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Kuprinenko N

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Congress Report

Bone and Joint Diseases and Age: Principal Study Outlines (The symposium review)*

N. Kuprinenko

At the beginning of May 2015, the International Symposium "Bone and Joint Diseases and Age" was held in the beautiful Ukrainian city of Lviv. The event was co-organized by the Ukrainian Association of Osteoporosis, the Austrian Society of Bone and Mineral Research, and the Slovak Society for Osteoporosis and Metabolic Bone Diseases under the aegis of the European Society for Clinical and

Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases. It must be said that Ukraine had witnessed the scientific event of such a scope centered on the problems of bone and joint diseases, featuring a staggering number of lecturers from abroad and hosted by the international committee for the first time.

On the opening ceremony, the welcoming letter from Professor Jean-Yves Reginster, President of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), was read. Prof. Reginster was quoted as saying: *"This meeting is a prime event in the sense that it has a vision of what will become, in the coming years, the major burden for all developed countries: aging and its consequences on bones, joints and muscles ... I am convinced that the quality of the presentations, together with the interaction between the audience and the speakers, will pave the way to provide solutions for our actual and future sufferers. On behalf of ESCEO, I wish you a wonderful Congress and I would like also to take this opportunity to thank, once*



Figure 1: The organization committee and lecturers of the symposium.

again, Professor Vladyslav Povoroznyuk for his permanent commitment to fight musculoskeletal diseases and to improve the well-being of our population."

In his welcoming speech, Professor Vladyslav Povoroznyuk, President of the Ukrainian Association of Osteoporosis, noted that the event was very important for the Ukrainian physicians and scientists, and for the country as a whole. On

behalf of the members of the Ukrainian Association of Osteoporosis, Prof. Povoroznyuk expressed his gratitude to the 8 leading scholars from 6 European countries for their assistance and attendance as well as for their presentations. Professor Heinrich Resch (Austrian Society of Bone and Mineral Research, Wien, Austria) reminded everyone that the idea of organizing the Austrian-Ukrainian medical symposium of bone and joint diseases there, in the Ukrainian city of Lviv, the center of the historical region of Galicia, had been discussed for several years by him and Prof. Povoroznyuk. At last they were honored to admit that the idea had become a reality. Professor Resch expressed his hope that similar scientific meetings in Lviv would become a tradition. Prof. Resch proceeded to read the letter from Professor Juraj Payer, President of the Slovak Society for Osteoporosis and Metabolic Bone Diseases, absent from the meeting, who nevertheless with a great pleasure wrote the greetings to all the participants and mentioned his hopes that the Slovak colleagues would have a chance to follow the tradition and to host their own symposium in future.

The scientific program of the symposium started with the lecture "Bone and joint diseases and age" by **Professor Vladyslav Povoroznyuk (Kyiv, Ukraine)**. Prof. Povoroznyuk paid attention to the problem of aging population, shared by Ukraine and all the other countries of the world. The average age of menopause onset typical of the Ukrainian women was 47 years. At that point onwards, the progressive loss of bone mass was registered. The same tendency was observed in the Ukrainian men aged 70 years and older. Aging was heterochromic, but in postmenopausal women it began progressing in all the skeleton sites and led to the bone loss. Before the age of 65 years, the frequency of fractures in women was lower in comparison with men; however, in those of 65 years and older the frequency of fractures increased. It was estimated that only 25 % of

fractures were clinically manifested. Over the years, in women the frequency of proximal hip fractures, vertebral fractures, and distal forearm fractures increased with the same characteristic of the frequency of proximal hip fractures and distal forearm fractures in men. In the recent years we had witnessed the advent of new methods of osteoporosis diagnostics, among those the trabecular bone score (TBS). TBS was used not only to diagnose osteoporosis but also to predict fractures. TBS had a greater sensitivity in comparison with the bone mineral density (BMD); however, the clinicians advised to use them both in conjunction. All over the world, 20 % of patients died during the first year after the hip fracture, and only 30 % of patients returned to their normal life, the rest requiring permanent care. Similar figures in Ukraine: 19.5 % patients died during 2 years after the hip fracture; 47 % of them died during the first 6 months after the fracture, and 12 % died during the first 6–12 months.

