10th SKELETAL ENDOCRINOLOGY MEETING

SCIENTIFIC PROGRAMME

26th/27th March 2023

Hotel Regina Palace

STRESA - ITALY

PRESIDENT

Andrea Giustina (IT)

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A.I.C. Asti Incentives & Congressi

Piazza San Uomobono, 30 - 56126 Pisa

Ph +39 050 598808 Fax +39 050 0987825

skeletal@aicgroup.it - www.aicgroup.it

CONGRESS VENUE

Regina Palace Hotel

Corso Umberto I, 29 - 28838 Stresa (VB)

Ph +39 0323 936936

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UNDER THE PATRONAGE OF

AIMN - Associazione Italiana di Medicina Nucleare

ASBMR - American Society for Bone and Mineral Research

Collegium P.O.E.M.A. - Collegium dei Professori Ordinari di Endocrinologia, Metabolismo e Andrologia

TES - The Endocrine Society

ESE - European Society of Endocrinology

IOF - International Osteoporosis Foundation

SIE - Società Italiana di Endocrinologia

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

SIOT - Società Italiana di Ortopedia e Traumatologia

SUNDAY 26 MARCH 2023

12.45 - 13.00 **Opening Ceremony**

13.00 - 14.20 **Satellite Symposium - Vitamina D: una terapia ormonale sostitutiva**

*Chairs: **R. Bernardini** (IT), **A. Giustina** (IT)*

Le dimensioni del problema in Italia e nel mondo - **S. Giannini** (IT)
Quando e come misurare la vitamin D - **S. Minisola** (IT)
Quando e come supplementare la vitamin D - **N. Napoli** (IT)
Il profilo costo beneficio della vitamina D e la nota 96 - **R. Bernardini** (IT)
Discussione

14.20 - 15.40 **Joint Symposium with SIOT: Osteoporotic fracture current challenges and perspectives**

*Chairs: **V. Salini** (IT), **P. Tranquilli Leali** (IT)*

The fracture secular trend - **P. Piscitelli** (IT)
Perioperative management of osteoporotic patients - **S. Bukata** (USA)
Fractures in people joint replaced - **U. Tarantino** (IT), **E. Piccirilli** (IT)
Devices for preventing femoral fracture - **M. Alessio Mazzola** (IT)
Discussion

15.40 - 16.40 **Joint Symposium with ESE: Bone Neuroendocrine Symposium**

*Chairs: **J. Bollerslev** (NO), **M. Reincke** (DE)*

Growth hormone, GHD and bone - **J.O. Jørgensen** (DK)
Medical treatment of acromegaly and osteopathy - **S. Chiloiro** (IT)
Management of Cushing osteopathy - **A. Colao** (IT)
Discussion

16.40 - 17.20 **Opening lectures**

*Chairs: **J.P. Bilezikian** (USA), **A. Giustina** (IT)*

One year in hormones and bone - basic - **R. Civitelli** (USA)
One year in hormones and bone - clinical - **D. Shoback** (USA)

17.20 - 18.40 **Joint Symposium with AIMN: Advancements in the assessment of fracture risk**

*Chairs: **R. Giubbini** (IT), **C. Messina** (IT)*

BSi and TBS - **F.M. Ulivieri** (IT)
R.E.M.S. technology (Radiofrequency Echographic Multi Spectrometry) - **G. Adami** (IT)
Microindentation - **A. Diez Perez** (ES)
Opportunistic fracture detection - **S. Frara** (IT)
Discussion

18.40 - 19.00 **ASBMR Lecture**

*Chairs: **E. Canalis** (USA), **C. Rosen** (USA)*

Novel mechanisms in Osteoporosis - **L. Calvi** (USA)

19.00 - 20.30 **Presidential Session**

*Chairs: **E. Ghigo** (IT), **A. Giustina** (IT)*

MONDAY 27 MARCH 2023

08.45 - 10.05 **Joint session with ECTS: Rare bone diseases**
*Chairs: **M.L. Brandi** (IT), **S. Cenci** (IT)*
FOP - **R.J. Pignolo** (USA)
Hypophosphatasia - **M.L. Brandi** (IT)
Non classical Osteogenesis imperfecta - **E. Canalis** (USA)
XLH - **S. Mora** (IT)
Discussion

10.05 - 10.25 **Collegium P.O.E.M.A. Lecture**
*Chair: **R. Bonadonna** (IT)*
Update in glucocorticoid induced osteoporosis - **A. Isidori** (IT)

10.25 - 11.25 **Joint session with the Endocrine Society: Clinical aspects of Hypoparathyroidism**
*Chairs: **J.P. Bilezikian** (USA), **D. Shoback** (USA)*
Determinants of skeletal phenotype - **J. Bollerslev** (NO)
Renal complications - **L. Rejnmark** (DK)
Quality of life - **H. Siggelkow** (DE)
Discussion

11.25 - 12.25 **Joint session with SIE: Treatment of Hypoparathyroidism**
*Chairs: **G. Aimaretti** (IT), **A. Colao** (IT)*
Standard treatment and PTH 1-84 - **C. Marcocci** (IT)
TransCon PTH - **N. Napoli** (IT)
Novel molecules - **A. Khan** (CA)
Discussion

12.25 - 12.45 **European Hormone and Metabolism Foundation Lecture**
*Chairs: **D. Macut** (SRB), **R. Nuti** (IT)*
Hyperparathyroidism clinical guidelines - **J.P. Bilezikian** (USA)

12.45 - 14.00 **Lunch**

14.00 - 15.20 **Joint session with IOF: The Osteo-muscular unit**
*Chairs: **F. Casanueva** (ES), **R. Rizzoli** (CH)*
Diagnostic criteria for sarcopenia - **L.M. Donini** (IT)
Clinical significance of osteosarcopenia - **E. Dennison** (UK)
Duchenne Syndrome - **G. Iolascon** (IT)
Prostate cancer - **A. Berruti** (IT)
Discussion

15.20 - 16.40 **Joint Session with SIOMMMS: Update on Bone targeted therapy**

*Chairs: **I. Chiodini** (IT), **B. Frediani** (IT)*

Bisphosphonates - **A. Giusti** (IT)

Denosumab - **S. Papapoulos** (NL)

Teriparatide and Abaloparatide - **S. Minisola** (IT)

Romosozumab - **S. Ferrari** (CH)

Discussion

16.40 - 17.00 **Closing lecture**

*Chairs: **L. Calvi** (USA), **E. Ghigo** (IT)*

Integrative biology of Bone - **C. Rosen** (USA)

17.00 - 17.10 **Final discussion and conclusive remarks**

*Chairs: **J.P. Bilezikian** (USA), **E. Canalis** (USA), **A. Giustina** (IT)*

17.10 - 17.20 **CME test instructions**

Skeletal Endocrinology Group
Glucocorticoid Induced Osteoporosis
HORMONES BONE
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ABSTRACT BOOK

LE DIMENSIONI DEL PROBLEMA IN ITALIA E NEL MONDO

Sandro Giannini
Clinica Medica 1, Dipartimento di Medicina, Università di Padova

L'ipovitaminosi D costituisce ancora un problema endemico in quasi tutti i Paesi del Mondo. Negli ultimi anni, le maggiori Società Scientifiche Internazionali e Nazionali del Settore hanno proposto, in modo sempre più attento, i criteri per la sua rilevazione, con un chiaro tentativo di identificare valori soglia in grado di rispondere alle necessità valutative e diagnostiche di popolazioni diverse. Oggi si ritiene che livelli superiori a 30 ng/ml (75 nmol/l) siano necessari per la salute di popolazioni specifiche, quali, ad esempio, quelle gravate da osteoporosi ed elevato rischio di frattura, Iperparatiroidismo Primario e molte altre osteopatie possibilmente fragilizzanti. Tali valori sono anche riconosciuti come normali per soggetti ad altro rischio, come ad esempio i pazienti istituzionalizzati. Negli ultimi anni, almeno in Italia, l'attenzione nei confronti della patologia, specie scheletrica, da ipovitaminosi D è progressivamente cresciuta. Tuttavia, molto studi hanno dimostrato che molto rimane ancora da fare. Nonostante l'evidenza, oggi ampiamente riconosciuta anche dalle Istituzioni Regolatorie in materia di Sanità Pubblica, della indispensabilità di una normalizzazione oltre i 30 ng/ml dei livelli sierici della vitamina D in soggetti in terapia per una storia di frattura di fragilità o ad altro rischio di frattura e quindi trattati con farmaci anti-osteoporotici, la proporzione di pazienti che ancora non ricevono una terapia vitaminica D idonea allo scopo rimane molto elevata. In un recente passato, è stato anche dimostrato come l'introduzione di alcune disposizioni normative in riguardo alla dispensazione SSN dei preparati a base di vitamina D da parte delle Istituzioni Regolatorie, ha indotto una repentina riduzione del consumo di vitamina D proprio nei soggetti già in terapia con farmaci anti-osteoporotici perché già fratturati o ad elevato rischio di frattura, rendendo così certamente meno efficace la terapia anti-osteoporotica stessa. Rimane la forte necessità, anche in Italia, di programmi in grado di contrastare gli effetti certamente dannosi dell'ipovitaminosi D.

WHEN AND HOW TO MEASURE VITAMIN D

Salvatore Minisola
"Sapienza" Rome University

Current guidelines agree on recommending 25 hydroxyvitamin D as the preferred indicator of body's Vitamin D stores.

However, there is no doubt that 25 hydroxyvitamin D is not easy to accurately measure. This is mainly due, among other factors, to its strong binding to vitamin D binding protein, coexistence of multiple chemically related molecule that may cross react and common matrix effects.

Methods that remove prior to analysis proteins and lipids by strong organic solvents are those that should be preferred (among them liquid chromatography-tandem mass spectrometry); however, these methods are sometimes cumbersome and time consuming. The automatic immunoassays use alternative strategies to release 25 hydroxyvitamin D from its carriers.

It would be important that manufacturers and local laboratories adhere to international initiatives (such as the Vitamin D Standardization Certification program or Vitamin D External Quality Assessment Scheme) to standardize assays. This would render possible comparisons of different studies and harmonization of data for meta-analyses.

Measurement of 25(OH)D is the gold standard for the diagnosis of vitamin D deficiency. There are a number of subjects that are at risk for a vitamin D deficiency or in a suboptimal Vitamin D status. Furthermore, 25(OH)D should be requested when there is a need for a differential diagnosis between rickets, osteomalacia and other metabolic bone diseases or when we want to see the effect of vitamin D supplementation or in very rare cases of intoxication.

QUANDO E COME SUPPLEMENTARE LA VITAMINA D

Nicola Napoli, MD PhD
Division of Osteo-Metabolic and thyroid Diseases, Fondazione Policlinico Campus Bio-Medico

Vitamin D is a key hormone for skeletal health and to maintain optimal vitamin D status is essential throughout lifespam. However, a large amount of data have shown positive effects also on the immune system, acute respiratory infections and, more recently, in clinical outcomes related to COVID-19. Less solid is the evidence that vitamin D may prevent diabetes, cancer, cardiovascular diseases or other chronic conditions. From these premises, it is clear that vitamin D should be firstly prescribed to subjects at risk of bone fragility and in clinical conditions that impair absorption of calcium (malabsorption etc) or vitamin D is usually lower available (obesity, etc). Use of vitamin D supplementation is often required, as sunlight exposure and dietary intake alone is usually insufficient in most individuals at risk of vitamin D deficiency.

Although recommendations differ in many countries, daily intake from 400 to 2000 IU daily is commonly believed to be optimal according to age, clinical conditions and risk of fracture. In case of vitamin D deficiency higher doses can be safely prescribed and upper safe range has been fixed from 4000 to 10.000 UI according to different scientific societies. In the last decade several regimen of administration have been proposed, ranging from daily, weekly, monthly or yearly. According to an Italian study, daily administration is associated with a higher systemic exposure to 25(OH)D (compared to weekly and bi-weekly administration, respectively), even when corrected for the cumulative dose (Fassio 2020). Given the low compliance in daily doses, many physicians prefer weekly, every 2 weeks or monthly doses (25.000/50.000 UI) which, again, are largely safe and able to maintain normal vitamin D range in most patients. In order to quickly reach normal vitamin D values, boluses with high doses of cholecalciferol have been used but with controversial results. Given the evidence of higher risk of falls and fractures in those receiving intermittent doses with more than 300.000 UI, it is not recommended that bolus should not exceed 100.000 UI for each dose. The oral route remain the easiest and common way while intramuscular injection should be limited to patients with malabsorption or in the morbid obese. In the intensive care, however, a typical daily dose is inefficient, and initial loading doses (followed by a daily dose) are necessary to improve vitamin D levels.

Toxicity from vitamin D is a rare condition and protracted daily dosed of 4000 UI have been safely tested in many clinical trials. There are also proofs of evidence with higher doses (up to 10.000 UI) although these dosages are rarely needed in clinical practice.

