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CEE Summit on Bone Diseases 2016 Vienna

December 8th and 9th, 2016

Abstracts

December 8th, 2016

Risk Factors of Lower Limb Fractures of Different Age

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Introduction Lower limb fractures (LLF) account for approximately one third of all fractures and may result in substantial mortality and morbidity. Age, osteoporosis, road collision, obesity and different diseases (osteoarthritis, Parkinsonism, cataract, dementia etc.) are the risk factors of LLF. Fractures are a considerable public health burden but information about its risk factors in Ukraine is limited.

The purpose was to study the risk factors of LLF of patients depending on age, sex, type of fracture, parameters of bone mineral density, the geometric parameters of the femur and the level of vitamin D in serum.

Material and Methods We identified 1265 subjects aged 10 years and more who had a first-time (incident) diagnosis of LLF. Methods: questionnaires (determination of sex, age, time and reason of fracture), dual-energy X-ray absorptiometry (DXA, Lunar, Prodigy), assessment of geometric parameters of the hip (traditional X-ray), biochemical analyses of serum (the evaluation of level of 25(OH)D_{total} by electrochemiluminescence method, Elecsys, Roche).

Results Our study confirmed the significant association between LLF and age and sex. Lower limb fractures were more common among males than among females in the younger age groups (up to 50 years old). 44.4 % from the total fractures were established in patient aged 50 years and older. In this group the incidence of LLF was higher in women than in men, and the difference has grown up with increasing age.

The most common anatomic site of LLF was the tibia and/or fibula (48.9 % of all incident LLF), followed by the hip (29.5 %), and the tarsal/metatarsal bones (21.6 %). Incidence of fracture in patients 50 years and older was 519.8 per 100,000 patients for all LLF, 226.9 per 100,000 patients for hip fractures and 212.3 per 100,000 patients for tibia and/or fibula fractures. Frequency of tibia and/or fibula fractures rose with ageing from 20–29 to 60–69 years and feet fractures increased from 20–29 to 50–59 years. The incidence of hip fractures was highest in the age group over 85 years. Most patients with hip fractures had vitamin D deficiency or insufficiency, only 5 % of patients had a normal value of vitamin D in serum. Also this study has shown that some geometric parameters of the hip have significant influence on hip fracture risk on older patients, especially hip axis length, neck-shaft angle and cortical bone thickness. BMD indices were lower in patients with hip fractures in men and women but did not differ in patients with feet or tibia and/or fibula fractures compared with healthy population.

Conclusion Age, sex, parameters of bone mineral density, the geometric parameters of the femur and the level of vitamin D in serum are significant risk factors for lower limb fractures. The presence of these risk factors should be considered when planning therapeutic interventions in patients with fractures.

Association between Lean Mass and Dietary Protein Intake in Postmenopausal Women

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Introduction The skeletal muscle is a key component of the body composition, and it is highly correlated with physical activity. There are many factors leading to age-related muscle mass loss. Recent studies attest to a strong connection of dietary peculiarities and the body composition of elderly people. In this context, protein with its prominent dietary status gains an especial standing as far as the older population's health is concerned.

The aim of the study was to evaluate the appendicular lean mass depending on the dietary protein intake in Ukrainian postmenopausal women.

Materials and Methods The study involved 63 women aged 52–89 years who, depending on their ages, were divided into groups: 52–59 years (n = 9), 60–69 years (n = 26), 70–79 years (n = 21), 80–89 years (n = 7). To assess the dietary habits of women, we used the three-day sampling method and SEC "Viria" software. Lean mass was evaluated using a dual-energy X-ray absorptiometry (Prodigy, GE). We also calculated appendicular lean mass index (ALMI) by the formula: ALMI = lean mass of upper and lower extremities (kg) / height (m²).

Results Examination of patients' dietary habits showed an age-related decrease. Women of 80–89 years consuming less than 1.0 grams of protein per 1 kg of body weight accounted for more than a half of their group (57.1 %), which is significantly different from the parameters established in women of 52–59 years (22.2 %). For the purpose of quartile analysis, women were divided into 4 groups depending on their ALMI values: Q1 – ALMI = 5.20–5.84 kg/m² (n = 15), Q2 – ALMI = 5.85–6.25 kg/m² (n = 17), Q3 – ALMI = 6.26–6.56 kg/m² (n = 16), Q4 – ALMI = 6.57–7.65 kg/m² (n = 15). Women with the lowest ALMI values consume the lowest amounts of dietary protein (F = 3.67; p = 0.02). Significant correlations among dietary protein, nonessential, essential amino acids and ALMI values (r = 0.40, t = 3.44, p = 0.001; r = 0.39, t = 3.30, p = 0.002; r = 0.35, t = 2.91, p = 0.005; accordingly) were determined.

