European Society of Endocrinology

the European hormone society

7th - 8th April 2017

Mantova, Italy

MAMU - Mantova Multicentre

Largo di Porta Pradella, 1B Mantova

8th Skeletal Endocrinology Meeting

3rd TRANSLATIONAL ESE BONE COURSE

SCIENTIFIC COMMITTEE

CHAIR PERSONS

JOHN BILEZIKIAN

JENS BOLLERSLEV

ERNESTO CANALIS

ANDREA GIUSTINA

BARBARA OBERMAYER-PIETSCH

www.ese-hormones.org

www.aicgroup.it

WELCOME

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Dear Friends and Colleagues,

we are pleased to welcome you all to Mantova for the Eigth Skeletal Endocrinology Meeting. It will be held in the MAMU Congress Center of the City of Mantova on April 7th-8th 2017. Again this year the Meeting will be in collaboration with the European Society of Endocrinology (ESE) as the "Third Translational ESE Bone Course".
Over the next 2 days, the Meeting will offer the opportunity for an exciting exchange of basic and clinical science and will explore new insights into the role of traditional hormones and novel signals in bone health. The program will feature an outstanding panel of invited speakers and an audience of interested scientists and clinicians from around the World. The Venue of the Meeting will be Mantova, where in Carlo Poma Hospital active research in the field of Bone and Mineral Metabolism is conducted.
We do hope that this Eight Skeletal Endocrinology Meeting and the Third ESE Translational Bone Course will be as successful previous ones We cordially invite all of you to the city of Mantova, which offers an extraordinary environment for scientific and social activities.

Welcome to Skeletal!


JOHN P. BILEZIKIAN


JENS BOLLERSLEV


ERNESTO CANALIS


ANDREA GIUSTINA


BARBARA OBERMAYER-PIETSCH

PATRONAGE

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Consiglio Nazionale delle Ricerche

Istituto Superiore di Sanità

Regione Lombardia

Provincia Mantova

Comune Mantova

Azienda Socio Sanitaria Territoriale "Carlo Poma"

Agenzia di Tutela della Salute Val Padana
Distretto Socio Sanitario di Mantova

Ordine dei Medici Chirurghi e Odontoiatri
della Provincia di Mantova

Università Vita-Salute San Raffaele

SIE Società Italiana di Endocrinologia

SIOMMMS Società Italiana dell'Osteoporosi
del Metabolismo Minerale e delle Malattie
dello Scheletro

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PROGRAM

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Friday, 7th April 2017

01.00 - 02.15 pm — **SATELLITE SYMPOSIUM: OSTEOPOROTIC FRACTURE CURRENT CHALLENGES AND PERSPECTIVES**
Chair: A. Giustina (I)
The paradox of fracture increase in Italy - P Piscitelli (I)
A new approach to fracture prevention: the Nota 79 algorithm - F. Vescini (I)
Bisphosphonates: the challenge of adherence in real life - S. Giannini (I)
Discussion

02.15 - 03.30 pm — **UPDATES ON HORMONES AND FRACTURES**
Chairs: V. Camozzi (I), A. Giustina (I)
Treatment of adrenal insufficiency and bone - L. De Marinis (I)
Acromegaly and Bone - G. Mazziotti (I)
Teriparatide and fracture: place in guidelines and in the real life - J.P. Bilezikian (US)
Discussion

03.30 - 04.00 pm — **OPENING LECTURE**
Chairs: L. Moro (I), A.J. Van der Lelij (NL)
Genetics of osteoporosis - W. Van Hul (NL)

04.00 - 05.15 pm — **SESSION I: ADVANCEMENTS IN THE ASSESSMENT OF FRACTURE RISK**
Chairs: I. Chiodini (I), S. Minisola (I)
TBS - F.M. Ulivieri (I)
QCT, pQCT & HRpQCT- M. Bouxsein (US)
TC Cone Beam - F. Maffezzoni (I)
Discussion

05.15 - 06.30 pm — **SESSION II: DENOSUMAB WHAT'S NEW**
Chairs: B. Obermayer-Pietsch (A), L. Sinigaglia (I)
Bone microarchitecture - S. Ferrari (CH)
Combination treatments - S. Polyzos (GR)
Use in cancer-related bone disease - F. Bertoldo (I)
Discussion

06.30 - 07.00 pm — **ESE LECTURE**
Chairs: G. Bianchi (I), J. Bollerslev (N)
Long-term management of osteoporosis, when and how to switch - M.C. Zillikens (NL)

07.00 - 07.45 pm — **SKELETAL HOT TOPICS I**
Chairs: S. Corbetta (I), P. D'Amelio (I)
Prevalence of malignant neoplasia in patients with primary hyperparathyroidism - E. Cairoli (I)
Exploring epigenetic changes in human parathyroid tumors: long non-coding RNA expression profile reveals heterogeneity among human parathyroid tumors - V. André (I)
The use of denosumab in primary hyperparathyroidism - B. Carloni (I)
Hypovitaminosis D in patients with heart failure: effects on functional capacity and patients' survival - F. Saponaro (I)
Efficacy and safety of PTH (1-34) treatment of hypoparathyroidism: a prospective observational single-centre study - M. Celico (I)

07.45 pm — **OPENING CEREMONY AND POSTER DISPLAY**

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Saturday, 8th April 2017

08.00 - 08.40 am **SKELETAL HOT TOPICS II**
Chairs: G. Mazziotti (I), F. Vescini (I)
Tumor-induced osteomalacia mimicking spondyloarthritis: a diagnostic challenge - V. Ravagnani (I)
Micro-RNA signatures in healthy vitamin D deficient men before and after supplementation V. Francic (A)
Factor affecting fracture risk in adult-onset growth hormone-deficient patients and role of the Growth hormone receptor isoforms - S. Chiloiro (I)
Atypical femoral fractures caused by Glucocorticoid and Bisphosphonate prolonged therapy in premenopausal women: a case report - G. Franceschet (I)
Effects of denosumab on quantitative ultrasound and Dual-Energy X-ray absorptiom try measurements in aromatase inhibitor-treated breast cancer women - F. Bellone (I)

08.40 - 09.10 am **LECTURE**
Chairs: G. Banfi (I), E. Canalis (US)
Muscle-bone interaction: The paradigm of Duchenne's Dystrophy - P. Roschger (A)

09.10 - 10.20 am **SESSION III: HYPOPARATHYROIDISM**
Chairs: J.P. Bilezikian (US), C. Marcocci (I)
Determinants of skeletal phenotype - R. Rizzoli (CH)
Clinical practice guidelines - J. Bollerslev (N)
Replacement therapy - L. Rejnmark (DK)
Discussion

10.20 - 11.30 am **SESSION IV: RARE BONE DISEASES**
Chairs: G. Arioli (I), A. Rubinacci (I)
Hypophosphatasia - M.L. Brandi (I)
Osteogenesis imperfecta and Ehelrs Danlos Syndrome - A.M. Formenti (I), G. Mazziotti (I)
Hajdu Cheney Syndrome - E. Canalis (US)
Discussion

11.30 - 12.40 pm **SESSION V: VITAMIN D AND BONE**
Chairs: E. Ghigo (I), R. Rizzoli (CH)
Definition, assays and variables in biochemical diagnosis of hypovitaminosis D - M. Plebani (I)
Hypovitaminosis D skeletal phenotype - R. Bouillon (B)
Treatment with Vitamin D - B. Obermayer-Pietsch (A)
Discussion

12.40 - 01.30 pm **SESSION VI: NEW HORIZONS ON ANTI-OSTEOPOROTIC THERAPY**
Chairs: A. Angeli (I), S. Gonnelli (I)
Romosozumab - C-C.J. Glüer (Ger)
Abaloparatide - J.P. Bilezikian (US)
Discussion

01.30 - 01.45 pm **CONCLUSIVE REMARKS**

PROGRAM

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Poster Display

Posters will be displayed on the 1st floor of the Congress Venue

P.1 Prevalence of malignant neoplasia in patients with primary hyperparathyroidism - E. Cairoli (I)

P.2 Exploring epigenetic changes in human parathyroid tumors: long non-coding RNA expression profile reveals heterogeneity among human parathyroid tumors - V. André (I)

P.3 The use of denosumab in primary hyperparathyroidism - B. Carloni (I)

P.4 Hypovitaminosis D in patients with heart failure: effects on functional capacity and patients' survival - F. Saponaro (I)

P.5 Efficacy and safety of PTH (1-34) treatment if hypoparathyroidism: a prospective observational single-centre study - M. Celico (I)

P.6 Tumor-induced osteomalacia mimicking spondyloarthritis: a diagnostic challenge - V. Ravagnani (I)

P.7 Micro-RNA signatures in healthy vitamin D deficient men before and after supplementation - V. Francic (A)

P.8 Factor affecting fracture risk in adult-onset growth hormone-deficient patients and role of the Growth hormone receptor isoforms - S. Chiloiro (I)

P.9 Atypical femoral fractures caused by Glucocorticoid and Bisphosphonate prolonged therapy in premenopausal women: a case report - G. Franceschet (I)

P.10 Effects of denosumab on quantitative ultrasound and Dual-Energy X-ray absorptiometry measurements in aromatase inhibitor-treated breast cancer women - F. Bellone (I)

P.11 Micro-rna targets associated with bone metabolism in chronic kidney disease patients before and after kidney transplantation - I. Foessl (A)

P.12 Phalangeal quantitative ultrasound detects changes of bone status in aromatase inhibitor-treated breast cancer receiving denosumab - F. Bellone (I)

P.13 Treatment with teriparatide: improvement of BMD in GHD's patient - C. Bima (I)

P.14 Proacro study: our proposal to improve acromegaly's osteoarthrosis - C. Bima (I)

P.15 Low calcium intake strongly predicts the risk of developing osteoporosis and vertebral fractures - S. Frara (I)

P.16 Sex-hormone binding globulin as determinant of radiological vertebral fractures in male HIV patients under antiretroviral therapy - T. Porcelli (I)

P.17 Body composition, size and hormonal parameters are associated with bone and glucose metabolism in a large cohort of volunteers - C.W. Haudum (A)

FACULTY

GIOSEG Glucocorticoid Induced Osteoporosis Skeletal Endocrinology Group

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V. Andrè (I)
A. Angeli (I)
G. Arioli (I)
G. Banfi (I)
F. Bellone (I)
F. Bertoldo (I)
G. Bianchi (I)
J.P. Bilezikian (US)
J. Bollerslev (N)
R. Bouillon (B)
M. Bouxsein (US)
M.L. Brandi (I)
E. Cairoli (I)
V. Camozzi (I)
E. Canalis (US)
B. Carloni (I)
M. Celico (I)
S. Chiloiro (I)
I. Chiodini (I)
S. Corbetta (I)
P. D'Amelio (I)
L. De Marinis (I)
S. Ferrari (CH)
A.M. Formenti (I)
G. Franceschet (I)
V. Francic (A)
E. Ghigo (I)
S. Giannini (I)
A. Giustina (I)
C. Glüer (Ger)
S. Gonnelli (I)
F. Maffezzoni (I)
C. Marcocci (I)
G. Mazziotti (I)
S. Minisola (I)
L. Moro (I)
B. Obermayer-Pietsch (A)
P. Piscitelli (I)
M. Plebani (I)
S. Polyzos (GR)
V. Ravagnani (I)
L. Rejnmark (DK)
R. Rizzoli (CH)
P. Roschger (A)
A. Rubinacci (I)
F. Saponaro (I)
L. Sinigaglia (I)
F.M. Ulivieri (I)
A.J. van der Lelij (NL)
W. Van Hul (NL)
F. Vescini (I)
M.C. Zillikens (NL)

