Congress Report: The II International Symposium “Bone and Joint Diseases and Age”: The Review of Basic Topics
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FRAX is available in 58 countries and lets cover about 70% of world population. This method of fracture risk prediction was incorporated into more than 80 assessment guidelines. There was no own model of FRAX in Ukraine, but we would work on it.

Prof. Jean-Yves Reginster, the ESCEO President (Liege, Belgium) presented two lectures – about vitamin D and calcium and about sarcopenia. The fact that calcium supplements with vitamin D are an important therapy to prevent bone loss and reduce the risk of fractures, especially in the elderly, was well-known and evidenced in numerous studies. But there were a lot of discussions about the influence of calcium supplements on cardiovascular risk. Prof. Jean-Yves Reginster presented the review of some large studies and meta-analysis where the role of calcium supplementations, vitamin D and both calcium and vitamin D supplements on risk of cardiovascular events, including myocardial infarction (MI), cardiovascular death and stroke, in various cohorts of people was investigated. The basic conclusions were: no effects of calcium supplements on stroke or mortality, coronary artery calcification were accelerated. In some trials calcium supplements (without vitamin D) in doses above 1400 mg/day, in women, were associated with higher death rates from all causes and cardiovascular diseases but not stroke. And none of the trials had cardiovascular outcomes as the primary endpoints, none of the trials had adjudicated cardiovascular outcomes in standardized manner, inconsistent data in individual studies, findings did not apply to combined use of calcium and vitamin D, all-cause mortality reduced in patients given calcium and vitamin D. In the conclusion of the lecture, Prof. Jean-Yves Reginster paid attention to the mandatory adjunction of vitamin D and calcium supplements in addition to anti-osteoporosis drugs. Calcium supplement in a dose of 500 mg/day is mandatory to use in patients who get risedronate; vitamin D in a dose of 400 IU and more is mandatory in case of using strontium; both calcium (in dose from 500 to 1200 mg/day) and vitamin D (in dose of 400 IU) are mandatory with raloxifene, teriparatide, ibandronate, zoledronate, PTH, bazedoxifene, lasofoxifene. Only in case of using alendronate the prescription of calcium supplement and vitamin D is not mandatory; these supplements are recommended in cases of low calcium and vitamin D plasma levels.

The second lecture of Prof. Jean-Yves Reginster was focused on the “pitfalls” in the problem of sarcopenia. Sarcopenia was characterized by progressive and generalized loss of skeletal muscle mass and strength which is associated with increased risk of negative outcomes, including mobility disability, falls, hospitalization, poor quality of life and death and it was a major pathway that led to physical frailty. Sarcopenia had a high prevalence in older population. Diagnostic criteria of sarcopenia were a decrease in muscle mass and strength and/or speed. The European Working Group on Sarcopenia in Older People (EWGSOP) recommended using the presence of both low muscle mass and low muscle function for diagnosis of sarcopenia. According to EWGSOP criteria, sarcopenia in older patients (> 65 y.o.) was diagnosed in cases of gait speed ≤ 0.8 m/sec, grip strength < 30 kg for men and < 20 kg for women, muscle mass < 7.25 kg/m² for men and < 5.5 kg/m² for women. FNHI (Foundation for the National Institutes of Health) criteria of sarcopenia included grip strength < 30 kg for men and < 20 kg for women, appendicular lean mass (ALM) < 0.789 for men and < 0.512 for women. Nevertheless both Consensuses have included objective measure of muscle/lean mass and both have incorporated muscle weakness or reduced physical functioning into the definition. In addition to the grip strength some other tests can be used for evaluation of muscle strength and function (4-meter walking speed, 6-min. walking test, 400-meter walking test, 5-time chair stand, lower and upper limb press, stair climbing, Short Physical Performance Battery [SPPB]). The SarQol questionnaire was recommended for patient self-assessment of quality of life. Potential treatments of sarcopenia were under development, but there were no guidelines to support regulatory studies for new chemical entities. In the conclusion Prof. Jean-Yves Reginster outlined the key issues of sarcopenia investigations that required the focusing of attention. They included the presence of numerous gaps in knowledge, particularly in risk assessment and the necessity to build the risk model similar to FRAX for osteoporosis. Also the value of indexing threshold values for sarcopenia measures and outcomes needs to be further investigated, using risk-based analysis for one of the strong clinical endpoints. The consensus core outcome set would bring standardization and comparability to research in sarcopenia and therefore would help improve the evidence base.