IL PROFILO COSTO BENEFICIO DELLA VITAMINA D E LA NOTA AIFA 96

Renato Bernardini[1,2,3], Antonio Munafò[1], Carlo Maria Bellanca[1,2], Giuseppina Cantarella[1]

[1]Sezione di Farmacologia, Dipartimento di Scienze Biomediche e Biotecnologiche; [2]UO Tossicologia e Farmacologia Clinica, AOU Policlinico, Università degli Studi di Catania; [3]CdA AIFA, Roma

L'apporto supplementare di vitamina D rappresenta uno dei temi più dibattuti in campo medico, fonte di controversie e di divergenze di raccomandazioni da parte dei diversi organismi scientifici. Negli ultimi tempi è cresciuto notevolmente l'interesse della comunità scientifica e dell'opinione pubblica nei riguardi del deficit di vitamina D e dell'opportunità di una terapia integrativa. L'aumento esponenziale delle prescrizioni di vitamina D ha indotto AIFA a pubblicare, nel 2014, un rapporto su questa crescita incontrollata [1]. Tra i fattori che hanno contribuito in maniera significativa a questo fenomeno vi è stata certamente la maggiore attenzione della classe medica per le patologie scheletriche correlate alla carenza di vitamina D e un reale aumento della prevalenza e dell'incidenza di ipovitaminosi D nella popolazione. Non si può tuttavia escludere che una parte di questo aumento sia stato effettivamente legato a fenomeni di inappropriatezza prescrittiva. La crescente acquisizione di prove scientifiche a sostegno dell'utilità della supplementazione con vitamina D solo in specifiche condizioni cliniche [2–5], unita all'evidenza di un uso massivo da parte della popolazione italiana dei medicinali a base di tale principio attivo, ha portato all'istituzione nel 2019 della Nota AIFA 96, al fine di declinare i criteri di appropriatezza prescrittiva della supplementazione con la vitamina D e i suoi analoghi con indicazione alla prevenzione e al trattamento della ipovitaminosi D nell'adulto [6]. Nei tredici mesi successivi all'introduzione della Nota 96 si è registrata una riduzione di circa il 33% dei consumi e della spesa; tuttavia, nel periodo successivo si è assistito ad una progressiva riduzione di tale effetto. In aggiunta ai dati di utilizzo provenienti dal monitoraggio periodico dei consumi dei farmaci in Nota, un recente aggiornamento delle evidenze scientifiche [7,8], ha reso necessaria l'introduzione di alcune modifiche con particolare riferimento alla ridefinizione dei livelli soglia di vitamina D e degli scenari clinici per cui è prevista la prescrizione a carico del SSN con conseguente diminuzione dei consumi e della spesa farmaceutica e maggiore aderenza a criteri scientifici.

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PERIOPERATIVE MANAGEMENT OF OSTEOPOROSIS PATIENTS

Susan V Bukata, MD, FAAOS, FAOA
University of California, San Diego

For over 30 years, attempts have been made to improve the rates of osteoporosis care after fragility fractures with varying success. Around the world, we also face a silver tsunami of patients with both osteoporosis and low bone mass as well as osteoarthritis and spinal stenosis. Patients desire high levels of physical function and independence well into their geriatric years and have high expectations of durable success from their orthopaedic surgical procedures. Improvements in orthopaedic instrumentation and medical management also now make surgical candidates of patients who historically would not have been offered procedures. While both surgeons and primary care doctors may recognize the disease of osteoporosis in fragility fracture patients, many do not consider osteoporosis as they plan for elective orthopaedic surgery. An opportunity exists for bone health intervention to occur as a part of perioperative care for orthopaedic procedures.

In the United States, up to 2/3 of patients over age 60 presenting for elective orthopaedic surgery have either low bone mass (osteopenia) or osteoporosis from DXA measurements alone. Identifying patients with osteoporosis and low bone mass early before elective joint and spine surgery can allow for perioperative treatment to improve bone strength prior to surgery and possibly prevent or decrease the risk of some of the complications that can occur due to osteoporosis. For patients that present at the time of surgical scheduling, medications are unlikely to make a major bone strength change in the first 6 to 12 months and many cannot delay surgery extended periods of time. Thinking about perioperative bone health as making a long-term investment in both the patient's bone health and the success of their orthopedic surgery is important. Surgeons are very aware of the complications such as periprosthetic fractures around total joints and adjacent segment fractures around spine fusions that dramatically change the results and overall success of the surgeries. The highly protocolized pathways for spine and joint surgery create a unique opportunity for us to add bone health assessment into these treatment pathways. Leveraging the extensive care teams for these patients which include nurses, physical therapists, primary care doctors, hospitalists and surgeons increases the opportunity for bone health intervention and treatment.

Choice of treatment for osteoporosis and low bone mass in the perioperative setting remains controversial, although individual patient needs can allow antiresorptives such as bisphosphonates and denosumab, as well as anabolic medications, as possible treatments. It takes approximately 12 months on treatment to obtain 5% improvements in lumbar spine and 3% improvements in hip bone mineral density (BMD) for both bisphosphonates and denosumab. While spine BMD changes greater than 5% at the lumbar spine can occur within the first six months with the anabolic agents abaloparatide, teriparatide, and romosozumab, it can take 12 months to see 3% changes in the hip BMD with abaloparatide and teriparatide. Romosozumab demonstrates gains greater than 3% in hip BMD within six months. These improvements are substantial, but we need to change the dialog from attempting perioperative bone strength miracles to getting the patient on track for a lifetime of success and bone health.

DEVICES FOR PREVENTING FEMORAL FRACTURE

Mattia Alessio Mazzola[1], Giacomo Placella[2], Vincenzo Salini[2]

1. San Raffaele Research Hospital, Via Olgettina 60, 20132, Milan, Italy
2. Vita-Salute Univeristy San Raffaele, Via Olgettina 59, 20132, Milan, Italy

Osteoporotic bone defects are a relevant problem with increasing prevalence in the general population. Is estimated that 200.000 subjects over 50 years and 30% of subjects over 65 years suffer from osteoporotic bone defects. This problem causes 9.000.000 fractures every year worldwide and is estimated that 40 % of women and 15-30 % of men will experience a fragility fracture over their life.

In 2017 proximal femoral fractures represented 20% of total fractures in Italy and were responsible for 59% of global healthcare costs with 2.400.000.000 € spent to manage patients affected by this condition. There will be a 26.2% increase in costs by 2030 with 3.500.000.000 € estimated expenses.

A second femoral fragility fracture occurs in 7% of patients affected by a first proximal femoral fracture at 1 year, in 16% of patients at 2 years, and in 33% of patients over 2 years (median: 1.5 years after surgery). The recognized risk factors are female sex, high DEXA score, and low physical capacity. Despite widespread diffusion of anti-osteoporotic agents only 30% of subjects use anti-osteoporotic agents at the second surgery due to low compliance.

A preventative action providing immediate strengthening of the proximal femur by internal prophylactic augmentation is desirable to overcome the main limitations of systemic drugs.

In the past, the femoroplasty was proposed to increase the proximal femoral failure load. The procedure consisted of injection of low viscosity bone cement (PMMA) in the femoral neck. However, PMMA toxicity, thermal damage, necrosis, embolism, and subtrochanteric secondary fractures were potential severe complications related to this surgical procedure that was abandoned.

On the other hand, prophylactic augmentation with a nail, cannulated screws or sliding hip screw has been recently studied to increase proximal femoral strength, but stiff hardware may result in a higher incidence of acetabular fractures.

The local osteoenhancement procedure (LOEP) is a minimally invasive surgical approach to provide a durable increase in femoral strength. This is performed through a small lateral cortical wall portal, debridement and irrigation of the femoral neck, and injection of calcium sulfate, tricalcium phosphate, and brushite (AGN1) that is resorbed and replaced by new bone over time. This procedure increases the failure load of the proximal femur (+19.2%; $p<0.001$), the work to failure (+30%; $p<0.001$) without increasing femoral stiffness ($p>0.05$).

In vivo animal studies reported increased trabecular number ($p<0.05$) and decreased trabecular spacing ($p<0.05$) in animals treated by LOEP.

The systemic and histological toxicity of AGN1 was also studied and compared with PMMA in a sheep model of pulmonary embolism created by injecting 0.5 mL of tested molecules directly into the femoral vein. There were minimal to slight changes in thrombin/antithrombin cascade in AGN1 tested animals compared to severe changes in PMMA with less presence of histological lung thrombi in the AGN1 group.

A human study involving 12 osteoporotic post-menopausal women who underwent LOEP procedure was conducted in 2020 reporting a significant increase in estimated femoral strength at all time points ($p<0.01$) and no procedure or device-related serious adverse events with progressive resorption of AGN1 after 5-7 years.

The objective of the RESTORE study is to investigate the effect of LOEP on the secondary incidence of contralateral hip fracture in a population of osteoporotic women affected by a first fragility femoral fracture treated with surgical fixation of the indexed hip and with LOEP of the contralateral side.

Disclosures: all authors certify that they have no disclosures.

GROWTH HORMONE DEFICIENCY AND BONE

Jens Otto Lunde Jørgensen
Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark

Growth hormone (GH) is essential for longitudinal bone growth in childhood and puberty and this anabolic effect is largely mediated via GH-dependent production and action of IGF-I. Complete GH-deficiency in childhood results in stunted growth and so-called pituitary dwarfism. This phenotype is reversed by GH replacement, which has been used for more than 50 years. GH is also important for bone health in adulthood, and GH-deficiency in adulthood is associated with osteopenia and increased fracture risk. Administration of GH in adults markedly increases bone turnover as reflected by grossly elevated levels of bone formation and degradation markers in serum. This increase in bone turnover may translate into an initial decline in bone mineral density (BMD) when GH replacement is initiated in adult patients. During prolonged treatment, however, BMD increases in most adult patients. Moreover, observational surveys indicate that the increase in BMD reduces fracture risk in GH replaced hypopituitary adults. On the other hand, there is no evidence that GH is useful for the treatment of osteoporosis in the general population.

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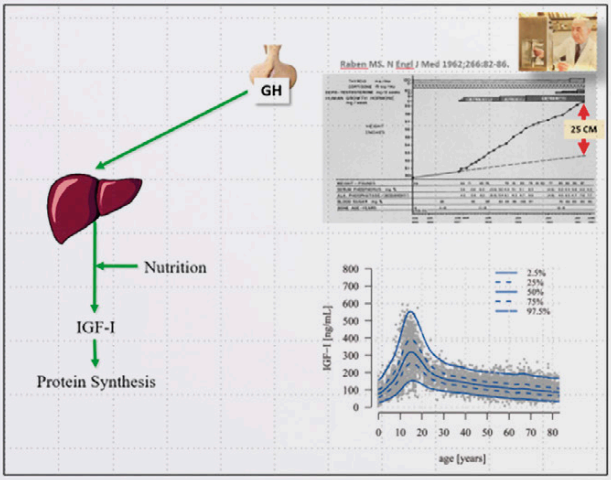

Figur 1. The anabolic effects of GH is largely mediated by IGF-I. GH replacement increases longitudinal growth in children with GHD.

CUSHING'S OSTEOPATHY

Rosario Pivonello, Chiara Simeoli, Angelica Larocca, Nicola Di Paola, Annamaria Colao

Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Italy

Endogenous Cushing's syndrome (CS) is a rare, severe, chronic, and systemic condition characterized by hypercortisolism. In approximately 75-80% of cases, endogenous CS is a consequence of an adrenocorticotrophin (ACTH) hypersecretion (ACTH-dependent CS), generally due to an ACTH-secreting pituitary tumor (Cushing's disease, CD, 70%), and, rarely, to an ACTH-secreting, or corticotrophin releasing hormone (CRH)-secreting, extra-pituitary tumor (Ectopic CS, ECS, 5-10%). In the remaining 20% of cases, CS is a direct consequence of autonomous cortisol overproduction by the adrenal glands (ACTH-independent CS, Adrenal CS), due to unilateral or bilateral adrenal diseases. Endogenous CS is associated with increased morbidity, mainly characterized by cardiovascular, metabolic, musculoskeletal, neuropsychiatric, dermatological, immune and sexual disorders. Skeletal fragility is a frequent and early complication of endogenous CS; indeed, fractures could be the first clinical manifestation of CS. Cortisol excess affects bone status through different mechanisms: uncoupling bone turnover, impaired calcium homeostasis, myopathy with reduction in muscle trophism. These mechanisms cause a prevalence of bone loss in 64-100% of CS patients. Particularly, the most prevalent skeletal manifestations in CS are osteopenia (40-78%), osteoporosis (22-57%), skeletal fractures (11-76%) and vertebral fractures (30-50% up to 78% if evaluated with a radiological morphometric approach). Therefore, the risk assessment for bone loss and fracture is recommended in all patients with CS. Conversely, in young patients with osteoporosis and in patients with several comorbidities typical of old age such as osteoporosis, diabetes and cardiovascular disorders, a screening of CS is suggested. Glucocorticoid-induced osteoporosis (GIOP) is the most common drug-induced cause of secondary osteoporosis, and its pathophysiology and clinical manifestations are similar to endogenous CS osteopathy. Age, daily dose, administration route, body mass index (BMI) and habits may influence GIOP degree: particularly, menopause in women and age > 50 in men, prednisolone equivalent doses (PED) ≥7,5 mg/day, intravenous pulses, low BMI, smoking and alcohol use, increase fracture risk. In both endogenous and exogenous hypercortisolism's osteopathy, dual energy X-ray absorptiometry (DXA) is the most common assessment used, evaluating quantitative, but not qualitative bone structure. High-resolution peripheral quantitative computed tomography acquires several parameters of bone quality, although this technique is not routinely available. Trabecular bone score (TBS) is a simple tool in the fracture risk prediction, able to evaluate bone micro-architecture based on a pixel greyscale. The first approach in the management of endogenous CS osteopathy is the resolution of the hypercortisolism and the identification and correction of coexistent factors increasing fracture risk (i.e. hypovitaminosis D, negative calcium balance, hypogonadism, growth hormone deficiency). In CS patients with low fracture risk, or when hypercortisolism is expected to be rapidly resolved by surgery, anti-osteoporotic drugs are not recommended; whereas, in patients with high fracture risk, anti-osteoporotic drugs are recommended, and teriparatide should be preferred. Placebo-controlled and randomized-controlled trials have evaluated the efficacy of oral bisphosphonates (alendronate, risedronate, zoledronate), denosumab and teriparatide in GIOP patients, suggesting that oral bisphosphonates are preferred in patients at high fracture risk, whereas parenteral zoledronate, denosumab and teriparatide in patients at very high fracture risk. To contain the risk of GIOP, the lowest effective GC dose, for the shortest amount of time, and the local administration rather than the systemic one, are recommended. In adults at risk of bone loss or fractures, including CS patients and glucocorticoid users, an optimal total daily calcium intake (1.2-2 g) together with vitamin D supplementation to achieve a total 25-hydroxyvitamin D target level of 20-50 ng/mL, is recommended. The prompt recognition of hypercortisolism and skeletal complications management are essential to reduce CS morbidity. Despite osteopathy is a common disease in the general population, osteopathy in CS requires a tailored therapeutic approach, which takes into account the complex state of CS patient.

