which can reliably measure such factors, and due to a lack of evidence and uncertainty of how to incorporate such factors in a care of an individual patient.

Bone size

Bone size becomes different in men and women after puberty due to the effects of estrogen in women and androgen in men. Androgens during puberty in boys increase periosteal apposition, bone diameter and cortical thickness, but in girls the increase of estrogen production decreases periosteal bone formation and eventually restricts bone diameter (figure 4) (17).

Periosteal Bone Formation



Seeman E. *NEJM.* 2003;349: 320-323

Figure 4

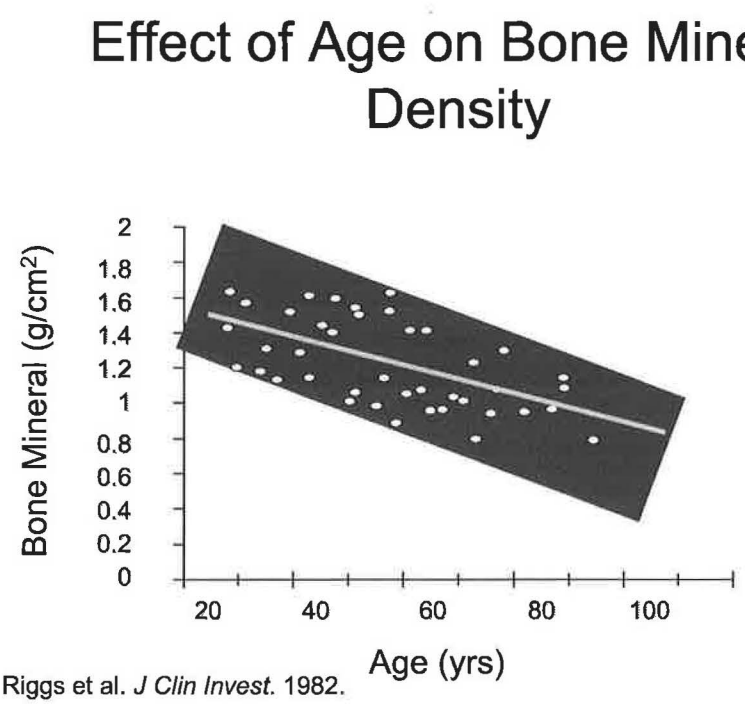
In menopause, the opposite happens. The lack of estrogen lifts the brake on periostal bone formation, but even more so it increases endocortical bone resorption (17). During aging, men have more periosteal bone apposition and have less net bone loss than women, so loads on bone for men are more evenly distributed and stress to the bone doesn't increase as much as in women. This results is fewer fractures. When Seeman et

al. looked at 95 men with spine fractures, 127 men with hip fractures and 395 healthy controls, he found that men with vertebral fractures have less vertebral body width then those men without fractures. Men with hip fractures had less femoral neck width but vertebral width was not different (18).

Bone Mineral Density

Even though measurement of BMD is not a perfect determinant of risk of future fractures it is comparable to the use of blood pressure to predict stroke, and substantially better than serum cholesterol to predict myocardial infarction (19). Physicians are becoming more and more comfortable interpreting the results and instituting treatment in response to that result. There are many caveats on reading BMD reports correctly but that is beyond the scope of this lecture. However, it must be remembered that BMD measurements must be done on the same machine and by the same technician if at all possible. This is necessary due to difficulty in cross-calibrating different brands of machines from different manufacturers and due to site specific calibration procedures or lack of such procedures in some instances (see International Society for Clinical Densitometry, www. ICSD.org).

We gain all of our bone strength and density from age 15 to mid-thirties. It is of paramount importance that young men and women in this age group consume adequate amounts of calcium and vitamin D and have enough exercise; otherwise their bone will never reach their "genetic bone strength potential". After age 40, on average men loose 1-2 % of BMD a year (figure 5) (20).



Riggs et al. *J Clin Invest.* 1982.

Figure 5

Because of this, it is clear that BMD depends on three main things: ***reached peak bone mineral density, rate of bone loss and lifespan.***

Hypothetically, if our lives would be indefinite, all of us would develop osteoporosis at some point.