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One of the problems recently in the limelight of medical attention was sarcopenia. The current reference database of patients with sarcopenia was established in Ukraine. It was estimated that the frequency of pre-sarcopenia among women of 65 y.o. and older was 10 % (women with obesity excluded). The prevalence of sarcopenia in Ukraine among women of 65–89 y.o. was 6.8 % [Povoroznyuk V, Dzerovych N, 2013]. Sarcopenia was a geriatric syndrome reducing physical capacity and quality of life in the elderly and senile age.

Another problem that needed further investigation was hyperuricemia. It was estimated that the level of uric acid increased depending on the age in men and women. The highest frequency of hyperuricemia was demonstrated in women aged 75–79 years (30.8 %) and in men aged 60–74 years (34.7 %) [Povoroznyuk V, Dubetska G, 2014]. Principal factors contributing to the increase of hyperuricemia (gout) are: increased life expectancy, increased occurrence of kidney diseases, frequent use of diuretics, epidemics of obesity, increased consumption of food containing high levels of purines.

The vitamin D (Vit. D) status was investigated in the Ukrainian population [Povoroznyuk V, Balatska N, 2012–2014]. It was estimated that 81.8 % of the adult population suffered from Vit. D deficiency; the frequency of Vit. D insufficiency was 13.6 %; only 4.6 % of the adult Ukrainian population had a normal Vit. D status. Analysis of various age groups showed that the significantly higher 25(OH)D levels (41.16 ± 2.53 nmol/l) were recorded in young people compared with people of 35–44 y.o. ($p < 0.01$), 60–74 y.o. ($p < 0.05$), and 75 y.o. and over ($p < 0.05$). Most cases of vitamin D deficiency were diagnosed in the group of people aged over 75 years (84.3 %). Risk factors for Vit. D deficiency among the population of Ukraine were female gender, obesity, insufficient weight, it also increased in the winter time and was typical of people who resided in other than the Southern regions of the country.

The statistical data on the prevalence of musculoskeletal diseases and treatment of bone and joint diseases were presented in the lecture of **Professor Heinrich Resch (Wien, Austria)**. Musculoskeletal disorders included joint diseases, osteoporosis, back pain, and skeletal trauma, and accounted for over three quarters of the burden of non-communicable diseases in Europe. During the recent decade, the number of people suffering from those disorders increased by 25 % and affected 1 of 4 adults worldwide. Joint diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA) were the leading causes of disability and half of all the chronic conditions over the age of 65.

The exact etiology of degenerative joint diseases was unclear, but genetics, obesity, inflammation, diabetes, immunoresponse, and aging were considered the predisposing factors. The main pharmacological therapeutic options were topical and systemic nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, symptomatic slow-acting drugs for OA (Diacerin), opioids, intraarticular injections of hyaluronic acids or steroids, orthovisc. The main aims of treatment were restoration of damaged cartilage at an early stage, bone marrow stimulation, osteochondral transfer.

The main therapeutic options in case of RA were drugs that eased the symptoms (NSAIDs) and drugs that slowed the disease activity (corticosteroids, disease-modifying antirheumatic drugs [DMARDs — methotrexate, sulfasalazine, azathioprine etc.]), biologics (infliximab, rituximab, abatacept etc.), inhibitors of Janus kinase, the pathways responsible for the body's immune response (tofacitinib).

About 75 millions of people in Europe suffered from osteoporosis. Globally, every 3 seconds a new osteoporosis-related fracture happened. Worldwide, 1 out of 2 females and 1 out of 5 males above 50 y.o. had to expect an osteoporosis-related fracture. The number of annual hip fractures in the Austrian population aged above 50 y.o. increased from year to year. The milestones in osteoporosis therapy changed from hormone replacement therapy in 1980-s to calcitonin, oral bisphosphonates, and raloxifene in 1990-s, from teriparatide in early 2000-s to strontium ranelate and IV bisphosphonates in the middle of 2000-s, and to denosumab in 2010. Now there were a lot of trials investigating the effects of anti-sclerostin and cathepsin K inhibitors in treatment of osteoporosis.