FIRST AUTHOR DISCLOSURES:

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ONE YEAR IN HORMONES AND BONE - CLINICAL

Dolores M. Shoback MD
Endocrine Research Unit, 111N, Department of Medicine, San Francisco Veterans Affairs Medical Center, University of California, San Francisco, CA, USA

Many developments during the past year influence our understanding of how hormones affect normal bone physiology and how their deficiency or excess produces skeletal consequences. Advances have also been made in clinical guidelines for several diseases. Both parathyroid hormone (PTH) and PTH-related protein (PTHrP) play prominent roles in bone physiology and disease pathogenesis. Trial data have been reported on the use of TransCon PTH (1-34) for the treatment of chronic hypoparathyroidism (PMID: 34347093; 36271471). Such treatment allows a reduction in conventional therapy with calcium (Ca salts) and activated vitamin D, stabilizes serum [Ca], and lowers urinary [Ca] to acceptable levels. Treatment of men with osteoporosis with the PTHrP analogue abaloparatide has been shown to raise bone mineral density (BMD) effectively in 2 trials (PMID: 36190391; 35977548). Studies over 10 years in the Scandinavian Investigation of Primary Hyperparathyroidism (SIPH) cohort reported improved BMD outcomes with parathyroidectomy vs observation of subjects with mild primary hyperparathyroidism (PHPT) (PMID: 36593641). There were no differences in mortality or fractures in the 2 groups of subjects (PMID: 35436153). New guidelines on management of PHPT (PMID: 36245251) and hypoparathyroidism (PMID: 36054621) were finalized this year by international task forces. The American College of Physicians published its guidelines for the pharmacologic treatment of osteoporosis in postmenopausal women and men (PMID: 36592456). The clinical value of supplementation of healthy middle-aged and older adults with vitamin D remains controversial. Results from the VITAL Trial demonstrated no significant effects on incident clinical fractures in men or women supplemented with vitamin D3 (50 mcg per day) vs placebo (PMID: 35939577). Several advances in fibroblast growth factor (FGF23)-mediated diseases were reported. Therapy with the FGF23 neutralizing monoclonal antibody burosumab was shown to be safe and effective in X-linked hypophosphatemia (XLH) in adults for up to 184 weeks (PMID: 36072994) and in children (age 5-12 years) for up to 160 weeks (PMID: 34636899) and in 2 patients with autosomal recessive hypophosphatemic rickets type 1 (due to inactivating mutations in dentin matrix protein 1) (PMID: 35896139). A consensus statement on management of XLH was also published (PMID: 35484227), along with comprehensive reviews on tumor-induced osteomalacia (TIO) due to the overproduction of FGF23 (PMID: 35857061; 36327295). A clinical series summarized 30 cases of intravenous iron-induced, FGF23-mediated with features strongly supportive of osteomalacia (PMID: 35426179). Determinants of cortical bone mass in type 1 diabetes (T1D) were investigated in the Epidemiology of Diabetes Interventions and Complications (EDIC) cohort and shown to include increases in Alc; increases in skin intrinsic fluorescence, reflecting advanced glycation end-product accumulation; and presence of renal disease (PMID: 35576955). Another analysis using the EDIC cohort showed that poorer glycemic control was associated significantly with low bone formation markers, and reduced renal function was associated with higher levels of bone resorption markers (PMID: 35188961), underscoring that the chronicity of insulin deficiency and diabetes complications were key factors mediating skeletal complications in T1D. The broad variety of hormones and diseases involved further emphasize the skeleton as a critical target tissue responsive to endocrine excess and deficiency states. Disclosure: trial investigator, Ascendis Pharmaceutical.

TRABECULAR BONE SCORE (TBS) AND BONE STRAIN INDEX (BSI)

Fabio Massimo Ulivieri
Institute of Endocrine and Metabolic Sciences
San Raffaele Vita-Salute University and IRCCS Hospital

For a proper assessment of osteoporotic fragility fracture prediction, all aspects regarding bone mineral density, bone texture, and information about strength are necessary, particularly in endocrinological diseases, where bone quality impairment is relevant. Data regarding bone quantity (bone mineral density, BMD) and bone quality (trabecular bone score, TBS and bone strain index, BSI) are obtained by the gold standard method of dual X-ray absorptiometry (DXA).

TBS is a DXA index of bone texture that evaluates bone mineral variations in lumbar DXA images in order to describe the internal structure of the bone. TBS is calculated based on the same mathematical matrix DXA source used for BMD measurement, but it represents a different feature of bone status and is able to discriminate between patients with similar BMD, but different trabecular microarchitecture. TBS can discriminate fractured patients and can predict fractures independently from BMD. TBS appears particularly useful in secondary osteoporosis, like diabetes, where fragility fractures are present despite a normal or slightly reduced BMD.

BSI is an DXA index of bone deformation, indicating the resistance of bone under load. It is based on the Finite Element Analysis (FEA) of a greyscale of density distribution measured on spine and femoral scans. BSI includes local information on density distribution, bone geometry and loadings and therefore it differs from BMD and TBS. BSI predict the first and further fragility fractures and it is useful to identify the osteoporotic patient's subgroup particularly prone to fragility fractures. Moreover, BSI characterises patients affected by secondary osteoporosis like mastocytosis and hyperparathyroidism. BSI is also able to monitor the effect of anabolic treatment for osteoporosis.

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REMS, RADIOFREQUENCY ECHOGRAPHIC MULTI SPECTROMETRY

Giovanni Adami MD
Rheumatology Section, University of Verona, Verona, Italy

Radiofrequency Echographic Multi Spectrometry (REMS) is a non-invasive technique for assessing bone mineral density and fracture risk. This technology uses radiofrequency signals to measure the properties of bone tissue, including its density, structure, and strength. REMS has shown promising results in clinical setting, with several studies demonstrating its ability to accurately predict fracture risk in patients with osteoporosis. This technology has also been shown to be effective in monitoring changes in bone density and structure over time, making it a useful tool for monitoring osteoporosis treatment and progression. One of the main advantages of REMS is its ability to provide detailed information about bone health without exposing patients to ionizing radiation, which is a concern with traditional bone density tests such as dual-energy x-ray absorptiometry (DXA). This makes REMS a safer option for patients who require regular bone health monitoring, such as those with a history of osteoporotic fractures or those undergoing long-term osteoporosis treatment as well as children or pregnant women. In special population, such as chronic kidney disease (CKD) patients or diabetic individuals, REMS have been shown to perform better than DXA, which might be biased by aortic calcifications and osteoarthritis. In summary, REMS is a promising technology for assessing bone health and fracture risk in patients with osteoporosis. Its non-invasive nature and ability to provide detailed information about bone density and structure make it a valuable tool for monitoring osteoporosis progression and treatment effectiveness.

BONE MICROINDENTATION

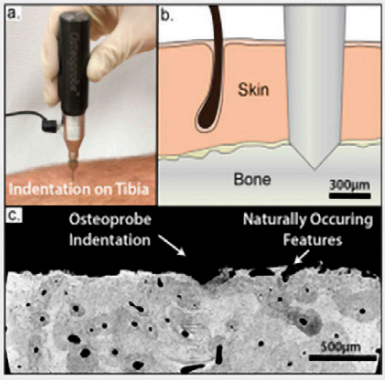
Adolfo Diez-Perez
Hospital del Mar Institute of Medical Investigation. Barcelona, Spain

Bone strength is the end result of the amount of bone, measurable by densitometry, plus the quality of the bone. The latter results from the combination of geometry, microarchitecture and different elements that exert an effect on the mechanical competence at the tissue level (stress risers, water content, fatigue damage, collagen and non-collagen components, etc.).

These bone tissue intrinsic mechanical properties can be indirectly estimated using different image analysis techniques. However, until the development of bone microindentation, a direct measurement, similar to the approach used in other materials engineering, has not been possible. The technique consists on a microscopic footprint in the anterior side of the midtibia at a fixed force and speed. The probe penetrates into the bone opening microcracks. Therefore, what measures is the resistance of bone to the opening of microcracks (i.e. the mechanism of a initiating fracture).

The units are expressed as BMSi (Bone Material Strength index) and the basis of the technique is displayed in the figure.

The reference values have been recently established in healthy adults in a multinational study. Clinical studies have been performed in postmenopausal osteoporosis, males and in special situations where BMD does not fully explains bone propensity to fractures.



Moreover, microindentation detects longitudinal changes independent of BMD in response to treatments for osteoporosis and clinical situations. The safety and tolerability of microindentation are excellent. In summary, this technique is complementary to the available tools for the assessment of bone fragility and adds valuable information to the measurements of bone density.

Disclosures: Shareholder of Active Life Sci, manufacturer of Osteoprobe®

CLINICAL ROLE OF OPPORTUNISTIC VERTEBRAL FRACTURE DETECTION

Frara Stefano, di Filippo Luigi, Doga Mauro, Giustina Andrea
Institute of Endocrine and Metabolic Sciences, Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy

Vertebral fractures (VFs) are among the most common complications in osteoporosis as well as in other conditions of skeletal fragility, and they have been associated with reduction in quality of life and life expectancy, as well as respiratory dysfunction and high risk for new (incident) vertebral and non-vertebral fractures ("domino effect"). Previous retrospective studies in post-menopausal women reported an incidence of new VFs of 10.7/1000 person-years, and a VFs prevalence ranged from 15% to 25%. Other European investigations in men older than 50 have reported a fragility fracture prevalence up to 20%, whereas in the United States the incidence of new VFs in men has been estimated between 15.3 and 33.4 per 100,000 person-years in 65 to 74 and over75 year-old patients, respectively. Since in only one third of VFs the diagnosis is clinical, as the majority of cases is actually asymptomatic or paucisymptomatic (self-limiting back pain after low trauma), spine X-ray, aimed specifically at studying and searching for these complications, still remain the gold standard for VFs diagnosis. This is a low-cost exam and particularly relevant in patients with secondary forms of osteoporosis (as in acromegaly or glucocorticoid-induced osteoporosis), where bone mineral density is not able to predict the risk for fracture. Nonetheless, the patient is exposed to significant amount of ionizing radiations, making it not appropriate as a screening test in general population.

VF assessment consists of a qualitative (morphology, shape, spatial alignment, study of the vertebral plates) and quantitative (measurement of the anterior, posterior and middle vertebral wall height and their relationships) evaluation of the thoracic and lumbar vertebrae in a lateral scan. Before 1993, there was no clear definition of VF and different studies may have reported discordant results, even in the same setting of patients. Genant standardized VF definition, classifying it according to a 20-25, 25-40% or more than 40% reduction in vertebral height as mild, moderate and severe VF, respectively. To date, we have different radiological techniques to perform a vertebral morphometry examination, each characterized by several advantages and limitations that take into account the amount of radiation to which the patient is exposed, the costs of the examination and image quality/resolution. Furthermore, to overcome these possible weakness, vertebral morphometry could be performed even on radiological exams executed for other reason (e.g., anesthesiological).

An examination that offers a valid compromise between costs, radiological resolution, minimum radiation exposure, being also time-saving (as it is performed with the same tool for DEXA), is lateral spine DEXA scans, that was characterized by a similar sensitivity and specificity than spine X-rays.

Moreover, several studies in different settings (patients with heart failure accessing emergency department, GH and TSH-secreting adenomas, COVID-19 patients...) reported consistent data performing VF assessment on lateral chest X-ray images, executed for pulmonary and/or cardiac pathology. Consistently, some retrospective Chinese studies demonstrated the usefulness also of antero-posterior images to detect moderate and severe thoracic VFs, with no lower precision as compared to lateral scans. In this context, the exam with the highest radiological power is represented by MRI, which can date VF onset (recent with bone edema or inveterate) and make differential diagnosis with pathological fractures. However, it is characterized by high costs and spotted availability worldwide. Recently, artificial intelligence was proposed to help clinicians analyzing CT scans, but further study are needed to validate these first, preliminary results.

