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WOMEN'S HEALTH

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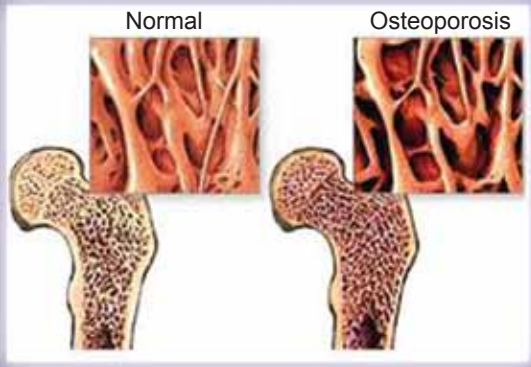

Editorial Note:

Dear Doctor,

It's our immense pleasure to inform you that we have published our newsletter, "Women's Health". In this issue we are focusing on Vitamin D and Female Fertility and Management of Postmenopausal Osteoporosis.

Your comments and suggestions will encourage us for upcoming issues. Please participate in quiz competition and win prizes.

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WOMEN'S HEALTH

Vitamin D and Female Fertility

Introduction

Vitamin D has been well known for its function in maintaining calcium homeostasis and promoting bone mineralization. Vitamin D is a steroid hormone and approximately 80-90% of vitamin D is produced in the skin after sunlight exposure. A small amount of the body's total vitamin D is also derived from diet and/or supplements. Vitamin D deficiency is highly prevalent among women of reproductive age. The increasing prevalence is caused by obesity, changes in lifestyle, and reduced sun exposure. There is some evidence that in addition to sex steroid hormones, vitamin D also modulates reproductive processes in women and men. This notion is supported by the fact that the vitamin D receptor (VDR) and vitamin D-metabolizing enzymes are found in human reproductive tissues.

In-vitro Fertilization

In 2010, a potential role of vitamin D in IVF has been suggested as pregnancy rates after IVF were reported to be higher in women who are vitamin D sufficient than in those who are vitamin D deficient. Rudicket al. in a retrospective cohort study among 188 infertile women undergoing IVF, observed a linear decline in pregnancy rate with decreasing vitamin D levels in non-Hispanic whites, whereas the opposite was true in Asian women. In a multivariate-adjusted model (age, number, and quality of embryos transferred), odds ratio (OR) of clinical pregnancy was four times higher in non-Hispanic white women with sufficient vitamin D levels (>30 ng/ml) compared with women with vitamin D deficiency (<20 ng/ml; P=0.01). Adjusted live birth rate was 47% in non-Hispanic white women with sufficient vitamin D levels compared with 14% in women with vitamin D deficiency (P=0.01). Interestingly, vitamin D status was not significantly associated with ovarian stimulation parameters or with markers of embryo quality. To further elucidate the role of vitamin D in reproduction, a retrospective cohort study examined the association of recipient vitamin D levels with pregnancy rates in donor-recipient IVF cycles in 99 recipients. Adjusted (embryo quality, recipient BMI, and race) clinical pregnancy rates were lower in vitamin D-deficient (<20 ng/ml) recipients than in vitamin D-sufficient (>30 ng/ml) women (37 versus 78%; P=0.004). Adjusted live birth rates were 31% in vitamin D-deficient women compared with 59% in vitamin D-sufficient women (P=0.04). As the design of the study allows a separate evaluation of endometrium (and not oocyte), the results suggest an important effect of vitamin D on the endometrium. Further, as clinical pregnancy and live birth rates in women with vitamin D insufficiency (20-30ng/ml) (37 and 30%, respectively) were similar to those in vitamin D-deficient women, a 25(OH)D level more than 30ng/ml should be achieved in women undergoing IVF.