Conclusion Further studies are needed to elaborate a set of recommendations aimed at correction of nutritional habits observed in older women of different countries.

Bone Mineral Density in Children with Epidermolysis Bullosa

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Introduction Epidermolysis bullosa is a group of inherited bullous disorders characterized by blister formation in response to mechanical trauma. Epidermolysis bullosa is classified into 3 major categories: epidermolysis bullosa simplex (intraepidermal skin separation), junctional epidermolysis bullosa (skin separation in lamina lucida or basement membrane zone) and dystrophic epidermolysis bullosa (sublamina densa basement membrane zone separation).

The aim of the study was to evaluate the peculiarities of bone mineral density in patients with epidermolysis bullosa.

Material and Methods There were examined 11 patients (4 males and 7 females) with generalized recessive dystrophic form of epidermolysis bullosa aged 10–38 yrs. (mean age was 19.18 ± 7.87 yrs.).

Bone mineral density of the lumbar spine and total body was measured by dual-energy X-ray absorptiometry (DXA) with “Prodigy”. Primary outcomes were areal bone mineral density (aBMD) based on chronologic age and adjusted for height Z-score.

Results Mean lumbar spine aBMD Z-scores $\pm$ SD were: -2.4 ± 1.9 for chronologic age, -1.8 ± 1.5 after adjusting for height Z-score. aBMD Z-scores were less than or equal to -2.0 SD in 72 % for chronologic age, and 36.4 % after adjusting for height Z-score. aBMD correlated with height Z-score, weight Z-score and erythrocyte sedimentation rate.

Limitation The small size of the patient group.

Conclusion Patients with generalized recessive dystrophic form of epidermolysis bullosa have low aBMD for age. Low aBMD was reduced after adjusting for small body size.

December 9th, 2016

Diagnosis of Osteoporosis in Clinical Rheumatology

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Osteoporosis is characterized by low bone mass, deterioration of bone microarchitecture, increased bone fragility, and susceptibility to fracture [Kanis JA, et al., 2005]. The issue took on a special sounding in the recent years due to a significant population ageing and increased number of postmenopausal women. The specialists consider the disease to be taking on the character of an epidemic. Therefore, it's important to set its diagnosis before the fracture occurrence. Fortunately, osteoporosis is easy to diagnose: BMD testing can detect it before the first fracture occurs.

Various internal and external factors are known to contribute to the risk, illustrating the multifactorial aetiology of the condition. The term “secondary osteoporosis” refers to disorders that are strongly associated with osteoporosis (diseases with systemic inflammation such as rheumatic diseases [rheumatoid arthritis, SLE, systemic sclerosis, ankylosing spondylitis and others], endocrine, malnutrition, malabsorption and others).

The presentation includes indications for bone mineral density testing (ISCD 2015), advantages of ultrasound and dual X-ray absorptiometry, peculiarities of diagnosis in rheumatic patients, review data of secondary osteoporosis in patients with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, gout, and relationship between glucocorticoids and bone.

