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**Congress Report: CEE Summit on
Bone Diseases: International
Experts' Forum**

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Congress Report

CEE Summit on Bone Diseases: International Experts' Forum*

December 8/9, 2016, Menopausekongress (Hilton am Stadtpark, Vienna)

N. Kuprinenko

The end of the year is a traditional time for summarizing our developments, professional achievements included. It is also the time for making new plans and sharing new thoughts with friends and colleagues. For the European medical community, early December of 2016 was marked with a significant event – the Central and Eastern European Summit on Bone Diseases held in Vienna, Austria. It was organized and held by the united efforts of the Austrian leaders in this field of medicine, Professor Gerold Holzer (Department of Orthopedic Surgery, Medical University of Vienna) and Professor Heinrich Resch (St. Vincent Hospital, Academic Teaching Hospital of the Medical University of Vienna). The primary aim of the meeting was to provide the platform to present and discuss latest findings by young, but also senior



clinicians and scientists in an open, friendly atmosphere. The CEE Summit on Bone Diseases was attended by scientists representing 8 countries. It should be proudly noted that among them there was a team of Ukrainian scientists headed by Professor Vladyslav Povoroznyuk, President of the Ukrainian Association of Osteoporosis (Kyiv, Ukraine). Reports and lectures presented during the Summit covered various aspects

of managing osteoporosis, vitamin D status, fractures, and osteoarthritis, as well as the Trabecular Bone Score (TBS) and changes in bone mineral density in various groups of population. All in all, 12 reports and lectures included 5 of those presented by the specialists on osteoporosis and bone diseases from Ukraine.

President of the Ukrainian Association of Osteoporosis Professor Vladyslav Povoroznyuk (D.F. Chebotarev Institute of Gerontology NAMS of Ukraine, Ukrainian scientific-medical center for the problems of osteoporosis, Kyiv, Ukraine) presented two reports. The first one covered the topic of diagnosis of osteoporosis in clinical rheumatology. Referring to the diagnostics of osteoporosis, Prof. V. Povoroznyuk noted that BMD testing might detect osteoporosis even before the first fracture occurrence. First and foremost, the following groups should undergo BMD testing [ISCD, 2015]: all women aged 65 and older; post-menopausal women younger than 65 with risk factors for low bone mass (low body weight, prior fracture, high-risk medication use, disease or condition associated with bone loss); women during menopausal transition with clinical risk factors for fracture (low body weight, prior fracture, or high-risk medication use); all men aged 70 and older; men < 70 years of age with risk factor for low bone mass (low body weight, prior fracture, high-risk medication use, disease or condition associated with bone loss); adults with a fragility fracture, adults with a disease or condition associated with low bone mass or bone loss, adults taking medications associated with low bone mass or bone loss, anyone being considered for pharmacologic therapy, anyone being treat-

ed, to monitor treatment effect; anyone not receiving therapy in whom evidence of bone loss would lead to treatment.

Prof. V. Povoroznyuk presented data of some recent studies of osteoporosis in patients with rheumatic diseases. It had been shown that the prevalence of osteoporosis in rheumatoid arthritis (RA) patients was approximately twice than in the general population. The frequency of generalized osteoporosis in patients with RA ranged from 12.3 to 38.9% at the lumbar spine and from 6.3 to 36.3 at the hip. Older age (≥ 70 years), low BMI (< 25), longer disease duration (≥ 10 years), higher HAQ score, and higher cumulative glucocorticoid dose were significantly associated with osteoporosis [J.-H. Lee, Y.-K. Sung, et al., 2016]. Results of another study [O. Hong, J. Xu, 2014] showed that 25(OH)D levels had been reduced in patients with RA and were negatively associated with disease activity, IL-17/IL-23 and bone loss in RA. Thus, vitamin D deficiency allegedly plays a role in the etiology of RA.