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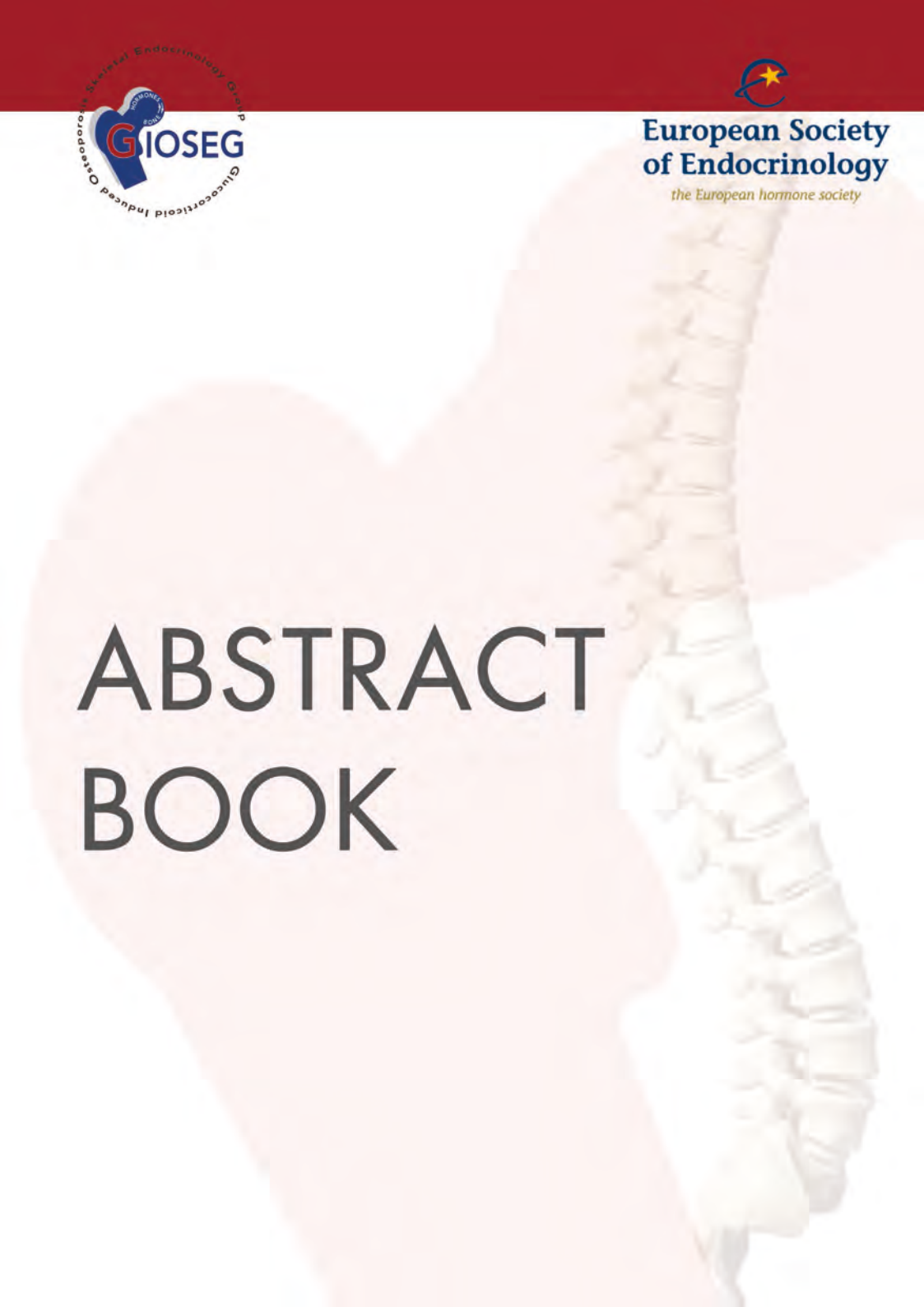
ABSTRACT BOOK



SKELETAL PHENOTYPE OF HYPOVITAMINOSIS D

Roger Bouillon

Clinic and laboratory of experimental medicine and endocrinology, KULeuven, Leuven 3000, Belgium.

The vitamin D endocrine system (D-endo) is essential for calcium and bone homeostasis. Absence of a functional VDR or CYP27B1 creates a severe rachitic bone phenotype in humans and mice as in severe vitamin D deficiency. There are three major hallmarks of rickets: abnormal growth plate structure with excess hypertrophic chondrocytes and lack of primary mineralization of the growth plate cartilage, resulting in stunted growth. In bone osteoid mineralization is impaired resulting in excess osteoid surface and thickness and above all delayed mineralization lag time. Evidently, this also results in less mineralized bone and or undermineralized bone. The intestine is the key target for VDR as a high calcium intake or selective VDR rescue in the intestine restores a normal bone and growth plate phenotype. Selective absence of VDR in osteoblasts or osteocytes does not create a bone phenotype when calcium intake is normal. Selective VDR deficiency in chondrocytes does not recapitulate the rachitic growth plate phenotype but causes a transient increase in bone mass and abnormal FGF23 signaling in the kidney. VDR signaling in the osteocytes may however become very important in case of calcium deficiency or exposure to excess 1,25(OH)2D, as in such case osteocytes may impair bone mineralization by regulating a coherent set of genes involved in regulating the mineralization process. Overall, tissue specific deletions of VDR or cyp27b1 have now better defined the role of vitamin D in different tissues. Indeed, the vitamin D endocrine system already exist early in the evolution of vertebrates and its primary role is to maintain a normal serum calcium homeostasis, whereas optimal mineralization of bone and teeth is the second role for this endocrine system. This implies that when calcium supply is sufficient, vitamin D will enhance the calcium balance and prevent or cure rickets/osteomalacia, largely indirectly. In case of severe calcium deficiency of lack of efficient calcium absorption, 1,25(OH)2D will stimulate both bone resorption and inhibit bone mineralization, thereby causing rickets/osteomalacia, as to maintain as long as possible a normal serum calcium homeostasis. The implications for humans are multiple: rickets is still endemic in different parts of the world and milder forms of vitamin D deficiency is present in more than a billion people worldwide so that appropriate large scale strategies are needed to correct this situation.

The guidelines from scientific societies and from governmental organizations to prevent vitamin D deficiency disorders are unanimous that serum 25OHD concentrations below 25 nmol/l should be avoided at all ages, but otherwise there is great discordance with regard to optimal levels and vitamin D intake. Based on a critical analysis of all existing data from randomized controlled trial, we suggest that serum 25OHD concentrations should be 50 nmol/l (20 ng/l) in all adults.

However the mean 25OHD found in normal adults around the world (n > 500 publications) is hardly higher than 50 nmol/l, indicating the widespread presence of mild to severe vitamin D deficiency. Some areas around the world are more prone to severe vitamin D deficiency such as the Middle East and Gulf States, Northern India and China (Mongolia being the worst of all). Populations in need of the highest attention are infants, the very elderly (oldest-old) and people with habitual low sun exposure for whatever reason. For these subjects a systematic approach to assure vitamin D supplementation is needed. The highest priority should be given to systematic vitamin D supplementation as general rule for all children till at least 3 years of age. All elderly subjects should also receive vitamin D supplementation up to about the equivalent of 800 IU of vitamin D3 per day keeping serum 25OHD levels above 20 ng/ml or 50 nmol/l.

VDR is ubiquitously expressed and about 3% of the mouse or human genome is regulated by the vitamin D endocrine system. This suggests that vitamin D may have many extra-skeletal effects. Prospective and intervention studies are needed and ongoing as to define the optimal vitamin D status for global health.

HYPOPHOSPHATASIA

Maria Luisa Brandi
University of Florence, Department of Surgery and Translational Medicine, Florence, Italy

Biomineralization is the process by which minerals are deposited within or outside the cells of a variety of organisms. In vertebrate tissues, the deposited minerals are composed of hydroxyapatite, and are found in the extracellular matrix. Alkaline phosphatases (ALPs) are membrane-bound ectoenzymes that hydrolyze monophosphate esters at a high pH (pH 8—10). Tissue-nonspecific alkaline phosphatase (TNAP) is expressed on the cell membrane of hypertrophic chondrocytes, osteoblasts, and odontoblasts, and is also concentrated on the membranes of the matrix vesicles budding from these cells. It hydrolyzes inorganic pyrophosphate (PPi) and provides inorganic phosphate (Pi) to promote mineralization. PPi, pyridoxal 5-phosphate, the activate form of vitamin B6 (PLP), and phosphoethanolamine (PEA) are their substrates. Hypophosphatasia (HPP, OMIM 146300, 241500, 241510)) is a heterogeneous rare metabolic bone disease caused by loss-of-function mutations in the tissue-nonspecific alkaline phosphatase gene (ALPL: MIM 171760) with a deficiency of TNAP. The presentation of HPP in adults demonstrated a wide range of clinical manifestations, many of which are nonspecific. The correct and differential diagnosis of adult HPP is difficult, and the disease is often misdiagnosed or not-diagnosed, and, subsequently, wrongly or non-treated. In most cases, diagnosis of adult HPP is made after a low serum ALP level and it is casually detected during routine blood screening, or when tested after a direct family member was diagnosed with the condition. The presentation will focus on the phenotype and genotype of adults with hypophosphatasia.

NOTCH AND HAJDU CHENEY SYNDROME

Ernesto Canalis
UConn Musculoskeletal Institute, UConn Health, Farmington, CT 06030

Notch 1 to 4 receptors are important determinants of cell fate and function, and Notch signaling plays an important role in skeletal development and bone remodeling. Following interactions with ligands of the Jagged and Delta-like families, Notch is activated to regulate the transcription of its target genes. Classic targets of Notch activation are Hairy and enhancer of split (Hes) and Hes-related with YRPW motif (Hey). Notch activation arrests osteoblast differentiation and causes bone loss. Notch1 inhibits, whereas Notch2 enhances, osteoclastogenesis and bone resorption. Congenital disorders of loss and gain-of-Notch function present with severe clinical manifestations, often affecting the skeleton. Hajdu Cheney Syndrome (HCS) is a rare disease associated with NOTCH2 mutations leading to the translation of a truncated NOTCH2 stable protein. As a consequence, a gain-of-NOTCH2 function is manifested. HCS is inherited as an autosomal dominant disease although sporadic cases exist. HCS is characterized by craniofacial developmental defects, osteoporosis with fractures and acroosteolysis. Subjects may suffer severe neurological complications. An experimental mouse model harboring an HCSNotch2 mutation exhibits osteopenia secondary to enhanced bone resorption, suggesting this as a possible mechanism for the skeletal disease. If the same mechanisms were operational in humans, anti-resorptive therapy could correct the bone loss, but not necessarily the acroosteolysis. Notch signaling can be controlled by the use of inhibitors of Notch activation, small peptides that interfere with the formation of a transcriptional complex or antibodies to Notch receptors or to their ligands. Treatment of HCSNotch2 mutant mice with antibodies to the Negative Regulatory Region of Notch2 reversed the osteopenic phenotype and the enhanced bone resorption. In conclusion, Notch plays a critical role in skeletal development and homeostasis and serious skeletal disorders can be attributed to alterations in Notch signaling.

TREATMENT OF ADRENAL INSUFFICIENCY AND BONE

De Marinis L, Bianchi A, Chiloiro S, Giampietro A
Pituitary Unit, Catholic University of the Sacred Heart, Rome

Glucocorticoids act on bone with a direct and an indirect mechanisms. Through a direct mechanism, glucocorticoids reduce the intestinal absorption and increase the renal excretion of the calcium, determining a negative calcium balance. Moreover, glucocorticoid act directly on the bone cells increasing the apoptosis and reducing the function of osteocytes and osteoblasts; reducing the differential potential of osteoblasts, the apoptosis of osteoclast and increasing osteoclast genesis. Through an indirect mechanism, glucocorticoids reduce the secretion of FSH, LH and sex steroids, stimulates the somatostatin and inhibit GH secretion (Giustina's effect). Consequently, though both a direct and an indirect mechanism, excess of glucocorticoid reduces bone quality, bone formation and increases bone resorption, inducing a reduction of bone mass and an increased risk of vertebral fractures.

Pituitary diseases are, consequently, strongly involved in bone metabolism: in Cushing disease as well as in cases of overtreatment of hypoadrenalism, a suppression of bone turnover marker occurred. In fact, in Cushing disease affected patients a severe trabecular bone rarefaction occurred. Moreover, also in other endogenous hypercortisolism conditions (as ACTH-secreting pituitary adenoma, adrenal adenoma and carcinomas and in ectopic ACTH excess), an higher prevalence of vertebral fractures, almost multiple, are reported, as compared to control cases. The increased bone turn-over is documented also in cases of overdosage of glucocorticoid replacement therapy both in central and primary hypoadrenalism: a higher prevalence of vertebral fractures was documented in hypopituitary patients treated with hydrocortisone doses greater than 28 mg per day.