Further, a prospective observational study examined the correlation of IVF outcome with 25(OH)D levels in the follicular fluid and serum of 221 infertile women. The fertilization rates associated with vitamin D status were 43.2, 53.4, and 58.8% for women with vitamin D deficiency, insufficiency, and sufficiency, respectively, (P=0.054), and the implantation rates were 17.3, 15.3, and 18.8 %, respectively (P=0.579). No significant correlation was seen between the pregnancy rate and the serum vitamin D level (P=0.094) or the follicular vitamin D level (P=0.170). The lack of statistical significance might be caused by the low number of women with vitamin D sufficiency (7.2%). Nevertheless, a trend toward higher fertilization and clinical pregnancy rates was observed in women with vitamin D sufficiency.

The majority of evidence from recent observational studies indicates an important role of vitamin D in IVF success. Those studies suggest that the most important factor is the vitamin D effect on endometrium. To date, there are no randomized controlled trials (RCTs) investigating the effect of vitamin D treatment on IVF outcome. Nevertheless, data from observational studies suggest that sufficient vitamin D levels at least 30ng/ml might be beneficial at least in non-Hispanic white women undergoing IVF.

Polycystic Ovary Syndrome

Vitamin D has been suggested to play an important role in PCOS regarding several aspects, including obesity, metabolic syndrome, and fertility. Most studies focused on vitamin D and metabolic risk factors, whereas only one study was published on vitamin D, PCOS, and fertility conducted a RCT in 110 infertile women with PCOS to investigate vitamin D effects on success rates of intrauterine insemination (IUI). The authors reported that endometrial thickness was significantly different in the vitamin D group, whereas no significant differences were found in pregnancy outcome, number of dominant follicles, duration of IUI cycles, and dose of human menopausal gonadotropin (HMG) used for IUI. The authors concluded that vitamin D induces endometrial proliferation in PCOS women during IUI cycle.

Because of the paucity of recent articles on vitamin D, PCOS, and fertility, there are two earlier studies on this important topic that are worth mentioning. At the beginning of 2012, Ottet al. published the results of a prospective cohort study including 91 anovulatory, infertile women with PCOS who underwent clomiphene citrate stimulation. In a multivariate model to predict both follicle development and pregnancy,BMI and 25(OH)D deficiency were significant predictive parameters. 25(OH)D levels less than 10 ng/ml were associated with a 67% reduced chance of follicle development and a 76% reduced possibility of becoming pregnant in multivariate regression analyses.

In 2011, Wehret al. examined the effects of 20 000 IU vitamin D weekly over 24 weeks on endocrine and metabolic parameters in 57 PCOS women.

After 12 weeks, 14 out of 46 PCOS women previously affected by menstrual disturbances (30.4%) reported improvement of menstrual frequency; after 24 weeks, 23 out of 46 women (50.0%), who were oligo-amenorrhoeic at baseline reported improvement. Moreover, four out of 16 women seeking pregnancy at baseline conceived during the study.

As metabolic disturbances including obesity and insulin resistance have a negative impact on fertility in PCOS, studies investigating the association of vitamin D with metabolic parameters in PCOS are also worth mentioning. In the last year, a RCT including 50 PCOS women with vitamin D deficiency investigated the effect of three oral capsules of 50000 IU vitamin D every 20 days over 2 months

versus placebo on cardiovascular risk factors. Vitamin D treatment significantly decreased total cholesterol, triglycerides, and very low density lipoprotein (VLDL) without a significant effect on high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, apolipoprotein AI (Apo-AI), and high-sensitivity C-reactive protein (hs-CRP). No significant change was observed in the placebo group.

Palet al. conducted a single arm open label trial to examine the effect of combined vitamin D (3533 IU per day, increased to 8533 after the first five participants) and calcium (530 mg per day) supplementation on hormonal and metabolic parameters in 12 overweight and vitamin D-deficient women with PCOS. Vitamin D and calcium supplementation resulted in a significant decrease of total testosterone and androstenedione levels. Further, in participants with baseline blood pressure levels at least 120/80 mmHg and in those with baseline 25(OH)D levels 20ng/ml or less, the intervention was associated with a significant reduction in blood pressure. The authors found no effect on glucose and insulin metabolism.