In the Ukrainian study of associations between serum level of 25(OH)D and disease activity in patients with RA [Povoroznyuk V et al.], deficiency of vit. D had been determined in 58%, insufficiency – in 37.6% of patients. No more than 7.6% of patients had a normal vitamin D status. The risk of a high RA activity appeared significantly increased when the level of 25(OH)D was lower than 20 ng/ml (OR = 3.00 (95-% CI: 1.01–

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8.86, $p < 0.05$). In another Ukrainian study, TBS and BMD in RA patients had been evaluated [V. Povorozyuk, T. Karasevska, 2015]. There was an influence of age on BMD of different skeletal parts and TBS at L1–L4; however, it significantly decreased starting from 50 years. TBS of patients using glucocorticoids (GC) in a dose of more than 5 mg of prednisolone for over 3 years was significantly lower than that of patients who did not use GC (TBS L1–L4: 1.147 ± 0.168 vs 1.250 ± 0.135 ; $t = -3.07$; $p = 0.003$) and of patients who took GC only at the advanced stage for less than 6 months (TBS L1–L4: 1.274 ± 0.138 ; $t = 3.95$; $p = 0.0002$).

Kang KY, Ju JH, et al. (2013) showed that TNF inhibitors could increase lumbar spine and total hip BMD and maintain femoral neck BMD for up to 2 years in patients with ankylosing spondylitis. The study of A. Khabazzi et al. (2014) suggested that alendronate is ineffective in preventing bone loss at the early stages of ankylosing spondylitis.

Patients with systemic sclerosis were likely to have a lower BMD than healthy controls [Y. N. Wan, 2014]. They also had a higher incidence rate of vertebral fractures, especially among the female, older groups using high doses of GC or experiencing bowel dysmobility [C. Lai et al., 2015]. TBS in patients with systemic sclerosis was significantly lower ($p < 0.001$) and did not differ from TBS in RA ($p = 0.128$) despite a lower cumulative and daily GC dose [E. Koumakis et al., 2015].

In his next report, Prof. V. Povorozyuk focused on osteoporosis in men. First of all Prof. V. Povorozyuk noted that the Ukrainian population is aging very fast and 46.7% of people are 65 years and more. Men of 65 years and over account for 11.1% of the overall Ukrainian population. At the same time, osteoporosis in men is growing. Prof. V. Povorozyuk presented data of recent Ukrainian studies of BMD and TBS in men of various ages. It had been estimated that BMD and TBS significantly decreases with age; there was also found a significant correlation between BMD and TBS of lumbar spine.

Prof. V. Povorozyuk characterized some aspects of secondary osteoporosis and referred to the key points of the Clinical Practice Guidelines 2012 on diagnosis, treatment and prevention of osteoporosis in men.

Risk factors of lower limb fractures in patients of different age were discussed in the report by **Nataliia Grygorieva (D.F. Chebotarev Institute of Gerontology NAMS of Ukraine, Ukrainian scientific-medical center for the problems of osteoporosis, Kyiv, Ukraine)**. The urgency of this topic was confirmed by the fact that lower limb fractures account for approximately one third of all fractures and might result in a substantial mortality and morbidity. In 2015, Adult Official Positions of the ISCD had been updated. Their amendments included information on hip geometry: hip axis length derived from DXA was associated with a hip fracture risk in postmenopausal women; however, hip geometry parameters derived from DXA (CSA, OD, SM, BR, CSMI, NSA) should not be used to assess hip fracture risk, to initiate treatment and for monitoring.

Fractures are viewed as a considerable public health burden; despite this fact, information about their risk factors in Ukraine is limited. This prompted a recent Ukrainian study of different risk factors for lower limb fractures in patients of various ages [N. Grygorieva, R. Vlasenko, O. Zubach, 2016]. 865 subjects aged 10 years old and over with a first-time diagnosis of fracture had been identified. Questionnaires, biochemical analysis of blood serum and hip geometry measurement had been used in the assessment. The study results had confirmed a significant association between lower limb fractures, age and sex. In the age group up to 50 years, lower limb fractures were more common among males than among females. In the age group 50 years and older, the incidence of low limb fractures was higher in women. The most common anatomic sites of low limb fractures were tibia and/or fibula (48.9%), hip fractures had been registered in 29.5% of patients. Frequency of tibia/fibula fractures had risen with age from 20–29 to 60–69 years; foot fractures – from 20–29 to 50–59 years. The incidence of hip fractures had been highest in the age group over 85 years. Vitamin D deficiency was registered in 81.1% of women and 88% of men with hip fractures and in 85% of women and 70% of men with tibia/fibula fractures. 85.3% of men and 52.1% of women had FRAX-hip 3 or more. It had been confirmed that age, sex, previous fractures, some geometric parameters of the femur and serum vitamin D levels are significant risk factors for lower limb fractures. The presence of those risk factors should be considered when planning therapeutic interventions in patients with fractures.