To evaluate the influence of glucocorticoid therapy (GC) on the trabecular bone score (TBS), a 1-year bone mineral density (BMD) and TBS dynamics was studied in Ukrainian patients with rheumatoid arthritis (RA) [Povoroznyuk V, Karasevska T, 2015]. 134 women with RA (age 52.5 ± 12.8 years; height 162.6 ± 6.4 cm, weight 68.2 ± 13.7 kg, duration of disease 9.1 ± 7.5 years, duration of postmenopausal period 7.6 ± 7.2 years) were examined. They were divided into three groups: first group, G1, includes 37 patients who did not use GC, second one, G2 – 50 patients who used GC in a dose of more than 5 mg of prednisolone for more than 3 years, third one, G3 – 47 patients who took GC only at the exacerbated stage for less than 6 months. All patients had been taking methotrexate as a basic treatment. BMD of total body, PA lumbar spine, proximal femur and forearm were measured using the DXA method (Prodigy, GEHC Lunar, Madison, WI, USA) and PA spine TBS was assessed by means of TBS iNsight® software package installed on our DXA machine (Med-Imaps, Pessac, France). A 1-year evaluation of TBS dynamics in the patients of G1 & G2 groups was conducted on the background of ongoing GC therapy (for the patients of the second group) and/or without any osteotropic treatment. The groups did not differ as to their age, basic anthropometric parameters, duration of disease and duration of postmenopausal period. TBS in G2 was significantly lower compared to G1 (TBS L1–L4: 1.147 ± 0.168 vs 1.250 ± 0.135 ; $t = -3.07$; $p = 0.003$), and in G3 compared to G1 (TBS L1–L4: 1.274 ± 0.138 ; $t = 3.95$; $p = 0.0002$). However, there were no differences in BMD of PA spine and hip among the groups. Only forearm BMD in the second group was significantly lower compared to the results in the first one (0.583 ± 0.176 g/cm² vs 0.675 ± 0.229 g/cm²; $t = -2.18$; $p = 0.032$). Spine TBS decreased by 1.4 % after one year for G1 and by 5.8 % for G2. Thus, for patients who are GC users, TBS rather than BMD reflects bone microarchitecture deterioration which is an indicator of a higher verte-

bral and non-vertebral risk of fracture. TBS is a determinant of bone state and must be monitored during the long-term GC treatment.

In conclusion, rheumatic diseases are strongly associated with osteoporosis and osteoporotic fractures. The patients who used glucocorticoid therapy have significantly lower bone mineral density and trabecular bone score data.

Less Strict High- versus Low-Risk Thresholds for the FRAX and TBS-Adjusted FRAX Predict Clinical Fractures in Osteopenic Postmenopausal Women with No Prior Fractures: A 5-Year Longitudinal Cohort Study

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Introduction Little is known about treating post-menopausal women with no prior history of fragility fracture and bone mineral densities (BMD) within the osteopenic range. In recent years, in addition to BMD and FRAX fracture probability assessments, a surrogate measure of bone micro-architecture quality, called trabecular bone score (TBS), has been proven to predict future fragility fractures independently of both BMD and FRAX.

Patients and Methods In this prospective, longitudinal cohort study, we compared three risk assessment instruments – the FRAX, the TBS, and a TBS-adjusted FRAX score – in their ability to predict future fragility fractures over a minimum of 5 years of follow-up among post-menopausal osteopenic women with no prior fragility fractures. We also sought to determine if more- versus less-stringent criteria were better when stratifying patients into higher-risk patients warranting osteoporosis-targeted intervention versus lower-risk patients in whom intervention would usually be deemed unnecessary.

Results Over a mean 5.2-year follow-up, 18 clinical fragility fractures were documented among 127 women aged 50 years and older (mean age = 66.1). On multivariate analysis utilizing regression models and Kaplan-Meier curve analysis, less-stringent criteria for the FRAX and TBS-adjusted FRAX were capable of predicting future fractures, while more-stringent criteria were incapable of doing so. Neither TBS threshold alone was a significant predictor of future fracture in our study. However, Hazard ratio analysis revealed slight superiority of the TBS-adjusted FRAX over the FRAX alone (HR = 3.09 vs 2.79).

Conclusions Adjusting the FRAX tool by incorporating the TBS may be useful as a means to optimize the detection of post-menopausal osteopenic women with no prior fractures who warrant osteoporosis-targeted therapy.

Trabecular Bone Score in Patients with Inflammatory Bowel Diseases

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Introduction Osteoporosis and osteopenia are known chronic complications of inflammatory bowel diseases (IBD). It is known that areal bone mineral density (aBMD) does not sufficiently reflect bone strength and quality. The trabecular bone score (TBS) provides an indirect measurement of bone microarchitecture, independent of areal bone mineral density (aBMD).

Aims and Methods The aim was to assess bone involvement in IBD patients with regard to disease behaviour using TBS in comparison with lumbar spine (LS) BMD. The cohort consisted of 84 IBD patients – 53 with Crohn's disease (CD) and 31 with ulcerative colitis (UC). Clinical characteristics of every patient were recorded, i.e. age, sex, anthropometry, clinical behaviour, location of disease according to the Montreal classification, medication. The BMD was determined by dual-energy X-ray absorptiometry (DXA, Hologic Discovery) at the lumbar spine. TBS was determined by TBS Insight® software (Medi-maps, France).