Lifestyle intervention is the first-line treatment for overweight and obese women with PCOS. Thomson et al. conducted a retrospective secondary analysis of two cohorts including overall 50 overweight/obese PCOS women undergoing a lifestyle modification program. One cohort started in winter and finished in summer and one started in summer and finished in winter. The winter cohort had lower 25(OH)D levels at baseline that increased over 20 weeks, whereas the summer cohort had higher levels at baseline that decreased. Interestingly, the changes in 25(OH)D levels inversely correlated with changes in waist circumference and cholesterol levels when controlling for baseline vitamin D levels. Increases in 25 (OH)D levels were associated with greater reductions in waist circumference and cholesterol, suggesting that the seasonal increase in 25(OH)D levels results in improved obesity and dyslipidemia in PCOS women. It is also worth mentioning that 98% of PCOS women were vitamin D deficient (<20 ng/ml) and 2% were vitamin D insufficient (20-29.9 ng/ml), whereas no PCOS women had sufficient vitamin D status. This highlights again the very high prevalence of hypovitaminosis D in PCOS women, particularly in overweight/obese PCOS women, who are most affectedby disturbed fertility.

Further studies focused on the association of vitamin D-related genetic variants and PCOS risk and phenotype. It has been shown that VDR gene polymorphism Taq-I is associated with increased risk of PCOS, whereas there was no association of VDR-related polymorphism Tru I with PCOS risk, but a significant association with severity of clinical features of PCOS. The association of genetically defined adult-type hypolactasia (ATH) with metabolic and endocrine parameters was examined in 504 PCOS and 366 healthy control women from Austria. ATH was associated with PCOS risk as well as with an adverse metabolic profile and low 25(OH)D levels. PCOS women within the highest quartile of calcium intake had significantly lower testosterone and androstenedione and significantly higher high-density lipoprotein cholesterol levels than PCOS women with lower calcium intake.

Further, 25(OH)D and calcium intake were independent predictors of androstenedione levels and calcium intake was an independent predictor of testosterone levels. That study contributed further evidence to the association of vitamin D and calcium metabolism with metabolic and endocrine arameters in PCOS.

Endometriosis

The role of vitamin D in the pathogenesis of endometriosis is biologicaly plausible due to its immune modulatory and anti-inflammatory properties. Endometrium is a target of vitamin D and VDR and vitamin D-metabolizing enzymes are found in the human endometrium. There is, however, conflicting evidence on the role of vitamin D in endometriosis. In a study investigating the global protein expression in ectopic endometrial tissue and normal endometrial tissue, vitamin D-binding protein (VDBP) was significantly increased in the ectopic endometrial tissue compared with the normal tissue. In another study on Rat model, Vitamin D treatment induced a reduction in endometriosis cyst cross-sectional area by 49% and produced fibrosis as well as apoptosis in the stroma, suggesting that vitamin D administration may have a beneficial effect in the treatment of endometriosis. It has been demonstrated that the VDR agonist elocalcitol inhibits lesion development and exerts a protective effect on the implantation as well as on organization of transferred endometrial tissue. Studies also found that predicted 25(OH)D levels were inversely associated with endometriosis and women in the highest predicted 25(OH)D quintile had a 24% lower risk of endometriosis compared with women in the lowest vitamin D quintile. Further,women in the highest quintile of vitamin D intake from food had a 21% reduced risk of incident endometriosis compared with women in the lowest quintile. Moreover, high dairy intake was associated with decreased risk of endometriosis suggesting high intake of vitamin D and dairy foods are associated with a lower risk of endometriosis and might be important modifiable risk factors for endometriosis

Primary Dysmenorrhea

As VDR is located in the human uterus and vitamin D inhibits synthesis of prostaglandins, a role of vitamin D has been suggested in primary dysmenorrhea, a condition characterized by excessive uterine production of prostaglandins. A RCT investigated the effect of a single loading dose of vitamin D (300000 IU) versus placebo on primary dysmenorrhea in 40 women with 25(OH)D levels less than 45ng/ml over 2 months. An inverse correlation of 25(OH)D levels with pain score as well as a significant reduction of pain in the vitamin D group with the greatest reduction in women with severe pain at baseline was observed. The use of analgetics was 40% in women in the placebo group, whereas no analgesic use was recorded in the vitamin D group.

