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RECENT ADVENCES IN MEDICAL TREATMENT OF OSTEOPOROSIS

OSTEOPOZUN MEDİKAL TEDAVİSİNDE GÜNCEL GELİŞMELER

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SUMMARY:

Osteoporosis is the most common bone disease, associated with low bone mineral density (BMD) and pathological fractures which lead to significant morbidity. It is defined clinically by a BMD of 2.5 standard deviations or more below the young adult mean (T-score = −2.5). Osteoporosis is also a huge global problem both socially and economically. Therefore preventative and therapeutic approaches are key to managing this problem within the aging population of today. Pharmacologic therapy for osteoporosis includes the use of antiresorptive agents to decrease bone resorption, such as bisphosphonates, the selective estrogen-receptor modulator (SERM) raloxifene, calcitonin, and denosumab. In addition, there are anabolic steroids that promote bone formation in patients with osteoporosis, such as teriparatide. Also new drugs are emerging for the treatment of osteoporosis, characterized by acting on very specific bone cell physiology.

Key words: Osteoporosis, medical treatment, new medicines.

Level of evidence: Review Article, Level V.

ÖZET:

Osteoporoz, düşük kemik mineral yoğunluğu ve patolojik kırıklarla seyreden ve belirgin morbiditelere yolaçan en sık görülen kemik hastalığıdır. Tanım olarak kemik mineral yoğunluğunun genç erişkinlere göre 2,5 standart sapma daha daha düşük olması olarak tarif edilebilir. Osteoporoz gerek sosyal, gerek ekonomik olarak da global bir problem halindedir ve bu nedenle giderek yaşlanan popülasyonumuzda koruyucu ve tedavi edici yaklaşımlar son derece önemli bir hale gelmiştir. Osteoporozun farmakololojik tedavisinde, kemik rezorbsiyonunu azaltan, bifosfonatlar, selektif östrojen modülatörü raloksifen, kalsitonin ve denosumab ile kemik yapımını arttıran teriparatid gibi ajanlar kullanılmaktadır. Son dönemde antisklerostin antikoru, katepsin K inhibitörü gibi kemik hücre fizyolojisi üzerine etkileri olan ilaçlar üzerine yapılan çalışmaların artması, osteoporoz tedavisinde daha iyi sonuçlara ulaşılacağını da düşündürmektedir.

Anahtar kelimeler: Osteoporoz, tıbbi tedavi, bifosfonatlar.

Kanıt Düzeyi: Derleme, Düzey V.

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INTRODUCTION:

Osteoporosis is defined by the World Health Organization as a value for bone mineral density (BMD) 2.5 standard deviations or more below the young female adult mean, referred to as a T-score of –2.5, where a T-score of zero is equal to the young female adult mean[8]. For the year 2000, there were an estimated 9 million new osteoporotic fractures, of which 1.6 million were at the hip, 1.7 million were at the forearm and 1.4 million were clinical vertebral fractures.

By 2005, the worldwide incidence of hip fracture in men is projected to increase by 310 % and 240 % in women. Europe and the Americas accounted for 51 % of all these fractures, while most of the remainder occurred in the Western Pacific region and Southeast Asia[16]. Although Turkey is still among the countries with low hip fracture rates in Europe, the incidence has increased markedly in the last 20 years.

In 2009, there were approximately 24,000 hip fractures estimated in Turkey, 73 % of which were found in women. Assuming no change in the age- and sex-specific incidence, the number of hip fractures was expected to increase to nearly 64,000 in 2035[33]. Osteoporosis takes a huge personal and economic toll. In Europe, the disability due to osteoporosis is greater than that caused by cancers (with the exception of lung cancer) and is comparable or greater than that lost to a variety of chronic noncommunicable diseases, such as rheumatoid arthritis, asthma and high blood pressure related heart disease[16].