Glucocorticoid replacement therapy impact on mineral bone density, also, in patients on treatment with rhGH for growth hormone deficiency, as the therapeutic response to GH replacement on BMD may, however, be less in patients receiving glucocorticoid replacement, in particular in the femur neck. However, the negative effects of glucocorticoid overtreatment were shown to be more evident in patients with untreated GH deficiency: in untreated GHD patients, high current cortisone dose increases frequency of vertebral fractures. In conclusion, both endogenous and exogenous glucocorticoid excess induce an increased vertebral fracture risk, particularly in patients with hypopituitarism as replacement therapies do not completely mirror the endogenous hormonal production, and their monitoring is also made difficult by the lack of good biomarkers of their action. Prospective trials comparing various glucocorticoid regimens and novel replacement modes such as modified-release tablets and continuous s.c. hydrocortisone infusion are expected to identify potential benefits for bone metabolism.

RARE BONE DISEASES: FRACTURE RISK IN OSTEOGENESIS IMPERFECTA AND EHLERS DANLOS SYNDROME

A.M. Formenti, G. Mazziotti, A. Giustina
University of Brescia; ASST C. Poma Mantova; Vita-Salute San Raffaele University Milano, Italy

Osteogenesis Imperfecta (OI) and Ehlers-Danlos syndrome (EDS) are both pathologic conditions caused by genetically determined collagen alterations. In OI type I collagen is mutated while in EDS more heterogeneous structural and functional collagen alterations are present variably involving also collagen type 3 and 5. Besides this different genotypic background, in both diseases the skeletal phenotype is characterized by an increased fracture risk . However, it is still unknown if differences in clinical presentation of skeletal fragility between these two diseases may exist. In a cross-sectional evaluation we found a greater percentage of patients wth hypovitaminosis D among EDS vs OI (85.2% vs. 22.2%; p<0.001) whereas BMD in OI was significantly lower vs EDS at all measured sites. Despite these densitometric differences, prevalence of VFs did not differ among the two groups (OI 55.6% vs.EDS 40.7%; p=0.44) although in OI multiple (44.4% vs. 11.1%; p=0.03) and/or severe (33% vs. 3.7%; p<0.001) VFs were more common than in ED. Based on our data it can be suggested that, despite EDS being only recently associated with increased fracture prevalence while OI being traditionally associated with a detrimental skeletal phenotype, OI and EDS appears to be burdened in adult patients by a similar risk of morphometric VFs. Interestingly, the predisposition to fracture could likely due to different underlying mechanisms, i.e low BMD in OI and hypovitaminosis D and hypomobility (reduced bone quality?) in EDS.

BISPHOSPHONATES: THE CHALLENGE OF ADHERENCE IN REAL LIFE

Sandro Giannini
Clinica Medica 1, Department of Medicine, University of Padova, Italy

The issue of adherence to prescribed medications is a key point in the treatment of almost all chronic diseases. This is particularly true in the elderly, because of the frequent presence of comorbidities and, thus, of the concomitant use of a large variety of drugs. Adherence is considered one of the major aspects in the therapy of osteoporosis, being able to affect the anti-fracture efficacy of the drugs used. It is well-known that loss of adherence is a common aspect for almost all the drugs used for the treatment of osteoporotic patients, in spite of the large variety of compounds and administration schedules that can be considered in this setting. The introduction of once-weekly oral bisphosphonates has increased the adherence to treatment. However, even in this case adherence remains relatively poor, reaching 50% of the patients included in several real-life observational studies. The most important consequence in terms of low adherence is the loss of efficacy of the treatment. It has been observed that a true anti-fracture effect can be seen only in patients taking at least 50% of the medication prescribed. To obtain a reduction in fracture risk similar to that observed for oral bisphosphonates in randomized clinical trials, patients need to be compliant and persistent for the 80%. Given these data, many studies have focused on the reasons for such a low adherence rate. These include the only modest perception of the risks and burden associated with osteoporotic fractures, the concomitant use of drugs for the treatment of other clinical conditions, age, socio-economic aspects and the possible presence of drug-associated side effects. Specific and effective strategies aimed to counteract the issue of adherence in the treatment of osteoporosis need a continuous revision and implementation.

HIGH RESOLUTION CONE-BEAM COMPUTED TOMOGRAPHY AS A NEW TOOL TO IDENTIFY SKELETAL FRAGILITY

Filippo Maffezzoni[1], Andrea Giustina[2]
[1]Department of Molecular and Translational Medicine, University of Brescia,
[2]Chair of Endocrinology, San Raffaele Vita-Salute University, Milan

The gold standard for studying bone microstructure is the histomorphometry (HM) of biopsies of the iliac crest. Alternatively to HM non-invasive diagnostic tools such as bone ultrasonometry, trabecular bone score (TBS) and high resolution peripheral quantitative computed tomography (HR-pQCT) have been proposed to study the bone framework in vivo. However, TBS software and HR-pQCT are technologies not routinely available.

Cone-beam computed tomography (CBCT) is a multitask tomography technique with plenty of benefits such as low radiation dose, cost effectiveness, scanning time and 3D modalities for evaluating bone structure (BS) in a clinically objective and quantitative way.

In particular, with the use of CBCT with high resolution (HR) protocol is possible to reconstruct tomographic images with a resolution up to 75 um. Such a spatial resolution is adequate for the detailed study of the BS and the accurate calculation of morphological trabecular and cortical parameters.

Using HR-CBCT protocols we investigated BS at distal radius in a population of acromegaly patients, a specific setting of secondary osteoporosis, with increased incidence and prevalence of vertebral fractures (VFs) even in patients with preserved bone mineral density (BMD). We also correlate trabecular and cortical parameters with morphometric VFs.

40 patients (24 females; median age 57 years, range 25–72) and 21 healthy volunteers (10 females; median age 60 years, range: 25–68) were evaluated for trabecular (bone volume/trabecular volume ratio, mean trabecular separation, and mean trabecular thickness) and cortical (thickness and porosity) parameters at distal radius using HR-CBCT. Acromegaly patients were evaluated for morphometrical VFs and for BMD with DXA at lumbar spine, total hip, femoral neck and distal radius.

Acromegaly patients with VFs (15 cases) had significantly ($p < 0.05$) lower bone volume/trabecular volume ratio, greater mean trabecular separation, and higher cortical porosity vs. non-fractured patients, without statistically significant differences in mean trabecular and cortical thickness. VFs were significantly associated with age, duration of active acromegaly and untreated hypogonadism. Fractured and non-fractured acromegaly patients did not have significant differences in terms of BMD at either skeletal site. Acromegaly patients showed lower bone volume/trabecular volume ratio ($p = 0.003$) and mean trabecular thickness ($p < 0.001$) and greater mean trabecular separation ($p = 0.02$) as compared to control subjects, without significant differences in cortical thickness and porosity.

This study shows for the first time that abnormalities of bone trabecular and cortical structure are associated with morphometric VFs in acromegaly. In our experience HR-CBCT at the distal radius may be a useful tool to evaluate bone microstructure and therefore predict skeletal fragility.

ACROMEGALY AND BONE

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Growth hormone (GH) and insulin-like growth factor-I (IGF-I) play a key role in the control of skeletal health and the effects of GH and IGF-I excess on bone metabolism and structure has been a matter of debate over the last 40 years. Former studies hypothesized that the effects of excess GH in the adults may be similar to those occurring in physiological conditions, by activation of periosteal growth, trabecular bone remodeling and an increase in both cortical and trabecular bone mass. During the recent years, however, it has become evident that GH excess may cause a specific bone disease, i.e. the "acromegalic osteopathy", characterized by high bone turnover and abnormalities in bone microstructure predisposing several patients to develop fragility vertebral fractures. In fact, vertebral fractures, as diagnosed by a radiological and morphometric approach, occur in about one third of acromegaly patients in close relationship with a more severe deterioration of trabecular microstructure. Vertebral fractures were shown to develop more frequently at the thoracic spine, possibly contributing to kyphosis of patients with acromegaly. The pathogenesis of acromegalic osteopathy is multifactorial involving either GH hypersecretion itself or coexistent risk factors for skeletal fragility. The duration of active acromegaly is the main determinant of skeletal fragility, although the risk of vertebral fracture may persist high even in patients with well controlled or cured acromegaly, in relationship with pre-existent fractures and hypogonadism. As in other forms of secondary osteoporosis, measurement of bone mineral density by dual-energy X-ray absorptiometry does not provide reliable information for predicting fracture risk in acromegaly, since vertebral fractures may occur even in patients with normal bone mineral density. In conclusion, "acromegalic osteopathy" is an emerging complication of acromegaly which management may be complex due to its multifactorial pathogenesis, lack of data on efficacy and safety of anti-osteoporotic drugs and also due to the still low awareness for this clinical condition.

TREATMENT WITH VITAMIN D

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Vitamin D is a pleiotropic hormone that ensures systemic calcium supply via an increase of calcium absorption in the gut and calcium reabsorption in the kidneys. It is therefore essential for the maintenance of skeletal health. Vitamin D deficiency due to malnutrition or low sunlight exposure results in impairment of bone mineralization, e.g. skeletal deformities such as rickets and osteomalacia.

In addition, vitamin D deficiency is associated with a large number of non-skeletal symptoms including fatigue and neuromuscular impairment, metabolic, hormonal, and immunological disturbances, but also cardiovascular diseases, cancer and fertility, published in a number of studies based on thresholds of 25(OH)vitamin D blood level measurements. However, results are conflicting for several topics and are currently under further investigation.

In historical medicine, long before the discovery of vitamin D, sunlight or ultraviolet B (UV-B) radiation - enhancing vitamin D synthesis in the skin - have been applied in the treatment and prevention of rickets, but also for patients with lung diseases and in general recovery.

Vitamin D supplementation in babies and children has been consented recently in the „Global Consensus Recommendations on Prevention and Management of Nutritional Rickets", (Munns CF and co-authors, J Clin Endo Metab 2016) with a large number of specific evidence-based recommendations to decrease vitamin D deficiency and the development of rickets. While vitamin D treatment was able to reduce the prevalence of rickets during the past decades in Western European countries, their high prevalence in Africa, the Middle East and Asia represents still a major health (and socioeconomic) burden.

400 IU (10 µg) daily intake of vitamin D is considered as sufficient for all children from birth to 12 months of age, independent of their mode of feeding. Thereafter, all children and adults should receive at least 600 IU (15 µg) daily, as recommended by the Institute of Medicine (IOM), but higher doses might be necessary in individual cases of vitamin D deficiency and potentially subsequent osteomalacia.

The implementation of international rickets prevention programs, including supplementation and food fortification, has been discussed as an important future health care requirement. A large number of randomized controlled studies whether or not to recommend vitamin D supplementation in various conditions and diseases are on the way or quite recently published; most of them can be found on clinicaltrials.gov or via www.ncbi.nlm.nih.gov/pubmed.

DEFINITION, ASSAYS AND VARIABLES IN BIOCHEMICAL DIAGNOSIS OF HYPOVITAMINOSIS

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Vitamin D deficiency has been described as being pandemic, but serum 25-hydroxyvitamin D [25(OH)D] distribution data for the European Union and worldwide are of very variable quality. Substantial variability is associated with laboratory measurement of serum total 25-hydroxyvitamin D [25(OH)D]. This, in turn, makes impossible any effort to achieve a consensus on 25(OH)D values defining stages of vitamin D status, and in particular hypovitaminosis. As resolving this situation requires standardized measurement of 25(OH)D some initiatives developend methodology to standardize thi assay to the reference measurement procedure (gold standard). The effect of such retrospective standardization on prevalence of "low" vitamin D status in several national studies was such that in NHANES III 25(OH)D values were lower than original values, while higher in another study (KIGGS). In NHANES III the percentage with values below 30, 50 and 75 mmol/L increased from 4% to 6%, 22% to 31% and 55% to 71%, respectively. In KIGGS, after standardization the percentage below 30, 50 and 75 mmol/L decreased from 28% to 13%, 64% to 47%, and 87% to 85%, respectively.

The importance of using standardized serum 25(OH)D data in the assessment of the prevalence of vitamin D deficiency in Europe was exemplified in the upward and downward revision of prevalence estimates after standardization in some studies. For example, 10.4 million fewer German adults and 267,000 more Irish adults had vitamin D deficiency by using the estimates based on standardized compared with the corresponding nonstandardized serum 25(OH)D data from these surveys.