Nataliia Dzerovych (D.F. Chebotarev Institute of Gerontology NAMS of Ukraine, Ukrainian scientific-medical center for the problems of osteoporosis, Kyiv, Ukraine) reported an association of lean mass and dietary protein intake in postmenopausal women. She noted that the aging process is associated with a gradual and progressive loss of muscle along with a lowered strength and physical endurance. Recent studies attested to a strong connection of dietary peculiarities and body composition of elderly people. Good nutrition, especially adequate protein and energy intake, could help limit and treat age-related declines in muscle mass, strength, and functional abilities. It was estimated that older participants in the highest quintile of protein intake (1.2 g/kg/day) had lost nearly 40% fewer appendicular lean mass than those in the lowest quintile (0.8 g/kg/day) over 3 years of follow-up [D. Houston, 2008]. An inadequate protein intake may be associated

with lean mass loss, and daily protein intake ≤ 0.8 g/kg was not sufficient to prevent lean mass loss in postmenopausal women [M. Bopp et al., 2008]. In women over 65 years, muscle mass had been significantly higher in cases of protein intake > 1.2 g/kg/day. So, protein and energy intake were significant predictors of muscle mass [P. Genaro et al., 2015]. Dependence of appendicular lean mass on the dietary protein intake had been evaluated in Ukrainian postmenopausal women [N. Dzerovych, V. Povoroznyuk, 2016]. It had been estimated that women with the lowest appendicular lean mass index (ALMI) consumed the lowest amounts of dietary protein. Significant correlations among dietary protein, nonessential, essential amino acids and ALMI values had been determined.

The issue of dietary protein amount consumed by elderly people with anabolic resistance was found to be very important. Nutritional recommendations for the management of sarcopenia showed that the total protein intake should be 1.0–1.5 g/kg/day [J. E. Morley et al., 2010]. According to the Nordic Nutrition recommendations (2014), 1.2–1.4 g protein/kg body weight/day with protein at the level of 15–20% of total energy intake is optimum for healthy older adults. Recommendations for dietary protein intake [R. Rizzoli, 2015] are daily 1.0–1.2 g protein/kg (body weight) with an optimal repartition over each meal to prevent sarcopenia.

Protein intake of 1.0–1.2 g/kg/day had been recommended for the preservation of healthy aging muscles, while 1.2–1.5 g/kg/day of protein might be necessary in older patients with

acute or chronic diseases. Elderly people with severe illness or malnutrition might need as much as 2.0 g/kg/day of protein [F. Landi et al., 2016].

Natalya Balatska (D.F. Chebotarev Institute of Gerontology NAMS of Ukraine, Ukrainian scientific-medical center for the problems of osteoporosis, Kyiv, Ukraine) raised a very interesting and unusual topic – BMD peculiarities in children with epidermolysis bullosa. Epidermolysis bullosa belongs to a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma. In addition to infections, sepsis, dehydration, eye disorders and skin cancer, severe forms of epidermolysis bullosa could cause fusion of fingers or toes and abnormal bending of joints (contractures), such as those of fingers, knees and elbows. It is not so long ago that the “Debra Ukraine” center was found for an express purpose of medical, psychological and financial help to children with epidermolysis bullosa and to their families in Ukraine.

Natalya Balatska told about a recent study where the BMD had been evaluated in 11 patients with epidermolysis bullosa aged 10–38 years. It had been estimated that 8 (72.7%) patients had a low BMD for their chronologic ages (mean lumbar spine aBMD Z-scores $\pm$ SD were -2.4 ± 1.9) and 4 (36.4%) – after adjusting for height Z-score (aBMD Z-scores $\pm$ SD were -1.8 ± 1.5). So, patients with a generalized recessive dystrophic form of epidermolysis bullosa had a low aBMD for their age. aBMD parameters had been reduced after adjusting for small body size.