In conclusion, opportunistic evaluation for VFs possibly with the aid of AI on radiological images of the spine obtained for other reasons is suggested to be currently the ethically sound approach of choice for either epidemiological studies on the clinical burden of osteoporosis in the general population or clinical purposes as establishing the indication to bone protective treatments and assessing the bone status in high fracture risk groups.

NOVEL MECHANISMS OF OSTEOPOROSIS: INTERACTIONS OF MESENCHYMAL STROMAL CELLS WITH NEUTROPHILS AND MACROPHAGES INDUCE SENESCENCE

Laura Calvi, MD
Department of Medicine, School of Medicine and Dentistry - University of Rochester

Pre-clinical studies show that senescent bone marrow-derived mesenchymal stromal (a.k.a. stem) cells (MSCs) and osteolineage cells contribute to age-dependent bone loss and bone marrow failure. Therefore, the identification of novel mechanisms that accelerate MSC dysfunction could enable mechanistic approaches to degenerative processes that impact the skeleton. A handful of in vitro studies previously demonstrated MSCs' ability to phagocytose apoptotic cells (efferocytosis). Data will be presented to support this MSC activity as a mechanism inducing senescence and contributing to bone loss. MSCs indeed efferocytose apoptotic neutrophils in vivo. We also found that, in aged mice, efferocytosis by MSCs is significantly increased. Moreover, transcriptional and functional data suggest that excessive efferocytosis by MSCs decreases osteoblastic differentiation and promotes senescence. Since efferocytosis is accompanied by oxidative stress and mitochondrial changes, which we previously found to modulate osteoblastic differentiation, mitochondrial disruption may mediate functional changes in MSCs that clear high numbers of apoptotic cells. Defining the role of facultative phagocytosis/efferocytosis in metabolic changes and senescence in MSC and their relevance to human aging and disease will provide innovative, actionable strategies impacting degenerative disorders that target the skeleton.

FIBRODYSPLASIA OSSIFCANS PROGRESSIVA (FOP): NATURAL HISTORY AND THEURAPEUTIC HORIZONS

Robert J. Pignolo, MD, PhD
Department of Medicine, School of Medicine and Dentistry - University of Rochester

Mayo Clinic School of Medicine, Rochester Minnesota, USA

Fibrodysplasia ossificans progressiva (FOP, OMIM #135100) is an ultra-rare genetic disease characterized by congenital malformed first toes as well as episodic and progressive development of heterotopic ossification (HO). Classic FOP, reported in about 97% of cases, is due to an activating pathogenic variant (c.617G>A; p.R206H) in the glycine-serine (GS) activation domain of Activin A receptor type I (ACVR1)/Activin-like kinase 2 (ALK2) receptor, a bone morphogenetic protein (BMP) type 1 receptor. FOP patients with the less common pathogenic variants can have either a milder or more severe phenotype and can have variable or atypical features. The development of heterotopic bone is usually preceded by flare-ups, painful soft tissue swellings that can occur spontaneously or due to viral illness, trauma, or muscular overuse. These painful swellings occur in soft connective tissue including skeletal muscles, tendons, ligaments, fascia and aponeuroses, and usually present in the first decade of life. The development of HO is episodic, but the disability is cumulative and can progress in characteristic patterns, initially affecting the dorsal, axial, cranial and proximal regions of the body and later in the ventral, appendicular, caudal and distal regions, respectively. About 50% of patients report progression of their disease without a preceding flare-up. Individuals with FOP are usually wheelchair bound by the second decade of life and disease is associated with early mortality (median life expectancy of 56 years) due to cardiopulmonary causes. There are several comorbidities associated with FOP including severe scoliosis, thoracic insufficiency syndrome, recurrent pneumonias and right-sided heart failure. Individuals with FOP are at increased risk of fall, fractures, nutritional deficiencies and kidney stones. They are also at risk of lymphedema and recurrent pressure ulcers. Hearing loss is common, and many patients have chronic pain, accelerated osteoarthritis, menstrual abnormalities, alopecia, gastrointestinal and neurological symptoms. FOP has been described as a premature ageing syndrome. Multiple therapeutic targets have now been identified in FOP and several drugs are being investigated as potential therapies in current clinical trials.

Disclosures: RJP is a principal investigator on clinical trials for FOP sponsored by Ipsen/Clementia, Regeneron, and Incyte.

HYPOPHOSPHATASIA

Maria Luisa Brandi, MD,PhD
FIRMO Foundation, Florence and HSR,Milan, Italy

Hypophosphatasia (HPP) is an inborn error of metabolism caused by reduced or absent activity of the tissue non-specific alkaline phosphatase (TNSALP) enzyme, resulting from pathogenic variants in the ALPL gene. Clinical presentation of HPP is highly variable, including lethal and severe forms in neonates and infants, a benign perinatal form, mild forms manifesting in adulthood and odonto-HPP. Diagnosis of HPP remains a challenge in adults, as signs and symptoms may be mild and non-specific. Disease presentation varies widely; there are no universal signs or symptoms, and the disease often remains underdiagnosed or misdiagnosed, particularly by clinicians who are not familiar with this rare disorder. The absence of diagnosis or a delayed diagnosis may prevent optimal management for patients with this condition. Formal guidelines for the diagnosis of adults with HPP do not exist, complicating efforts for consistent diagnosis. To address this issue, the HPP International Working Group selected 119 papers that explicitly address the diagnosis of HPP in adults through a Medline, Medline In-Process, and Embase search for the terms “hypophosphatasia” and “HPP”, and evaluated the pooled prevalence of 17 diagnostic characteristics, initially selected by a group of HPP clinical experts, in eligible studies and in patients included in these studies. Six diagnostic findings showed a pooled prevalence value over 50% and were considered for inclusion as major diagnostic criteria. Based on these results and according to discussion and consideration among members of by the Working Group, were finally defined 4 major diagnostic criteria and 5 minor diagnostic criteria for HPP in adults. I suggested the integrated use of the identified major and minor diagnostic criteria, which either includes two major criteria, or one major criterion and two minor criteria, for the diagnosis of HPP in adults.

NON CLASSICAL OSTEOGENESIS IMPERFECTA

Canalis Ernesto
Department of Orthopaedic Surgery and Medicine and The Musculoskeletal Institute, UConn Health, Farmington, CT 06030

Osteogenesis Imperfecta (OI) is a heterogeneous group of inherited bone dysplasias affecting connective tissue. OI is caused by pathogenic allelic variants in COL1A1, COL2A1 and in genes that modify type 1 collagen post translationally or result in compromised collagen processing or cross-linking or in defective bone mineralization. In addition, pathogenetic variants of genes associated with abnormal osteoblast differentiation/function are associated with bone fragility and can be considered non classical forms of OI. Notch receptors play a significant role in bone remodeling and affect cells of the osteoblast and osteoclast lineages. Pathogenic variants of Notch receptors are known to be associated with a variety of monogenic disorders of the skeleton, including Hajdu Cheney and Alagille Syndromes, but they have not been associated with OI. A young child presented with a low trauma femoral fracture, and exome sequencing revealed a heterozygous mutation in exon 25 affecting the extracellular domain of NOTCH2. To gain an understanding of the disease, CRISPR/Cas9 technology was used to recreate the mutation in a *Notch2*^{em1Ecan} mouse model. Homozygous Notch2em1Ecan mutant mice were active, appeared healthy and weights and femoral length were not different from controls. μCT of the distal femur revealed a 25% decrease in trabecular bone volume and a substantial decrease in total, bone and marrow area, in periosteal and endocortical perimeters and in polar moment of inertia. This reveals that bones from *Notch2*^{em1Ecan} mice are small and fragile like those found in some forms of OI. Confocal microscopy using either polarization or backscatter second harmonic generation revealed no abnormalities in collagen fibers and procollagen chains isolated from osteoblast cultures did not reveal apparent alterations in collagen chains in *Notch2*^{em1Ecan} mutant cells suggesting an absence of collagen abnormalities. A structure homology model of NOTCH2 revealed that the mutation likely disrupts the local NOTCH2 structure and possibly affects NOTCH2-ligand interactions and activity. In conclusion, a novel NOTCH2 mutation is associated with small and fragile bones, and a phenotype consistent with OI.

XLH

Stefano Mora
Pediatric Endocrinology, Department of Pediatrics, San Raffaele Scientific Institute, Milan, Italy

X-Linked Hypophosphatemia (XLH) is a rare disorder of phosphate metabolism, and it is the commonest inherited form of rickets. The tight regulation of phosphate serum concentration is disrupted by an unbalanced synthesis of the hormone fibroblast growth factor 23 (FGF23), leading to reduced tubular reabsorption of phosphate, reduced renal 1α-hydroxylase activity, and increased renal 24-hydroxylase activity. Responsible for the disease are pathogenic variants of the PHEX gene, located on the short arm of the X chromosome (Xp22.11). To date, more than 700 variants have been reported, and all kind of molecular defects have been described.

Age-related hypophosphatemia associated with renal phosphate wasting, normal serum concentration of calcium, parathyroid hormone, and 25-hydroxy-vitamin D represents the main biochemical picture in affected patients. Patients with XLH have rickets and osteomalacia, and they often present severe deformities of the lower limbs, bone and muscular pain, and stunted growth. XLH is not an exclusively skeletal disease, but it is rather as a multisystemic disorder requiring multidisciplinary approaches in specialized subdisciplines. Severe complications may occur in patients with XLH including craniosynostosis, hearing loss, progressive bone deformities, dental and periodontal recurrent lesions, and psychosocial distress. Moreover, long-term conventional treatment may cause endocrinological complications such as secondary or tertiary hyperparathyroidism, and adverse events in kidney as hypercalciuria, nephrocalcinosis, and nephrolithiasis.

Treatment of XLH is classically performed by giving active vitamin D metabolites and oral inorganic phosphate salts. Although vitamin D is usually given as a single dose daily, inorganic phosphate requires multiple administration during the day and often during the night. Such treatment does not improve phosphate metabolism and it shows modest and slow effects in improving rickets lesions and linear growth. The use of a recombinant human IgG1 monoclonal antibody that targets FGF23 (burosumab) leads to a marked improvement of serum phosphate concentration and renal tubular reabsorption of phosphate. These findings are associated with a rapid healing of radiologic signs of rickets, reduced muscular and osteoarticular pain, and improved physical function.

Regardless of the kind of treatment, it is important to implement a global approach to the disease that includes the involvement of a multidisciplinary team of experts.

Disclosure: Alexion, Ascendis Pharma, Biomarin, Kyowa Kirin.

UPDATE IN GLUCOCORTICOID INDUCED OSTEOPOROSIS

Andrea Isidori
Department of Experimental Medicine, "Sapienza" University of Rome, Rome, Italy

Introduction: Glucocorticoid-induced Osteoporosis (GIO) is the third most common condition of pathological bone loss following post-menopause and aging, and is the most frequent cause of secondary osteoporosis. Glucocorticoids (GC) negatively impact all skeletal cell types, and most recent epidemiological data report a 5.1% annual incidence of vertebral fractures in GC initiators. Oral and infusional bisphosphonates, Teriparatide and, more recently, Denosumab are currently approved for the treatment of GIO, while other therapies such as Abaloparatide and Romosozumab are still under study. GC, however, are needed for physiological bone development and metabolism and adrenal insufficiency (AI) is also characterized by altered bone metabolism and increased risk of fractures. While data on conventional glucocorticoid replacement may be influenced by the heterogeneity of regimens, novel therapies such as modified-release hydrocortisone have shown a reassuring safety profile.

Methods: We studied patients with AI on short-acting, immediate-release GC therapy (hydrocortisone or cortisone acetate) before and up to 60 months after the switch to an equivalent dose of DR-HC, collecting data on bone turnover markers, femoral and lumbar spine areal bone mineral density (aBMD) and trabecular bone score (TBS). Any concomitant condition (hypo- or hyperparathyroidism, early menopause, malignancies) or medication (PTH, anti-resorptive therapy) that could influence bone parameters was considered as exclusionary.

Results: 31 patients (18 PAI and 13 SAI, 18 females, 9 post-menopausal) with a median age of 51 (range 20-77) years, were included. Patients on established immediate-release glucocorticoid therapy were switched to an equivalent dose of DR-HC at baseline. Median duration of AI at baseline was 36 months (range 12-432). Median daily hydrocortisone- equivalent doses before switching to DR-HC were 14.7 [12.0-17.3] mg/kg/m2 in PAI and 11.0 [10.1 – 13.2] mg/kg/m2 in SAI. Any other hormonal disorders (i.e. diabetes, hypothyroidism, hypogonadism, Growth Hormone deficiency) were adequately controlled throughout the study. All patients had normal calcium and phosphate levels and most were under cholecalciferol therapy, with mean Vit D 30.0 ± 13.2 ng/mL at baseline. At baseline, 48% of patients had aBMD values compatible with osteopenia and 16% had a diagnosis of osteoporosis in at least one site. Compared to baseline, no significant difference was observed in aBMD at femur neck, total hip and total lumbar spine at 24 (p= .825; p=.453; p=.637), 36 (p=.637; p=.460; p=.607), 48 (p=.202; p=.996; p=.379) and 60 months (p=.175; p=.528; p=.983) of DR-HC therapy. According to published data on the effects of aging on bone microarchitecture, TBS values decreased after 48 (p=.021) and 60 months (p=.032). Alkaline phosphatase, C-terminal telopeptide and osteocalcin levels showed no differences in all timepoints. Moreover, no differences were found between PAI and SAI patients in all the evaluated parameters. No osteoporotic or other fractures were reported during the study timeframe.