Several variables affect the realiability and accuracy of 25(OH)D measurement and in particular, the method of choice (immunoassay versus LC-MS/MS), calibration procedures, interference of Vitamin D Binding Protein (VDBP), and cross reactivity with 3-epi-25(OH)D. Standardization and harmonitation initiatives are required to provide more "robust" data to define hypovitaminosis.

DENOSUMAB: COMBINATION TREATMENTS

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The rationale of combining antiresorptive with osteoanabolic medications is to attain additive or synergistic effects on bone mass and strength compared with either monotherapy. In this regard, denosumab, an antiresorptive medication, has been combined with teriparatide, an osteoanabolic medication, in women with postmenopausal osteoporosis (DATA trial and its extensions). Initially, Tsai et al. showed in a 12-month randomized controlled trial that combined teriparatide and denosumab increased bone mineral density (BMD) more than either agent alone. Specifically, lumbar spine, femoral neck and total hip BMD increased more after teriparatide and denosumab combination (9.1, 4.2 and 4.9%, respectively) than teriparatide monotherapy (6.2, 0.8 and 0.7%, respectively) or denosumab monotherapy (5.5, 2.1 and 2.5%, respectively). Increase in radius BMD was higher with combination therapy (2.6%) compared with teriparatide monotherapy (-1.8%), but similar to denosumab monotherapy (1.7%). Interestingly, bone turnover markers (osteocalcin, PINP and CTX) followed a pattern more similar to denosumab monotherapy and different to that of teriparatide monotherapy. The 12-month extension of DATA trial (Leder et al.) showed that the superiority of the combination therapy at lumbar spine, femoral neck and total hip BMD was sustained over either monotherapy. However, there were no group differences in the magnitude of these increments in the second year among groups, possibly implying that there is no advantage of the combination of teriparatide and denosumab vs. either monotherapy after the first year, which however warrants further research. Although studies with fractures as main outcome are to-date lacking, combination therapy with teriparatide and denosumab might be useful to treat patients at high risk of fracture.

Apart from the concomitant administration of denosumab with osteoanabolic medications, another clinically relevant issue is the sequential combinations with denosumab. According to DATA-Switch study, the order in which denosumab and teriparatide monotherapy are used affects overall treatment efficacy. Teriparatide does not adequately prevent bone loss after denosumab, whereas denosumab stabilizes and further increases BMD, when used after teriparatide or combination therapy. The largest increases in BMD at the hip and wrist were achieved in women treated with combined teriparatide and denosumab for 24 months, followed by 24 months of denosumab monotherapy. Regarding transitioning from bisphosphonates to denosumab in postmenopausal women with low bone mass, Kendler et al. showed that the 12-month lumbar spine, femoral neck, total hip and radius BMD increases were higher after transitioning from alendronate to denosumab than continuing on alendronate. Moreover, in a head-to-head comparative study, Ebina et al. showed that transitioning from teriparatide to denosumab increased lumbar spine, femoral neck and total hip BMD, and decreased bone resorption more effectively compared with switching from teriparatide to oral bisphosphonates for 12 months. These studies warrant further research on sequential treatment with low-energy fractures as main outcome.

HYPOPARATHYROIDISM: REPLACEMENT THERAPY

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Hypoparathyroidism (HypoPT) is characterized by hypocalcaemia due to inappropriate low plasma levels of parathyroid hormone (PTH). Supplementation with calcium and (active) vitamin D has for many years been the only treatment option. However, despite a normalization of plasma calcium levels in response to conventional treatment, patients often have a number of complaints including fatigue, muscle weakness, and paresthesia. Moreover, patients are at increased risk of long-term complications such as impaired kidney function, renal stones, development of cataracts, and calcification of soft tissues.

In a number of recent studies, PTH replacement therapy has been studied as an alternative treatment option. Subcutaneous injections with either intact PTH(1-84) or N-terminal PTH (1-34) have been shown to reduce the need for calcium and active vitamin D while maintaining normocalcemia. Moreover, plasma phosphate levels and renal calcium excretion may be lowered in response to PTH therapy. Data from randomized double-blind studies have so far not documented a consistently improved quality of life in response to PTH therapy, although data from cohort studies suggest that PTH treatment may improve patient's well-being.

In 2015, the U.S. Food and Drug Administration approved treatment with PTH(1-84) for the treatment of HypoPT and European Medicines Agency (EMA) has in February 2017 recommended conditional approval for treatment with PTH(1-84) in the European Union.

So far, therapy with PTH(1-84) has been marketed as an injection once-a-day in a fixed dose of either 25, 50, 75 or 100 microgram. However, studies have suggested that dosing regimens with two daily injections (or continuous pump-infusion) are more feasible than a higher dose injected only once-a-day. If injected twice-a-day, the total daily dose needed to maintain normocalcemia is only half the dose needed if PTH is injected only once-a-day. The total daily dose may be further reduced by continuous infusion of PTH by an insulin pump. Even more importantly, diurnal variations in plasma calcium levels may be rather pronounced if PTH is injected in a relatively high dose only once-a-day. If delivered by pump or injected twice-a-day, the diurnal variations are less marked thereby allowing for mimicking the normal variation in calcium homeostasis.

The daily dose of PTH needed to maintain normal plasma calcium levels varies between patients with postsurgical HypoPT and according to the etiology. For example, studies have shown that patients with autosomal dominant hypocalcemia (ADH) on averages need twice the dose of PTH than patients with post-surgical HypoPT.

Overall, PTH replacement therapy seems to be a promising new therapeutic option in HypoPT, especially if the drug will be available for twice-a-day injections in individualized doses allowing for careful titration of the dose according to the need of the individual patient. Further studies are needed to assess whether replacement therapy will reduce risk of long-term complications.

SKELETAL PHENOTYPE IN HYPOPARATHYROIDISM

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About 1% of total bone calcium exchanges every month, through bidirectional fluxes, under the stimulation of parathyroid hormone (PTH) and/or calcitriol. In the absence of PTH or in case of resistance to its action, bone turnover and bidirectional calcium fluxes are markedly low, as assessed by bone turnover markers and/or dynamic histomorphometry, with deeply suppressed mineralization surfaces. Bone mass is higher than in sex- and age-matched normal individuals in transiliac bone biopsies. This increase concerns cancellous bone, trabecular and cortical thickness. Higher bone mineral mass and areal mineral density values are confirmed at all skeletal sites investigated by DXA. High-resolution peripheral quantitative computerized tomography analysis reveals higher cortical volumetric BMD and lower cortical porosity in PTH deprive subjects. However, distal tibia cortical thickness is lower. Interestingly, calculated bone strength and stress of distal radius and tibia, using finite element analysis, are not different in hypoparathyroidism and controls. Fracture risk in hypoparathyroidism was neither increased (except morphometric vertebral fracture in one study and upper extremities in non surgical hypoparathroidism in another study) nor decreased as compared with controls. This indicates that long-term low bone turnover is at least not consistently associated with higher bone fragility. However, a non-commensurate reduction of fracture risk despite higher bone mass in hypoparathyroidism further underlines the major role of PTH in the control of bone strength.

MUSCLE-BONE INTERACTION: THE PARADIGM OF DUCHENNE'S DYSTROPHY

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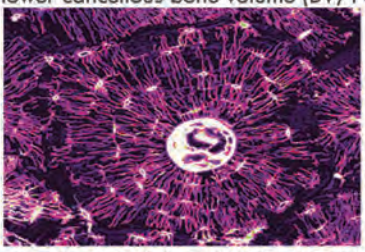
Duchenne muscular dystrophy (DMD): DMD is caused by a mutation in the dystrophin gene (X-linked and recessive) leading to a progressive muscle weakness. Dystrophin is found exclusively in skeletal and heart muscle cells with little amounts in brain. Its primary function is the mechanical stabilization of the plasma membrane in the muscle fiber cells (myocytes). The absence of dystrophin results in mechanical damage of the cell membrane leading to micro-lesion, influx of Ca++, fiber necrosis, inflammation processes, invasion of macrophages and accumulation of fat cells into the muscle tissue.

DMD characteristics: The prevalence of DMD is about 1 : 3500 live male births. Typically the first symptoms are recognized within 3 to 5 years of age. The progression of muscle weakness is leading to loss of ambulation between 8 and 15 years. DMD is accompanied by severe osteoporosis, significant bone fragility and scoliosis. Due to cardiac and respiratory dysfunction patients die early around 20 years of age. The treatment with glucocorticoids (GC) distinctly slows down muscle degeneration progression and increases life expectancy.

DMD impact on bone mineral density (BMD) and fracture incidence: In untreated DMD patients there is a relatively slight decrease in spine BMD with increasing muscle weakness, while proximal femur BMD is already low at the beginning of the development of muscle weakness (Z-score of -2), which declines progressively to levels below -3. The fractures occur mainly in femur and long bones, but not in vertebrae. However, GC treatment decreases dramatically spine BMD Z-scores below -3 and induces vertebral fractures accompanied with back pain. Treatment with bisphosphonates (BP) were shown to resolve back pain and to stabilize the vertebral BMD.

DMD impact on bone tissue and material level: Data from transiliac bone biopsy samples are only available from GC treated patients so far. These showed significant lower cancellous bone volume (BV/TV) and cortical thickness (Ct.Wi) versus healthy average. The mineralizing surface (MS/BS) was in the lower normal range. The average degree of bone matrix mineralization of cancellous (Cn.CaMean) and cortical compartments (Ct.CaMean) was not different from healthy reference. After iv bisphosphonates, BV/TV and Ct.Wi were on average unchanged, while MS/BS was decreased and Cn.CaMean increased in line with the further decrease in bone turnover. These observations point to the need of novel therapies with less or absent suppression of bone formation.



osteocyte lacunae canaliculi network – it plays a key role in mechanosening and muscleskeletal metabolism

Muscle-bone interaction: In recent years there is evidence, that the interaction between muscle and bone is not limited in dictating bone by mechanical loading, but there exists also an extensive biochemical and molecular communication. Muscle and bone tissue has been found to have an important endocrine function for the whole body. For instance, they secret growth factors and specific factors regulating muscle and bone mass like myostatin and sclerostin, respectively. Further the osteocytes, which represent about 95% of the bone cells appear to play a central role in homeostasis of bone mass, calcium and phosphate levels as well as for bone matrix mineralization. These new insights in muscle-bone interaction open a new field of potential therapies for DMD. Promising strategies seem to be the inhibition of the negative regulators of muscle and bone mass, myostatin and sclerostin.

TRABECULAR BONE SCORE AS AN INDEX OF BONE QUALITY: SOMETHING NEW?

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The gold standard exam for the quantitative measurement of BMD is the dual X-ray photon absorptiometry (DXA) [1]. However, a relevant number of fragility fractures occurs in the range of normal BMD values, meaning that also microarchitecture aspects of bone play a role, directly investigated by invasive approaches with a biopsy. A new tools, namely trabecular bone score (TBS) obtained during DXA, can supply informations about bone structure in a not invasive way. TBS is a gray-level textural measure that can be extracted from the 2-dimensional lumbar spine DXA image to estimate trabecular microstructure. TBS provides information that is not captured by the standard BMD measurement [2]. The relationship between TBS texture and 3-dimensional microarchitecture parameters is documented by several ex vivo studies that reported significant correlations with the bone histology parameters defined by Parfitt (trabecular space and number, connective density); these correlations are independent from areal bone mineral density [3]. A high TBS value correlates with better skeletal texture, reflecting a better microarchitecture. Recent studies demonstrated that TBS predicts fracture risk, partially independently from BMD, in primary and secondary osteoporosis and after pharmacological treatment [4-7]. However, nowadays a debate awakes about what TBS really represents and particularly about its true relation to vertebral strength [8]. A few study of in vitro and in vivo LSC of TBS have demonstrated that it is almost double than LSC of BMD [9,10]. Data from the studies show that increases of TBS values after pharmacological therapy for osteoporosis are small and very close to the least significant change at the end of the usual period of treatment. Therefore, it is questionable if TBS is really helpful in monitoring bone quality and in defining reduction of individual fragility fracture risk during osteoporosis treatment with anti resorptive and anabolic agents [11].