Aside from this, it is clear that as BMD worsens in postmenopausal women and older men, the risk of fracture increases. General "rule of thumb" is that with each standard deviation below normal young adult BMD, risk of fracture doubles (21,22). In some groups such as young healthy men the baseline absolute risk of fracture is so low that even hypothetical quadrupling of this risk (in case of BMD of -2 SD below normal) the risk of future fracture risk may be too low to warrant therapy. Recently presented data from the Osteoporotic Fractures in Men Study (MrOS), showed that elderly men with BMD of -2.5 SD and below had absolute risk of fracture 3.7% (baseline without osteoporosis is 0.1%) and 7.4% (baseline 1%) in hip and spine respectively (23). When data from MrOS and the Study of Osteoporotic Fractures (SOF) in women were compared, it was clear that men with BMD below -2.5 SD in fact have the higher risk of non-spine fracture, 9.5% versus 7.9% in women (24).

BMD measurement in men should be considered in the following categories:
1. Age 70 and above
2. Adults with fragility fracture
3. Family history of fracture
4. Hypogonadism
5. Cigarette smoking
6. Glucocorticoid use > 3 month
7. Use of GnRH agonist
8. Loss of height

Case History (continued)

Spine film conformed T12 and L1 compression fractures. BMD T score shows -1.7 SD in LS and -2.2 SD in total hip. 25 hydroxy-D 15ng/dl (normal above 30), Ca 9.5 mg/dl and PTH 80 pg/ml (normal below 65) and am pooled testosterone 250 ng/dl with elevated LH.

Bone Turnover

Broadly speaking, bone turnover markers can be divided into two categories, one representing bone resorption and the other bone formation. In the first category would be markers such as deoxypyridinoline (DPD), N-telopetides of type I collagen (NTX), C-telopeptides of type I collagen (CTX). In the second would be osteocalcin (OC), bone alkaline phosphatase (BALP), procollagen type I C-terminal propeptide (PICP) and procollagen type I N-terminal propeptide (PINP). Generally speaking, bone turnover increases with age due to decreased level of sex hormones, vitamin D deficiency and hyperparathyroidism, etc. This increase has been clearly associated with increased fracture risk in women but has not been well studied in men. Bone resorption markers above pre-menopausal range have been associated with doubling of fracture risk in hip (25). This association is as strong as decrease in BMD by 1SD (26). However, there is a suppression threshold for bone markers below which risk of fracture will not be reduced and in fact may be increased (27,28). The combination of high bone turnover and low BMD places women in particularly high risk for fracture. Results on an association between BMD and rate of bone turnover at baseline have been very sparse in men.

In fact, the only study published so far was by Luukinen et al., and showed no association between level of bone formation marker total osteocalcin and fractures in elderly Finnish men (Figure 6) (29).

Baseline biochemical parameters in men who sustained a fracture during a 5-year follow-up

	Fractures (n = 21)	Controls (n = 280)	
Total OC (tOC) (ng/ml)	9.5 ± 4.8	9.3 ± 4.7	0.79
Carboxylated OC (cOC)	6.7 ± 4.2	8.6 ± 4.0	0.02
cOC / tOC	**0.74 ± 0.36**	0.96 ± 0.30	0.002

Luukinen et al. *JBMR*, 2000

Figure 6

Changes in Trabecular Architecture

With aging, a decrease in trabecular thickness takes place. This is caused by misbalance between bone resorption and formation. Bone resorption is primarily accomplished by osteocalsts, and bone formation by osteoblasts. Complete cycle of remodeling in trabecular bone takes on average 200 days (50 days for bone resorption and 150 days for bone formation) (30). It is more pronounced in non load-bearing horizontal trabeculae than vertical.

If bone loss is not prevented, trabeculae perforate and connection between them is disrupted. The disruption and loss of connections between horizontal trabeculae increases susceptibility to fracture and cannot be detected by BMD measurement. Several new "virtual" biopsy techniques based on quantitative computed tomography (31) and magnetic resonance imaging (32) may help in the future, but at this point are research tools only.

High resolution MRI is able to discern individual trabaculae. As a result, it can depict bone microarhitecture and different parameters that reflect the integrity of trabecular network which can be quantified. In a study by Bonito et al. it was clearly shown that male bones with similar BMD can have substantially different microarhitectural structure (16). Though it appears tempting to believe that more precise assessment of microarhitecture will also be a better predictor of fracture risk, it has yet to be proven in prospective trials.