Identifying and treating patients at risk of fracture, but who have not yet sustained a fracture, will substantially reduce the long term burden of osteoporosis. Reducing the risk of first fracture from 8 % to 2 % can reduce the 5-year fracture incidence from approximately 34 % to 10 % [21]. Treatment of established osteoporosis is cost-effective irrespective of age and therapies with proven rapid efficacy may offer important value to healthcare payers, providers and patients[17]. There is a range of drug treatment available for postmenopausal osteoporosis. Different studies have consistently shown that, depending on the drug and the patient population, treatment reduces the risk of vertebral fracture by between 30-70 %, nonvertebral fractures by between 15-20 %, and hip fractures up to 40 %[18].

Postmenopausal women and men age 50 and older presenting with the following should be considered for treatment: A hip or vertebral fracture (clinically apparent or found on vertebral imaging). T-score ≤–2.5 at the femoral neck, total hip, or lumbar spine.

Low bone mass (T-score between –1.0 and –2.5 at the femoral neck or lumbar spine) and a 10-year probability of a hip fracture ≥3 % or a 10-year probability of a major osteoporosis-related fracture ≥20 % based on the FRAX calculation[1]. All patients being considered for treatment of osteoporosis should also be counseled on risk factor reduction including the importance of calcium, vitamin D, and exercise as part of any treatment program for osteoporosis.

All patients with low bone mass should have an adequate daily intake of calcium and vitamin D in addition to what ever bone strengthening medication they may be using. It is generally recommend a daily calcium intake of 1,200 mg with most of the calcium derived from dietary sources if possible[7]. There is no evidence that calcium intake in excess of these amounts confers additional bone strength. There have been a number of studies questioning the cardiovascular safety of calcium supplementation, but a recent analysis of the Women's Health Initiative data involving over 93,000 postmenopausal women failed to find evidence for an adverse influence of calcium and vitamin D supplementation on the risk for myocardial infarction, coronary heart disease, total heart disease, stroke, or total cardiovascular disease[27]. While there are a number of different recommendations for daily vitamin D intake, the recommended daily vitamin D dose to a level that provides an adequate serum level (30 ng/ml and above), a goal that is usually met with daily vitamin D intake of 1,000 to 2,000 IU[15].

The prescription drugs approved for the treatment of fracture prevention are often classified by whether they reduce bone loss (antiresorptive) or promote bone growth. All of the approved drugs have been shown to improve bone mineral density and to prevent some fragility or osteoporosis related fractures. The approach to treatment is tailored to the clinical needs of each individual patient. Treatment decisions should be individualized according the patient's age, bone density values, prior fracture history, underlying general health, and concomitant medications.

Current FDA-approved pharmacologic options for the prevention and/or treatment of osteoporosis include, in alphabetical order: bisphosphonates (alendronate, alendronate plus D, ibandronate, risedronate and zoledronic acid), calcitonin, estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene), tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone (PTH [1–34], teriparatide), and the receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) inhibitor denosumab[8].

BISPHOSPHONATES:

Bisphosphonates are the most commonly used drugs for the treatment of osteoporosis. They avidly bind to bone and are internalized by osteoclasts to inhibit resorption. Alendronate is the most commonly prescribed drug for the treatment of postmenopausal osteoporosis and is associated with increased BMD . Alendronate sodium is approved by the FDA for the prevention and treatment of postmenopausal osteoporosis. Alendronate is also approved for treatment to increase bone

mass in men with osteoporosis and for the treatment of osteoporosis in men and women taking glucocorticoids[30]. It increases spine and hip bone mineral density and reduces the relative risk of fracture of the spine, hip, and wrist by about 50 %[3]. Risedronate was introduced several years after alendronate and is a widely used oral bisphosphonate. It is approved for use of osteoporosis in men and women. Risedronate has been shown to reduce vertebral fractures by 41 % and nonvertebral fractures by 39 % over 3 years[14].