Uterine Leiomyoma

Vitamin D insufficiency has been suggested as a risk factor in the development of uterine leiomyoma. To further test this hypothesis, a case-control study investigated the association of 25(OH)D levels with leiomyoma in 128 cases and 256 age-matched controls. The mean 25(OH)D levels were significantly lower in women with leiomyoma compared with controls. Further, the adjusted (BMI, parity, black ethnicity) OR for the presence of leiomyoma was 2.4 (P_0.016) in women with vitamin D deficiency (<10 ng/ml) compared with women with sufficient vitamin D levels (20 ng/ml). Thus, the potential role of vitamin D in human fertility is also supported by the association of vitamin D deficiency with uterine leiomyoma development.

Ovarian Reserve

The association between circulating 25(OH)D and anti-mullerian hormone (AMH) levels studied in a cross-sectional study included 388 premenopausal women with regular menstrual cycles. The authors observed a positive independent association of 25(OH)D levels with AMH in women aged at least 40 years (n=141). Thus, vitamin D deficiency might be associated with lower ovarian reserve in late reproductive aged women.

Conclusion

Evidence from observational studies indicates an important role of vitamin D in IVF success, which is probably mediated through vitamin D effects on endometrium. Although there are no RCTs investigating the effect of vitamin D treatment on IVF outcome, data from observational studies suggest that sufficient vitamin D might be beneficial in women undergoing IVF. Further, sufficient vitamin D levels might be favorable for reproductive and metabolic health of PCOS women as well as for the prevention of endometriosis. Further beneficial effects of vitamin D and female fertility include improvement of primary dysmenorrhea following vitamin D supplementation and a possible association of high vitamin D levels with better ovarian reserve in women of late reproductive age. As the majority of evidence derives from observational studies, well designed RCTs with a large sample size are required to evaluate the effect of vitamin D supplementation on female fertilit