Results The mean age of the cohort was 42 ± 14.2 years with the average disease duration of 11 ± 7 years. 12/84 (14 %) of the cohort were postmenopausal women. 39.6 % (21/53) of CD patients had prior resection of the ileum. At the time of assessment 8/84 (9.5 %) of the IBD patients (3 CD vs 5 UC patients) were on glucocorticoid therapy with > 5 mg equivalent to prednisolone daily. The percentage of patients with substitution of vitamin D₃ (800 IU) and calcium (0.5–1 g) was similar between CD and UC (24.5 % vs 29 %), none of the patients were on anti-osteoporotic treatment. Biological treatment was common in the study population (48.4 % UC vs 50.9 % CD). The average LS BMD was 0.964 ± 0.113 g/cm² and TBS 1.36 ± 0.14 . The median serum 25(OH)D level was in the deficiency range in IBD patients (mean $\pm$ SD, 20.3 ± 8.2 ng/mL). There was a modest correlation between LS BMD and spine TBS ($r = 0.42$). Significantly lower TBS although not LS BMD was found in patients with fistulising CD as compared to those with luminal disease ($p = 0.0039$). We did not observe any difference in TBS or BMD in UC patients according to the disease behaviour.

Conclusion We observed that spine TBS can identify quality of bone mineral density in patients with Crohn's disease better than BMD itself. CD patients with severe disease are at higher risk of low bone mineral density.

Atypical Femoral Fracture as a Sign of Adult Hypophosphatasia

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Hypophosphatasia (HPP) is a genetic disease characterized by low levels of serum alkaline phosphatase (ALP). Assays for two natural substrates for "tissue-nonspecific" isoenzyme of ALP (TNSALP) and TNSALP mutation analysis are available in commercial laboratories. In contrast to severe forms in infants, HPP in adults shows a different pattern including loss of primary dentition, pseudofractures or recurrent poorly healing metatarsal stress fractures. Because the skeletal disease of HPP results from extracellular accumulation of the TNSALP substrate inorganic pyrophosphate (PPi) and its inhibitory effect on mineralization, perhaps HPP patients or carriers will have adverse effects from specific osteoporosis drugs like BPs. Less is known about microarchitecture in adult HPP patients with a preceding low-traumatic fracture.

Our report is one of the first showing bone structure analysis by HR-pQCT at the radius and tibia apart from other diagnostic measures like bone density measurement by DXA, TBS, quantitative QCT as well as biochemical markers and gen analysis in a 25-year-old male patient suffering from HPP with spontaneous atypical subtrochanteric femoral fractures (ASFF) after inadequate trauma and evidence of severe osteoporosis. The data of this patient are the first in a series of 7 cases we have been collecting during the last 5 years. Meanwhile, clinicians must suspect HPP when clinical or laboratory clues include premature loss of primary dentition, pseudofractures or recurrent poorly healing metatarsal stress fractures, a family history suggestive of HPP, or low serum ALP activity. To establish the diagnosis of HPP, assays for two natural substrates for TNSALP and TNSALP mutation

analysis should be done. With positive findings, radiological or bone biopsy evidence of acquired osteomalacia would indicate the adult form of this inborn-error-of-metabolism. As soon as the diagnosis is established ultimate benefit of a therapy with the new compound asfotase alfa should be considered.

Metabolic Compensation of Type-2 Diabetes and Bone Quality

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Introduction Patients with type-2 diabetes (T2DM) are at an increased risk of osteoporotic fracture despite increased bone mineral density (BMD), which can be caused by compromised bone quality. Poor glycaemic control is associated with higher incidence of all types of fracture risk.

Objective To determine the role of metabolic compensation measured by glycated haemoglobin (A_{1c}) on BMD and on bone quality measured by trabecular bone score (TBS) in T2DM patients.

Patients and Methods A retrospective cross-sectional trial in 56 women with T2DM treated only with metformin and DPP-4 inhibitors (drugs with neutral effect on bone metabolism) and 58 healthy controls without diabetes. The diagnosis of diabetes was confirmed according diagnostic criteria of ADA 2011, using the value of fasting plasma glucose and A_{1c}. The BMD at lumbar spine (LS) and femoral neck (FN) was measured by dual energy X-ray absorptiometry (DXA, Hologic). TBS Insight® tool was used to assess TBS derived from L-spine DXA scans.