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THE GENETICS OF OSTEOPOROSIS

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An large number of clinical entities are associated with abnormal bone mineral density. On the one end of the spectrum , the sclerosing bone dysplasias are characterized by an excess of bone tissue. These conditions are, in most cases, monogenic diseases with involvement of one gene resulting in a clear mode of inheritance. Molecular genetic studies over the last decennia revealed the underlying genetic causes for many of them indicating that the pathogenic mechanism can either be a decreased bone resorption, as in different forms of osteopetrosis, or an increased bone formation.

Osteoporosis is, on the other end of the spectrum, the best known example of a condition with decreased bone mass resulting in an increased risk for low trauma fractures in the elderly. The risk for osteoporosis is influenced by both environmental and genetic factors and is determined both by the peak bone mass reached at young age and by the subsequent bone loss later on in life. Calculation of the heritability indicates that 50-80% of the variance in different bone parameters and subsequently in the risk for osteoporotic fractures can be explained by genetic factors.

Especially genome wide association studies in the last decade have been very useful for dissecting the genetic basis for the regulation of bone mineral density. However, despite extremely large scale studies by very extended consortia, the obtained results so far can explain less than 10% of the assumed genetic variability and further studies are needed. But these genome wide association studies definitely contributed to our current understanding of bone homeostasis by the identification of a large number of novel genes of relevance. Furthermore, the pathways involved in sclerosing bone dysplasias and osteoporosis are overlapping clearly highlighting the interdependency between these two groups of skeletal diseases. These include genes involved in osteoblast differentiation, the genes encoding RANK-RANKL-OPG and genes encoding proteins from the Wnt-signaling pathway. In this way, several genes were identified with high potential for the development of novel therapeutic targets for osteoporosis.

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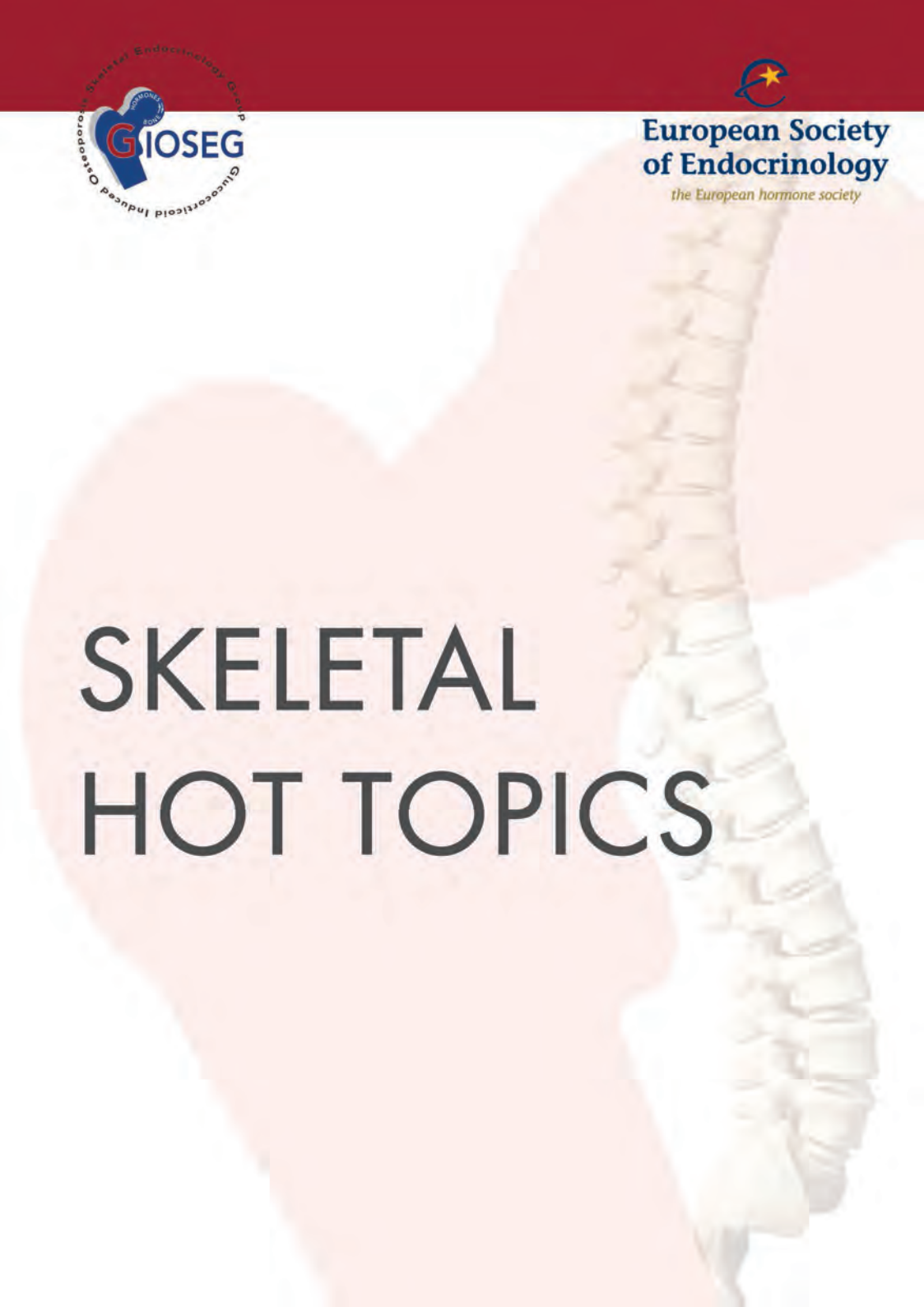

SKELETAL HOT TOPICS

EXPLORING EPIGENETIC CHANGES IN HUMAN PARATHYROID TUMORS: LONG NON-CODING RNA EXPRESSION PROFILE REVEALS HETEROGENEITY AMONG HUMAN PARATHYROID TUMORS.

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Aberrant epigenetic signatures occur in parathyroid tumors: microRNAs (miRNAs) and methylome deregulations have been recently described. Here we extended the investigation of epigenetic changes by profiling the expression of 90 long non-coding (lnc) RNAs in 4 parathyroid carcinomas (PCas), 12 parathyroid adenomas (PAds) and 2 parathyroid glands from normocalcemic patients (PaNs). Unsupervised clustering clearly distinguished PCas from PaNs, whereas 8 PAds clustered with PaNs and 4 with PCas. Most deregulated lncRNAs are downregulated in parathyroid tumors compared with normal glands. Investigating lncRNAs differentially expressed between classes, SAMR analysis identified 10 lncRNAs significantly deregulated between PCas and PaNs, 14 lncRNAs between PAds and PaNs, and 26 lncRNAs between PAds and PCas. Four mostly deregulated lncRNAs, namely HAR1B, MEG3, NEAT1 and KCNQ1OT1 were validated by qPCR in an independent series of 3 PCas, 4 atypical PAds, 22 PAds and 2 PaNs. PCas and atypical PAds showed similar expression levels of the 4 lncRNAs, whereas PAds were distinguished in two clusters with 10 PAds similar to normal glands and 12 PAds with a distinct profile. Clinically, PAds with lncRNA profiles similar to normal glands had lower mean serum total calcium and ionized calcium than the PAds with the distinct profile as well as than the cluster of atypical PAds and PCas (10.2±0.5 vs 11.5±0.8 vs 12.1±0.2 mg/dL; P=0.006 and 1.36±0.06 vs 1.51±0.08 vs 1.81±0.11 mmol/L; P=0.0001 by ANOVA). Furthermore, 10 PAds were characterized for the MEN1 protein expression level; interestingly, PAds with lower nuclear menin expression had decreased expression of two lncRNAs mapping on chromosome 11: KCNQ1OT1 and NEAT1. KCNQ1OT1 is known to interact with chromatin, with H3K9- and H3K27- specific histone methyltransferase and with polycomb repressor complex 2 (EZH2 and Suz12), whose deregulation has been described in parathyroid tumors, while NEAT1 produces a lncRNA transcribed from the MEN1 locus, and it is predicted to interact with microRNAs. In conclusion, lncRNAs are deregulated in parathyroid tumors and identify 3 distinct groups of parathyroid tumors with different clinical activity. Moreover, lncRNAs deregulation in PAds may be related to the genetic background. Analysis of the lncRNAs' potential interaction with microRNAs is ongoing.

EFFECTS OF DENOSUMAB ON QUANTITATIVE ULTRASOUND AND DUAL-ENERGY X-RAY ABSORPTIOMETRY MEASUREMENTS IN AROMATASE INHIBITOR-TREATED BREAST CANCER WOMEN

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Objective: Bone loss has been reported in postmenopausal women receiving aromatase inhibitors (AIs) for the management of breast cancer (BC), and denosumab has been shown to prevent fractures in these subjects. We recently observed phalangeal quantitative ultrasound (QUS) to be associated with dual energy X-ray absorptiometry (DXA) measurements in BC women receiving AIs. Aim of this research was to evaluate bone status by QUS and DXA in women taking denosumab to prevent AIs associated bone loss.
Materials and Methods: 35 postmenopausal BC women, with at least one mild vertebral fracture, who started adjuvant treatment with AIs (i.e. anastrozole, letrozole, exemestane) were enrolled (mean age 61.2 ± 4.5 yr.) and received subcutaneous denosumab (60 mg every 6 months) and oral cholecalciferol (25000 IU bimonthly). Phalangeal QUS parameters [Amplitude Dependent Speed of Sound (AD-SoS), Ultrasound Bone Profile Index (UBPI), Bone Transmission Time (BTT)] and DXA at lumbar spine and femoral neck were performed at baseline and after 24 months. At baseline, 12 and 24 months, C-telopeptide of type 1 collagen (CTX) and bone specific alkaline phosphatase (BSAP) were measured. The main outcomes were compared with a control group not receiving denosumab (n=39).
Results: Differently from controls, women receiving denosumab had a significant improvement of lumbar spine and femoral neck BMD and a significant improvement of all the QUS parameters. The percent changes (Δ) of QUS measurements were significantly associated with ΔBMD at femoral neck. A significant reduction of CTX and BSAP values was detected and ΔCTX and ΔBSAP were associated with ΔBMD at lumbar spine (r=-0.39, P=0.02; r=-0.49, P=0.01, respectively).
Conclusions: This is the first time phalangeal QUS has been used in the follow-up of bone health in a set of AIs treated BC women receiving denosumab. Beyond DXA, phalangeal QUS may also provide additional information on the physical properties of bone tissue (e.g. structure and elasticity) that contribute to bone strength.

PREVALENCE OF MALIGNANT NEOPLASIA IN PATIENTS WITH PRIMARY HYPERPARATHYROIDISM

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Background: The increased cancer risk in patients with primary hyperparathyroidism (1HPT) is debated. The aim of the present study was to investigate the occurrence of neoplasia in 1HPT.

Patients and methods: All patients (n=1750, 1532 females, 218 males) referred to our "Osteoporosis and Metabolic Disease" outpatients clinic were considered eligible for the study. The exclusion criteria were: finding of osteoporosis and/or fragility fracture and/or increased calcium and/or parathyroid hormone (PTH) levels in the context of investigations for the staging or follow-up of malignancy; intake of drug and/or presence of chronic diseases known to influence the cancer risk; neoplasia in the context of familiar and/or hereditary syndrome; heavy smoking habit. Eventually 1606 patients (1407 females, 199 males) were recruited; 163 patients (148 females, 15 males) were found to be affected with 1HPT while 1443 (1259 females and 184 males) were not and were used as control group.

In all patients serum calcium, phosphorous, PTH, 25hydroxy-cholecalciferol, 24-h urine calcium and creatinine excretion levels were measured and data regarding the occurrence of cancer during the 10 years prior the study inclusion were recorded. In 40 patients with 1HPT we found that the hypercalcemia was already present at least 5 years before the enrolment. In this subgroup of 1HPT patients we assessed the occurrence of malignancies during the period of time between the first finding of hypercalcemia and the study entry. These data were compared with those of 120 age-, and gender-matched subjects without 1HPT, who had been randomly selected from the whole group of control subjects.