The lecture of Prof. Heinrich Resch (Austrian Society of Bone and Mineral Research, Wien, Austria) has proved that medicine is an art, and art can help physicians, patients and investigators. During the lecture all participants could forget about modern serious scientific topics and fly away in their thoughts to the world of art legacy. Professor Heinrich Resch demonstrated some well-known pictures of famous artists of last centuries and noticed that if we look at their characters not only watching on story, dresses and background, but paying attention to details, such as the skin colour, skin condition, joints, limbs, nails, we’ll see symptoms of some diseases. For example, there were a lot of cases of rheumatoid arthritis, gout, osteoporosis and osteoarthritis in characters of pictures of Sandro Botticelli, Pierre Renoir, Jacob Jordaens, Marc Hodler, Diego Velázquez, Pinturicchio Bernardino di Betto, El Greco, Vincent van Gogh etc. This let us conclude that these diseases were widespread in last century and were the cause of short life expectancy.

Prof. Juraj Payer, President of the Slovak Society for Osteoporosis and Metabolic Bone Diseases (Bratislava, Slovakia), presented the lecture about effects of growth hormone (GH) on bone. GH had an anabolic effect on bone in vitro and in vivo. Effects were mediated by insulin-like growth factor 1 (IGF-1) which was produced mostly by the liver. The impact of GH on bone in various periods of life included the stimulation of longitudinal bone growth in childhood, stimulation of bone maturation to achieve “peak bone mass” (main predictor of fracture) in adolescence and maintenance of bone mass through bone regulation in adulthood. Data about bone quality in patients with growth hormone deficiency (GHD) were scarce as well as the effect of GH on trabecular bone score (TBS) was not well documented yet. Professor Juraj Payer presented results of a study that was made by his colleges and him. The objective was to compare effect of recombinant GH (rhGH) on BMD and TBS, to assess risk factors of rhGH effect on bone and to
Sarcopenia and Dysmobility Syndrome

Some reports were devoted to sarcopenia – a topic that has been widely discussed in recent years.

In his report Prof. Edward Czerwinski (Krakow, Poland) noticed that sarcopenia incidence increased with age, ranging from 15 % after 60 to as much as 50 % over 85, and aging was one of the main causes of sarcopenia. The development of sarcopenia was also affected by hormonal factors (testosterone, estrogen, growth hormone/IGF-1), humoral factors (subliminal chronic inflammation) and environmental factors (diet, sedentary lifestyle). The only effective methods for both prevention and treatment of sarcopenia were regular physical activity and proper diet. The most effective exercises were resistance exercises, particularly progressive resistance training, affecting both the increase in strength and muscle mass. In turn, the lack of physical activity triggers muscle atrophy. Diet recommendations were focused on proper protein and vitamin D3 intake. The recommended consumption equaled 0.8–1.2 g of protein per kg of body weight per day. Proteins provided the appropriate course of post-exercise regeneration processes and were an important anabolic stimulus for skeletal muscle. Vitamin D3 stimulated the synthesis of myocytes and their differentiation, inhibited apoptosis, affected the conductivity and muscle contraction. Sarcopenia was a fall risk factor. Due to such aging factors as depleting biologic reserves, slow reflexes and osteopenia or osteoporosis, a seemingly harmless fall from own height could have serious consequences and the most serious are fractures. In the elderly people fractures could cause not only pain and temporary immobilisation, but also a permanent impairment of mobility, functional deterioration, increasing morbidity and mortality. Various forms of physical activity were recommended for fall prevention. Regular exercise of moderate intensity was recommended at least 3 times a week: Nordic Walking, Tai-Chi, dancing, brisk walking.

Results of studying sarcopenia in Ukrainian women were presented by Natalia Dzerovych (D. F. Chebotarev Institute of Gerontology NAMS of Ukraine, Kyiv, Ukraine). 311 healthy women-volunteers aged 20–87 years (mean age = 57.3 ± 0.9 yrs; mean height = 1.62 ± 0.004 m; mean weight = 63.5 ± 0.5 kg, BMI = 24.2 ± 0.2 kg/m²) were examined. No subject had any systemic disorders or took medications known to affect the skeletal and muscle metabolism. Appendicular lean mass (ALM) was measured at all four limbs with DXA. The appendicular lean mass index (ALMI) was also calculated according to the formula: ALM/height (kg/m2). The frequency of sarcopenia increased with age and was the highest in women aged over 80 years (30.8 %). The frequency of sarcopenia in women aged over 65 years was 21.3 %. Also it was determined that dietary protein intake significantly decreases in women with age. In women with lower appendicular lean mass, lower dietary protein was observed. Results confirmed the literature data on the association between dietary protein, amino acids intake and lean (skeletal muscle) mass in older people. In another Ukrainian study (38 postmenopausal women aged 53–82 years) it was determined that using individually targeted vitamin D therapy and OTAGO Exercise Programme during 12 months significantly improves daily activity, muscle strength, quality of life and reduces fall frequency in postmenopausal women.