Results Mean age was similar in both groups (50.3 ± 7.1 vs 52.2 ± 6.9 yrs, $p = 0.01$). Patients in the study group had greater BMI in comparison to controls (33.1 ± 5.3 kg/m² vs 28.6 ± 8.1 kg/m², $p = 0.04$). Duration of diabetes was 5.3 ± 3.8 years. The mean A_{1c} in the study group was 7.6 ± 0.6 % DCCT. Diabetes was associated with higher BMD than the control group (1.008 ± 0.175 g/cm² vs 0.961 ± 0.176 g/cm², $p = 0.05$). LS-TBS was lower in T2DM than in the control group (1.172 ± 0.120 vs 1.304 ± 0.018 , $p < 0.001$). Patients with a cut-off of A_{1c} ≤ 7.4 % had significantly higher TBS (1.203 ± 0.089 vs 1.117 ± 0.065 , $p < 0.05$), but there was no difference in BMD.

Conclusion Good glycaemic compensation is an important determinant for BMD as a marker of bone quantity and also TBS, a marker of bone quality. It seems that the cut-off levels of A_{1c} are others for BMD and TBS, respectively. Reliable A_{1c} cut-offs need to be determined in larger prospective studies. There can be other factors affecting the correlations like duration of diabetes, treatment modalities and other diabetic complications.

In the Aim of Rising Treatment Efficiency

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Despite significant progress in osteoporosis screening tools (FRAX, Garvan, X-Fracture) and the availability of several effective registered treatment options against osteoporosis, only 20 % of potential patients are selected and treated.

In the aim of improvement of the present situation, the possibility of broader utilization of BTM markers in protocols of patients diagnostic, outlines of drug selection and monitoring of the treatment are discussed.

Several issues supporting this view appeared lately. The IOF BTM Working Group inserted new recommendations pointing to a selection of the most promising assays. The automatization procedure significantly improved availability and reproducibility of assays. The assays have also started to be much broadly used in the treatment monitoring procedure.

Last but not least it should be pointed out that the broader utilization of BTM in routine clinical practice could in some way extend examination of metabolic status of treated patients and, when simultaneously passed to patients, influence presently low compliance and motivation for treatment.

Osteoporosis in Men

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Osteoporosis in men is substantially underdiagnosed and undertreated worldwide. Men of 65 years and over account for 11.1 % of the overall Ukrainian population. A 60-year-old white man has a 25-% lifetime risk for an osteoporotic fracture, and the consequences of this fracture may be severe. The 1-year mortality rate in men after hip fracture is twice than in women. Diagnostic evaluation and treatment of men at high risk for fracture remains low, despite the prevalence of this condition in men [Hau L, et al., 2008].

This presentation includes data on epidemiology and causes of osteoporosis, osteoporotic fractures in men, ISCD indications for BMD testing of osteoporosis in men, peculiarities of diagnosis, prevention and treatment of osteoporosis in men.

To evaluate the trabecular bone score (TBS), bone mineral density (BMD) and body composition in the Ukrainian men of various ages, 300 men aged 40–87 years (mean age – 60.5 ± 0.6 yrs; mean height – 1.61 ± 0.003 m; mean weight – 84.1 ± 0.9 kg) were examined [Povoznyuk V, Musiienko A, 2015]. The patients were divided into the following age-dependent groups: 40–49 yrs (n = 52), 50–59 yrs (n = 90), 60–69 yrs (n = 88), 70–79 yrs (n = 58), 80–87 yrs (n = 12). The BMD of total body, PA lumbar spine and proximal femur were measured by the DXA method (Prodigy, GEHC Lunar, Madison, WI, USA), and PA spine TBS was assessed by the TBS iNsight® software package installed on our DXA machine (Med-Imaps, Pessac, France). We observed a significant decrease of TBS (L1–L4) as a function of age (40–49 yrs – 1.161 ± 0.022 ; 50–59 yrs – 1.108 ± 0.018 ; 60–69 yrs – 1.114 ± 0.016 ; 70–79 yrs – 1.061 ± 0.024 ; 80–87 yrs – 1.105 ± 0.049 ; $F = 2.49$; $p = 0.04$). We also found the age-related decrease of BMD of lumbar spine (40–49 yrs – 1.186 ± 0.003 g/cm²; 50–59 yrs – 1.128 ± 0.021 g/cm²; 60–69 yrs – 1.224 ± 0.026 g/cm²; 70–79 yrs – 1.247 ± 0.034 g/cm²; 80–87 yrs – 1.131 ± 0.064 g/cm²; $F = 3.25$; $p = 0.01$) and proximal femur (40–49 yrs – 1.050 ± 0.021 g/cm²; 50–59 yrs – 0.996 ± 0.018 g/cm²; 60–69 yrs – 1.032 ± 0.018 g/cm²; 70–79 yrs – 1.004 ± 0.021 g/cm²; 80–87 yrs – 0.879 ± 0.050 g/cm²; $F = 3.34$; $p = 0.01$). Significant correlation was observed between TBS and BMD of lumbar spine [$TBS = 1.017 + 0.079 \times BMD (L_1-L_4)$; $r = 0.11$; $t = 1.90$; $p < 0.05$] and lean mass [$TBS = 1.441 - 0.000006 \times \text{Lean mass (g)}$; $r = -0.25$; $t = -4.50$; $p = 0.00001$]. Thus, TBS and BMD in examined men significantly decreased with ageing. We have also found a significant correlation between TBS and BMD of lumbar spine, along with lean mass.