The main points in musculoskeletal disorders treatment were awareness, compliance, data of medical researchers on the efficacy, and economic justification.

● Genetic Risk Factors: Epidemiology of Osteoporosis

Professor Vladyslav Bezrukov, head of the Institute of Gerontology named after D. F. Chebotarev NAMS of Ukraine (Kyiv, Ukraine), highlighted the genetic factors of osteoporosis. He noted that the human life span depended from the genetic factors by 20 %. Recently there had been more and more trials on the influence of genetic factors on osteoporosis and other diseases.

Studies of genetic risk factors for Alzheimer's disease, Parkinson's disease, diseases of the immune, endocrine and cardiovascular systems as well as researches of the influence of genetic factors on the development of osteoporosis, osteoarthritis and low back pain are conducted in the Institute of Gerontology named after D. F. Chebotarev NAMS of Ukraine. Prof. V. Bezrukov presented the results of studying the frequency of alleles of bone metabolism gene-regulators in patients with osteoporosis. The aim of the trial was to determine the influence of specific gene polymorphisms on the osteoporosis risk. Results showed that the Collagene type I (increase frequency of G-allele) gene polymorphism was proved to increase the osteoporosis risk by 2.8 times, while the Vit. D receptor – VDR 60890 A/G polymorphism – by 3.2 times; however, there were no changes in polymorphism of 764 T/G gene ERα. Researches continued.

Some epidemiological aspects of aging and osteoporosis were presented in the report of **President of the Romanian Association for Osteoporosis Prevention (ASPOR), Professor Andreia Ildiko Gasparik (Romania)**. Prof. Gasparik emphasized that $\frac{2}{3}$ of all people ever reaching the age of 65 were still living. On the one hand, it meant that the humanity won fight for the longevity, but on the other, it was a challenge to face the burden

of an aging population, as (illustrated by the Ukrainian demographic data) “a small group will care for a wide majority”. At the same time, however, aging was not a disease, just a growing susceptibility to it – the prevalence of almost all chronic diseases increased after 65 y.o., and arthritis and osteoporosis among them. Nowadays over 200 million people worldwide had osteoporosis. The prevalence of it was higher in women vs men and in white vs black. The trend was that hip fractures would substantially increase due to the demographic changes. It was predicted that by 2050 its level would increase by 240 % in women and by 320 % in men.

Vertebral fractures were among the most common osteoporosis fractures and they were also a good marker of osteoporosis and predictors of future fractures, the same as distal forearm fractures. After the age of 65, the growing rates of vertebral and hip fractures were similar, as well as excessive mortality 5 years after the vertebral and hip fractures. The prevention of aging-associated diseases, including osteoporosis and osteoporotic fractures, must be one of the main goals in modern healthcare. Lifestyle, education, and social support factors were as yet unexplored in terms of their efficiency.

● Using Trabecular Bone Score

During the recent years, the Trabecular Bone Score method (TBS) became a new standard in diagnosis of osteoporosis. It was the topic of **Professor Didier Hans's (Lausanne, Switzerland)** lecture. Prof. Hans presented the results of some clinical trials and meta-analyses that showed consistent association between the TBS and fracture risk, as well as the similar predictive power of TBS in men and women. He also noted the value of TBS as an additive component to FRAX and emphasized that an incremental improvement in fracture identification was seen by using lumbar spine TBS in combination with FRAX. Formulas for calculating of fracture probabilities according to TBS were also presented in the lecture.

Another aspect of TBS was in its indicating of treatment effects – efficacious therapies for osteoporosis differed in the extent to which they influence the TBS [Krieg, 2013; Popp, 2013; Senn, 2014; Del Rio, 2015]. For example, teriparatide induced the highest TBS changes after 24 months of treatment. Denosumab took the second place in the gradation of efficacy in terms of the TBS changes. There were almost no TBS changes in cases of treatment with bisphosphonates.