Ibandronate sodium is approved by the FDA for the treatment of postmenopausal osteoporosis. Ibandronate reduces the incidence of vertebral fractures by about 50 % over 3 years, but reduction in risk of nonvertebral fracture with ibandronate has not been documented[6]. Zoledronic acid is approved by the FDA for the prevention and treatment of osteoporosis in postmenopausal women. It is also approved to improve bone mass in men with osteoporosis and for the prevention and treatment of osteoporosis in men and women expected to be on glucocorticoid therapy for at least 12 months. Zoledronic acid is also indicated for the prevention of new clinical fractures in patients (both women and men) who have recently had a low- trauma (osteoporosis-related) hip fracture. Zoledronic acid reduces the incidence of vertebral fractures by 70 % (with significant reduction at 1 year), hip fractures by 41 %, and nonvertebral fractures by 25 % over 3 years in patients with osteoporosis defined by prevalent vertebral fractures and osteoporosis by BMD of the hip[5].

Contraindications to bisphosphonate therapy include hypersensitivity or hypocalcemia. Bisphosphonates should be used with caution, if at all, in patients with reduced kidney function (glomerular filtration rate below 30 mL/ min for risedronate and ibandronate or below 35 mL/min for alendronate and zoledronate)[19].

Orally administered bisphosphonates should be used with caution in patients with active upper GI disease, inability to follow the dosing regimen for oral use (that is, inability to remain upright for 30 to 60 minutes), or presence of anatomic or functional esophageal abnormalities that might delay transit of the tablet (for example, achalasia or stricture). Intravenous administration of nitrogen-containing bisphosphonates, such as pamidronate, ibandronate and zoledronate, circumvented this problem. Intravenous bisphosphonates are generally well tolerated, and the most commonly observed side effect is self-limiting flu-like symptoms which persist for about 3 days following the first administration. Osteonecrosis of the jaw is a rare but recognized side effect resulting from long-term bisphosphonate use[20]. It is most prevalent in individuals who have received high dose IV bisphosphonate therapy for malignant disease and rare in osteoporotic patients. Although rare, low-trauma atypical femur fractures (subtrochanteric or femoral shaft) may be associated with the long-term use of bisphosphonates diagnosed upon presentation with a characteristic combination of features to distinguish from typical femoral fractures[32].

The limited trial data available regarding long-term treatment with bisphosphonates has raised questions about the optimal length of treatment with these medications. This issue has become more important, given newly recognized complications of bisphosphonate use, including osteonecrosis of the jaw and atypical femur fractures. In 2016, the American Society for Bone and Mineral Research published guidelines on long-term bisphosphonate treatment that included the following recommendations[1]:

a. After 5 years of oral bisphosphonates or 3 years of intravenous bisphosphonates, reassessment of risk should be considered.

b. In women at high risk (eg, older women, those with a low hip *T*-score or high fracture risk score, those with previous major osteoporotic fracture, or those who fracture on therapy), continuation of treatment for up to 10 years (oral) or 6 years (intravenous), with periodic evaluation, should be considered.

c. The risk of atypical femoral fracture, but not osteonecrosis of the jaw, clearly increases with the duration of bisphosphonate therapy, but such rare events are outweighed by vertebral fracture risk reduction in high-risk patients.

d. For women not at high fracture risk, a drug holiday of 2 to 3 years can be considered after 3 to 5 years of BP treatment.

CALCITONIN:

Calcitonin is a naturally occurring peptide hormone synthesized and secreted by the thyroidal C-cells. Mature osteoclasts express calcitonin receptors and, in vitro, calcitonin acts directly on osteoclasts to inhibit resorption. Calcitonin reduces vertebral fracture occurrence by about 30 % in those with prior vertebral fractures but has not been shown to reduce the risk of nonvertebral fractures. In 2013, an FDA post-marketing review was prompted after studies showed increased risk of malignancies in calcitonin-treated patients. In a meta-analysis of 21 randomized, controlled clinical trials with calcitonin-salmon (nasal spray or investigational oral formulations), the incidence of malignances in calcitonin-treated patients was 4.1 %, versus 2.9 % in placebo-treated patients. The data were not sufficient for further analysis by specific malignancies and a definitive causal relationship between calcitonin use and malignancies could not be established. The FDA has recommended that health care professionals assess a patient's need for osteoporosis therapy as well as benefits and risk of

available treatments[26]. Calcitonin is an option for patients who are not candidates for other available osteoporosis treatments.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