Conclusions: DR-HC is a valuable treatment option in terms of bone health in patients with AI, maintaining stable bone mass, bone quality and bone turnover while aging.

DETERMINANTS OF SKELETAL PHENOTYPE IN CHRONIC HYPOPARATHYROIDISM

Jens Bollerslev, MD; DMSc
Professor in Endocrinology
Faculty of Medicine, University of Oslo, Oslo, Norway

Chronic hypothyroidism in adults (HypoPT) is an orphan disease most often secondary to neck surgery, so far treated in an un-physiological manner either indirectly with Vitamin D, activated Vitamin D and Calcium supplements, or with daily injections of recombinant human parathyroid hormone (rhPTH), (available since 2015) (1, 2). Neither of these treatment modalities restore the normal action of PTH in target tissues. The PTH receptor is widely expressed in the body, including bone. PTH increase bone turnover by binding to its receptor, which for bone seems to be exclusively expressed on the formative side. Thereby, bone resorption is indirectly stimulated from the formative cells, among others by the RANKL/OPG/RANK system (3, 4).

With the inappropriately low PTH in HypoPT, bone remodelling and turn-over is low followed by an increased bone mass in most compartments, when evaluated by conventional osteodensitometry (DXA) (4). A high BMD is normally associated with increased bone strength and thus reduced fracture rate. However, a chronic low turn-over state, as in HypoPT may lead to over-mineralized bone tissue with compromised biomechanical properties, and thereby potentially increased fracture risk. Moreover, trabecular thickness and separation have been shown to be deteriorated in by various techniques. For cortical bone, porosity is decreased as expected in HypoPT, whereas the endosteal and periosteal surfaces are scarcely studied (5).

From a clinical point of view, fracture rate is the natural endpoint. So far fracture rate in HopoPT, being vertebral or appendicular has not been shown to be different from the background population. However, based on morphometry by Genant's method, some but not all studies have indicated a higher risk of more severe, or overall risk of vertebral fractures, as compared to the background population or normal controls (6, 7). However, careful register studies from Denmark did not demonstrate an increased risk of all fractures neither in Post-Surgical (8), nor in Non-Surgical HypoPT (9).

Long-term treatment with rhPTH (up to 12 years) seems to be safe and to maintain skeletal integrity (5). Upcoming new and potentially more physiological treatment modalities seems promising (10), at least from a safety perspective. The long-term skeletal outcomes are however so far unknown.

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HYPOPARATHYROIDISM: RENAL COMPLICATIONS

Lars Rejnmark, MD, PhD, DMSc
Professor in Endocrinology
Dept. of Endocrinology and Internal Medicine, Aarhus University Hospital and Department of Clinical Medicine, Aarhus University, Denmark

Chronic hypoparathyroidism (HypoPT) is associated with a high risk of impaired kidney function compared with the general population. The disease is associated with an increased renal calcium excretion causing hypercalciuria, which has been suggested as an explanation for nephrolithiasis and nephrocalcinosis often encountered in HypoPT. However, although this may impair kidney function, studies have so far not shown the reduced kidney function in HypoPT to be unequivocally attributable to hypercalciuria or renal calcifications. A case-control study showed renal diseases in HypoPT was associated with episodes of hypercalcemia, a high calcium-phosphate produce and a long disease duration. In addition, parathyroid hormone (PTH) may by itself affect renal function. In primary hyperparathyroidism, patients with initial normal kidney function who have lowering of PTH levels following parathyroidectomy have been shown to have a decline in kidney function despite normalization of calcium levels. In HypoPT, observational studies have suggested beneficial effects on kidney function of treatment with rhPTH(1-84) compared with conventional therapy (calcium supplements plus active vitamin D). A PTH analogue with a long duration of action is currently being develop (palopegteriparatide) and has been shown to lower urinary calcium in clinical trials with HypoPT patients. Long-term experiences are not yet available, but a beneficial effect on kidney health can probably be expected from PTH treatment of HypoPT.

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QUALITY OF LIFE IN PATIENTS WITH HYPOPARATHYROIDISM

Heide Siggelkow MD PhD
MVZ Endokrinologikum Göttingen, Göttingen, Germany
Clinic of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center Göttingen, Göttingen, Germany

Patients with hypoparathyroidism (HypoPT) on conventional therapy with calcium and active vitamin D often suffer from physical, mental, or emotional symptoms, even when their calcium values are within the target range recommended for this disease. Multiple studies have shown reduced Quality of life (QoL) in patients with hypoPT. When using standard validated instruments such as the Short Form Health Survey (SF-36), QoL in HypoPT is reduced and comparable to or lower than scores in patients with other chronic diseases, such as heart disease, hematologic disorders, diabetes, and cancer. However, comparing HypoPT patients to healthy population may be suboptimal due to presence of other impairments in HypoPT. Indeed, when comparing HypoPT patients to more suitable controls, such as those who had thyroidectomy but had preserved parathyroid function, the differences are still seen albeit less striking.

To date it is still debated whether the disturbed calcium homeostasis or rather PTH deficiency directly impairs QOL. With the development of PTH and its analogues for HypoPT, the question is whether QoL would improve with their use, since conventional therapy does not substitute the missing hormone. Open label trials from New York with PTH 1-84, and Italy with PTH 1-34 demonstrated an improvement in QoL during treatment with benefits occurring early and lasting through all 8 years of therapy studied to date. In contrast, QoL response to PTH in double-blind placebo-controlled studies has been less consistent with no improvement in a Danish study and some improvement in a multicenter registration trial REPLACE. Greater improvement in QoL was observed in patients with lower-baseline QoL scores and in those with greater reduction in calcium and calcitriol requirements in response to PTH.

One of the difficulties in assessing QoL in HypoPT may be lack of a disease specific instrument suitable for capturing the impairments HypoPT patients experience. In most of the studies the investigators used SF-36, which has been widely used and validated, but may not have enough sensitivity to detect the QoL deficiencies specific to HypoPT. In response, several groups have developed disease-specific instruments. Future studies are needed to demonstrate the effectiveness of these different tools to better understand the QoL in patients with hypoparathyroidism and to assess the effects of various pharmacologic therapies. A recent phase two trial on TransCon PTH-treated HypoPT patients demonstrated significant improvement in QoL even after short time treatment including specific QoL instruments. These are promising results by showing the effectiveness of specific tools to quantify QoL and that adaption of treatment may improve the complex symptoms in hypoparathyroidism.

NOVEL MOLECULES FOR THE TREATMENT OF HYPOPARATHYROIDISM

Aliya A. Khan MD
FRCPC, FACP, FACE, FASBMR
Professor Of Clinical Medicine
McMaster University - Hamilton, Canada

Treatment of hypoparathyroidism with conventional therapy consisting of active vitamin D and calcium has been associated with fluctuations in serum calcium, inadequate control of symptoms in addition to long term complications. (1) Recently PTH and PTH analogue therapy has been shown to lower the pill burden, improve quality of life and in some studies was shown to lower urine calcium as well as serum phosphate and is a welcome addition to therapeutic options in hypoparathyroidism. (1)

Novel molecules are also being evaluated in hypoparathyroidism. This presentation will review data from the phase 2 trial with Eneboparatide and the phase 2 trial with Encalaret in Autosomal Dominant Hypocalcemia type 1(ADH1).

An orally administered agonist of the PTHR1 PCO371 molecule was being evaluated for the treatment of hypoparathyroidism. However due to increases in liver enzymes the study was terminated. (2)

Eneboparatide (AZP-3601) is a parathyroid hormone receptor 1 (PTHR1) agonist with a novel mechanism of action being developed as a replacement therapy for hypoPT. This molecule targets the R0 conformation of the PTH receptor and induces long-acting effects.

It also enhances renal calcium reabsorption. Phase 2 data will be presented (3)

Encaleret a calcilytic molecule is being developed for ADH1 which results from gain of function mutations in the CaSR gene. Data from phase 2 studies will be presented (4) demonstrating normalization of serum calcium while off all supplements as well as normalization of urinary calcium with encalaret dosing in ADH1.

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PRIMARY HYPERPARATHYROIDISM: NEW CONCEPTS AND NEW GUIDELINES

John P. Bilezikian, MD, PhD (hon)
Silberberg Professor of Medicine, Vice-Chair Department of Medicine for International Education and Research Vagelos College of Physicians and Surgeons - Columbia University

Since the proceedings of the 4th international workshop on the evaluation and management of primary hyperparathyroidism (PHPT) were published, in 2014, advances in many aspects of this disease led to the fifth international workshop, 2020-2022. About 100 international experts in the parathyroid diseases convened virtually, over a 2-year period, to review new information that has become available over the past decade. Workshop participants addressed in Four Task Forces the following aspects of PHPT: epidemiology, genetics, physiology, pathophysiology, clinical presentations, new imaging modalities, target and other organ systems, diagnosis, pregnancy, evaluation, management, and outcomes. A summary statement incorporated the conclusions of all four task forces and revised guidelines for evaluation and management of this disease.

We recognized three phenotypes of PHPT: symptomatic, asymptomatic, and normocalcemic. Among those with hypercalcemic and normocalcemic forms of asymptomatic PHPT, we acknowledged that after evaluation, some individuals will have evidence for target organ involvement (e.g., skeleton and/or kidney) while others will not. Thus, we can consider those with asymptomatic or normocalcemic PHPT as either having or not having target organ involvement.

After the diagnosis has been established, all patients should be further evaluated with a measurement of 25-hydroxyvitamin D. The serum phosphorus concentration and bone turnover markers can be helpful. Skeletal imaging with 3-site dual energy X-ray absorptiometry (DXA: lumbar spine, hip, and distal 1/3 radius) is an essential component of the evaluation. Based upon the need for additional information about the skeleton, another vertebral imaging modality such as X-Ray, vertebral fracture assessment or trabecular bone score) should be done. Evaluation of the kidney starts with an accurate measure of creatinine clearance and 24-hour urinary calcium. A urinary stone risk profile may be indicated. An assessment of renal calcifications or silent nephrolithiasis requires non-invasive imaging, either by abdominal X-ray, ultrasound, or CT. Since non-classical manifestations of PHPT are still controversial, we do not recommend specific evaluation of neurocognitive, quality of life, or cardiovascular aspects.

Parathyroidectomy should be recommended in anyone with symptomatic PHPT, defined as overt complications of the skeleton (e.g., fractures) or kidneys (e.g., kidney stones). Surgery can also be recommended in anyone with the diagnosis, even if they do not meet surgical criteria, and in whom there are no contraindications.

Any one of the following criteria meets the revised guidelines for a recommendation of parathyroid surgery:

a. hypercalcemia > 1 mg/dL (> 0.25 mmol/L) above normal.

b. T-score (≤ -2.5 at lumbar spine, total hip, femoral neck, or distal 1/3 radius) or a fracture by VFA or vertebral X-ray;

c. creatinine clearance < 60 cc/min; nephrocalcinosis or nephrolithiasis; hypercalciuria (> 250 mg/day in women; > 300 mg/day in men).

d. Age, < 50.

The workshop participants evaluated the evidence for normocalcemic PHPT, an increasingly frequent phenotype of this disease. While it is clearly a recognizable entity, there are not sufficient data, at this time, to recommend the aforementioned guidelines in those with normocalcemic PHPT. However, the guidelines for hypercalcemic PHPT can be a useful guide in this newer form of PHPT.

Preoperative imaging is important to conduct when the decision for surgery is made. Popular parathyroid imaging modalities include ultrasound, technetium-99m-sestamibi subtraction scintigraphy, and contrast-enhanced 4D-CT. The decision as to which parathyroid imaging test to use depends upon the local experience. At Columbia and many other centers in the United States, contrast-enhanced 4D-CT is the procedure of choice.

Parathyroid surgery should be performed by an experienced parathyroid surgeon, defined as someone who performs at least 50 parathyroidectomies per year. The success rate of these experienced parathyroid surgeons is over 95%. Intraoperative measurement of the parathyroid hormone is helpful in ascertaining the complete removal of all overactive parathyroid tissue. The post removal PTH level will typically fall by over 50% into the normal range within 10 minutes after parathyroidectomy.

In those who meet criteria for parathyroid surgery but in whom surgery is not to be performed, pharmacological management can include cinacalcet to lower the serum calcium. Alendronate or denosumab can be used to increase bone mineral density.

In those who are not going to have parathyroid surgery, annual measurements of the serum calcium, PTH, and 25-hydroxyvitamin D are recommended. Yearly or every 2-year assessment by DXA is recommended with other spine imaging as clinically needed. Yearly assessment of renal function (creatinine clearance or eGFR) with renal imaging as clinically indicated is also recommended. In those who develop any criterion for surgery during monitoring, they should be recommended for surgery, if there are no contraindications.

Nutritional guidelines include calcium and Vitamin D according to local or national guidelines. Recommendations in the United States for this disease are for the 25-hydroxyvitamin D level to be maintained > 30 ng/mL (> 75 nmol/l). Calcium intake should be between 1,000 and 1,200 mg, preferably from food sources. Calcium supplements are used only to supplement.