Prof. Neil Binkley (University of Wisconsin Osteoporosis Clinical Research Program, Madison, Wisconsin, USA) presented the report about dysmobility syndrome. Prof. N. Binkley mentioned that osteoporosis and sarcopenia contributed to falls and fractures risk, but we must remember obesity as a risk factor especially in postmenopausal women. Also the combination of low muscle mass and function (sarcopenia) and high fat mass (obesity) had poor prognosis. It was termed “sarcopenic obesity”. However, rather than focusing on each condition individually, an opportunity existed to combine clinical factors to potentially improve identification of older adults at risk for falls and fractures. Such combination was termed “dysmobility syndrome”. Dysmobility defined as 3 or more symptoms such as high body fat, osteoporosis, low muscle mass, low muscle strength, slow gait or falling risk. To reduce falls and fractures in patients with dysmobility syndrome, all components of it, especially obesity, must be corrected. 2000 IU of vitamin D daily would be a reasonable place to start for optimizing the vitamin D status. Using existing osteoporosis medications to treat the bones were recommended.
Healthy Aging and Focus on Patients

Prof. Vidmantas Alekna (Vilnius, Lithuania) discussed problems of healthy aging and interface between lifestyle and geriatric syndromes. First of all Prof. V. Alekna mentioned some interesting historical and statistical points about aging. It was known that from the Bronze Age to 1900 (the 6000-year period), the average human life expectancy has risen by only 0.3% per year, and in early 2016, the average life expectancy at birth was 68.7 years. In humans, aging represents the accumulation of changes in a human being over time, encompassing significant physical, psychological and social change, and at a biological level, aging is associated with the gradual accumulation of a wide variety of molecular and cellular damage. Physical health is of key importance in healthy aging. Poor health is a characteristic of older people—they have many chronic diseases. But nowadays geriatrics deals with so-called geriatric syndromes. Common multifactorial geriatric syndromes such as dementia, malnutrition, gait and balance problems, sarcopenia, falls, frailty, urinary incontinence and chronic inflammation/increased frequency of infection have shared the risk factors and pathophysiology mechanisms with multiple chronic diseases. This calls for a unified approach to treatment and prevention of these syndromes, in order to improve health care systems so that the needs of our rapidly aging population can be addressed adequately. In the conclusion Prof. V. Alekna noticed that a change towards a healthy lifestyle made early in life and continued to older ages increases the chance of survival, is most effective for the prevention of diseases and delays the onset of deterioration of health. As healthy lifestyle behaviors are related to survival and health at the age of 70–75 years, and are likely to contribute to healthy aging. Nevertheless, healthy lifestyle does not eliminate all risk factors, that is why a number of older people will anyway suffer from geriatric syndromes.

TBS in Fracture Risk Assessment

Prof. Didier Hans (Lausanne, Switzerland) is the world expert of using the Trabecular Bone Score method (TBS). In his report he reminded that TBS was a DXA software program that estimated bone texture information and provided fracture risk information that was additive to BMD and clinical risk factors. A higher TBS was correlated with better bone microstructure, and a lower TBS correlated with a worse one. TBS was officially recognised worldwide as an independent fracture risk prediction tool. TBS was associated with fracture, in women and men, predicted fracture independently from BMD, CRF and FRAX®, including cases of fracture in secondary osteoporosis context (type-2 diabetes, hyperparathyreosis, glucocorticoid-induced osteoporosis). But TBS should not be used alone to determine treatment recommendations in clinical practice.

In the second part of the report Prof. D. Hans presented series of clinical cases where the TBS estimating of fracture risk was used.