In conclusion, Ukrainian population is ageing very fast. The prevalence of osteoporosis in men is growing. The burden of fractures in men will probably increase in the nearest future.

Renal Insufficiency and Hip Fractures – A Slovenian Survey

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Osteoporosis is a condition that causes a systemic bone loss which starts with no apparent problems and is typically diagnosed only after a complication – a fracture. The most problematic are proximal femur fractures, which of all the typical osteoporosis fractures occur last and have the worst prognosis in terms of mortality and maintenance of the independent ability to manage daily activities of the elderly.

Besides the well-established method of bone mineral density (BMD) measurement with dual energy X-ray absorptiometry (DXA), in recognition of the importance of metabolic processes of bone tissue and calciotropic modulators, today increasing attention is paid to the role of kidneys as an important factor in these processes. Impairment of kidney function presents an important risk factor, the development of which can be at least partially influenced and thus also reduced.

The goal of the study was to determine the difference between bone mineral density of patients who sustained proximal femur fracture with those who did not sustain this fracture and to find out what role the observed kidney function plays in this. Further to that, we also wanted to determine correlations with some of the metabolites which affect the remodulation of bone tissue.

The study was carried out on 38 patients who sustained proximal femur fracture and 29 patients who did not sustain an osteoporotic fracture. For all the patients central dual energy X-ray absorptiometry was used to assess bone mineral density. In addition to that, serum concentrations of calcium, phosphate, parathormone, 25-hydroxycholecalciferol, 1,25-dihydroxycholecalciferol, urea and creatinine were also measured. A modified formula for the calculation of glomerular filtration was used to calculate kidney function.

The results of the study show that there is a difference in bone mineral density, which is lower with patients who sustained a fracture. No differences in the concentrations of calcium, phosphate, PTH and 1,25-dihydroxycholecalciferol were detected, while an increased concentration of 25-hydroxycholecalciferol was observed in the group of patients who sustained a fracture, the increase being due to a substitute therapy with vitamin D. In the group with impaired kidney function (GFR < 60 ml) the ratio of patients with osteoporotic fracture was statistically higher. The relation between bone mineral density of lumbar spine and serum creatinine was observed. Patients with fractures had higher values of urea than the control group, which we ascribed to the initial dehydration accompanying the fracture.

Craniosynostosis Malformation and Importance of Early Diagnosis

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Craniosynostosis is the premature closure of one or several sutures of the skull. It causes distorted head shape, which makes an increased risk of elevated intracranial pressure. Regarding to the best available sources till 2011, its ranges were from 3.1 to 6.4 in 10,000, also some evidence showed its prevalence between 1 in 2100 to 1 in 3000, 79 % of them considered as non-syndromic craniosynostosis and 21 % caused by a known genetic disorder. Raised awareness among Paediatrics, Obstetrics, Midwives and other health care providers causes early diagnosis of craniosynostosis, which is very helpful for on-time referring of these patients to a craniofacial and paediatric neurosurgeon. The timing of surgery is individualized and focuses on the correction of the abnormal skull, reshapes and repositions those bones to give a more normal skull shape for better function with prevention of associated morbidity and mortality. The first reported surgical procedure for correction of craniosynostosis was performed in 1890 by Lanne-longue. Now through the pioneering work of Jimenez and Barone, minimally invasive approaches to the surgical correction of craniosynostosis are gaining wide acceptance. Jimenez et al. (2002) reported 100 patients with documented diagnosis of craniosynostosis treated with endoscopic strip craniectomies. They emphasize that it is a safe and valuable therapeutic alternative to the current extensive surgical treatment modalities with significantly less blood loss, length of stay and decreased costs. Referring to the importance of early diagnosis of craniosynostosis, various photos of improved patients from pre-operation time till years after operation will be shown during the presentation of this article.