The deliberations, conclusions, and guidelines of the 5th International workshop on Primary Hyperparathyroidism were published in 8 papers in the November, 2022, issue of the Journal of Bone and Mineral Research.

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DIAGNOSTIC CRITERIA for SARCOPENIA

Lorenzo M Donini, Francesco Frigerio, Eleonora Poggiogalle
Department of Experimental Medicine, Sapienza University, Rome (Italy)

In 1989, IH Rosenberg proposed the term 'sarcopenia' (Greek 'sarx' or flesh + 'penia' or loss) to describe this age-related decrease of muscle mass. The European Society for Clinical Nutrition and Metabolism (ESPEN) defined sarcopenia as a syndrome of its own characterized by the progressive and generalised loss of skeletal muscle mass, strength and function (performance) with a consequent risk of adverse outcomes. Sarcopenia can be classified as "primary" (no causes other than aging) or "secondary" [activity-related (due to e bedridden state or weightlessness), disease-related (due to severe organ dysfunction, inflammatory disease or malignant tumor), nutrition-related (due to protein and energy deficiencies associated with malabsorption, gastrointestinal.disease and /or medication)].

Currently, no general consensus exists on the definition of muscle mass depletion, partly due to diverse measurement tools in assessing skeletal muscle mass and conceptual confusion between the disease or condition related to low muscle mass and frailty.

Moreover imaging technologies (CT and MRI), are precise and valid but cannot be used in general population because of high cost and lack of feasibility. Most operational definitions of low muscle mass have been assessed by dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). However, DXA and BIA have limitations in assessing muscle mass.

Fat-free mass (FFM) assessed by DXA or BIA is a heterogeneous compartment that consists of muscle and connective tissues. It does not correctly reflect muscle mass with increasing age, advancing body fat mass or disturbance of hydration in FFM such as chronic heart and renal failure.

Different diagnostic criteria have been proposed considering muscle mass, muscle strength, impaired physical performance.

	Reduced Muscle Mass	Reduced Muscle Strength	Impaired physical performance
ESPEN (2010)	Yes	No	Yes
EWGSOP (2010-2019)	Yes	Yes	Yes
International Working Group on Sarcopenia (2011)	Yes	No	No
Soc of Sarcopenia Cachexia & Wasting Disorders (2011)	Yes	No	Yes
Asian Working Group for Sarcopenia (2013)	Yes	Yes	Yes
Nat Inst of Health Sarcopenia Project (2014)	Yes	Yes	Yes

At the moment the most accredited algorithm for the diagnosis seems to be the one proposed in 2018 by the European Working Group on Sarcopenia in Older People (EWGSOP). It is based on a 4 steps procedure

1. Find-cases: using the SARC-F questionnaire or clinical suspicion to find sarcopenia-associated symptoms.

2. Assess: using grip strength or a chair stand measure with specific cut-off-points for each test.

3. Confirm: by detection of low muscle quantity and quality, DXA is advised in clinical practice, and DXA, BIA, CT or MRI in research studies.

4. Determine Severity: by performance measures; gait speed, SPPB, TUG and 400-m walk tests can be used.and characterise sarcopenia.

CLINICAL IMPLICATIONS OF OSTEOSARCOPENIA

Elaine M Dennison
MRC Lifecourse Epidemiology Centre, Southampton SO16 6YD

Osteosarcopenia refers to the coexistence of osteoporosis (OP) and sarcopenia (SP). The concept was introduced to acknowledge the co-existence of OP and SP in older adults and recognises common risk factors for OP and SP and the muscle-bone unit. It has been hypothesised that a combination of OP and SP may place the individual at higher risk of falls, fractures and institutionalisation - the so-called 'hazardous duet'. A number of definitional approaches have been recommended, and this presentation will consider these. Clearly the prevalence of the condition will vary according to the approach taken, but previous studies have suggested that the prevalence of osteosarcopenia ranges in community-dwelling older adults from 5-37% in those aged ≥65 years with the highest rates observed in those with fractures (low-trauma fracture: ~46%; hip fracture: 17.1-96.3%). The condition is more common with advancing age, low BMI and reduced physical activity. It has been associated with an increased risk of falls, and increased mortality, and is linked with many comorbidities including type 2 diabetes and other risk factors of cardiovascular disease and renal dysfunction. Increased activity (weight bearing and resistance exercise) has been promoted as a possible therapeutic approach, while possible future therapeutic targets include myosin, irisin and TGF beta.

Disclosure information

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DUCHENNE MUSCULAR DYSTROPHY

Giovanni Iolascon
Full Professor of Physical Medicine and Rehabilitation- University of Campania "L. Vanvitelli"

Muscular dystrophy is a group of genetic disorders characterized by progressive weakness and loss of muscle mass. Among the best-known forms is Duchenne Muscular Dystrophy (DMD), which is a rare X-linked neuromuscular disease, affecting approximately 1 in 6,000 live male births and is characterized by progressive muscle weakness, leading to loss of independent ambulation at age 13. This disabling condition has several consequences for musculoskeletal health, including a reduction in bone density and strength and an increased risk of fragility fractures. Bone loss in people with DMD depends on mechanical and biochemical mechanisms. Muscle weakness and progressive loss of mobility are the main culprits for poor mechanical stimulation of bone tissue. Chronic muscle inflammation, observed in these patients, negatively affects the signaling pathways that modulate muscle-bone cross talk. Several cytokines (i.e. interleukin-6, leukemia inhibitory factor), osteokines (i.e. osteopontin) and myokines (fibroblast growth factor 21, FGF21) are upregulated in DMD patients contributing to bone loss. Furthermore, destabilization of the dystrophin-associated protein complex (DAPC) and structural changes in the elastic properties of myotendinous junctions reduced the transmission of force and mechanical stimuli to bone tissue.

TERIPARATIDE AND ABALOPARATIDE

Salvatore Minisola
"Sapienza" Rome University

Medications used to reduce the risk of osteoporosis related fractures are traditionally classified as antiresorptive agents (they suppress osteoclast mediated bone resorption) or anabolic therapies. Anabolic treatment for osteoporosis is able to stimulate bone formation, inducing large increases in bone mass and improving both cortical and trabecular architecture. Previous studies have shown the superiority of anabolic therapy over bisphosphonates in reducing fracture risk; therefore, these agents should be initially chosen for the treatment of patients at very high risk of fracture.

Teriparatide and abaloparatide were the first anabolic agents marketed. They both stimulate parathyroid hormone receptor 1. Teriparatide is a synthetic peptide composed of the first 34 amino acid of parathyroid hormone. Abaloparatide is a synthetic analogue of the first 34 amino acids of parathyroid hormone related peptide with 8 amino acid substitutions in the 20-34 region.

In phase 3 clinical trials, treatment with teriparatide and abaloparatide resulted in significant mean percent difference from placebo both at the lumbar spine (8.6 and 10.4, respectively) and total hip (3.6 and 4.3%, respectively). There was a significant vertebral and non-vertebral fracture risk reduction with both teriparatide and abaloparatide. A meta analysis of clinical trials carried out with teriparatide supports an effect of this agent also on hip fractures risk reduction.

In the Active trial teriparatide and abaloparatide were directly compared. Bone mineral density increases were greater with abaloparatide than with teriparatide. The effect of abaloparatide on major osteoporotic fractures (78% reduction) was significantly greater than that seen with teriparatide (23% reduction, p= 0.007).

Both teriparatide and abaloparatide are well tolerated with very few side effects being reported, among which are orthostatic hypotension, dizziness and nausea. Incidence of hypercalcemia has been reported to be higher with teriparatide than with abaloparatide.

Since osteoporosis is a chronic condition, the availability of anabolic drugs with different mechanism of action give us the possibility of extending the period of therapy with sequential schedule. Furthermore, owing to their peculiar mechanism of action, anabolic regimens represent the first line treatment in patients at very high risk of fracture.

ROMOSOZUMAB UPDATE

Serge Ferrari, MD
Service of Bone Diseases, Department of Medicine, Geneva University Hospital, Switzerland

Romosozumab (Romo), a monoclonal anCbody against sclerosCn, is a biological treatment of severe osteoporosis with a unique mode of acCon, namely a bone-forming together with an anC-resorpCve effect. It has been shown to reduce vertebral and clinical fractures from the first year of therapy as compared to both placebo and alendronate, and further to reduce all fracture types in high risk paCents when sequenced by an anC-resorpCve drug. Recent comparison between Romo followed by denosumab vs denosumab alone for two years from the FRAME study shows a significant reducCon of vertebral fractures in the Romo-first arm. As compared to teriparaCde, Romo significantly improves vertebral and hip BMD, both in the trabecular and corCcal compartments. Recent analyses using 3D reconstrucCons from 2D DXA at hip (3D-shaper) further illustrate the beneficial effects of Romo on hip corCcal thickness and sBMD. However Romo effects on BMD are less when started aQer another osteoporosis drug, parCcularly aQer denosumab, probably since the bone turnover rebound aQer the laRer is only parCally prevented by Romo. With regards to its cardiovascular safety, accumulaCng experimental evidence points towards a role of sclerosCn in relaCon to vascular calcificaCons and atheroscleroCc plaque stabilizaCon, however it remains unsure whether the treatment should be avoided in such paCents but in absence of a prior MI or stroke.

UPDATE ON BONE TARGETED THERAPIES: DENOSUMAB

Socrates Papapoulos
The Leiden Center for Bone Quality, Leiden University Medical Center, The Netherlands
Department of Medical Research, 251 Hellenic Air Force and VA General Hospital, Athens, Greece

Denosumab (Dmab), a human monoclonal antibody that binds with high specificity Receptor Activator of Nuclear Factor kappa B ligand (RANKL), reduces osteoclast number and activity, and thereby decreases bone resorption. In the 7-year extension of the pivotal 3-year placebo-controlled clinical trial (FREEDOM) in women with osteoporosis, Dmab treatment increased BMD at both the spine and the hip to levels within the range of osteopenia in a substantial number of patients, reduced further the risk of fractures while the incidence of rare but serious adverse events (osteonecrosis of the jaw and atypical femur fractures) was very low. An analysis employing the virtual twin model, which uses the information obtained during the placebo-controlled phase of the trial to model fracture incidence if placebo was continued for 10 years, demonstrated a continuous positive benefit/risk ratio in postmenopausal women at risk of fractures. Notably and differently from other antiresorptive therapies, mean BMD continued to increase significantly at each time point measured during the Extension, for cumulative 10-year gains of 21.6% and 9.1% at the lumbar spine and total hip, respectively, from the FREEDOM baseline. The mechanism(s), however, responsible for the continuous increase in BMD still need to be determined. These data demonstrated that Dmab treatment for up to 10 years is associated with persistent reductions of bone turnover markers, continued BMD gains without therapeutic plateau, low fracture incidence, and a favorable benefit/risk profile in an aging population of women with postmenopausal osteoporosis. Dmab has also been shown to improve BMD in men with osteoporosis and in patients with glucocorticoid-induced osteoporosis; in addition, it has been investigated, in a different dosing schedule, in the management of patients with metastatic bone disease, which is characterized by RANKL-induced focal osteoclastic bone resorption and was found to reduce the incidence of skeletal-related events in patients with multiple myeloma, prostate, breast, and other solid cancers. A clinically important area of current investigation is the clarification of the pathophysiology and, consequently, the design of optimal management of the transient rebound in bone turnover associated with rapid bone loss and increased risk of vertebral fractures that follows discontinuation of Dmab therapy.

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INTEGRATIVE BIOLOGY OF BONE

Clifford J. Rosen
Maine Health Institute for Research

There is now indisputable evidence that bone is an endocrine tissue. Several components of the skeleton, osteoblasts, osteocytes, and marrow adipocytes, are responsible for whole body homeostasis. For example, during remodeling and bone resorption, osteocalcin, produced by osteoblasts and stored in the matrix, is released to modulate insulin sensitivity, brain function and gonadal status. Osteocytes make sclerostin which can regulate adipose tissue function in an endocrine fashion and bone turnover in a paracrine manner. FGF-23 is also generated by osteocytes and it regulates phosphate homeostasis, vitamin D and PTH. Independent of those hormonal modulators, the bone marrow also can mediate responses to many stresses, both environmental and nutritional. Emerging evidence supports the role of bone marrow adipose tissue in a regulatory circuit that also modulates metabolic homeostasis. Adiponectin, an insulin sensitizing hormone, regulated by PPARG activation, is produced by bone marrow adipose tissue during calorie restriction, and in the clinical syndrome of anorexia nervosa. Adipsin, the first adipokine described, when produced by peripheral adipocytes circulates and is associated with age and obesity, in a manner analogous to leptin. During calorie restriction in mice and humans, or with aging, adipsin is also produced and secreted by marrow adipocytes. In a paracrine manner it suppresses osteoblast differentiation, while at the same time promoting marrow adipogenesis in a feed forward manner. In those conditions, circulating adipsin is unchanged, in contrast to obesity. It is likely that there are other systemic mediators regulating insulin sensitivity and lipid metabolism, but these are yet to be discovered. Taken together, the skeleton is the largest endocrine organ in the body, excepting adipose tissue.

Dr. Rosen has nothing to disclose.