Selective estrogen receptor modulators (SERMs) are considered to provide the beneficial effects of estrogen without the potentially adverse outcomes. Raloxifene is a selective estrogen receptor modulator and inhibits bone resorption. It is approved for the treatment and prevention of osteoporosis in postmenopausal women, at a dose of 60 mg daily. Raloxifene reduces the risk of vertebral fractures by about 30 % in patients with a prior vertebral fracture and by about 55 % in patients without a prior vertebral fracture over 3 years[11]. Reduction in risk of nonvertebral fracture with raloxifene has not been documented. Raloxifene is also indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis[2].

Pooled mortality data from large clinical trials of raloxifene (60 mg/day) were analyzed by Grady et al in 2010. When compared with placebo, all-cause mortality was 10% lower in older postmenopausal women receiving raloxifene. The primary reduction was in noncardiovascular, noncancer deaths[13].

The combination product of bazedoxifene, a SERM, and conjugated estrogens (CEs) was approved by the FDA in October 2013 for prevention of osteoporosis and treatment of vasomotor symptoms in postmenopausal women. Combining a SERM with CEs lowers the risk of uterine hyperplasia caused by estrogens. This eliminates the need for a progestin and its associated risks (eg, breast cancer, myocardial infarction, venous thromboembolism). In clinical trials, this combination decreased bone turnover and bone loss in postmenopausal women at risk for osteoporosis. Bone mineral density increased significantly more with all bazedoxifene/CE doses compared with placebo at the lumbar spine and total hip and with most bazedoxifene/CE doses compared with raloxifene at the lumbar spine[22].

PARATHYROID HORMONE:

Parathyroid hormone (PTH) 1-34 and PTH 1-84 are peptides of the parathyroid hormone family. They represent the intact molecule (1-84) or the 1-34 N-terminal fragment (teriparatide). Unlike endogenous PTH which leads to mobilisation of calcium from skeletal sites (loss of bone mineral) the intermittent exposure to once daily exogenous PTH increases bone formation more than bone resorption resulting in an anabolic effect and increased bone mass. The exact mechanism leading to the anabolic effect of teriparatide is not fully understood, but it has been shown to enhance osteoblast formation from its circulating precursors and prevent osteoblast apoptosis[10]. The effects of parathyroid hormone are maximal at skeletal sites which are predominantly composed of trabecular bone such as the spine.

Teriparatide (Forteo) is a recombinant human parathyroid hormone (1-34) (PTH [1-34]) and is the only available anabolic agent for the treatment of osteoporosis. It is indicated for the treatment of women with postmenopausal osteoporosis who are at high risk of fracture, who have been intolerant of previous osteoporosis therapy, or in whom osteoporosis treatment has failed to increase bone mass. It is indicated in men with idiopathic or hypogonadal osteoporosis who are at high risk of fracture, who have been intolerant of previous osteoporosis therapy, or in whom osteoporosis therapy has failed. Teriparatide is also approved for the treatment of patients with glucocorticoid-induced osteoporosis. The approved dosage of teriparatide is 20 μg once daily injected subcutaneously. Teriparatide is dispensed in a glass cartridge that is preassembled into a disposable multiple-dose pen syringe device designed to provide 28 doses[28].

It is contraindicated in patients with pre-existing hypercalcemia, severe renal impairment, pregnancy, breast-feeding mothers, history of bone metastases or skeletal malignancies, and patients who are at an increased baseline risk for osteosarcoma including those with Paget disease, unexplained elevated alkaline phosphatase, children and young adults with open epiphyses or prior radiotherapy of the skeleton[28]. Patients with monoclonal gammopathies of uncertain significance (MGUS) should also not be given teriparatide. Before treatment with teriparatide, levels of serum calcium, PTH, and 25(OH)D need to be monitored.