The take home message is this: BEST PREDICTORS OF FUTURE FRACTUTRES ARE PREVIOUS FRACTURE, AGE AND BMD !!!!!!! THE ONLY WAY TO SELECT OUT MEN WITH NON-CLINICAL SPINE FRACTURES IS TO MEASURE THEIR HEIGHT. It is clear that those who have sustained minimal trauma fracture regardless of their BMD have poor bone quality and have to be treated. The same is true for men who are older and have low BMD. Age is an independent predictor of bone quality. Young men with low BMD need work-up for secondary causes of bone loss. If no secondary cause is found and no fractures are present they do not need treatment for osteoporosis.

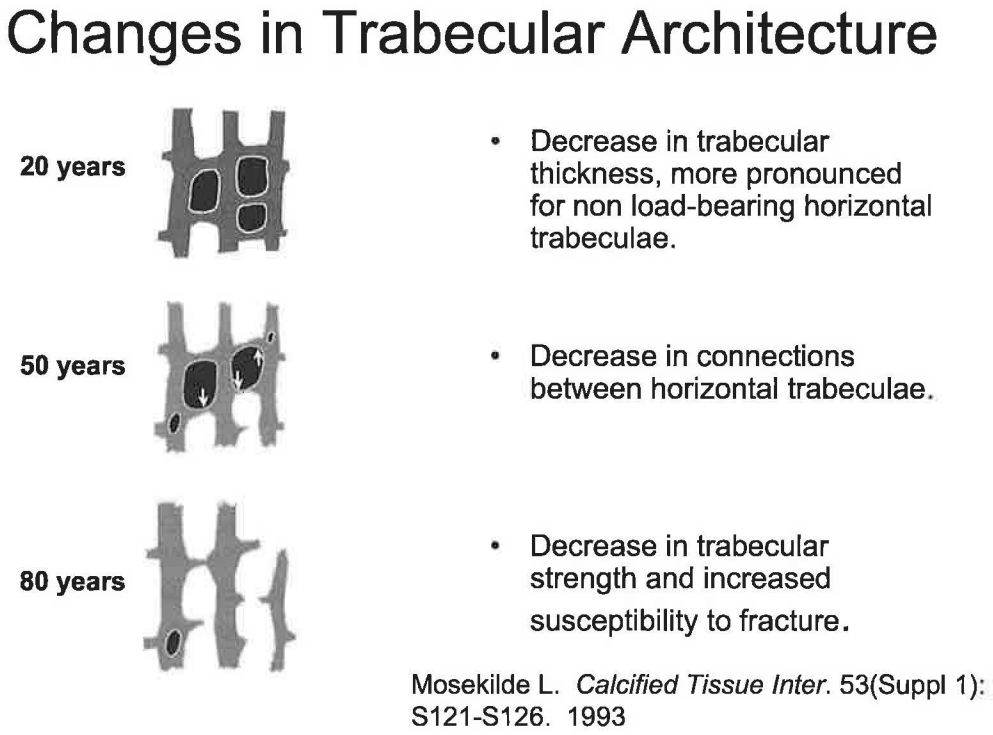


Figure 7

What about men with osteopenia?

The World Health Organization defines osteopenia as -1 to -2.5 SD below normal peak BMD (T score). In men and women 50% and more fractures occur while BMD is in osteopenia range (36,33). In the U.S. alone we have approximately 12 million men and 20 million women with osteopenia in the hip (4). It would be unnecessary and impossible to screen all of them, yet how do we select the ones with highest risk of fracture?

In 1995, Cummings et al. in New England Journal of Medicine presented a study where it was shown that combining risk factors with BMD is a better predictor of fractures risk than BMD alone (34). In 1999, Burger et al. looked at 2,193 men from a Rotterdam study and depending on presence or absence of seven risk factors, estimated a four year hip

fracture risk (36). Each of the factors (age, height, use of walking aid, smoking, BMD and weight) had an assigned risk point value. Combining the points, physicians can tell with more certainty what the four year risk of hip fracture would be. A Fracture Risk Score have also been developed in women from Study of Osteoporotic Fractures (SOF) Research Group and Épidémiologie de l'Ostéoporose (EPIDOS) study (36,37).
One would think that data on absolute risk of fracture would be also more meaningful than BMD results for a patient.
At this point however, there are no clear guidelines what risk is acceptable and at what threshold treatment is necessary for women and men. Hopefully, the guidelines for women will be published this summer by a World Health Organization expert panel led by John Kanis.