Results: Patients with and without 1HPT were comparable as far as age and gender. In 1HPT patients the occurrence of all, breast, kidney and skin cancer was significantly higher (21.5%, 12.2%, 2.5%, 1.8%, respectively) than in patients without 1HPT (12.4%, 6.9%, 0.3%, 0.3%, $p<0.05$ for all comparisons). The period of time between the study entry and the occurrence of neoplasia was lower in patients with 1HPT (56.3±23.1 months, range 36-116 months) than in those without 1HPT (89.0±33.6 months, range 24-120 months). The prevalence of subjects in whom the neoplasia occurred less than 5 years before the study entry was higher in 1HPT patients (26/35, 74.3%) than in controls (40/179, 22.3%, $p <0.0001$). In the 40 patients with 1HPT, in whom the hypercalcemia was already evident at least 5 years before the study entry, the occurrence of neoplasia during this period of time tended to be higher (9/40 cases, 22.5%) than that in the 120 subjects without 1HPT randomly selected as controls (14/120 cases, 11.7%, $p=0.06$). The logistic regression analysis showed that the diagnosis of 1HPT was significantly associated with the occurrence of all neoplasia and of breast, skin and kidney neoplasia (odds ratio, 95% confidence interval, p value: 1.93, 1.27-2.92, 0.002; 1.93, 1.11-3.35, 0.002; 9.18, 2.16-38.8, 0.003; 8.23, 1.71-39.5, 0.008, respectively) even after adjusting for age, gender (as appropriate), smoking habit and hypovitaminosis D.

Conclusions: During the 10 years prior the diagnosis of 1HPT, the occurrence of all, breast, skin and kidney neoplasia is increased.

THE USE OF DENOSUMAB IN PRIMARY HYPERPARATHYROIDISM

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Introduction: Denosumab is a monoclonal antibody with a bone antiresorptive effect used in the treatment of osteoporosis or bone metastasis breast or prostate cancer. Recently, this drug has been proposed in the treatment of parathyroid carcinoma. However, in the literature are not reported studies on the use of denosumab in patients with mild or asymptomatic primary hyperparathyroidism (PHPT).
The aim of this study was to evaluate the effects of denosumab in PHPT patients.
Material and methods: we evaluated 9 patients with PHPT, aged 63-90 years, sent for treatment with denosumab at least one year. A group of 9 PHPT patients with similar characteristics, in treatment with bisphosphonates at least one year, were used as control group. All patients were subjected to clinical examination, neck ultrasonography, densitometry, blood tests, before and during the bone antiresorptive treatment.
Results: All patients have graves osteoporosis. Bone failures were present in 4 cases. Patients in treatment with denosumab showed improvement in BMD (9.8% hip, 13.4% lumb; $P<0.05$) as in patients treated with bisphosphonates (5.9% hip, 11.7% lumb; $P=0.5$ e 0.8, respectively). The levels of calcium show an improvement in both groups with no significant differences (denosumab Ca $P=0.1$, -9.11%; bisphosphonates Ca $P=0.5$; -4.44%). The levels of PTH show an improvement on bisphosphonates ($P<0.005$, -42.4%) more significant what in patient on denosumab ($P=0.5$; -38.7%). However, the improvement of Ca and PTH were not significant before groups, at basal (PTH $P=0.9$; Ca $P=0.84$) and 2nd (PTH $P=0.4$; Ca $P=0.42$) evaluation. Finally, phosphorus, vitamin D, alkaline phosphatase and urinary calcium showed no change during treatment in both groups. In all cases the drug was well tolerated. No adverse events attributable to the drug was found.
Conclusions: Denosumb can be used safely and effectively in reducing the levels of calcium and parathyroid hormone as an adjuvant therapy in the PHPT compromised bone.

EFFICACY AND SAFETY OF PTH (1-34) TREATMENT OF HYPOPARATHYROIDISM: A PROSPECTIVE OBSERVATIONAL SINGLE-CENTRE STUDY

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Hypoparathyroidism is usually managed with calcium and active vitamin D treatment. However an adequate control of calcium serum levels often cannot be achieved with conventional therapy or requires very high doses that might lead to gastrointestinal side effects or kidney complications. The aim of our study was to investigate at our centre efficacy and safety of PTH (1-34) treatment in adult subjects with chronic hypoparathyroidism. Between 2013 and 2016 we enrolled 9 subjects with documented hypoparathyroidism meeting the Italian inclusion criteria for the prescription of PTH (1-34) (age >18 years old; surgical hypoparathyroidism symptomatic and non responsive to conventional therapy and/or with renal complications; subjects with autoimmune, congenital or infiltrative disease; subjects with kidney dysfunction). All subjects, after adequate training, self-administered a sc injection of 20 mcg PTH (1-34) once or twice-daily. We evaluated calcium and vitamin D supplementation requirements and serum calcium, phosphate, alkaline phosphatise (ALP), uric acid, 24-hour urinary calcium excretion at baseline and after 15 days and 1,2,3,6,12,18,24 months of PTH (1-34) treatment. DEXA was evaluated at baseline and after 12 and 24 months of treatment. In the present study, we report data of 7 (4 females, 3 males, mean age 40.2±6.9 yrs) out of 9 patients with a minimum follow up of 3 months: 5 with surgical hypoparathyroidism and 2 with hypoparathyroidism secondary to thalassemia major. PTH (1-34) therapy was performed for 24 months in 2 cases, 18 months in 1 case, 12 months in 2 cases, 6 months in 1 case, and 3 months in 1 case. One patient was lost to follow up after 12 months and one discontinued therapy after 18 months for pregnancy. Mean calcium levels significantly increased from baseline (1.88±0.12 mmol/l) to 15 days 2.17±0.23 mmol/l) and 3 months (2.23±0.37 mmol/l), remaining stable until the end of the observational period. A significant reduction in calcium and vitamin D supplementation was recorded from baseline (2.71±1.25 g calcium/die; 1.17±0.98 mcg calcitriol/die) to 3 (1.14±0.56 g calcium/die; 0.61±0.28 mcg calcitriol/die) and 6 months (1.25±0.76 g calcium/die; 0.5±0.27 mcg calcitriol/die), remaining stable until the end of the observational period. We observed a modest increase in urinary calcium levels during the first 3 months of therapy, reverting to baseline at 6 months and until the end of the study period. ALP increased significantly from baseline at 3, 6 and 12 months. We also observed a trend toward an increase in uric acid levels without clinical significance. Lumbar BMD increased significantly at 12 months and remained stable at 24 months. No serious adverse events occurred during the study. One patient discontinued treatment after 3 months due to asymptomatic hypercalcemia and another experienced important muscle and bone pain that lead to therapy discontinuation after 6 months; one patient discontinued after 12 months because of pollakiuria and inadequate response to therapy. Transient injection-site erythema was observed in two patients (2/7). Other adverse events such as nausea (1/7), mild muscle and bone pain (2/7) and tachycardia with higher dose (1/7) were recorded. In conclusion, in our population we observed an increase in serum calcium and a reduction in supplemental calcium and calcitriol daily doses, without serious adverse events, confirming the usefulness of PTH (1-34) treatment in selected cases of patients with hypoparathyroidism non responsive to conventional therapy.

FACTOR AFFECTING FRACTURE RISK IN ADULT-ONSET GROWTH HORMONE-DEFICIENT PATIENTS AND ROLE OF THE GROWTH HORMONE RECEPTOR ISOFORMS

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INTRODUCTION: Growth hormone (GH) and insulin-like growth factor-1 (IGF-I) play a substantial anabolic role on bone tissue with an endocrine and paracrine mechanism. In fact, osteoblasts and chondrocytes express growth hormone (GH) receptor. The GHR consists of an extracellular, a transmembrane and an intracellular domain, whereas the GHR gene consists of nine exons encoding the receptor protein and several additional untranslated exons. Two isoforms of human GHR have been identified: a full-length (fl-GHR) isoform retaining the protein fragment encoded by exon 3 and an exon 3 deleted (d3-GHR) isoform excluding this fragment.3 Exon 3 encodes a segment in the extracellular domain of the receptor; although both the isoforms retain the capacity of binding GH with a high affinity, there are significant functional differences between the two isoforms. Specifically, the d3-GHR isoforms may confer an higher sensitivity to GH. Vertebral fractures (VFs) occur in a relevant percentage of adult patients with hypopituitarism, and growth hormone deficiency (GHD) is considered as the most important factor determining skeletal fragility in these patients. However, no information is yet available on predictive factors for the skeletal events in GHD patient with the exception of GH treatment. Aim of our study was to evaluate the potential role of GHR polymorphism in the risk of fractures in GHD patients treated or untreated with rhGH.

SUBJECTS AND METHODS: A cross-sectional study was conducted to investigate the association between the GHR isoform and the prevalence of morphometric vertebral fractures (VFs) in AO-GHD. All patients were followed-up to the Pituitary Unit of the Endocrinology Department of the Catholic University of the Sacred Heart in Rome and underwent clinical and biochemical evaluation of thyroid, adrenal and gonadal status and bone metabolism, though lumbar and femoral neck dual energy X-ray absorptiometry (DXA) scan and vertebral X-ray assessment, though dosage of serum 25-hydroxy vitamin D, serum parathyroid hormone. Patients underwent genetic test for the detection of the GHR gene polymorphism. Were excluded from the study all the patients with a diagnosis of an active neoplastic disease, with an ongoing or previous treatment with anti-osteoporotic drugs with the exception of calcium and vitamin D supplements, with ongoing treatment with drugs causing osteoporosis (with the exception of glucocorticoid replacement therapy in hypopituitaric patients), with a clear history of moderate or high-energy vertebral fractures (VF, with an history of spine surgery and with a prolonged immobilization (more than 6 weeks).

RESULTS: Ninety-three AO-GHD were enrolled. Forty-nine patients carried flfl-GHRi (52.7%), and 44 patients (47.3%) carried at least one allele of the d3-GHR isoform. Thirty-two VFs were documented. Fifty-seven patients underwent rhGH replacement therapy. Fractured AO-GHD patients did not differ for gender, anthropometric features, bone metabolism markers as compared to nonfractured AO-GHD patients. Median age was significantly higher in fractured patients as compared to nonfractured ones (55 years vs 51 years). IGF-I levels, rhGH replacement treatment duration and rhGH mean weekly dose, female and male gonadal status, glucocorticoid, testosterone or estro-progestin replacement therapy did not differ in fractured and nonfractured AO-GHD patients. Percentage of patients on GH treatment was slightly but not significantly higher in nonfractured vs fractured patients. The prevalence of vertebral fractures was significantly higher in fl-carriers patients as compared to d3-carriers ($P < 0.0001$). As to confirm the prognostic role of GHRi, we evaluated it separately in patients undergoing rhGH replacement treatment and in patients not undergoing rhGH replacement treatment and we found that only in patients on rh-GH replacement therapy, d3 polymorphism was associated with a lower facture prevalence (OR: 0.37, 95% IC:0.24-0.55, $P < 0.0001$)

CONCLUSION: Our data suggest for the first time that the d3- GH receptor polymorphism may represent an important protective factor for vertebral fractures, in patients with GHD. The observation that in GHD patients treated with rhGH the d3-GHR polymorphism may play an additional protective role with respect to treatment per se may suggest that genetic testing for GH receptor polymorphism could represent an additional tool for stratification of the risk of VFs in AO-GHD patients and treatment indication.

ATYPICAL FEMORAL FRACTURES CAUSED BY GLUCOCORTICOID AND BISPHOSPHONATE PROLONGED THERAPY IN PREMENOPAUSAL WOMEN: A CASE REPORT

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Atypical femoral fracture (AFF) is defined as a fracture occurring along the femoral diaphysis, from a point just distal to the lesser trochanter to a point just proximal to the supracondylar flare that exhibits features of a stress fracture. The pathogenesis of AFF is related to a severe suppressed bone turnover, accompanied by a decrease of the osteoblastic and osteoclastic surfaces on cancellous bone and a delay of bone micro damage remodelling. Bisphosphonates (BPs) are potent inhibitors of osteoclast-mediated bone resorption widely used in the treatment of osteoporosis. They localize in areas in which stress fractures are developing: the suppression of targeted intracortical remodelling at the site of an AFF may impair the processes by which stress fractures normally heal. Moreover, prolonged glucocorticoid (GCs) therapy, induces a suppression in bone turnover. Thus, it is possible that an additive effect of BPs and GCs on bone turnover can lead to AFF onset.