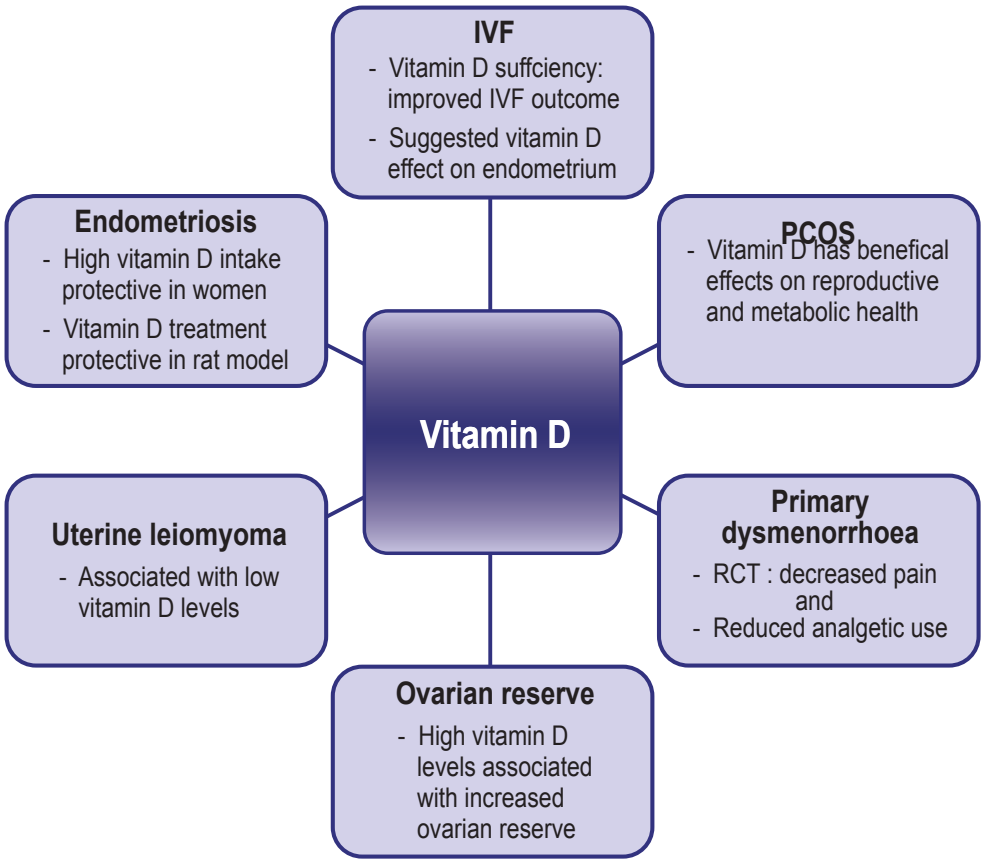

FIGURE 1.Suggested vitamin D effects on female fertility.

IVF- in-vitro fertilization; PCOS- polycystic ovary syndrome; RCT- randomized controlled trial.

Reference: Lerchbaum, Elisabeth, and Thomas Rabe. "Vitamin D and female fertility."Current Opinion in Obstetrics and Gynecology 26.3 (2014): 145-150.

WOMEN'S HEALTH

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Management of Postmenopausal Osteoporosis

Genetically determined low bone mass along with the loss of bone associated with estrogen deficiency probably account for the majority of patients with postmenopausal osteoporosis. Nevertheless, all postmenopausal patients with osteoporosis should be evaluated for secondary causes of bone loss, such as long-term (more than three months) administration of systemic glucocorticoids, including high doses of inhaled steroids and endogenous hypercortisolism; rheumatoid arthritis; chronic liver disease; alcoholism; untreated hypogonadism following bilateral oophorectomy; anorexia nervosa or other severe eating disorders; administration of chemotherapy or aromatase inhibitors; hypopituitarism; prolonged immobility associated with spinal cord injury, Parkinson's disease, stroke, muscular dystrophy or ankylosing spondylitis; immunosuppression in organ transplantation patients; diabetes mellitus type 1 or type 2; untreated hyperthyroidism and over replacement in hypothyroidism; inflammatory bowel disease; and chronic obstructive pulmonary disease. This article focuses on newer issues in postmenopausal osteoporosis that are not attributable to secondary conditions.

Identifying Patients At Risk

Bone mineral density (BMD) is an assessment of the mineral content in key skeletal regions. The World Health Organization (WHO) has defined osteoporosis using a BMD score derived from dual-energy X-ray absorptiometry (DXA). Central DXA is used for measurement of BMD of the spine and hip. It has proven utility for the diagnosis of osteoporosis, assessment of fracture risk, and monitoring of response to treatment. This method is widely available with readily interpretable results. The risk of fracture exponentially increases as BMD decreases at the spine, hip, forearm, humerus, and pelvis. Peripheral DXA measurements of the BMD of the forearm, heel or hand correlate less well with central DXA measurements, and they have little utility as serial measurements to assess treatment efficacy.

The WHO's Fracture Risk Assessment Tool (FRAX) is a fracture risk prediction model that utilizes the femoral neck BMD as measured by DXA and incorporates clinical risk factors for bone loss in order to better estimate the 10-year probability of hip and other major osteoporotic fractures (spine, humerus, forearm). Newly developed advances in DXA methods have greatly expanded their functionality and a relationship between 3D bone characteristics, mechanical parameters, and the trabecular bone score (TBS) has been established. Many studies have demonstrated that TBS predicts current and future fragility fractures in osteoporosis beyond those predicted by BMD and clinical risk factors and has value in monitoring response to treatment. TBS may have additional value in secondary osteoporosis when abnormal trabecular microarchitecture may help explain the paradox of increased fractures at a higher BMD in specific diseases or conditions (e.g., diabetes, rheumatoid arthritis, glucocorticoid-induced osteoporosis). One way of interpreting TBS would be to provide clinically relevant ranges (Table 1). The WHO is considering possible inclusion of TBS in the FRAX calculation.