Case History (continued)

Mr. R gets 64 points from the fracture risk score: 24 points for age, 12 points for height, 8 points for being a smoker, and 20 points for BMD. His cumulative 4 year hip fracture risk is 2-3% (baseline risk with normal BMD is 0.1%).

Contributors to bone loss

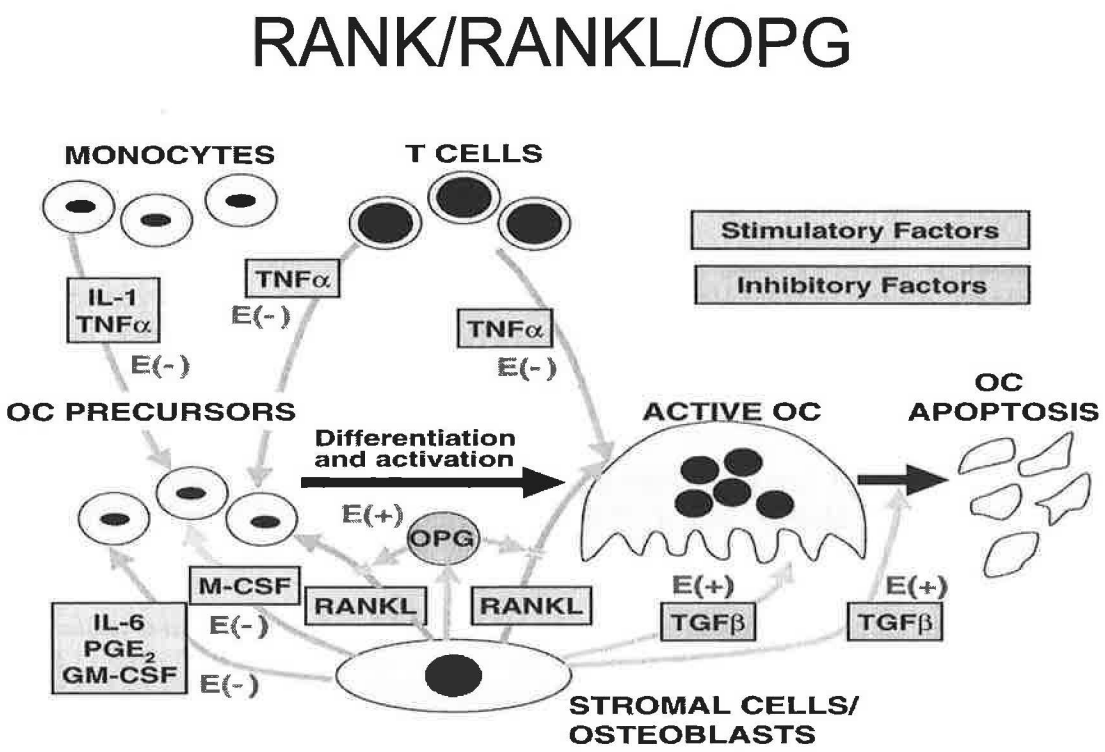
Between 50-60% of men with osteoporosis have disorders known to produce bone loss including hyperparathyroidism, hypogonadism, vitamin D deficiency, hypercalciuria, intestinal disorders, malignancies, and conditions resulting in immobilization (38,39,40).
What the contribution of each factor is so far can only be answered from population studies which have been done in rather limited geographical areas and may not be representative for all men in the U.S.
The MrOS study hopefully will answer many questions we need to know. It is the largest longitudinal, prospective study today on older healthy men, and includes 5,989 men above age 65. Approximately 10% of the cohort is minorities, and 18% of the men are 80 and older, from six different geographical areas (41). The men will be followed for seven years, including yearly questionnaires on lifestyle, activity, diet, fracture data (conformed by X-ray films), BMD, bone micro CT and measurement of sex hormones, metabolites of vitamin D, PTH etc.
Aadequate vitamin D level is necessary to keep the bone resorption process from accelerating. It is believed that a 25-hydroxy vitamin D level above ~35ng/ml is adequate. Levels above this threshold keeps vitamin dependent calcium absorption at its maximum and PTH level is at low normal levels.
Vitamin D deficiency is common in men. In winter 43.9% of African Americans (AA), 30% of Hispanics and 16.8% of Caucasian men have vitamin D insufficiency (42). In summer, the percentage decreases by approximately half in Caucasians and Hispanics but in AA vitamin D insufficiency remains at 44%. A recently presented abstract by Holick et al. showed that ~50% of women who are presently treated for osteoporosis and are in good health are vitamin D insufficient (43). Vitamin D insufficiency is common in adolescents and reaches 42% in the Boston area. Similar data have been reported from France. In hospitalized and nursing home patients, vitamin D deficiency reaches 60% (44). The National Academy of Sciences recommends calcium intake between 1,200 and 2,500mg and vitamin D intake between 400 and 2,000IU a day. This recommendation is