Prof. Vladyslav Povoroznyuk (Kyiv, Ukraine) presented the results of evaluating TBS changes with age and the role of TBS in fracture risk assessment according to recent literature and Ukrainian studies. In studies of correlation of TBS and age, the significant decrease in TBS values (14.5 % in Dufour R et al. [2013] study; 16.0 % in Simonelli C et al. [2013] study) was obtained for all lumbar vertebral combinations between 45 and 85 years of age. Age-related declines in lumbar spine BMD and TBS were also observed in a large cross-sectional study of 29,407 women ≥ 50 years from the province of Manitoba, Canada [Leslie WD et al., 2013]. Similarly, a negative correlation between L2–L4 TBS and age (r = -0.39, p < 0.001) was observed in 4907 Lebanese women from 20 to 90 years of age [El Hage R et al., 2013]. In cross-sectional analysis from two facilities in Ukraine and Spain, TBS values were obtained for all lumbar vertebral combinations (L1, L2, L3, L4) [Povoroznyuk V, Del Rio L, Di Gregorio S et al., 2014]. There was a linear decline of 13.5 % (~ -1.75 T-score) in TBS at L1–L4 between 40 and 90 years of age in men whereas a decline of 16.7 % (~ -2.58 T-score) was observed in women. Conversely to women, it seems that there is no modification of TBS decline rate after 65 years in men. The retrospective case-control study by Pothuaud L et al. (2009) evaluated 135 postmenopausal women (45 women had radiographically confirmed osteoporotic fractures). Women with any fracture had significantly lower TBS values than controls (0.784 ± 0.176 versus 0.899 ± 0.177; p = 0.005).

TBS in contrast to spine bone mineral density could predict vertebral fractures in men. TBS value ≤ 0.987 was a cut-off point related to over 5× higher risk of vertebral fracture. TBS is significantly lower in fractured men and no significant difference was found for bone mineral density [Lorenc R, 2012].

To evaluate the TBS values (L1–L4) in Ukrainian men depending on vertebral fractures presence, 197 men aged 45–89 years were examined [Povoroznyuk V et al., 2012]. The basic group consisted of 52 men with osteoporotic vertebral fractures in the anamnesis and the control group – of 145 men without fractures. In all age groups (45–59 yrs [n = 83], 60–74 yrs [n = 86], 75–89 yrs [n = 28]) of men with osteoporotic vertebral frac-
tures the TBS values were significantly lower than in men of the control group and were decreased with age.

Thus, it would be concluded that TBS significantly decreased with age; TBS results were lower in women who had sustained a fragility fracture but in whom DXA did not indicate osteoporosis or even osteopenia; TBS predicted fracture risk as well as lumbar spine BMD measurements in postmenopausal women; the combination of any BMD measurement with TBS significantly improved fracture prediction compared with BMD or TBS alone.

### Secondary Osteoporosis

The section of secondary osteoporosis was started with the report of [Prof. Heinrich Resch (Wien, Austria)](5) about diabetes and bone, in which molecular and clinical findings of diabetic bone disease were introduced. Prof. H. Resch reminded that the anabolic effect of insulin on bone provided the strong association of type-1 diabetes with osteoporosis. Insulin deficiency associated with low BMD altered bone architecture that resulted in increased propensity to fall and higher fracture risk. In the same time during many years type-2 diabetic (T2DM) patients were considered to be protected from fragility fractures. Nevertheless, data of some recent studies have improved the increased risks of fractures in T2DM patients. Specific risk factors were more prevalent in T2DM in cases of poor glycemic control, long-term duration of the diseases, as well as some of the diabetic medications may exacerbate fracture risk. For example, oral glitazones (more in females), thiazolidinediones doubled the fracture risk. Fragility fractures in T2DM may result from diabetes-related alterations in skeletal properties not captured by DXA. In such cases TBS could be an alternative assessment tool. Furthermore, in cases of prescribing medications for the T2DM patients we must remember that even some of the new oral antidiabetic drugs also can harm bone metabolism.

The association of male hypogonadism and bone mass was discussed in the report of [Prof. Mario Rui Mascarenhas (Lisboa, Portugal)](5). Normal testosterone levels provided proper protein formation, muscle strength and volume, and bone density. Androgens contributed to osteoblast growth, differentiation, proliferation, increased protein synthesis of bone matrix (osteocalcin, type-I collagen, osteopontin), caused calcium retention and optimized peak bone mass. Hypogonadism is one of the major causes of osteoporosis and osteoporotic fractures in adult men. It was detected a significant low BMD at several skeletal sites in men with postpubertal onset of hypogonadism, as compared with a group with normal gonadal function. Low BMD was in 26.0 % of hypogonadal men vs 9.6 % of men from the control group; osteoporosis was in 39.8 % of hypogonadal men vs 1.4 % of men from the control group. The BMD in men with late onset hypogonadism was reduced at the hip, as compared with the normal gonadal function group. In the same time BMD at L1–L4, at the distal radius and at the whole body was similar between the groups. In hypogonadal elderly men, vitamin D deficiency modified bone and muscle masses. Testosterone therapy (injectable testosterone 200 mg 2–4 weeks, transdermal patch 5 mg nightly and transdermal gel 5 mg daily) inhibited osteoclast activity and increased bone formation. After a mean 3 years of therapy 31 % of the hypogonadal men had a normal BMD (7 % more than before treatment). But no reduction in fracture risk was shown in men under androgen therapy and with osteoporosis.