HOT TOPICs

GENETIC ACTIVATION OF GLYCOLYSIS IN OSTEOBLASTS PRESERVES BONE MASS IN TYPE I DIABETES

Xing Ji[1], Rebecca Seeley[1], Ke Li[1], Fangfang Song[1], Xueyang Liao[1], Chao Song[1], Marco Angelozzi[1], Yu Shi[1], Wen-Chih Lee[1], Arianna Valeri[1], Tyler Marmo[1], Fanxin Long[1,2]

[1]Translational Research Program in Pediatric Orthopedics, Department of Surgery, The Children's Hospital of Philadelphia, Philadelphia, PA

[2]Deaprtment of Orthopedic Surgery, University of Pennsylvania, Philadelphia, PA

BACKGROUD:

Mounting evidence indicates that diabetes is associated with increased bone fracture risks. As most studies show that both bone formation and resorption are suppressed in diabetic patients, bone anabolic therapies are likely needed for effective treatment of diabetic bone frailty. The current options, however, are limited; there remains an unmet need for safe anabolic therapies to combat diabetic bone frailty especially in children. Recent studies have demonstrated that osteoblast metabolism particularly the glycolysis flux is highly attuned to bone anabolic needs in response to paracrine and endocrine signals. Potential metabolic defects in osteoblasts could contribute to diabetic osteopenia but have not been demonstrated to date.

OBJECTIVES:

1) To demonstrate potential defects in glucose metabolism in the bones of diabetic mice; 2) To deterimine the effect of insulin deficiency and hyperglycemia, the two hallmarks of T1D, on glucose metabolism in osteoblasts; 3) To test whether osteoblast-specific activation of glucose metabolism prevents osteopenia in T1D mice.

METHODS:

We have used the Akita mouse as a T1D model. Akita mice harbor a single nucleotide mutation in the Ins2 gene. The heterozygous male Akita mice in the C57BL6 background develop clear diabetes by 4 weeks and offer an advantageous choice for studying the effects of hypoinsulinemia and hyperglycemia. In vivo glucose tracing with stable isotope is used to compare the metabolic flux rates of glucose in bone between normal and T1D mice. Seahorse technology is used to detect the rates of oxidative phosphorylation and glycolysis in osteoblasts. Single-cell RNA-seq is used to detect gene expression changes in bone marrow stromal cells. Tissue-specific knockout of insulin receptor is used to assess the contribution of hypoinsulinemia to bone loss. Transgenic overexpression of Pfkfb3 is used to activate glycolysis in the bones of T1D mice.

RESULTS:

T1D in Akita mice suppresses bone formation resulting in a rapid loss of both cortical and trabecular bone. Single-cell RNA sequencing uncovers metabolic dysregulation in bone marrow osteogenic cells of the diabetic mice. In vivo stable isotope tracing reveals impaired glycolysis in diabetic bone that is highly responsive to insulin stimulation. Deletion of the insulin receptor reduces cortical but not trabecular bone. Activation of glycolysis by Pfkfb3 overexpression preserves both trabecular and cortical bone mass in the face of diabetes.

CONCLUSIONS:

Defective glucose metabolism in osteoblasts is a pathogenic mechanism for osteopenia in T1D. Boosting osteoblast glycolysis can be explored as a potential anabolic therapy.

EFFECTS OF A KETOGENIC DIET ON THE PROGRESSION OF OSTEOARTHRITIS IN OBESE MICE - ARTICULAR, METABOLIC AND EPIGENETIC CHARACTERIZATION

Thomas Solé[1,2], Sara Delon[1], Margaux Digonnet[1], Asmaa El Maarbani[1], Souad Nasser[3], Nathalie Vega[3], Emiline Groult[4], Jérôme Lafont[4], Thierry Thomas[1,2], Laurence Vico[1], Luciano Pirola[3], Maura Strigini[1]

[1]Université Jean Monnet Saint-Étienne, Mines Saint Etienne, INSERM, SAINBIOSE U1059, F-42023, SAINT-ÉTIENNE, FRANCE; [2]University Hospital CHU Saint-Etienne, France; [3]INSERM U1060 CARMEN and UCBL1 Lyon, Lyon, France; [4]LBTI UMR5305, CNRS and UCBL1 Lyon, Lyon, France

Background

In obese individuals, osteoarthritis (OA) incidence is increased by low-grade metabolic inflammation, a damaging adipokine profile and weight-related joint overload. A ketogenic diet (KD) can induce weight-loss, decrease metabolic inflammation and increase the circulating levels of the ketone body beta-hydroxybutyrate (BHB). BHB is a putative histone deacetylase (HDAC) inhibitor, a class of molecules known to slow-down OA progression in in vitro and in vivo model. KD could thus be beneficial in obesity-linked OA treatment.

Objectives

We want to determine the extent to which a ketogenic diet can limit osteoarthritis progression in a murine model of obesity compounded OA and to understand the accompanying epigenetic changes.

Material and Methods

We induced obesity by a high fat diet (HFD) in mice and OA by medial meniscus destabilization, then we fed mice one of three diets ad libitum: HFD; KD; Standard Diet (STD) for 8 weeks. Disease progression was evaluated by OARSI score on knee paraffin sections, microCT analysis of peri-articular bone and RT-PCR. We analysed histone modifications by Western blots.

Results

BHB levels increased tenfold in KD group only. Glycemia remained high in HFD mice, but decreased in STD and even more in KD ($p< 0,001$). HFD mice continued gaining weight, while STD and KD lost weight. OA progression was particularly slowed down in KD: MMP13 expression in cartilage was two-fold lower in KD compared to HFD ($p=0.005$) and to STD ($p=0.02$); osteophytes were smaller (HFD: 101247 AU; STD: 61863 AU; KD: 4325 8AU, $p< 0.001$); severe OA cases (OARSI score>2.5) were less frequent (HFD>STD>KD, $p=0.037$).

KD increased histone beta-hydroxy-butyrylation of peripheral tissues, with no obvious effect on histone acetylation.

Conclusion

KD has a moderate beneficial effect on OA progression in our murine preclinical model. Modulation of the novel histone modification beta-hydroxy-butyrylation, but not acetylation, may contribute to the beneficial effects of KD on obesity-linked OA.

EXPLORING THE EFFECTS OF THE ILEAL ENTEROKINE FGF19 ON BONES AND BONE CELLS IN PRECLINICAL OSTEOSARCOPENIA MODELS

Hao Zhang[1], Priyanka Garg[1], Bérengère Benoit[2], Jérôme Ruzzin[3], Hubert Vidal[2], Laurence Vico[1], Maura Strigini[1]

[1]Université Jean Monnet Saint-Étienne, Mines Saint Etienne, INSERM, SAINBIOSE U1059, F-42023, SAINT-ÉTIENNE, FRANCE; [2]INSERM, U1060 CARMEN, Lyon, France; [3]University of Oslo, Norway

Background

Osteoporosis and sarcopenia, often coupled, are common diseases for the elderly. No efficient treatment is currently available to protect against muscle and bone wasting and associated morbidity. Inter-organ communication, via myokine, osteokine and other long-range acting molecules is crucial to musculoskeletal physiology. The fibroblast growth factor 19 (FGF19), member of the atypical endocrine subfamily of FGFs, produced by ileal enterocytes, significantly increases skeletal muscle mass and improves muscle wasting when injected in different experimental sarcopenia mouse models (Benoit et al 2017).

Objectives

We want to determine the action of FGF19 on bone in an osteosarcopenia mouse model (aging) and to determine if FGF19 can signal directly to bone cells.

Material and Methods:

22-month old mice were injected with FGF19 (0.1mg/kg) or vehicle daily for 3 weeks (n=32); bone femur microarchitecture was assessed by micro-Computed Tomography (microCT) at 10.5 µm isotropic cubic resolution. Bone cell lines or mouse primary cells were differentiated into osteoblasts or osteoclasts under different FGF19 concentrations (0, 0.5, 5 or 50 ng/ml) and their differentiation assessed by enzymatic activity (ALP or TRAP) and RT-PCR.

Results

FGF19 injections in aged mice has known anti-sarcopenic activities. microCT analysis of bones from new experiments show a clear increase in the bone cross-sectional area of treated mice measured at the femur distal metaphysis (median: Veh.: 3.4 mm2; FGF19: 3.7 mm2, P=0.006), confirmed by 2D slice by slice analysis, suggesting a beneficial effect on bone. On the other hand, FGF19 also decreases cortical thickness and increases cortical porosity, which may undermine the extent of a positive biomechanical impact. Trabecular bone and mid-cortical bone are not affected. No effect on osteoblasts and a non-significant decrease in osteoclast number (p=0.06) can be seen by histomorphometry of femur sections.

For osteoblasts and osteoclasts, there is no difference in ALP or TRAP activity, respectively, or marker gene expression, regardless of the FGF19 concentration.

Conclusion

In aged mice, FGF19 injections improve not only muscle physiology but also increase bone cross-sectional area at femur distal metaphysis, suggesting a potential as an anti-osteosarcopenia agent. At the cellular level, a direct effect of FGF19 on bone cells remains to be shown. Positive impacts of FGF19 on bone may be indirect and secondary to muscle effects.

THE CHALLENGES OF A POLYOSTOTIC FIBROUS DYSPLASIA CASE WITH MILD HYPERPARATHYROIDISM AND A NEUROENDOCRINE TUMOR OBSERVATION

Diana-Elena Niță[1], Nicoleta Chelaru[1], Diana-Cristina Andrei[1], Cristina Preda[1,2], Maria-Christina Ungureanu[1,2]

1- "Sf. Spiridon" Hospital, Iași, Romania – Endocrinology Department

2- "Grigore T. Popa" University of Medicine and Pharmacy, Iași, Romania

Background

Polyostotic fibrous dysplasia is a rare skeletal condition where the normal bone tissue is replaced with fibrous tissue with high risk of fracture. The association with hyperparathyroidism can be sporadic or it can be part of the McCune-Albright syndrome, being a challenge in terms of diagnosis and treatment.

Objective: We present the case of a 39-year old patient, underweight, being followed in the Endocrinology Department for approximately 10 years, diagnosed with polyostotic fibrous dysplasia (lesions of the femur and the tibia on MRI) and hyperparathyroidism.

Case report

Laboratory results show high-normal levels of PTH, with normal calcium levels and hypocalciuria. The scintigraphic parathyroid imaging performed three times didn't show any parathyroid adenoma. The patient had no densitometric diagnosis of osteoporosis but was treated for a few years with bisphosphonates to prevent the possible fractures that are expected in a fibrous dysplasia, constantly monitoring the bone turnover markers. The clinical examination shows a low BMI and one small café au lait spot on the right leg. Genetic test for McCune-Albright syndrome is on pending at the moment. During the numerous evaluations in the Endocrinology department, the laboratory results revealed high levels of neuroendocrine tumor markers (chromogranin, serotonin and gastrin) without any signs or symptoms. The patient run multiple imaging tests, the whole-body scintigraphic evaluation with Tektrotyd identifies a retrohepatosplenic nodular fixation area, without any change in the numerous CT scans or at the capsule endoscopy. The last CT exam describes a pulmonary nodule in the lower left lobe of 7.2/6 mm, stationary compared to the previous evaluation, an observation of right parathyroid hyperplasia and multiple osteolytic areas on the left ischiopubic ramus and left femur.

Conclusions

The fibrous dysplasia diagnosis and the association with hyperparathyroidism with no osteoporosis or fracture history, the suspicion of neuroendocrine tumor based on high levels of neuroendocrine tumor markers, but with no clinical expression or imaging findings, represent a challenge for the clinician that needs increased attention and constant follow-up of the patient in order to make the right medical decisions.

Disclosure of interest: None declared.

TRABECULAR BONE SCORE, BONE MARROW FAT AND VERTEBRAL FRACTURES IN CUSHING'S SYNDROME PATIENTS

F. Ferraù[1,2], S. Giovinazzo[1], Y. Alessi[2], A. Catalano[3], A. Tessitore[4], E. Mormina[4], F. Bellone[3], G. Giuffrida[1], G. Paola[2], O.R. Cotta[2], M. Ragonese[1,2], F. Granata[5], A.G. Lania[6,7], G. Mazziotti[6,7], S. Cannavò[1,2]

[1]Department of Human Pathology of Adulthood and Childhood "G. Barresi", University of Messina, Italy; [2]Unit of Endocrinology, "G. Martino" University Hospital, Messina, Italy; [3]Department of Clinical and Experimental Medicine, University of Messina, Italy; [4]Neuroradiology Unit, Radiology Department "G. Martino" University Hospital, Messina, Italy; [5]Department of Biomedical, Dental, Morphological and Functional Imaging Sciences, University of Messina, Italy; [6]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy; [7]Endocrinology, Diabetology and Andrology Unit, Metabolic Bone Diseases and Osteoporosis Section, IRCCS Humanitas Research Hospital, Rozzano (MI), Italy

Background

Evaluation of skeletal fragility in Cushing's syndrome (CS) is a clinical challenge. Glucocorticoid excess causes abnormalities in bone microstructure and increases the risk of fragility fractures that may occureven in presence of normal bone mineral density. Increased bone marrow fat (BMF) has been associated with prevalent VFs in Cushing syndrome (CS) patients. Trabecular bone score (TBS) provides information on bone microarchitecture and has been proposed as a predictor of fragility fractures.