very difficult to fulfil by diet alone unless one drinks 4-8 cups of 8fl oz of milk a day. Without sun exposure one would need to drink 4-20 cups of 8fl oz of milk a day or eat 6 oz of baked salmon every day to have recommended vitamin D intake. Sun exposure of the arms and legs or hands, arms, and face, 2 or 3 times a week for 5-10min and increased dietary and supplemental D intake are a reasonable approach to guarantee vitamin D sufficiency.

Sex hormones (androgens and estrogens) play an important role in bone acquisition and loss. Both regulate bone formation and resorption through balance between RANK/RANKL (receptor activator of nuclear factor-kB ligand) and OPG (osteoprotegerin, a soluble decoy receptor that neutralizes RANKL) systems (Figure 8)(45).

The testosterone and estradiol levels decrease with age (46,47).

Free testosterone decreases by ~1-2% per year after age 30 in otherwise healthy individuals. It is well documented from epidemiological studies that close to 70% of men by age 70-79 are hypogonadal if free testosterone level is measured (46). The concurrent age-related increase in the incidence of chronic diseases and obesity undoubtedly accelerates this decline. Due to unreliability of free testosterone assays many experts recommend measurement of bioavailable testosterone instead.



Riggs et al. *Endo Rev.* 2002.

Figure 8

As recommended by the Second Andropouse Consensus Conference, the cutoff value for diagnosing hypogonadism in aging males is total morning testosterone level below 350ng/dl (with symptoms) or below 200ng/dl (regardless of symptoms).
In the Rancho Bernardo study where 352 men were followed for 13 years, low total estradiol level was shown to be a much stronger predictor of fracture than testosterone (48). The role of testosterone and estradiol in construction and conservation of male skeleton has been proven in men with prostate cancer who undergo androgen deprivation therapy. In a study by Smith et al. lumbar spine BMD declined by ~4% while testosterone decreased five fold from 355 to 51ng/dl and estradiol four fold from 26 to 7pg/dl during 48 weeks of the study (49). A recently published Medicare study of 50,613 men with prostate cancer showed 70% higher relative risk of fracture for those who received androgen deprivation therapy (50).
In summary, all men who are at increased risk for osteoporosis need to undergo the following work-up (38,39):

1. Physical examination: Height measurement and fall risk assessment

2. Laboratory evaluation: Serum creatinine, calcium, phosphorus, alkaline phosphatase, am pooled testosterone, 25-hydroxyvitamin D, PTH, liver function test, complete blood count, electrophoresis if patient is anemic and 24-hour urine calcium/creatinine.

Treatment of male osteoporosis/fractures

From the start, we have to remember one important thing:

- **all the data from treatment trials are on older men and postmenopausal women and can not be applied for younger patients**

Treatment modalities for osteoporosis/fractures have to focus on three different components; prevention of falls, decreasing the impact from the fall and lastly improving bone strength. A combination of appropriate interventions will improve our chances of decreasing fracture risk.
Approaches in prevention of fractures can be divided into pharmacological and non-pharmacological. Non-pharmacological approaches include physical therapy to strengthen "stability" muscles, appropriate home adjustments for fall prevention (falls account for 90% of hip fractures and over 50% of vertebral fractures), discontinuation of psychotropic medications, and correction of vision. If a patient is still prone to falls, hip protectors can help in softening the impact from the fall.
Results of different strategies are compiled by Tinetti et al. in a recent article of the NEJM and are shown below in table 1 (51).
A pivotal study from Finland by Kannus et al. included 653 subjects in a hip protector group (149 men) and 1,148 in a control group (243 men) (52).
The risk reduction for hip fractures was 60%. Nine of the subjects in hip protector group fractured a hip while not wearing it. If those patients were to be excluded, risk reduction would be 80%. The significant problem however is compliance, because many patients stop using hip protectors as they may feel tight and a bit bulky.

