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TREATMENT OF SEVERE OSTEOPOROSIS IN RUSSIA
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Objective: To review and analyze peculiarity of medical therapy and treatment results in patients with severe osteoporosis in selected clinics in Russia.

Methods: Within the study source, data analysis was performed for the patients who were observed for at least 1 y. Total number of patients included in analysis was 1000: 955 women and 45 men aged from 35-95 y. Observation period was 2864.5 person-years.

Results: At the time of diagnosis of osteoporosis, more than 90% of the patients had at least one fracture in their history, and 70% of the patients had multiple vertebral fractures. During the observation period, new fractures occurred in 23.9% of patients, frequency of hip fractures was 28.8%, vertebral fractures - 24.8%. There was registered high level used of oral and parenteral bisphosphonates at baseline (55% and 30.2%, respectively). Antiestoporosis treatment was changed or canceled in 48.3% patients with severe osteoporosis. The most often reasons were low efficacy, adverse events and the patient's inability to pay for treatment. Oral bisphosphonates were the most frequently canceled medications (71.3%). Parenteral bisphosphonates and denosumab were more frequently used at the time of last observation (42.8% and 36.6%, respectively). Over 5% of patients with severe osteoporosis received anabolic therapy (teriparatide). The best results of treatment were observed in patients who was initially prescribed intensive therapy (parenteral bisphosphonates at least 3 y, denosumab or teriparatide at least 1 y). In this group, new fractures occurred with a lower frequency than in other patients (22.1% and 29.6% for all fractures, 9.9% and 17.1% for vertebral fractures, and 0.6% and 3.5% for hip fractures, respectively).

Conclusion: Treatment of patients with severe osteoporosis should be started with intensive therapy (parenteral bisphosphonates, denosumab, teriparatide) in order to reduce the risk of fractures.

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PRE-ANALYTICAL VARIABILITY OF BONE TURNOVER MARKERS IN AND ELDERLY POPULATION IN IRAN: BUSHEHR ELDERLY HEALTH (BEH) PROGRAM
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Objective: To evaluate the pre-analytical variability of four BTMs, osteocalcin (OC), C-terminal telopeptide of type I collagen (CTX), bone specific alkaline phosphatase (bALP), and tartrate-resistant acid phosphatase (TRAP) in an elderly population.

Methods: A random subsample of 400 individuals (186 men and 214 women) from the baseline survey of the Bushehr Elderly Health (BEH) programme, a population-based prospective cohort study being conducted in Bushehr, a southern province of Iran, was selected for this study. OC and CTX were measured using electrochemiluminescence method (Roche Diagnostics, cobas e 411) and bALP and TRAP were measured using ELISA method (immunodiagnostic systems). Robust multiple linear regression models (Hampel’s M-estimator) were used adjusted for age, sex, smoking, alcohol, history fractures, drugs, bed/rest immobility, circadian, physical activity, taking corticosteroids more than three months, renal disease, liver disease, type 2 diabetes mellitus (T2DM), thyroid disorder, menopausal status, delivery, and years after menopause (<10 y as early post menopause vs. ≥10 y as late post menopause). To avoid sparsity, low-frequency variables were omitted from the analysis.

Results: The coefficients of multiple determination of the models for men and women, respectively, were as follows: OC [R2=0.09 (P<0.01), R2=0.21 (P<0.01)], CTX [R2=0.14 (P<0.01), R2=0.12 (P<0.01)], bALP [R2=0.03 (P=0.64), R2=0.03 (P<0.19), and TRAP [R2=0.06 (P=0.03), R2=0.07 (P<0.05)]. Age had significant effect on the OC and CTX in both genders and on TRAP in men, the most important determinant of OC and CTX in both genders was T2DM
that causes severe decrease in BTM levels. Late postmenopause women experienced significant decrease on their TRAP levels vs. early postmenopause women (this variable explained 56% of variability that accounted for by the model). Physical activity changed the CTX levels in men and women in opposite directions.

**Conclusion:** Pre-analytical sources of variability should be taken into account when interpreting BTMs in clinical practice. This may be very important in elderly, in whom several coexisting factors may influence the level of BTMs.