Objectives

The aim of this study was to investigate the relationship between TBS, BMF and vertebral fractures in a cohort of CS patients.

Methods. Thirty subjects (7 M and 23 F, mean age 44.8±13.4 yrs, range: 25-71) with active hypercortisolism were evaluated for VFs by quantitative morphometry, BMD and TBS by lumbar spine DXA and BMF by single-voxel magnetic resonance spectroscopy of vertebral body of L3. Lumbar spine MRS was obtained by MRI acquisition with a 1.5-Tesla unit and BMD by a dual-energy X-ray absorptiometry (DXA) densitometer (Hologic Discovery); TBS was obtained from DXA images by iNsight software (version 3.0; Medimaps group, Geneva, Switzerland).

Results

CS patients with VFs (n=17) showed lower BMD in comparison with CS patients without fractures (P=0.012). The median TBS value was lower in patients with VFs in comparison with patients without VFs (1.2 Vs 1.4, P=0.004). Patients with VFs showed also higher BMF than the other ones (53 vs 22%, p=0.014). Prevalence of VFs resulted to be significantly higher in individuals with impaired TBS as compared to those with normal TBS (77.8% vs. 25.0%; P=0.008). Among patients with VFs, only 6 (35.3%) had either osteoporosis or "low BMD for age". In logistic regression analysis, impaired TBS maintained the significant association with VFs (P=0.042) independently of BMF (P=0.152).

Conclusions

Low TBS values is associated with BMF increase and VFs in CS patients. BMF and TBS should represent a predictors of bone health in CS patients. TBS might be more accurate than BMF in identifying subjects with active CS and skeletal fragility at risk of VFs.

FRAGILITY FRACTURES – AN EARLY, YET A LATE DIAGNOSTIC TOOL IN CUSHING'S DISEASE

Nicoleta Chelaru[1], Diana-Elena Niță[1], Diana-Cristina Andrei[1], Daniel Rotariu[2], Cristina Preda[1,3], Maria Christina Ungureanu[1,3]

[1]Saint Spiridon County Hospital, Iași, Romania, Endocrinology Department, [2]Emergency Hospital "Professor Doctor Nicolae Oblu", Iași, Romania, Neurosurgery Department, [3]"Grigore T. Popa" University of Medicine and Pharmacy of Iași, Romania

Background

Cortisol excess exerts an early negative impact on musculoskeletal homeostasis. If not diagnosed and treated on time, Cushing's disease (CD) significantly decreases the quality of life of the affected individual on account of the complications of the disease, among which, fractures may represent the trigger that leads the patient to the physician. Fractures may occur early in the setting of hypercortisolism, even when the bone mineral density (BMD) is in the normal range.

Objective

We present the case of a 30-year-old female patient who was diagnosed with CD after she presented at the hospital for multiple fractures.

Case report

During a 5-month period, the patient had multiple fragility fractures which required orthopedic care: incomplete fracture of the left femoral neck, right iliac wing fracture, left iliopubic and ischiopubic ram fracture, and right calcaneus fracture. Given the clinical aspect at her last orthopaedic check-up, she was referred to the endocrinologist in order to investigate the etiology of her bone fragility: she had a facial plethora, moon facies, was overweight with dorsocervical and supraclavicular distribution of the fat, proximal muscle weakness, broad and violaceous striae distributed over the upper thighs, thin nails and skin, easy bruising. Moreover, she complained of persistent headaches and she had a medical history of depression (treatment with valproate, lorazepam and quetiapine for over 3 years). Laboratory tests confirmed the diagnosis of Cushing's disease, with a well-defined macroadenoma of 10/12/10 mm, in the left half of the pituitary gland. The DXA result showed a low BMD: Z score L1-L4= -3,1 SD, Z score total hip = - 1,5 SD, Z score Neck = - 1,1 SD, Z score ⅓ distal radius = - 1,6 SD. The calcium - phosphate metabolism parameters were within the normal range. Shortly after the diagnosis, surgery was performed, then glucocorticoid substitution and vitamin D were initiated. Postoperatively, the patient's aspect and physical status improved radically. There was a significant increase of the BMD on the lumbar spine and ⅓ distal radius, documented 9 months following the surgical cure.

Discussions and conclusion

After the surgical cure, BMD improved significantly in our patient's case, in concordance with literature data which report an early improvement at 3 to 6 months following the cure. Skeletal fragility in hypercortisolism is explained by the glucocorticoid - mediated osteoblast differentiation and function, apoptosis of the osteoblasts and osteocytes, an increase of the osteoclastic activity, and the negative interaction of glucocorticoids with GH/IGF-I axis, gonadal axis and PTH/vitamin D axis. Among CD's clinical features, fractures may be the starting point for the investigation of a hypercatabolic status, considering bone's increased sensitivity to even mild cortisol excess.

Disclosure of interest: None declared

BONE STRAIN INDEX AS A RELIABLE BONE PARAMETER IN A COHORT OF MALE PATIENTS

Luigi di Filippo[1], Stefano Frara[1], Filippo Bolamperti[1], Fabio Massimo Uliveri[1], Andrea Giustina[1]

[1]Institute of Endocrine and Metabolic Sciences, Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy

Background

The bone Strain Index (BSI) is an innovative index of bone strength that provides information about skeletal resistance based on a finite element model from dual X-ray absorptiometry (DXA) scans. BSI calculation includes information on bone density distribution and geometry obtained by a greyscale density distribution measured at lumbar spine and hip. This index has been recently proposed to help clinicians to improve bone impairment prediction. This could be particularly useful in specific patient groups that can hardly effectively analyse with only a conventional bone assessment such as male subjects.

Objectives

This study aimed to evaluate the relationship between BSI and densitometric data and morphometric vertebral fractures (VFs) in a cohort of male subjects attending a single bone-clinic centre.

Methods

In this retrospective study, we evaluated BSI parameters, Bone Mineral Density (BMD) and T-score levels obtained at spine (S) and femoral scans (Neck [FN] and Total Hip [TH]), by DXA scans (Discovery Wi, Hologic®) in all male patients who attended the Bone Center, IRCCS Ospedale San Raffaele, a tertiary health-care centre in Milan, Italy in 2022 performing a VFs assessment by lateral spine DXA (MMXA), using a quantitative morphometric assessment.

Results

A total of 18 male subjects were enrolled. The median [IQR] age was 55 [37-60] years with a median Body Mass Index (BMI) of 26.7 [23-30]. Median S-BSI, FN- and TH-BSI were 1.98 [1.43-2.39], 1.62 [1.47-1.96] and 1.33 [1.14-1.74], respectively. An impaired BSI, defined as a value of BSI ≥2.4 in one of the three sites, was found in 3 (16.7%) patients. Prevalent VFs were detected in 2 (11.1%) patients. We found statistically significant lower BMD and T-score levels in those with an impaired BSI (S-BMD 0.79 [0.77-0.8] vs 1.1 [0.9-1.2] p=0.01) (FN-BMD 0.49 [0.51-0.46] vs 0.79 [0.67-0.84] p=0.017) (TH-BMD 0.64 [0.58-0.66] vs 0.94 [0.89-1.05] p=0.005) (S-T-scores -2.7 [-2.6 – -2.8] vs -0.4 [-0.3 - +1] p=0.005) (FN-T-score -3.2 [-3.1 - -3.4] vs -1 [-1.8 - -0.6] p=0.01) (TH-T-score -2.6 [-2.5 - -3] vs –0.6 [-0.9 - +1] p=0.005). Linear regression analyses showed negative correlations between S-BSI and S-BMD (p<0.001) and S-T-score (p<0.001) levels; between FN-BSI and FN-BMD (p=0.012) and FN-T-score levels (p=0.015); and between TH-BSI and TH-BMD (p<0.001) and TH-T-score levels (p<0.001). FN-BSI and TH-BSI were negatively correlated with BMI (p=0.029 and p=0.045, respectively). No differences were observed regarding BSI in fractured and non-fractured patients.

Discussion

In this one-year single bone-clinic centre experience focused, we showed that BSI values were strictly associated with densitometric data in a cohort of male patients. It could be hypothesized that BSI may integrate conventional bone evaluation in assessing fracture risk in male osteoporosis.

Disclosures: Luigi di Filippo has no competing interests to declare

NOVEL CIRCULATING MICRORNAS AS POTENTIAL BIOMARKER ASSOCIATING DISEASE SEVERITY AND VITAMIN D STATUS IN COVID-19 PATIENTS

Luigi di Filippo[1], Stefano Frara[1], Umberto Terenzi[1], Santina Battaglia[2], Silvano Bonaretti[3], Silvia Trasciatti[3], Fabrizio Nannipieri[2], Andrea Giustina[1]

[1]Institute of Endocrine and Metabolic Sciences, Università Vita-Salute San Raffaele, IRCCS Ospedale San Raffaele, Milan, Italy

[2]Galileo Research Srl, Pisa, Italy

[3]Clinical Research, Abiogen Pharma, Pisa, Italy

Background

MicroRNAs are small non-coding RNAs involved in the post-transcriptional regulation of gene expression influencing cellular activities regulating cell growth, differentiation, and apoptosis. MicroRNAs have been recently linked to many pathological conditions as promising novel potential non-invasive diagnostic and prognostic biomarkers, including also for skeletal and inflammatory diseases such as osteoporosis and COVID-19. The negative role of hypovitaminosis D in patients affected by COVID-19 was consistently reported as a risk factor for worse outcomes.

Objectives

The aim of this pilot study was to evaluate the expression of circulating microRNAs in patients with COVID-19, and to correlate the circulating microRNAs expression pattern to the patient's vitamin D status.

Methods

This was a prospective study performed at IRCCS Ospedale San Raffaele, Italy. At hospital admission, COVID-19 patients were consecutively enrolled, matched for age, sex and comorbidities in a 1:1 ratio, and classified on the basis of presence or absence of a severe disease. 25(OH) vitamin D levels were measured at admission, and vitamin D deficiency was defined as 25(OH) vitamin D levels below 20 ng/mL. The expression levels of circulating microRNAs were estimated using qRT-PCR technique on patients' blood samples collected at admission and processed according to manufacturer recommendations.

Results: A total of 73 COVID-19 patients (36 severe and 37 non-severe) were enrolled. Median [IQR] 25(OH) vitamin D level was 13.8 [8.8-20.1] ng/mL and vitamin D deficiency was found in 75% of the cohort. In patients affected by a severe disease we observed higher expression of two specific microRNAs, hsa-miR-3115 and hsa-miR-7151-3p, as compared to those affected by a non-severe condition. On the other hand, we observed in patients affected by vitamin D deficiency higher expression of two other specific microRNAs, hsa-miR-33a-5p and hsa-miR-642a-3p/642b, as compared to those without vitamin D deficiency.

Discussion

This is the first seminal observation reporting a different microRNAs expression pattern related to patient's vitamin D status in COVID-19. So far, very few studies have reported the potential role of specific microRNAs as predictive biomarkers for COVID-19 severity. We observed that hsa-miR-3115 and hsa-miR-7151-3p were highly expressed in those affected by a severe disease, and, to date, no previous data are available in literature regarding the biological role of these two microRNAs. Moreover, it has to be noted that hsa-miR-33a-5p, typically highly expressed in inflammatory conditions, and hsa-miR-7151-3p, previously reported to be highly expressed in patients with osteopenia and osteoporosis, were differentially expressed in patients with hypovitaminosis D. In conclusion, we firstly reported on the expression of novel microRNAs as potentially useful biomarker for COVID-19 severity, and secondly the expression of microRNAs involved in inflammatory response and bone health, in patients with vitamin D deficiency and COVID-19, possibly linking these two conditions and the negative effects of hypovitaminosis D on COVID-19 outcomes.

Disclosures: Luigi di Filippo has no competing interests to declare

GIOSEG Skeletal Endocrinology Group Glucocorticoid Induced Osteoporosis

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GENERAL INFORMATION

CME ACCREDITATION

The Skeletal endocrinology Meeting (event ID: 5468-374409 - edition n.1 - Scientific Coordinator Dr. Stefano Frara, Assistant Professor "Vita-Salute San Raffaele" University - Milan) obtained **n. 9,1 credits** for the following professions: Physician (Clinical Biochemistry, Clinical Pathology, Continuity of Care, Endocrinology, Emergency Medicine and Surgery, Epidemiology, Food science and dietetics, General Medicine, general Surgery, Geriatric, Gynaecology and Obstetrics, Internal Medicine, Laboratory of Medical Genetics, Legal Medicine, Metabolic Diseases and Diabetology, Nephrology, Neurosurgery, Ophthalmology, Oncology, Orthopaedics and Traumatology, Palliative Care, Pediatrics, Pharmacology and Toxicology, Physical Medicine and Rehabilitation, Rheumatology, Sport Medicine, Urology), Biomedical Laboratory Health Technicians, Medical Radiology Health Technicians, Physiotherapists, Nurses, Paediatric Nurses, Biologists, Dieticians

EDUCATIONAL TARGET

Application of Evidence-Based-Practice (EBM-EBN-EBP) principles and procedures in daily practice

CME ACCREDITATION

To receive the CME credits all forms must be returned on-site to the Provider A.I.C. Asti Incentives & Congressi that will check:

- if all sessions have been attended
- if the 75% of the answers of the quiz are correct
- if all forms are well completed

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. Translation will not be provided

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