Pharmacological modalities can be divided in two broad categories, drugs which stimulate bone formation and ones which decrease bone resorption.

The first category includes parathyroid hormone, possibly fluoride, and strontium ranelate (not tested in men). The second group is much larger and includes calcium plus vitamin D, calcitonin (Miacalcin), SERMs (selective estrogen modulators such as Evista), testosterone, and biphosphonates. Future antiresorptive treatments for osteoporosis in men may include fully human monoclonal IgG2 antibody to RANKL and OPG (osteoprotegerin), both so far studied in women only.

Table 1. Strategies Shown in Randomized Clinical Trials to Be Effective in Reducing the Occurrence of Falls among Elderly Persons Living in the Community.*

Strategy	Estimated Risk Reduction	No. of Trials with Positive Results†
	%	
Health care–based strategy‡:		
Balance and gait training and strengthening exercise	14–27	2 of 3
Reduction in home hazards after hospitalization	19	1 of 1
Discontinuation of psychotropic medication	39	1 of 1
Multifactorial risk assessment with targeted management§	25–39	3 of 3
Community-based strategy¶		
Specific balance or strength exercise programs	29–49	2 of 2

* The trials are those reported in the Cochrane review[14] that included at least six months of follow-up and involved persons living in the community. Among the strategies that have not been shown to be effective are multifactorial risk assessment without targeted management (none of three trials with positive results[28-30]), low-intensity general exercise programs (none of seven trials with positive results[31-37]), and cognitive–behavioral, educational, and self-management programs (one of six trials with positive results[38-43]).

† Positive results were defined as relative risks with 95 percent confidence intervals that did not include 1.[15,16,19-21]

‡ Participants were recruited from clinical settings, and interventions were carried out by health care professionals. Participants had reported previous falls or balance or gait difficulties or had one or more risk factors for falling.

§ The specific assessments and interventions varied among the trials. The trial personnel directed or carried out specific interventions on the basis of the results of the assessments.

¶ Participants were recruited from community sites, and interventions were not carried out by health care professionals. Participants were not recruited on the basis of previous falls, balance or gait difficulties, or risk factors.[44,45]

Drugs which increase bone formation

Teriparatide (1-34 molecule) (Forteo) have shown 5.9% increase in LS BMD over a 10 month period as compared with calcium and vitamin D alone (53). The same data was presented as a poster presentation and demonstrated 50% relative risk reduction in fracture; however, the numbers of fractures were small: 12 in placebo and 10 in parathyroid hormone (1-34) group (54).

In women, teriparatide for 18 months reduced vertebral fractures by 65% when compared to placebo (55).

With fluoride, in one randomized controlled study of 64 males, BMD increased at all sites (56). In addition, a significant difference in small number of vertebral and non-vertebral fractures was documented between calcium alone and monofluorophosphate and calcium combination. In a different uncontrolled study fracture rates were reduced from 33% in the first year to 11% in the second year in both men and women. Another promising agent which has been studied in women, is strontium renelate. In a study of

1,649 women it decreased vertebral fractures by 41% in three years and increased BMD by 14.4% and 8.3% in spine and femoral neck respectively (57). What is very perplexing is that this agent increases bone formation and decreases bone resorption at the same time. None of the other drugs do that. All of the antiresorptive drugs decrease bone formation and bone resorption at the same time.