Table 1 Proposed trabecular bone score (TBS) ranges for postmenopausal women.

TBS	Microarchitecture
<1.2	Degraded=higher risk of fracture
1.2-1.35	Partially degraded=medium risk of fracture
>1.35	Normal=lower risk of fracture

Interventional Strategies

A strategic approach to postmenopausal osteoporosis would embrace early detection and staged interventions. Bone mass is largely genetically determined. More than one-third of women reach menopause with low bone density, which is frequently worsened by years of inadequate calcium and/or vitamin D intake. This can lead to regions of under mineralized bone and loss of structural elements, resulting in increased skeletal fragility that is often undetected by bone density measurements alone.

Therefore, a starting point for proper risk assessment includes a detailed medical, activity, and nutritional history. Bone density measurement by DXA provides an excellent surrogate measure of fracture risk. A narrow femoral neck or radial shaft resulting in a low moment of inertia can be a predictor of low bone strength. Assessing trabecular bone structure by calculating TBS may provide insights into the structural integrity.

Starting early to prevent osteoporosis means ensuring adequate calcium, vitamin D, and exercise during the formative years to build bone mass to its genetically programmed ideal level. Deficiencies in calcium and vitamin D intake during the peri-menopausal years can accelerate the rate of bone loss, as can diets high in phosphate or acid content. Therefore, initiating and maintaining a healthy bone program as early as possible is one starting point.

Calcium

Thousands of milligrams of calcium passively diffuse into and out of bone daily and are bioactively moved into and out of the bone matrix during cell-mediated bone remodeling. As much as 10,000 mg of calcium are filtered by the kidneys daily, and more than 98% of that is reabsorbed. Minor increments in the renal filtered load over a prolonged period of time can lead to chronic deficits in calcium balance. Inadequate dietary calcium can result in a compensatory loss of calcium from bone-a negative spending-that

can have detrimental consequences for skeletal integrity. During normal bone homeostasis, there are obligatory losses of calcium by the kidneys, gastrointestinal tract, and skin; replenishment via dietary intake is necessary to maintain a positive calcium balance. Beyond calcium homeostasis, several studies suggest additional bone benefits from calcium supplementation. Evidence that calcium supplementation reduces fracture incidence would be the most convincing proof of skeletal benefit. Post hoc analyses have shown a positive effect of calcium supplementation on fractures in compliant patients; however, intent-to-treat analyses have not shown an effect. In a meta-analysis of 17 trials with 52,625 participants, there was a 12% risk reduction. In the subgroup that had calcium supplementation alone, an analysis of only 6,517 participants, the reduction in fracture risk was even greater (24%) when compliance was high (greater than 80%) and when calcium supplementation was equal to or greater than 1,200 mg per day.

Recently, controversy has raged over the incidence of myocardial infarction in patients receiving calcium supplements. Randomized controlled trials and meta-analyses have not resolved the controversy, and the disagreement persists. In 2013, a study in patients with osteoporosis who were followed for 10 years reported that calcium supplements, up to 1,000 mg per day, along with increased dietary intake of calcium may be associated with a reduced risk of mortality in women (45).

Vitamin D

Based on data from randomized placebo-controlled clinical trials evaluating falls and fractures, the US Institute of Medicine recently recommended that a circulating level of 25-hydroxy vitamin D (25OHD) at 20 ng/ml is sufficient for 97.5% of the population, although up to 50 ng/mL is safe. Adults up to 70 years old need 600 IU vitamin D daily to meet the goal of 20 ng 25OHD, although up to 4,000 IU daily is considered safe. However, several experts consider these recommendations to be too strict, given data from other relevant studies. Parathyroid hormone levels increase at 25OHD levels less than 30ng/mL, and intestinal calcium transport increases at 25OHD levels greater than 32ng/mL. Epidemiological studies have shown that both BMD and muscle function (e.g., walking speed) positively correlate with 25OHD levels. BMD improves in elderly individuals receiving a combination of Vitamin D and calcium supplements. Supplementation with at least 800 IU of Vitamin D daily is associated with improved lower extremity function, greater balance, and reduced falls, as well as fracture prevention.