In conclusion Prof. Hans noted that TBS was integrated into the guidelines for the diagnostics and management of osteoporosis (the DVO guidelines, the ESCEO guidelines, the ISCD guidelines).

The TBS studies in the Portuguese population were presented in the lecture by **Professor Mario Rui Mascarenhas (Lisboa, Portugal)**. The aim of one of those [Mascarenhas et al., 2012] was to correlate bone quality, as assessed by the TBS, and vitamin D and the intact PTH (iPTH) in adults. In that study with participation of 72 normal adults aged above 60 y.o. (39 postmenopausal women and 33 men), no significant correlation between BMD vs iPTH and between BMD vs 25(OH)D was detected. The negative aging influence on bone quality was de-

termined, according to the TBS. Vitamin D₃ might play a role in determining the bone quality. Indeed, the men and postmenopausal women with a low 25(OH)D had a low TBS and worse bone quality. The next study [Mascarenhas, 2012] was devoted to the impact of androgens on the bone quality in normal adult men. It was determined that normal men with a low total testosterone plasma level may tend to have both a diminished BMD and bone quality, and thus a weaker bone strength. Another study [Mascarenhas, 2015] showed the role of osteocalcin (by TBS): normal men with a low osteocalcin blood level tended to have a reduced spine TBS. In the evaluation [Mascarenhas, 2012] of the impact of male hypogonadism on bone quality (by TBS), the reduction in both BMD and bone quality were determined. The results suggested an important negative impact on bone strength of hypogonadal men and increased osteoporotic fracture risk. According to the data from a last-year study [Mascarenhas, 2014], the postmenopausal women with osteoporotic fractures had a significant reduction of TBS. Nevertheless, there was an overlap of BMD values in both groups, without a clear differentiation of women with and without osteoporotic fractures. In another study [Mascarenhas, 2015] the significant reduction of TBS in the groups of women with obesity and in men with a resistance to insulin was determined. Spine TBS may be an important method of evaluating the bone quality and determining secondary osteoporosis risk in the endocrine patients.

● Secondary Osteoporosis

The lecture of **Professor Ana Paula Barbosa (Lisboa, Portugal)** focused on the bone mass and osteoporotic fractures in hyperthyroid adults. Prof. Barbosa noted that the potential risks of hyperthyroidism were diverse and could vary from patient to patient, but heart and bone complications were relatively common, especially among the elderly. Hyperthyroidism was an important cause of secondary osteoporosis and a risk factor for hip fracture in women. Moreover, those osteoporotic fractures were associated with a risk of precocious mortality, namely in the elderly. In the adult life, after the acquisition of the peak bone mass, the excess of circulating thyroid hormones could lead to an increase in bone resorption, either by acting directly on osteoclasts or indirectly on osteoblasts. Bone remodeling accelerated while bone formation was decreased, originating an incomplete substitution with new bone cells and loss of mineralized bone. Hypercalcemia, hypercalciuria, and a negative balance of calcium were also described. Recent studies had shown that low TSH levels, *per se*, could lead to osteoporosis and fragility fractures. In old and young Portuguese patients with endogenous hyperthyroidism, both men and women, significant decreases in the BMD in several skeletal regions and an increase in the prevalence of osteoporosis/low BMD were observed. In young Portuguese men with hyperthyroidism, the trend for an increased prevalence of osteoporotic vertebral fractures was found.

● Some Aspects of Osteoporosis Therapy

The problem of monitoring osteoporosis treatment was discussed in the lecture of **Professor Vidmantas Alekna (Vilnius, Lithuania)**. Prof. Alekna mentioned the categories of population that should be considered for treatment. They are