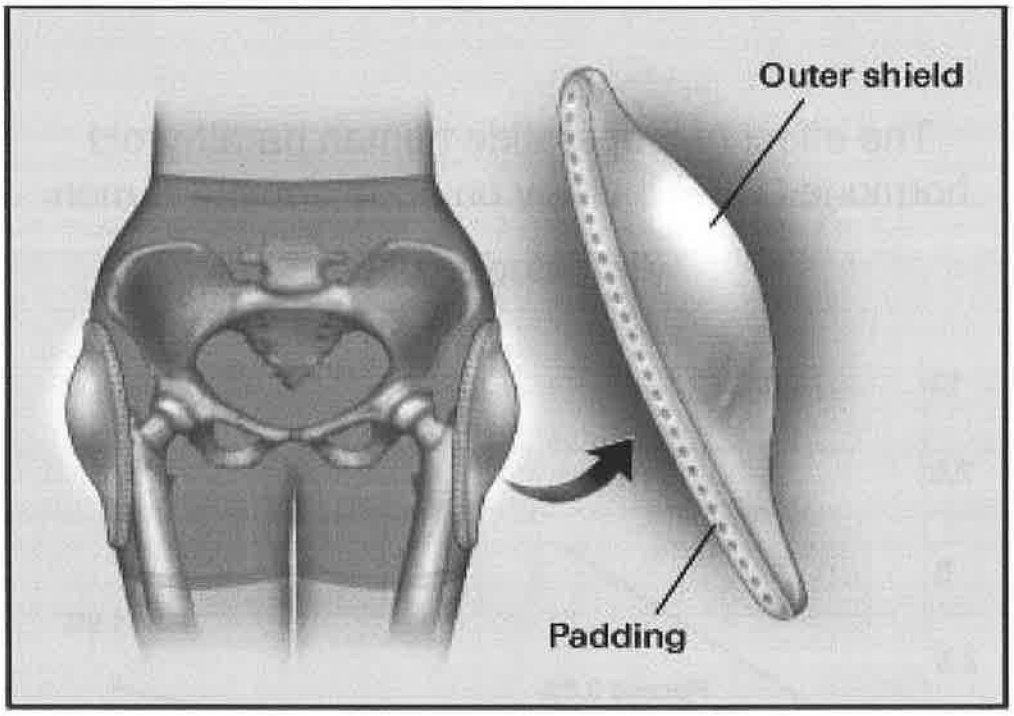


Figure 9

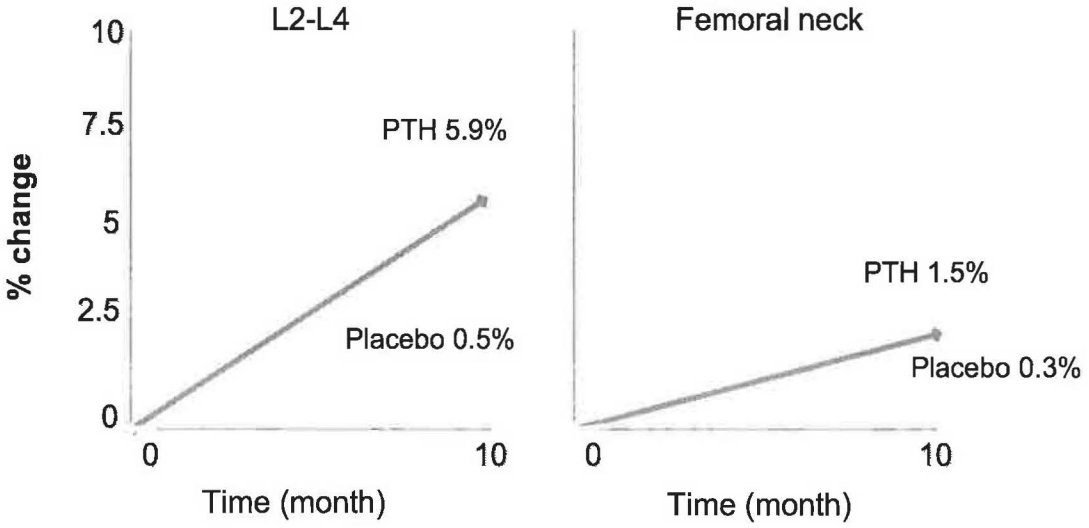
Drugs which increase bone formation such as PTH also increases bone resorption. Mechanism through which strontium renelate exerts this dissociating effect between bone formation and resorption remains unclear. Strontium renelate has not been studied in men.

Drugs which decrease bone resorption

In a placebo controlled study by Dawson-Hughes et al., 389 (176 men) subjects were taking 500mg of calcium and 700IU of vitamin D daily. At the end of three year follow-up, risk of non-vertebral fracture was decreased by 64% despite no change in BMD (58). With calcitonin, a study which included 41% men, calcitonin stabilized BMD. In the placebo group, men lost 15% of BMD as compared with 1% in calcitonin combination with calcium and vitamin D (59). In another small randomized study, calcitonin treatment for two years resulted in reduced vertebral fracture incident when compared with calcium and vitamin D alone (60). Testosterone replacement consistently increases BMD in men

who are hypogonadal (61). The BMD increase is greater in men with lower testosterone levels (62).
Only two drugs have shown fracture reduction in males: alendronate (Fosomax) and risedronate (Actonel) (63,64). The Food and Drug Administration has approved only alendronate and teriparatide (Forteo) for treatment of non-steroid induced osteoporosis in men. Risedronate is approved for the prevention and treatment of steroid induced osteoporosis in men.