The same results were described in earlier studies. For example, in the study by A. L. Bruckner et al. (2011), aBMD Z-scores were found less than or equal to -2 in 64% for chronological age, 50% for bone age, and 28% after adjusting for height Z-score. And aBMD correlated with height Z-score, weight Z-score, extensive blistering, immobility, albumin, hemoglobin, iron, erythrocyte sedimentation rate, and C-reactive protein values. M. S. Fewtrell et al. (2006) had shown that children with recessive dystrophic and junctional epidermolysis bullosa had lower BMD SD scores than controls; differences remained after adjusting for the smaller body size of the patients. Bone mass was best predicted by mobility rating.

The meeting continued with another interesting report presented by **Professor Heinrich Resch (St. Vincent Hospital, Academic Teaching Hospital of the Medical University of Vienna, Austria)** on atypical femoral fracture as a sign of adult hypophosphatasia (HPP). HPP is a life-threatening, progressive, systemic, inherited metabolic disorder caused by loss-of-function mutations in the ALPL gene, which encodes tissue-nonspecific alkaline phosphatase (TNSALP). Low alkaline phosphatase (ALP) activity inhibits bone mineralization, which could lead to premature death, progressive physical disability, and poor quality of life in children. HPP in adults shows different patterns, such as loss of primary dentition, pseudofractures and recurrent poorly healing metatarsal stress fractures. Diagnosis of HPP is confirmed by a low ALP level and proper clinical symptoms. The prominent symptoms are dental (premature or nontraumatic tooth loss with the root intact), skeletal (severe hypomineralization, skeletal deformities, craniosynostosis, rachitic chest, rickets, bowing, short stature, osteomalacia, bone pain, frequent fractures) and muscular (muscle weakness, hypotonia, muscular/joint pain, waddling gait, difficulty to walk). Respiratory insufficiency, vitamin B₆-responsive seizures, hypercalciuria, nephrocalcinosis, renal damage as well as delayed or missed motor milestones and short stature might also be included.

Prof. H. Resch presented the case report of a 24-y.o. male with a congenital, infantile, juvenile form of HPP. The patient had complained of pain in the right knee and thigh accompanied by cramps. He had low levels of alkaline phosphatase, PLP and vitamin D. Radiographic evaluation showed cystic lucencies in a greater trochanter on both sides, a fissure on the medial side of the left proximal femur and a sclerotic lesion with thickening of cortical bone on the right femur.

Professor Roman Lorenc (Warsaw, Poland) told about raising the efficacy of osteoporosis treatment with broader utilization of bone turnover markers (BTM). He noted that including BMT in protocols and in routine clinical practice of diagnostics, drug selection and monitoring of the treatment could improve the present situation with management of osteoporosis. BMT is an independent (from BMD) fracture risk factor and serves for the identification of postmenopausal women with increased bone turnover operating. Professor R. Lorenc presented an algorithm of using BMT for monitoring the treatment in patients with osteoporosis.

Professor Catalina Poiana (Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bu-

charest, Romania) described the influence of vitamin D on musculoskeletal health. She reminded that concentrations of 25(OH)D below the suggested level of 30 ng/ml (75 nmol/L) appear to be associated with a suboptimal calcium absorption and increased PTH. Serum 25(OH)D concentrations below 20–25 nmol/L determine an increased risk of rickets and osteomalacia. By contrast, high 25(OH)D serum levels are correlated to higher bone mineral density (BMD). Vitamin D deficiency is associated with myopathy; both vitamin D deficiency and age-related sarcopenia have been associated with a preferential atrophy of type-II fibers [C. M. Girgis et al., 2013]. Proximal myopathy is often associated with proximal myalgia or with more diffuse muscle pain. There exist conflicting data regarding an association between vit. D deficiency and fibromyalgia [C. M. Girgis et al., 2014]. Fat infiltration in muscle is one of the suggested manifestations of vitamin D deficiency. Low physiological concentrations of 1,25(OH)₂D representing a vitamin D-deficient state induce myoblasts to transdifferentiate into adipogenic lineage and appear to involve activation of PPAR γ 2 (C2C12 muscle cell line) [K. Ryan, 2013].

A number of organizations recommend vitamin D in order to lower the risk of falls in the elderly. According to recommendations of the Scientific Advisory Committee on Nutrition (2016), beneficial effects are only noted if larger doses are used (800–1000 IU) and if post-treatment serum concentrations of 25(OH)D are over 60 nmol/L. There are also evidences that vitamin D is helpful in fracture prevention and 800 IU is the minimum recommended dose.