postmenopausal women and men aged 50 years and older, presenting with a hip or vertebral fracture (clinically apparent or found on 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 10-year probability of a hip fracture $\geq 3\%$ or a major osteoporosis-related fracture $\geq 20\%$, based on the U.S.-adapted WHO algorithm. According to European guidelines on osteoporosis (2012), drugs with anti-fracture efficacy in cases of postmenopausal osteoporosis were alendronate, risedronate, zoledronic acid, strontium ranelate, and denosumab. Proposals for an operative definition of response for treatment were: no incidence fracture and no decrease in BMD superior to 2 % of the least significant change (LSC) meant the adequate response; incidence fracture or decrease in BMD superior to 2 % of the LSC meant possible inadequate response; incidence fracture and decrease in BMD superior to 2 % of the LSC meant inadequate response. Common causes of failure to respond to therapy included poor compliance and persistence, inadequate calcium and/or vitamin D intake, malabsorption, comorbid conditions, medications. Clinical tools for monitoring treatment were incident fractures, the changes of bone mineral density (BMD), the changes of bone turnover markers. During the monitoring of osteoporosis treatment the following points should be considered: checking for poor adherence, comorbidities, deficiency of calcium and Vit. D, malabsorption and metabolic factors, lack of efficacy, unapparent secondary causes; treatment required a period of time to act at the tissue level; fracture had been shown to decrease after 6–12 months on treatment; one year on treatment constituted a conservative estimate.

Professor Jerzy Konstantynowicz (Białystok, Poland) made a report about the old and new therapies of osteoporosis in children and adolescents. He presented a list of cases when osteoporosis should be suspected in children: multiple/recurrent fractures, special phenotype/clinical features associated with rare genetic disorders affecting skeleton, chronic diseases possibly affecting bone metabolism, nutritional deficiencies, long-term use of medications that have bone-specific side effects, rickets/osteomalacia, non-characteristic musculoskeletal pain. Clinically significant fractures that should be determined as low-energy fractures in children were: at least 3 fractures of major bones (confirmed by X-ray), at least one fracture of long bone of lower limb (confirmed by X-ray), non-traumatic fractures of vertebral bodies (confirmed by X-ray), and fractures resulting from a minimal injury. Among all groups of medicines only the supplementation of Vit. D and Ca (and calcitonin in Poland) are actually permitted. So, pharmacological treatment of osteoporosis in children and adolescents was extremely limited. New protocols were under investigation regarding their safety and efficacy, and may be implemented soon.

● Vitamin D Levels in Population

Professor Pawel Pludowski (Warsaw, Poland) gave a lecture about the phenomenon of vitamin D. He noted that Vit. D deficiency should be considered an endocrine problem rather than a nutritional one. The effect of Vit. D on the endocrine system depends on the circulating concentration of 25(OH)D. The optimal 25(OH)D level for both skeletal and extra-skeletal action

is 30–50 ng/ml or 75–125 nmol/l. It was proved that in case of 25(OH)D > 24 ng/ml, the risk of falls decreased by 19 %, fracture risk at femur decreased by 37 %, the risk of other fractures decreased by 31 %. In case of 25(OH)D = 30–40 ng/ml, the risk of falls was lower compared to both < 30 ng/ml and > 50 ng/ml. According to the data of meta-analysis of 11 randomized trials [Bergman, 2013], people with the level of 25(OH)D of more than 38 ng/ml and regular using of Vit. D supplementation had a by 36 % reduced risk of infections. With Vit. D supplementation in the dose of 1000 IU/d, school children had a reduced risk of influenza type A (but not type B) by 67 %. According to the data of an 18-study meta-analysis [Song, 2013], in case of 25(OH)D = 40 ng/ml there was a 33 % reduced risk of type 2 diabetes. Increased risk of cardiovascular diseases was registered when 25(OH)D level was < 24 ng/ml [Wang, 2012]. Vitamin D deficiency (25(OH)D < 17 ng/ml) in children aged 10 ± 5 years was associated with a high risk of intima media thickness, measured at the age of 37 ± 5 years [Luonala M, 2015]. During pregnancy every 10 ng/ml of increased 25(OH)D decreased the risk of preeclampsia, preterm birth, gestational diabetes, cesarean section, and bacterial vaginosis. Obtaining and maintaining 25(OH)D at 30 ng/ml seemed to be related to the all-cause mortality risk reduction of 9–28 %. Once Vitamin D was an epiphenomenon or marker of bad health status, people must not believe that Vit. D was a panacea. One of the most recent trials [Bolland et al., 2014] presented data that using Vit. D for improving various clinical outcomes was wasting of time and money.