The effect of teriparatide human parathyroid hormone (1-34) therapy on bone density in men with osteoporosis



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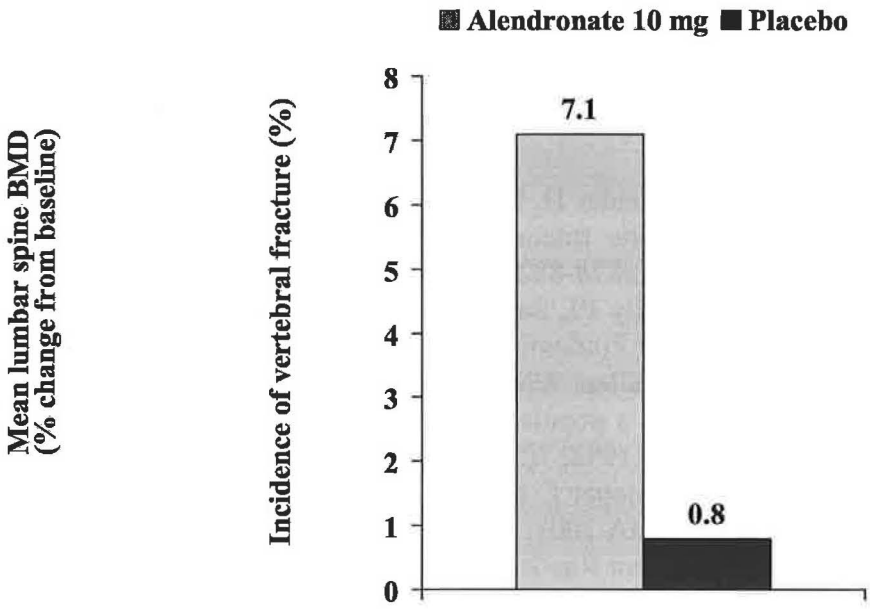
Other biphosphonates such as ibandronate (Boniva) and zoledronic acid (Zometa) are not approved for use in the treatment of male osteoporosis in the U.S. However, zoledronic acid could be used in patients who can not tolerate oral biphosphonates and risk of fracture is high. The yearly dose of 4mg of zoledronic acid intravenously would be the recommended dose. In women who received zoledronic acid once yearly, BMD improved by 4.5% in the spine and 2.5% in the femoral neck (65). The zoledronic acid and pamidronate (Aredia) also prevents decline in BMD in men who receive GnRH agonists for treatment of prostate cancer (49). Effect on fracture reduction with ibandronate, pamidronate and zoledronic acid are unknown.

Combination therapy in men with osteoporosis

It was anticipated that combining the drugs which decrease bone resorption and increase bone formation would increase BMD more than each of the drugs used separately. Yet a study by Finkelstein et al. proved this concept untrue. In a study of 83 men, spine BMD in 30 months improved by 18.1% in teriparatide, by 7.9% in alendronate and by 14.8% in combination groups. In total hip, BMD increases were 6.4%, 4.8% and 5.3% respectively (66).

Similar results were seen by our group who studied a combination of testosterone and bisphosphonates in 116 men. Yearly percent change in BMD was 2% in testosterone, 2.6% in bisphosphonate and 2.4% in combination groups (p=NS) (67). The conclusion is that at this point there is no evidence to use combination therapy in men with decreased BMD.

Effect of Alendronate on BMD and Fracture Risk in Men with Osteoporosis



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Treatment

Replete vitamin D stores with 50000U Ergocalciferol Q week (for 8 weeks) and start 500mg of Ca+vit D BID with meals. Recheck 25-hydroxyvitamin D in 8-12 weeks.

Initiate testosterone replacement for erectile dysfunction.

Have a discussion with patient on what treatment to start him on, Fosomax/Actonel versus Forteo.

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