Here, we describe the case of a 39 year old female affected by Takayasu's Arteritis since she was 28. She was treated with oral prednisolone at a starting dosage of 50 mg/day, gradually reduced to 5 mg/day, with periods of increased dosage in case of disease flares.
To prevent glucocorticoid-induced osteoporosis (GIOP) the patient was treated with oral vitamin D and risedronate for 6 years (from 32 to 38 years), starting 4 years after GCs therapy was undertaken.
In June 2016, the patient was admitted to the hospital for increasing pain and right leg loss of function, with no trauma. She reported also a discontinuous bilateral leg pain during prolonged walk in the last year. The radiography detected a right femoral sub-trochanteric fracture and initial signs of left femoral sub-trochanteric fracture, typical features compatible with AFF. These fractures were treated with intramedullary nail.

GIOP is the most common cause of secondary osteoporosis. Due to inadequate data, the American College of Rheumatology Guidelines show insufficient recommendations for the prevention and treatment of GIOP in premenopausal women without prevalent fragility fractures: which is the best strategy in this subset of subjects is still an open question. Instead they recommend to treat premenopausal women if they have an history of previous fractures, like our patient. We decided to treat our patient with teriparatide, that currently is the gold standard therapy in GIOP complicated with fractures.
Fortunately, AFFs rarely occur: we have found only one other similar case reported in literature, regarding premenopausal women presenting AFF during GCs therapy associated to BPs.
These cases highlight the necessity to find the most correct strategy for premenopausal women treated with GCs before a fracture occurs.

MICRO-RNA SIGNATURES IN HEALTHY VITAMIN D DEFICIENT MEN BEFORE AND AFTER SUPPLEMENTATION

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Introduction: Small, non-coding transcripts called microRNAs (miRNAs) that provide an important and pervasive layer of post-transcriptional gene regulation are the subject of intense research. It is becoming evident that miRNAs are playing a significant role in regulatory mechanisms at important steps in bone and glucose metabolism.

We aim to detect miRNA signatures differentially expressed before and after 6 and 12 weeks of vitamin D or placebo (PBO) treatment in healthy vitamin D deficient men.

Methods: For a first pilot investigation, we randomly selected 4 men with a significant increase of 25OHD levels ($p<0.001$) and 3 with no increase, from a randomized double blind-blind placebo controlled trial including healthy but 25(OH)vitamin D (25OHD) deficient (<30 ng/ml) men treated with either 20,000 IU of vitamin D or PBO per week (NCT01748370). The miRCURY LNA PCR panel 1 (Exiqon) was used for targeted screening of miRNA expression in plasma samples obtained at the baseline, interim and final study visit.

Results: 372 miRNAs were tested, with 111 detectable miRNAs in all screened samples. Of these, 10 miRNAs showed a more than 2fold significant change in their expression pattern compared to baseline in plasma from patients with an increase in 25OHD levels. Some of these miRNAs have already been associated with β-cell-function in previous studies (e.g. miR-194-5p, miR-326).

Discussion: We demonstrate that vitamin D treatment has direct effects on the expression of miRNAs in plasma of healthy vitamin D deficient men after vitamin D supplementation as compared to PBO. Interestingly, some of these miRNAs were of relevance in the regulation of vitamin D and glucose metabolism. Further characterization of these miRNA signatures is ongoing.

TUMOR-INDUCED OSTEOMALACIA MIMICKING SPONDYLOARTHRITIS: A DIAGNOSTIC CHALLENGE

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Fibroblast-growth factor 23 (FGF-23) is a fosfaturic hormone secreted by osteocytes in response to high serum phosphate levels. Tumor-induced osteomalacia (TIO) is an emerging clinical condition sustained by a mesenchimal tumor producing an excess in FGF-23 leading to renal phosphate wasting and hypophosphatemia. In its early phases, TIO can cause axial pain and radiological findings similar to ankylosing spondylitis (AS). The case here described is paradigmatic of the confounding factors making difficult the correct identification of disease and leading to delayed diagnosis for patient and potential waste of resources for the Health System.

In 2015, a 56 year old man with a diagnosis of AS was referred to our Rheumatology outpatient clinic. The disease was diagnosed 3 years before. From 2010, he suffered from inflammatory back pain and heel pain and once reported symptoms consistent with an acute arthritis of the third finger of the right hand. Even in absence of the classical radiological signs of AS in the spine, in 2013 the MRI of the pelvis showed pathological findings similar to bone oedema of the right sacral ala and of the left iliac ala, that was interpreted as a bilateral sacroileitis. An ultrasonography of the heels reported an interruption of the cortical bone with power Doppler signal inside, evocative of a bone erosion at the insertion of the Achilles' tendon to the right calcaneus. These findings made the clinicians confident of the diagnosis of AS. The patient was treated with prednisone, indometacine, aceclofenac, methotrexate without achievement any significant improvements in clinical signs and symptoms. According to the current guidelines for AS, an TNF blocker was proposed. Etanercept was administered for 5 month and interrupted because of the occurrence of lesions similar to vasculitis in the lower limbs. Then adalimumab was started and rapidly interrupted after a month for the same adverse event. Finally, golimumab was started three months before our first visit. The patient did not referred any clinical improvement with TNF blocker therapies and the AS disease activity indexes were increased (BASDAI= 4.8, BASFI 2.6), with pain being referred progressively increased involving the pelvis, the spine, the ribs and particularly the right hip. Before defining the subsequent therapeutic protocol, patient underwent a new panel of exams which revealed low serum phosphate values (1 mg/dl) associated with increased urinary phosphate (992 mg/24 h) high serum alkaline phosphate(227 Uk /l), with normal serum calcium, parathyroid hormone and 25OH-vitamin D values. A CT scan revealed a fracture of the right femoral head and some lines of fractures in the iliac wings, near to sacroiliac joints. Similarly the XRay showed fractures of the VIII and IX dorsal vertebra, of the X and XI left ribs, of the VI and VII right ribs. The total body bone scintigraphy showed an increased concentration of the tracer in a large amount of lesions. The clinical suspicion of a FGF23 secreting neoplasia was confirmed by the high levels of FGF23 (5.07 pmol/l, normal value <0.8) and by a total body GA68 PET, that detected a pathological lesion close to the right patella. Patient underwent surgical removal of the lesion and the histological analysis confirmed its mesenchimal origin.

The pain of the patient progressively disappeared after conservative treatment of the fractures, after introduction of phospathe supplements and after the surgical removal of the tumor in the right knee in July 2015. Presently the patient keep to be perfectly asymptomatic, his phosphate levels are normal and he does not assume any therapy. The previously described arthritis of the right finger, was interpreted as an isolated attack of calcium pyrophosphate dihydrate crystal deposition disease (CPPD), also known as pseudogout, that may be associated with osteomalacia.

HYPOVITAMINOSIS D IN PATIENTS WITH HEART FAILURE: EFFECTS ON FUNCTIONAL CAPACITY AND PATIENTS' SURVIVAL

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Chronic heart failure (HF) is a major cause of morbidity and mortality, but its prognosis remains poor. Vitamin D hormone has many extra-skeletal functions including a positive impact on the cardiovascular system, and has been proposed for mortality risk evaluation in HF patients. The aim of the present study was to evaluate vitamin D status in HF patients, measured by high performance liquid chromatography coupled with mass spectrometry (HPLC-MS-MS) and to correlate serum 25 hydroxy-vitamin D (25OHD) levels with functional (peak VO2%) and mortality (MECKI score) HF parameters. We enrolled 261 consecutive patients diagnosed with HF: all patients underwent a comprehensive clinical and biochemical characterization, and serum 25OHD levels were measured by HPLC-MS-MS. Cardio-pulmonary test (CPET) parameters and MECKI score of mortality risk were measured in all patients. Serum 25OHD levels ranged between 2 and 45 ng/ml (mean 17±9 ng/ml); most patients (87%) showed hypovitaminosis D, and 25% showed severe vitamin D deficiency (serum 25OHD <10ng/ml). Patients with 25OHD <10ng/ml had significantly lower CPET VO2/kg, peak VO2% and significantly higher NT-proBNP and MECKI score, than patients with 25OHD>10 ng/ml. Patients with peak VO2% <50% showed significantly lower 25OHD compared to those with peak VO2% > 50%. There was a significant, positive correlation (r=0.16, p=0.008) between 25OHD levels and peak VO2% and an inverse correlation with MECKI score (r=-0.21, p<0.001), even when adjusted for age, BMI, MDRD, NT-proBNP. In conclusion, our findings show that vitamin D levels are associated with functional and mortality HF prognosis parameters.

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POSTER

PHALANGEAL QUANTITATIVE ULTRASOUND DETECTS CHANGES OF BONE STATUS IN AROMATASE INHIBITOR-TREATED BREAST CANCER RECEIVING DENOSUMAB.

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In breast cancer (BC) women receiving aromatase inhibitors, accelerated bone loss and increased risk of fractures are frequently observed due to near-complete ablation of estrogen production.

Denosumab is a fully human IgG2 monoclonal antibody that is able to prevent the interaction of RANKL with its receptor RANK, on osteoclasts and their precursors, and to reversibly inhibit osteoclast-mediated bone resorption, leading to a reduction of fracture risk. We recently reported phalangeal quantitative ultrasound (QUS) to be associated to dual-energy X-ray absorptiometry (DXA) measurements in BC women receiving AIs.

Aim of this research is to correlate phalangeal QUS with DXA measurements in the follow-up of women receiving denosumab to prevent AIs associated bone loss in BC women.

Thirty-eight Caucasian postmenopausal women, with early BC who started (within the last 12 months previous enrollment) adjuvant treatment with AIs (i.e. anastrozole, letrozole, exemestane) were enrolled if low bone mass (osteopenia/osteoporosis with or without fractures) in accordance to WHO criteria was detected at recruitment.

Subcutaneous denosumab 60 mg every 6 months and oral cholecalciferol (25.000 IU bimonthly) were administered to participants; moreover, women with an estimated poor dietary calcium intake were supplied with calcium carbonate (500 to 1000 mg, daily) in order to reach the recommended daily allowance of calcium.

QUS at phalangeal site, DXA at lumbar spine and femoral neck and vertebral morphometry by X-ray were performed at baseline and after 24 months.

At baseline, 12 and 24 months, C-telopeptide of type 1 collagen (CTX), as a marker of bone resorption, bone specific alkaline phosphatase (BSAP), as a marker of bone formation, 25-hydroxyvitamin D (25(OH)D), albumin corrected calcium, phosphorus, creatinine, were measured.

Denosumab treatment was associated to significant improvement of DXA derived BMD (at lumbar spine and femoral neck), but also to significant improvement of all the QUS parameters evaluated (Amplitude Dependent Speed of Sound - Ad-SoS -, Ultrasound Bone Profiler Index - UBPI -, Bone Trasmission Time - BTT -). As expected, a significant reduction of CTX and BSAP at 12 and 24 months vs. baseline was detected. The percent changes (Δ) of QUS measurements were significantly associated with Δ BMD at femoral neck, and the highest degree of association was observed for AD-SoS ($r=0.5$, $p=0.003$). Δ CTX and Δ BSAP were associated with Δ BMD at lumbar spine ($r=-0.39$, $p=0.02$; $r=-0.49$, $p=0.01$, respectively). No incident vertebral fractures were detected over the observation period.

This is the first time phalangeal QUS has been used in the follow-up of bone health in a set of AIs treated postmenopausal women receiving denosumab. Denosumab 60 mg twice per year preserve bone health as measured by phalangeal QUS and DXA.

TREATMENT WITH TERIPARATIDE: IMPROVEMENT OF BMD IN GHD'S PATIENT

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Teriparatide is the first anabolic agent shown to reduce the risk of fractures in patients with osteoporosis.
We presented a clinical case in order to report the effectiveness and safety of Teriparatide in treatment-naïve patients affected by osteoporosis.
This patient was affected by GH (Growth Hormone) deficiency, diagnosed in June 2005, after neurosurgery for a prolactin-secreting pituitary adenoma. Patient was treated with rhGH from December 2007. Densitometry documented a severe osteoporosis without vertebral fractures.
In April 2015 he strated treatment with Teriparatide, with excellent results.
In fact, after 20 months of therapy, densitometry documented a state of osteopenia (T-score at lumbar spine of -1.5 sd; T-score at femur neck of -1.3 sd).
This clinical case shows how Teriparatide can be effective in the treatment of patients with osteoporosis at high risk of fracture.