Therapeutic Interventions

The average bone loss in the five years around menopause (perimenopause) can reach 15%, which puts women who come to menopause with low bone density at significant risk for future fracture. These women need to be identified early so that appropriate measures can be implemented to preserve and protect their skeletal mass. In the early perimenopausal period, simple antiresorptive agents can preserve and protect skeletal mass. Late in the perimenopausal period, only prolonged therapy with costly anabolic agents can partially repair the skeletal loss. Premenopausal women at increased risk for osteoporosis, such as those with a strong family history of osteoporosis; history of inflammatory vascular, musculoskeletal, or bowel diseases; diabetes; history of disordered eating; and medical treatments such as steroids or aromatase inhibitors merit full evaluation. These women, prior to menopause or in their early perimenopause, should undergo a bone density determination; a biochemical evaluation of bone turnover, urinary calcium loss, and vitamin D levels; and a detailed history of lifestyle factors that might contribute to bone loss.

Antiresorptives

The use of estrogen replacement therapy to prevent or treat postmenopausal osteoporosis is limited due to its adverse effects in the uterus, breast, and cardiovascular system. The Women's Health Initiative confirmed that oral estrogen (0.625 mg daily) with progestin in women with an intact uterus, or without progestin after hysterectomy, prevents bone loss and is associated with a reduction in fracture risk; however, this diminishes within a year after discontinuation. Selective estrogen receptor modulators, such as raloxifene, exert an antiestrogen effect in the uterus and breast, whereas they have an estrogen agonist effect in bone. Raloxifene reduces the incidence of vertebral fractures; however, evidence regarding hip and nonvertebral fractures is lacking, and its efficacy is lower than that of other antiresorptives. The increased risk of venous thromboembolic events persists, and it may aggravate menopausal vasomotor effects.

Bisphosphonates (BPs), such as alendronate, risedronate, ibandronate, and zoledronic acid, have unique properties that enable them to decrease bone resorption by inactivating osteoclasts (partly by inducing their apoptosis). This results in the maintenance of bone microarchitecture and mineralization, and leads to a reduced fracture risk. BPs remain embedded in bone and are slowly released from the skeleton over time; this long elimination half-life likely explains the delayed reversal of their antiresorptive effect after discontinuation.

These agents are generally safe with few adverse events, mainly the gastrointestinal reflux symptoms associated with oral BPs. Due to BPs' renal clearance, they are contraindicated in severe renal impairment. Greatest safety concerns are with regard to rare adverse events, such as osteonecrosis of the jaw and atypical fractures that may occur with higher frequency during BP therapy lasting longer than 5 years. Osteonecrosis of the jaw has been extensively discussed in recent consensus papers. Atypical low energy or low-trauma fractures of the femoral shaft have been reported as a rare occurrence in BP-treated patients. However, reductions in morbidity and mortality have been reported with BP therapy following hip fracture and in frail, elderly women. Overall, the reduced fracture risk with BP treatment in the appropriate patient population greatly outweighs the risks of extremely rare adverse events.

Only one anabolic agent, teriparatide (TPTD), has been approved by the US Food and Drug Administration as a treatment for severe osteoporosis. TPTD, a 34-amino-acid peptide, is the biologically active N-terminal portion of recombinant human parathyroid hormone. When injected subcutaneously daily at 20_g, a brief spike in active hormone levels lasting only minutes results in an anabolic response in bone. Bone morphometric studies show increased osteoblast activation and new bone formation within a few months of initiating therapy. However, the newly formed matrix mineralizes slowly, as changes in BMD at the spine, with its high trabecular bone content, start to be seen only after 10 or 12 months of treatment. At the hip, which has a much higher cortical, or dense, bone content, increasing BMD is more likely to be seen after 18 months of treatment. Following TPTD therapy, the increase in BMD is slowly lost unless the newly formed and probably undermineralized bone is protected by administration of an effective antiresorptive agent. Thus, successful anabolic treatment with TPTD requires combination therapy.