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**BONE MINERAL DENSITY CHANGES IN PATIENTS RECEIVING LIVER TRANSPLANTATION AND INFLUENCE OF TREATMENTS TARGETING BONE REMODELING**

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**Objectives:** Chronic hepatic diseases and liver transplantation can be responsible for bone fragility with an increase morbidity and mortality. The objectives of this study were to determine the prevalence of osteoporosis before transplantation, its evolution along the follow-up and the influence of treatments targeting bone remodeling and BMD.

**Methods:** This prospective, monocentric cohort study included liver transplant patients between 2006-2015. Patients were assessed with a systematic rheumatologic evaluation before their transplantation (VO) including clinical and biological evaluations, radiographs of the thoracolumbar spine and bone densitometry by DXA. They were then followed in outpatient visits of rheumatology 6 months (V1) and 3 y (V2) after the transplant.

**Results:** 251 patients were included at VO, 202 attended V1 and 112 V2. Our patients were 75.3% of men, mean age 54.9±8.8 y. Prevalence of osteoporosis before transplantation at least at one site according to the results of DXA was 26%. An antosteoporotic treatment was introduced at V0 for 34.3% of the patients, 40.6% at V1 and 43.7% at V2. Alendronate was mainly prescribed (in 55 cases or 64%). In the whole of the transplanted population, BMD lowered significantly between V0 and V1 at the femoral neck (−4.82%, p<0.0001) and at the total hip (−3.63%, p<0.0001). Between V1 and V2, it increased significantly at the total hip (+4.88%, p<0.0001), at the femoral neck (+2.14%, p=0.0224) and at the spine (+6.83%, p<0.0001). Bisphosphonates (BP) allowed a significant increase at the spine between V0 and V1 (2.11%, p=0.043) and between V1 to V2 (3.1%, p=0.05) and at the femoral neck between V1 and V2 (0.5%, p<0.0001) in comparison with untreated patients. Zoledronic acid (n=18, 22%) allowed a higher gain than the oral BP between V0 and V1 at the spine.

**Conclusion:** The liver transplanted patients presented with a greater bone fragility before and after the transplant. A significant improvement was found with BP treatment, particularly with zoledronic acid.

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**OSSEOTIDE, SYNTHETIC SELECTIVE OSTEOCGENIC PEPTIDE FOR THE TREATMENT OF OSTEOPOOROSIS: FROM DISCOVERY OF AND EFFICACY EVALUATION**

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**Objective:** Osseotide, a new synthetic peptide has been identified from the protein-protein interaction between collagen and osteopontin during bone tissue mineralization procedure. Osseotide has been developed to selectively target and distribute to skeletal tissue thereby enhancing osteogenesis. The objective of the study is to demonstrate the selective bone formation by the peptide Osseotide is through the stimulation of osteoblast differentiation, which is clear contrast to current therapy targeting osteoclast.

**Methods:** The osteogenic differentiation activity and cell signal pathway by Osseotide peptide were examined through stem cell culture to delineate the mode of action. In vivo tissue distribution of Osseotide was measured by imaging of the animal after IV and SC injection. Therapeutic effect of Osseotide was examined using osteoporosis mice models. Further GLP based safety evaluation was conducted for phase I clinical study.

**Results:** Osseotide increased osteogenic differentiation as reflected by the upregulation of osteogenic markers including RUNX2. In contrast, PPARY level, which is the marker of adipogenesis was decreased by Osseotide, indicating the peptide has selective target differentiation primarily to bone formation. The selective bone targeting by Osseotide has been further evidenced by the skeletal-selective distribution after IV and SC injection. The selective bone distribution of Osseotide is anticipated to prevent side effects by nonspecific tissue distribution. In an osteoporosis animal model, Osseotide restored bone mass with significant bone formation, which is even better than the other marketed medication, PTH. In addition, significant decrease in total fat and subcutaneous fat was observed in Osseotide treated group, which is additional advantage of this peptide over the other medication. From the GLP toxicity study result demonstrated that there has been no specific toxicity related to Osseotide even at high dose.

**Conclusion:** These results suggest that Osseotide could be an effective therapeutic agent for osteoporosis and other skeletal bone regenerative practice due to its new mode of action such as selective targeting osteogenic differentiation.

**Acknowledgments:** This study was supported by the Bio and Medical Technology Development Program of the National Research Foundation funded by the Ministry of Science and ICT (NRF 2017M3A9B3063635).