PROACRO STUDY: OUR PROPOSAL TO IMPROVE ACROMEGALY'S OSTEOARTHROSIS

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Growth Hormone (GH) and its effector Insuline-like Growth factor-1 (IGF-1) are important regulators of bone homeostasis and have a central role in the longitudinal bone growth and maintenance of bone mass. It was hypothesized that there are two phases in the pathogenesis of acromegalic arthropathy.

First, elevated GH and IGF-1 levels induce cartilage hypertrophy and laxity of the peri-articular ligaments, which result in limited range of motion. In this phase, radiographic abnormalities include joint space widening and peri-articular soft tissue hypertrophy. This early stage is thought to be at least partially reversible by adequate treatment. However when the GH excess persists, the disease acquires features of a degenerative joint disease, resulting in scar, cyst and osteophyte formation with further deterioration of joint architecture. In this late phase, changes become irreversible and may be GH-independent, and acromegaly treatment has only limited effects on joint symptoms.

Arthropathy is one of the most prevalent and invalidating complications of acromegaly, affecting all, both weight and non-weight bearing joints and it worsens the quality of life of these patients. In 50-70% of patients, arthropathy is one of the presenting symptoms at diagnosis. Also despite long-term biochemical disease control, prevalence of arthropathy is 4 to 12 fold increased when compared to the general population, impairing quality of life.

Until now, information on the course of acromegalic arthropathy in cured patients during long-term follow-up is relatively scarce. For this reasons, we consider the importance of a study aimed at the qualitative and quantitative assessment of osteo-articular disability in patients with acromegaly.

Therefore, we have initiated a multi-center study (PROACRO STUDY) lasting three years in which we enrolled a large patient series with acromegaly, which are subjected to a physiatrist assessment, in particular a measurement of the forearm strength by hand grip. These patients fill out two specific questionnaires to assess quality of life (AcroQL and PASQ), two scales to measure disability (ADL and IADL), two scales to measure arthritis/arthrosis (AIMS and WOMAC) and a form of assessment of work capacity (WPAI: GH) already experienced in other types of chronic diseases such as diabetes.

MICRO-RNA TARGETS ASSOCIATED WITH BONE METABOLISM IN CHRONIC KIDNEY DISEASE PATIENTS BEFORE AND AFTER KIDNEY TRANSPLANTATION

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Objective

Chronic kidney disease (CKD) causes CKD-MBD, the CKD-associated 'mineral and bone disorder'. We recently published changes in expression levels of circulating miRNAs (Ulbing M et al, Bone 2016). These changes were shown to be reversed after kidney transplantation (KT). Bioinformatical target predictions were aimed to expand our knowledge on relevant underlying pathways for the respective miRNA signatures.

Methods

Out of 73 serum samples from patients at CDK stages 3-5 without haemodialysis, 67 patients after renal transplantation and 36 healthy controls and a large number of surrogate biomarkers, miRNAs were associated with kidney function, inflammation and bone metabolism. Target predictions were performed using respective online databases and target prediction tools (miRWalk, TargetScan, MiRTarBase, KEGG Pathway Database).

Results

MiR-223-3p and miR-93-5p have been shown do decrease systemically in late-stage CDK patients compared to healthy controls, which was reversed after KT even at comparable preoperative renal function. Downstream targets such as IKKalpha, interleukin-6-signal transducer, ribosomal protein S6 kinase beta-1 (RPS6KB1), signal transducer and activator of transcription 3 (STAT3), receptor activator of NF-κB ligand (RANKL), SMAD6 or bone morphogenetic protein receptor type 2 (BMR2) were identified to be related to these miRNAs.

Summary and Conclusions

Specific signatures of circulating miRNAs were shown to be altered during CKD, but normalized after KT. For miR-223-3p and miR-93-5p, we found significant associations to bone metabolism and inflammation parameters as well as a large number of downstream pathways that may be of relevance in CKD-MBD.

LOW CALCIUM INTAKE STRONGLY PREDICTS THE RISK OF DEVELOPING OSTEOPOROSIS AND VERTEBRAL FRACTURES.

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Introduction. Osteoporosis is a systemic disease that involves the whole skeleton with a higher prevalence in women and it is characterized by a reduction in bone mineral density (BMD) as well as a derangement in bone microarchitecture. In this clinical setting, clinicians frequently observe fragility fractures, in particular at vertebral (VF) and hip sites. The most common cause of osteoporosis is the post-menopausal status when the protective role of estrogens is abruptly interrupted. Dietary calcium usually comes from milk and dairy products, and, in a minor proportion, from water, fruits, vegetables and proteic foods (fish, meat, beans). In the past, low calcium intake and hypovitaminosis D have been pointed out as co-factors in inducing osteoporosis. However, recent findings did not report a significant correlation between low calcium intake and risk of VFs.

Aim of this cross-sectional study was to evaluate the relationship between calcium intake and BMD or VFs in a cohort of post-menopausal women without any other causes of secondary osteoporosis.

Patients and Methods. We enrolled 312 consecutive women (mean age 63.5±9.6 years, mean BMI 24.13±4.3Kg/m2, mean menopause duration 14±5.3years). In 304 subjects we obtained bone mineral density (BMD) as assessed by lumbar and femoral dual-energy X-ray absorptiometry (DXA) (Hologic QDR4500W). Quantitative DXA vertebral morphometry was performed in 106 subjects. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Hm/Hp) were calculated for each vertebra from T5 to L4. Fractures were defined mild, moderate and severe based on a height ratio decrease of 20-25%, 26-40% and more than 40%, respectively. Finally, women were asked to complete a validated questionnaire with 15 items in order to establish their daily calcium intake together with its prevalent origin.

Results. Based on these questionnaire answers, three groups were defined: calcium intake >1200mg/die (43pt/312; 13.8%), calcium intake between 800mg and 1200mg/die (138pt/312; 44.2%) and calcium intake <800mg/die (131pt/312; 42%). No significant differences in BMI ($p=0.983$) and age ($p=0.27$) were observed between the three groups. The highest calcium intake group had a significantly higher BMD with respect to the others, both at lumbar spine (-1.5DS vs -1.95DS and-2.4DS; $p<0.05$) and femoral neck (-1.0DS vs -1.7DS vs -2.7DS; $p<0.05$). Moreover, 49 (46.2%) women had morphometric VFs and their calcium intake was significantly lower than in patients without VFs ($p=0.017$). The origin of calcium was prevalently from milk and dairy products in patients with no VFs, whereas it derived from proteic products in women with VFs (71% vs 53%, $p<0.05$). At the logistic regression, subjects with calcium intake <800 mg/die showed an OR 2.84 to develop osteoporosis ($p=0.006$) and an OR 10.00 to have at least one VF ($p=0.037$) as compared to women with calcium intake >1200mg/die.

Conclusions. Our study showed that the calcium intake of a high percentage of post-menopausal women is insufficient. In this clinical context, lower calcium intake appears to correlate with high risk to develop osteoporosis and, most importantly, morphometric VFs.

BODY COMPOSITION, SIZE AND HORMONAL PARAMETERS ARE ASSOCIATED WITH BONE AND GLUCOSE METABOLISM IN A LARGE COHORT OF VOLUNTEERS

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1. Objective

Both type 1 and type 2 diabetes (T1DM, T2DM) not only bear micro- and macrovascular disease risk, but have a tremendous effect on bone metabolism and strength. We have shown that 25-OH-Vitamin-D3 (25OHD) as well as testosterone play an important role in bone homeostasis. In this study, we investigate the interaction between bone metabolism and 25OHD and testosterone levels in patients with T2DM, prediabetes and healthy controls in a large cohort study, the BioPersMed cohort (Biomarkers for personalized Medicine).

2. Methods

To identify putative alterations in bone metabolism between healthy, pre-diabetic and diabetic patients, biochemical and clinical parameters of 966 female (531) and male (435) volunteers were analysed. Differences in metabolic and anthropometric parameters of obese (BMI > 30kg/m2) patients compared to overweight or lean people were addressed. Osteocalcin, 25OHD and androgen measurements were analysed in association with DXA-derived data for bone density, TBS and body composition. .

3. Results

The findings of our study confirm previous reports on significantly lowered osteocalcin concentrations in patients with T2DM compared to healthy controls. This effect was pronounced in men ($p < 0.0001$) and less in women ($p=0.122$). Significant differences in osteocalcin levels occurred already in pre-diabetic men ($p=0.007$). 25OHD ($p=0.038$), free testosterone ($p=0.022$) and testosterone ($p= 0.002$) levels significantly followed this trend in pre-diabetic men. These parameters, among others, were significantly (25OHD ($p= 0.005$), testosterone ($p< 0.001$)) decreased in obese compared to lean volunteers.

4. Summary and Conclusions

Our results underline the influence of T2DM on bone metabolism. Differences between female and male patients in the regulation of bone and glucose metabolism might be of great importance for pathophysiological and clinical purposes, with an early association of osteocalcin changes in pre-diabetic men and specific 25OHD and androgen influences depending on body size and composition.

The author declares that he has no relevant or material financial interests that relate to the research described.

SEX-HORMONE BINDING GLOBULIN AS DETERMINANT OF RADIOLOGICAL VERTEBRAL FRACTURES IN MALE HIV PATIENTS UNDER ANTIRETROVIRAL THERAPY.

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Introduction. Differently from what has been observed in the general population, patients infected by HIV and treated with Highly Active AntiRetroviral Therapy (HAART) have increased risk of fragility fractures without significant differences between males and females. Moreover, HIV infection is frequently associated with hypogonadism the diagnosis of which is often challenging, due to variable values of gonadotropins and elevated circulating levels of sex-steroid biding globulin (SHBG). Whether hypogonadism may influence skeletal fragility in HIV patients is still matter of debate.

Aim of the study. In this cross-sectional study, we aimed at evaluating the association between bone mineral density (BMD, Hologic DEXA), radiological vertebral fractures (VFs) and serum gonadotropins (LH and FSH), total testosterone (TT), SHBG and calculated free (fT) testosterone in 103 subjects infected by HIV.

Results. VFs were found in 34 patients (33%); 15 had multiple fractures and 7 had at least one moderate-to-severe VF. Only 26% showed osteoporosis, whilst 13% had normal BMD and 61% had osteopenia. 26% had an increase in FSH and/or LH, but only 4 patients showed contextually a reduction in TT. We observed increased SHBG values with reduced fT in 29% of subjects. In univariate analysis, VFs were significantly associated with high levels of FSH (OR 4.2; p=0.02), high SHBG (OR 3.6; p=0,02), patients' age (OR 1.1; p=0,01) and pathological T-scores (OR 4.0; p=0,001), whereas no association was observed between VFs and TT (p=0.47), fT (p=0.5) or LH (p=0.59). Elevated SHBG, but not FSH, also correlated with pathological T-score values (OR 2.7; p=0,03).

Conclusion. Our study suggested an influence of gonadal status on VFs risk in males affected by HIV, consistently with the concept that increased levels of SHBG and FSH might be markers of hypogonadism. However, we cannot exclude that high circulating SHBG may have a direct and independent effect on skeletal health in HIV patients, such as already demonstrated in male patients with primary osteoporosis

INFO

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MANTOVA WELCOMES YOU TO THE 8th SKELETAL ENDOCRINOLOGY MEETING
3rd TRANSLATIONAL ESE BONE COURSE

Mantova, a Unesco heritage city, will amaze you with its rich artistic cultural heritage. It is a unique city, where history and ancient art are in continuous contact with modern life. Placed in the centre of the Po Valley, the city of Mantova is surrounded by lakes. The first inhabitants were Etruscans in Sordello Square. From the XIV century, the Gonzagas developed the cultural and artistic profile of the city, whose urban and architectural structure still exists today. Through four centuries of governments, the Dukes of Mantova engaged the most famous artists of that time, such as Leon Battista Alberti, Pisanello, Andrea Mantegna, Giulio Romano, Rubens and others. Their work, still mark the splendor of the town.

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The 8th Skeletal Endocrinology Meeting has received the following credits for physician:

No. 6 EACCME credits (ID EACCME 15395)

No. 8,4 CME credits (ID CME 5468-184418)

CERTIFICATE OF ATTENDANCE

Certificate of Attendance can be collected at registration desk only at the end of the Meeting.

LANGUAGE

The official language is English. No translation will be provided.

WEBSITE

For further informatian, please visit the official website of the Meeting: www.aicgroup.it

SCIENTIFIC SECRETARIAT

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