Combined Therapy

In an effort to improve outcomes with TPTD, a number of studies have varied the doses, agents and regimens of combined therapy. Early studies examining concurrent use (often starting with BP before TPTD) reported attenuation of the BMD response when compared with the anabolic agent alone. Treatment with one year of TPTD alone followed by BP alone resulted in improved bone density and mass at year two. Denosumab combined with TPTD increased BMD at the lumbar spine and hip more than either denosumab alone or TPTD alone after one and two years, and it produced favorable structural changes in cortical parameters. Altering the sequence of anabolic and antiresorptive BP therapy has improved BMD outcomes, particularly in year two of combined therapy.

The critical time during which TPTD induces increased bone formation, which is presumed to precede bone resorption, the so-called anabolic window, was not defined. When bone markers were tracked during the first 4-8 months of TPTD treatment, patients with an early rise in bone resorption, reflecting early closure of the anabolic window, showed a poor response to TPTD in terms of BMD change at 2 years. The early closure of the anabolic window helps explain data showing that the initial anabolic stimulus was augmented by the delayed administration of an antiresorptive agent. However, neither study provided insights on how to identify those patients receiving anabolic therapy who are most likely to benefit from appropriately timed combination therapy.

Newer anabolic therapies that are not constrained by an anabolic window are in clinical trials or are being developed. These agents act more directly on bone-forming pathways to enhance bone formation without provoking an osteoclast-mediated bone-resorptive response. One such agent is a humanized monoclonal antibody directed against sclerostin, an inhibitor of the bone-forming Wnt pathway. The earlier human trials have reported an excellent safety and efficacy response. Intermittent therapy with a pure anabolic could achieve treatment to goal, with a significant reduction in fracture risk.

Conclusion

The approach to osteoporosis should in principle follow a treatment-to-goal strategy. A therapeutic regimen to lower fracture risk should be individually applied, reassessed, and then changed to meet endpoints that best predict outcome. For example, treatment with raloxifene usually results in little or no significant increase in BMD. Therefore, there is little benefit to monitoring BMD to assess the reduction in fracture risk. However, a significant decline in BMD could indicate increasing fracture risk. By contrast, anabolic therapy with TPTD typically results in a significant increase in BMD, and this change is strongly correlated with a reduction in fracture risk. Regrettably, specific treatment goals have yet to be defined. Therefore, a pragmatic approach to treatment is advised. This starts with making the best assessment of fracture risk based on BMD, microstructure as determined either by CT or TBS analysis, and clinical evidence of prior skeletal fragility.

Those at highest fracture risk are likely to require parenteral antiresorptives or anabolic therapy. In these high-risk patients, it is often appropriate to monitor the increase in BMD and perhaps to set a goal that would be associated with a significantly lowered fracture risk. For low-risk patients with a BMD T-score at or near -2.5 and evidence of normal bone structure, normal geometry, and normal bone turnover, along with a negative history of skeletal fragility, a less intense regimen may be sufficient-for example, ensuring adequate calcium and vitamin intake and sufficient exercise. In all cases, periodic reassessment of BMD, skeletal and general health, and new medication use, is necessary because all of these may affect risk status and may require treatment modification.

Reference: Andreopoulou, Panagiota, and Richard S. Bockman. "Management of postmenopausal osteoporosis." Annual review of medicine 66 (2015): 329-342.

Congratulations !

The Winners of WOMEN'S HEALTH *Quiz Competition*

Volume : 8, No. :1, Jan - June 2015

1. **Dr. Farjana Raihan**
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2. **Dr. Mukta Sultana**
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   Kishoregonj

3. **Dr. Fedousi Akter**
   MBBS, MO
   250 bedded General Hospital
   Maizdee, Noakhali

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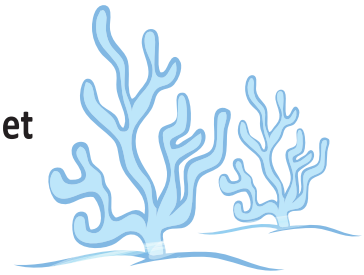

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