Teriparatide is given for a maximum of 2 years, Initial studies using a combination of concurrent PTH and bisphosphonate therapy showed decreased benefit compared with therapy with either agent alone; therefore, the general recommendation is that these drugs be given separately and in sequence[12]. When use of teriparatide is stopped, bone density declines quickly during the following year, although fracture reduction may persist for 1 or 2 years. Use of alendronate after teriparatide therapy prevents this loss and in some cases will be associated with a further increase in BMD[4].

Most studies with PTH have been performed on women. The medication decreases the risk of vertebral and nonvertebral fractures to the same extent as bisphosphonates. It has been shown to increase bone mineral density at the spine and hip and to reduce the relative risk of vertebral fractures by 65 % and nonvertebral fractures by 55 % over 18 months compared to placebo[24].

A study performed by an Austrian group using PTH 1-84 to treat pelvic fractures in postmenopausal women with osteoporosis demonstrated that this anabolic agent has

the ability to both increase the rate of union and enhance the speed of the process. In addition to improved fracture healing, treatment with PTH 1-84 was also associated with a significant decrease of pain and improved function over the placebo arm. This clinical study supports the extensive animal data that predicted a clear role for PTH in fracture repair[25].

DENOSUMAB:

Denosumab (Prolia) is a humanized monoclonal antibody directed against the receptor activator of the nuclear factor-kappa B ligand (RANKL), which is a key mediator of the resorptive phase of bone remodeling. It decreases bone resorption by inhibiting osteoclast activity. Denosumab is approved by the FDA for the treatment of osteoporosis in postmenopausal women at high risk of fracture. Denosumab reduces the incidence of vertebral fractures by about 68 %, hip fractures by about 40 %, and nonvertebral fractures by about 20 % over 3 years[9]. Denosumab is also indicated to increase bone mass in men at high risk of fracture, treat bone loss in women with breast cancer on aromatase inhibitor therapies, and to treat bone loss in men receiving gonadotropin-reducing hormone treatment for prostate cancer who are at high risk for fracture. Because the overactivity of RANKL is a major factor in bone loss in patients with autoimmune and inflammatory disorders, such as ulcerative colitis, denosumab may become first-line therapy for these patients[31]. No dose adjustment is required in patients with renal impairment. Hypocalcaemia should be corrected by adequate intake of calcium and vitamin D before initiating therapy. Side-effects include skin infection, predominantly cellulitis, and hypocalcaemia.

STRONTİUM RANELATE:

Strontium ranelate is not approved by the FDA, but is licensed (oral formulation of 2 g/day) for restricted use for the prevention of vertebral and nonvertebral osteoporotic fractures in the EU, in patients where bisphosphonate treatment has failed or is contraindicated. Divalent strontium ions have the capacity to substitute for calcium within bone without adversely affecting mineralization. Strontium ranelate (Protelos) increases BMD and reduces the risk of vertebral and nonvertebral fractures[23]. Because of an increase in the risk of myocardial infarction in individuals taking strontium ranelate, this drug should only be used to treat severe osteoporosis in postmenopausal women and men at high risk of fracture, for whom treatment with other approved drugs is not possible. It should not be used in patients with established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, or those with uncontrolled hypertension[29].

THE NEXT GENERATION THERAPEUTICS:

It is demonstrated that further therapeutic advances are continuing in the management of osteoporosis. The long-term follow studies with denosumab give comfort that treatment up to 10 years will show continued benefits in terms of bone mass and structural changes with, in all likelihood, maintained antifracture efficacy. Studies presented examining the potential for the antiresorptive agents, odanacatib (Cathepsin K Inhibitor) and abaloparatide,(Recombinant PTHrP analogue) suggest that these new treatments may well have a role in the clinic very soon when approved by licensing authorities. There are some very encouraging results about the romosuzumab, the antisclerostin antibody, as being the new anabolic therapy.

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