Vitamin D and Musculoskeletal Health

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Vitamin D (VD) has an essential role in the regulation of calcium and phosphorus metabolism and in maintaining musculoskeletal health.

VD deficiency is correlated with a number of negative health outcomes, mainly affecting the musculoskeletal system. The risk of rickets and osteomalacia is increased at serum 25-hydroxyvitamin D [25(OH)D] concentrations below 20–25 nmol/L. In contrast, high 25(OH)D serum levels are correlated to higher bone mass density (BMD). Native VD supplementation was associated with a small increase in femoral neck BMD, but had no effect at other skeletal sites.

In postmenopausal women, serum 25(OH)D concentration is inversely correlated with fracture risk. Oral VD supplementation has

a small effect in preventing non-vertebral and hip fractures in the elderly. Other meta-analyses or Cochrane analyses only support the anti-fracture effect for the combination of VD and calcium, a combination leading to a significant reduction in hip, non-vertebral or any fracture risk. Daily VD doses of at least 800 IU are needed. Whether the effect is present in all populations is currently unknown. For instance in one meta-analysis VD plus calcium reduced hip fracture in institutionalised individuals but not in community-dwelling individuals.

The anti-fracture effects of these daily doses of VD are the combined result of the minimal effect on BMD and the more significant decrease in the incidence of falling episodes. VD supplementation consistently reduces the risk of falling in the elderly. Such 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.

VD status was also directly correlated in numerous studies with measures of neuromuscular function and VD supplementation was shown to improve muscle strength and function especially in the elderly. Beneficial results have also been reported in younger adults with VD deficiency (as we and others have previously shown). However, the evidence supporting these beneficial effects is considered insufficiently conclusive at present.

The evidence overall suggests that risk of poor musculoskeletal health is increased at serum 25(OH)D concentrations below 20–30 nmol/L. In the elderly daily supplementation doses of 800–1000 IU VD associated with calcium are currently recommended for fall and fracture prevention and a serum 25(OH)D level of at least 50 nmol/l is aimed for proper muscle functioning.

Evidence on vitamin D effects on a wide range of non-musculoskeletal health outcomes (malignancy, cardiovascular diseases, immune diseases, reproductive health, infectious diseases etc.) is drawn mainly from observational studies. Currently there is insufficient evidence on the beneficial effects of VD supplementation for these non-musculoskeletal health outcomes.

Conclusions Despite of the lack of very robust and consistent data, published data support positive effects of VD replacement on the muscle force, falls and fracture risk in various population groups. Many other positive health outcomes are claimed but insufficiently proven to date.

The Blood Level of Vitamin D in Patients with Hypertension and Coronary Disease According to Age and Sex

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Purpose of the Research To assess the difference of 25-hydroxycholecalciferol [25(OH)D] level in blood plasma in patients with arterial hypertension (AH) and coronary artery disease (CAD) according to age, sex and diagnosis.

Materials and Methods We examined 539 individuals (152 men and 387 women) aged 30–79 years. Among them 71 participants did not have any cardiovascular disease, 221 had II degree of AH, 247 suffered from CHD. Vitamin D status was assessed by the serum level of vitamin D total [25(OH)D total = 25(OH)D₃+25(OH)D₂] using immunoenzymatic assay with the help of original DRG reagents. Level of parathyroid hormone (PTH) in blood plasma was estimated by means of the same method. Statistical analysis was carried out by "STATISTICA 10.0" software.