The importance of early diagnosis of craniosynostosis malformation was discussed in the report by **Simin Taavoni (Tehran University of Medical Sciences, Tehran, Iran)**. Craniosynostosis is the premature closure of one or several sutures of the skull and causes increased risk of elevated intracranial pressure. The early diagnosis of this disorder is very helpful for on-time referring of those patients to craniofacial and pediatric neurosurgeons. The timing of surgery is individualized. But in recent times minimally invasive approaches to the surgical corrections of craniosynostosis, such as endoscopic strip craniectomy, are gaining a wide acceptance.

The team of Slovak scientists presented 2 reports: **A. Krajčovičová (5th Department of Internal Medicine, Medical Faculty Comenius University in Bratislava and University Hospital Bratislava, Slovakia)** introduced the study of TBS in patients with inflammatory bowel diseases (IBD). She noticed that osteoporosis and osteopenia are known chronic complications of IBD: osteoporosis was diagnosed in 12–42% of patients; prevalence of osteopenia was typical in ⅓ of IBD patients.

84 patients (mean age 42 ± 14 years) with an average disease duration of 11 ± 7 years had taken part in the study. Lower BMD had been seen in 53.6% of IBD patients. There had been a significantly lower TBS in patients with Crohn's disease with fistulising compared to those with non-structuring/non-fistulising disease. There was no association with BMD at the lumbar spine. It had been concluded that TBS reflected better the degradation of bone (trabecular) tissue in connection with IBD severity. And patients with severe IBD form were at a higher risk for osteoporotic fractures.

Peter Jackuliak (5th Department of Internal Medicine, Medical Faculty Comenius University in Bratislava and University Hospital Bratislava, Slovakia) presented the findings on the influence of metabolic compensation of type-2 diabetes (T2DM) on bone quality. A retrospective cross-sectional trial in 88 women with T2DM and 130 controls without DM had been held to determine the role of metabolic compensation measured by HbA_{1c} on BMD and on bone quality measured by TBS in T2DM patients. Mean age of the patients was 51.2 ± 6.1 years, the mean duration of diabetes was 10.3 ± 5.8 years. All patients were treated only by oral antidiabetic drugs (metformin and DPP-4), not by insulin. Diabetes had been associated with higher BMD than the control group, and TBS in lumbar spine had been lower in T2DM. Patients with a cut-off HbA_{1c} less than 7.4% had significantly higher TBS, but there had been no difference in BMD. So, good glycemic compensation was an important determinant for BMD as a marker of bone quantity and also TBS as a marker of bone quality. But there are many questions for further investigations, for example, how to evaluate patients with T2DM at high risk for osteoporosis; the effect of antidiabetic drugs on bone; reliable HbA_{1c} cut-offs for BMD and TBS; all other factors affecting the correlations of diabetes and osteoporosis.

And last but not the least, a report on chronic kidney disease as a risk factor for proximal femur fractures in elderly by **Franci Vindišar** (General and Teaching Hospital Celje, Slovenia) presented data of his study of 38 patients with proximal femur fracture (fracture group) and 29 patients with hip joint

arthrosis receiving endoprosthetic treatment (control group). For all patients, BMD, markers of vitamin D metabolism and kidney function had been measured. The results had shown a difference in BMD, which was lower in patients with fractures. There had been no difference in the concentration of biochemical markers of bone metabolism (calcium, phosphate, PTH). There had been a correlation between kidney function and concentration of the active form of vitamin D in the fracture group. In a group of patients with reduced kidney function ($\text{GFR} < 60 \text{ ml/min/1.73 m}^2$), there had been observed an increased incidence of osteoporotic fractures.

To summarize, it must be said that each report was followed by a stimulating discussion. All participants enjoyed a warm and open-minded atmosphere letting everyone hear something new, but also share their own thoughts about each discussed topic.

At the end of the scientific program, one of the chiefs of the Organizing Committee, Professor Heinrich Resch, opened before the attendees the vistas of future plans and invited everybody to take part in the Meeting of the CEE Osteoporosis Summit Working Group to be held on May 12, 2017 in Salzburg, Austria.

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