Today there were some guidelines and recommendations that declared the new procedures for assessing and correction of Vit. D status. According to the Practical Guidelines for the supplementation of Vit. D and treatment of deficits in Central Europe (2013), the recommended therapeutic doses for groups with verified Vit. D deficiency (25(OH)D < 20 ng/ml [< 50 nmol/l]) were: for neonates – 1000 IU/d, for infants aged 1–12 months – 1000–3000 IU/d, for children and adolescents aged 1–18 years – 3000–5000 IU/d, for adults – 7000–10,000 IU/d (depending on body weight) or 50,000 IU/week. According to some other guidelines (2010), the treatment with a 3-month dose (IU) of Vit. D for adults should be calculated by the formula: $40 \times [75 - \text{patient's } 25(\text{OH})\text{D}] \times \text{patient's body weight}$.

Serum 25(OH)D should be monitored 3–4 months after the therapy implementation, and then semi-annually. When applicable, ALP, P and Ca as well as calciuria may be monitored every 1–3 months.

Finishing the lecture, Prof. Pludowski urged everybody to attend the EVIDAS (European Vitamin D Association) 2015 meeting that would take place in Warsaw (Poland) in October, 16–17.

Liudmila Yankouskaya (Grodno, Belarus) presented her thoughts on the role the vitamin D level played in the development of cardiovascular diseases (CVD), including arterial hypertension (AH). First of all, the reporter emphasized that the role of Vit. D was confirmed more and more often, and the decreased level of Vit. D considered a potential significant risk factor for AH. The level of 25(OH)D in plasma lower than 17 nmol/l was associated with an increased systolic blood pres-

sure. Inverse correlation was established between the 25(OH)D plasma level and diastolic blood pressure [Snezhitskiy VA, Yankouskaya LV, Povoroznyuk VV, et al., 2012]. Numerous cell types, including the vascular smooth muscle cells, endothelial cells, and cardiomyocytes, were known to be capable of producing 1- α -hydroxylase enzyme. Thanks to the latter, intracellular conversion of 25(OH)D to 1,25(OH)₂D occurred. It had been established that Vit. D acted as an inhibitor of the synthesis of rennin, and the activated Vit. D receptor reduced the RAAS activity and the severity of myocardial hypertrophy. The aim of the randomized prospective study made at the Grodno State Medical University was to assess the effect of cholecalciferol therapy in the subjects with AH (n = 204, age = 53.3 $\pm$ 8.2 years) using the indices of calcium-phosphorus exchange. It had been established that the cholecalciferol supplementation (dose – 2000 IU/day during 3 months) allowed compensating for the Vit. D deficit in 89 % cases, insufficiency in 81 % cases and did not change the 25(OH)D plasma level under its optimal baseline level. The blood level of calcium and phosphorus did not change irrespective of long-term administration of Vit. D at the dose of 2000 IU/day. Regular intake of strong tea and coffee (3 cups a day or more than 500 ml) reduced the urinary excretion of phosphorus.

To conclude, it must be said that all the lectures presented by the medical scientists from various parts of Europe empha-

sized the commonality of bone and joint diseases in all those countries. Presentations and scientific reports helped the participants to get new knowledge and skills required for the prevention, diagnosis and treatment of musculoskeletal system diseases. Thanks to the international team of presenters, the choice of English language as *lingua franca* and the organization committee comprising scholars from many European countries, the symposium turned into a truly cosmopolitan event of a high academic value. Besides hard work the participants, especially foreign guests, had an opportunity to discover for themselves the noble ancient Lviv. Lviv is the vibrant city situated on the crossroads between the East and West of Europe, the city where history could be found at every corner. So, let's meet in Lviv for the next International Symposium of Bone and Joint Diseases and Age to enjoy it together again!

Correspondance to:

Nataliia Kuprinenko
Journal "Pain. Joints. Spine"
Publishing House Zaslavskyy
PO Box 74
Kyiv, 04107, Ukraine
Tel: +380502103212
E-mail: medredactor@i.ua

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