Results We found a negative correlation between age and level of 25(OH)D in blood plasma in a whole group ($R = -0.21$; $p = 0.000001$) and in the joint group with AH and CAD ($R = 0.198$; $p = 0.000015$, $n = 468$), but after dividing patients into 3 groups by diagnosis this correlation appeared to be not significant in each group. To assess the effect of age, sex and diagnosis on the level of 25(OH)D, we performed multiple linear regression analysis by forward stepwise method. Formed regression relationship was significant ($R^2 = 0.10$; $F(2,42) = 19.77$; $p < 0.000001$), b coefficient for the independent vari-

ables included in the model was significant for age and PTH and valued at -0.18 ($p = 0.001$) and -0.097 ($p = 0.000001$), respectively, which indicates their negative association with the level of 25(OH)D. Also another regression equation was significant ($R^2 = 0.07$; $F(6,44) = 5.58$; $p < 0.00001$), b coefficient for the independent variables included in the model was significant for sex and diagnosis and valued at -0.10 ($p = 0.027$) and -0.18 ($p = 0.003$), which also indicates their negative correlation with the level of 25(OH)D. After separation of the entire group by the age into 5 subgroups: 3b – 30–39; 4b – 40–49; 5b – 50–59; 6b – 60–69; 7b – 70–79 years, we found differences ($p = 0.00002$) in the level of 25(OH)D between the group 3b, where the level was highest (25.3 ± 11.3 ng/ml), and other four groups; between group 7b, where the level of 25(OH)D was the lowest (14.97 ± 9.2 ng/ml), and group 3b ($p = 0.000004$), 4b ($p = 0.007$), 5b ($p = 0.006$). However, after separation of groups by diagnosis in each of them there were no differences by level of 25(OH)D between age groups. After separation into groups by diagnosis, ANOVA analysis revealed that the CAD group was older (64.6 ± 8.1 years) than the control group (46.1 ± 6.7 years; $p = 0.00001$) and the AH group (52.4 ± 7.6 years; $p = 0.000009$). Levels of 25(OH)D in blood plasma in the CAD group was 13.2 [8.3 ; 21.1] ng/ml and was lower ($p = 0.00001$) than in the AH group (20.1 [12.4 ; 29.1] ng/ml) and lower ($p = 0.00001$) than in the control group (20.8 [11.4 ; 27.9] ng/ml). Furthermore, PTH level in the CAD group was the highest (46.16 [33.19 ; 71.57] pg/ml); higher ($p = 0.0001$) than in the AH group (36.67 [25.22 ; 51.29] pg/ml) and the control group (43.12 [28.54 ; 55.26] pg/ml; $p = 0.002$). After separation of groups by sex no significant differences in 25(OH)D levels were found in a whole group and in groups separated by diagnosis, as well as in comparison of 5 subgroups comparable by age.

Thus, 25(OH)D level in blood plasma is negatively associated with age and it is dependent on cardiovascular diseases, in particular it is lower in individuals with CAD compared to individuals with AH II degree. Gender does not have a significant effect on the level of 25(OH)D in the blood plasma.

Microstructural Analysis of Subchondral Bone in Knee Osteoarthritis

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Objective Subchondral bone changes seem to contribute to the progression of knee osteoarthritis (OA). This study aimed to analyze subchondral bone microstructure in specimens of late-stage knee OA in respect to articular cartilage damage, meniscus integrity and knee joint alignment.

Methods and Materials 30 proximal tibiae of 30 patients (20 female and 10 male) with late-stage OA retrieved during total knee arthroplasty (TKA) were scanned using a high-resolution micro-computed tomography (μ CT). The scans were semi-automatically segmented into five volumes of interest (VOIs). The VOIs were then further analyzed using commercially available software. The degree of articular cartilage damage was assessed semi-quantitatively by magnetic resonance imaging (MRI) before surgery.

Results The mean bone fraction volume (BV/TV) in all weight-bearing locations was significantly higher compared to the non weight-bearing reference point below the anterior cruciate ligament ($p = 0.000$). The mean BV/TV in the medial compartment was significantly higher compared to the lateral compartment ($p = 0.007$). The BV/TV in intact menisci, there was a significantly lower subchondral BV/TV compared to subluxated or luxated menisci in the medial ($p = 0.020$) and lateral compartment ($p = 0.005$). Varus alignment had a significantly higher subchondral BV/TV in the medial compartment, whereas valgus alignment had a significantly higher subchondral BV/TV in the lateral compartment ($p = 0.011$).

Conclusion The results show significant differences of subchondral bone microstructural parameters in respect to cartilage damage, meniscus' structural integrity and knee joint alignment. Therefore, subchondral bone changes seem to be a secondary process in the late-stage OA of knee caused by mechanical changes.

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