[Prof. Ana Paula Barbosa (Lisboa, Portugal)](5) paid attention to the topic of the influence of hypopituitarism on bone structure. Pituitary disorders made different influence on bone and fractures. For example, acromegalia, hypogonadism, hyperprolactinemia increased bone turnover, but hypopituitarism, Cushing’s disease, growth hormone (GH) deficiency decreased it. In cases of all these disorders BMD and fracture risk were increased. GH deficiency was the major determinant of bone loss in hypopituitarism. The mechanisms underlying other hormonal deficiencies (ACTH/TSH) were not clarified. Fragility fractures are frequent complications in patients with hypopituitarism, and relatively underestimated and not strictly dependent on BMD (may occur with normal BMD). Higher prevalence of vertebral fractures was in hypopituitary adult patients treated with hydrocortisone in dose > 28 mg/day, thyroxine in dose > 1.35 mcg/kg/day. The negative effects of glucocorticoid overtreatment are more evident in patients with untreated GH deficiency. The negative effects of thyroxine overtreatment are more evident in patients with treated GH deficiency.

[Prof. Nenad Prodanovic (Bosnia and Herzegovina)](5) in his report focused on bone changes in cases of chronic diseases. It was noticed that patients suffering from chronic neuromuscular, inflammatory rheumatic and bowel diseases had a tendency to bone mineral density loss. People living with Parkinson disease had the highest incidence of accidental falling down, but osteoporotic bone fracture occurred more frequently among patients suffering Crohn’s disease and ulcerative colitis. Deficiency of vitamin D and calcium are common in patients with multiple sclerosis, inflammatory bowel diseases, rheumatoid arthritis and ankylosing spondylitis.

[Prof. Sekib Sokolovic (Bosnia and Herzegovina)](5) mentioned about the impact of nutrition on osteoporosis and cardiovascular diseases. He noted that common factors for osteoporosis, atherosclerosis and cardiovascular diseases were lipid abnormalities, smoking, aging, underlying disorders and using
of corticosteroids. Bone metabolism directly correlated to dietary acid/base balance. In disbalance the bones released calcium to keep normal levels of hydrogen and pH = 7.35–7.45. Excess of acid in the body for a long time could result in loss of calcium and bone and muscle breakdown. Vitamin D inadequacy with low BMD increased fracture risk, secondary hyperparathyroidism, calcified coronary arteries and cardiovascular events. Correlation of atherosclerosis and osteoporosis indicated the parallel progression of two tissue destruction processes with increased fatal and non-fatal coronary events and higher fracture risk.

Innovations in Pain Management in Osteoarthritis

Prof. Laszlo Hodinka (Budapest, Hungary) focused on questions of innovative pain management in patients with osteoarthritis. He noticed that the perception of chronic pain was projected in well defined areas of the brain where pain experience, emotions and behavioral patterns were coupled to the nociceptive input (insula, amygdala, hypothalamus and prefrontal cortex) and this complex resulted in chronic central pain. Descending modification was generated mostly in the anterior cingulate cortex and in the midbrain (cuneiform nucleus, periaqueductal grey material, dorsolateral pontine tegment and rostroventromedial medulla) and resulted in pain behaviour. In osteoarthritis tissue injury evoked the nociceptive input for the central sensitization and antidromic neurogenic inflammation. Among small molecular neurotransmitters, Nerve Growth Factor (NGF) and Calcitonin-Gene-Related Peptide (CGRP) neuropeptides played a crucial role in the maintenance of central pain. They were evaluated as therapeutic targets in pain management of osteoarthritis. In recent studies possibilities of modulation of pain perception by biological response modifying bioproteins, as monoclonal antibodies to NGF and CGRP, were evaluated.

Of course it would be difficult to overview all the lectures and reports that were presented during three working days of international symposium. Vitamin D status and gout also were among discussed topics.

All the time the lecture hall was full of participants, and all presentations continued with discussions. That suggested that the problem of musculoskeletal diseases is constantly being studied, and specialists in this field of medicine always have something new to discuss, especially when so many scientists from various countries meet together.

To be concluded, it must be said, that besides hard work the participants of the symposium had an opportunity to discover the City of Lviv for themselves, to walk by its ancient streets, to admire old buildings, chapels and cathedrals, to visit the famous Lviv Opera.

And let’s continue this fantastic tradition to meet in Lviv at the next International Symposium of Bone and Joint Diseases and Age again and again!

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