METABOLIC BONE DISEASE

SATELLITE MEETING

EUROMEDLAB 2017

JUNE **10** 2017

ATHENS WAR MUSEUM
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FINAL PROGRAM

IFCC-IOF Working Group for the Standardization of Bone Markers

International Osteoporosis Foundation

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

Belgian Bone Club

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Professor Etienne Cavalier
University of Liège, CHU Sart-Tilman, Domaine du Sart-Tilman, B-4000 Liège, Belgium.

Professor Evangelos Terpos
Medical School, University of Athens, Greece

Dr. Konstantinos Makris Ph.D
Clinical biochemistry Department, KAT General Hospital, Kifissia, Greece

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ORGANIZED BY

IFCC International Federation of Clinical Chemistry and Laboratory Medicine

IN COOPERATION WITH

GSCC-CB GREEK SOCIETY OF CLINICAL CHEMISTRY CLINICAL BIOCHEMISTRY

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EFLM EUROPEAN FEDERATION OF CLINICAL CHEMISTRY AND LABORATORY MEDICINE

Professor Howard Morris
University of South Australia, Adelaide, Australia

Dear Colleagues and Friends,

On behalf of the Organizing Committee it is a great pleasure to invite you to the Metabolic Bone Disease Satellite Meeting being held in conjunction with EuroMedlab Athens 2017 Congress. This meeting will bring together leading metabolic bone disease clinicians with laboratory medicine specialists providing clinical laboratory services to support their patients. Topics will address new therapies for osteoporosis, clinical practice for metabolic bone disease as a consequence of chronic kidney disease and other diseases of bone. These will be accompanied by presentations on the requirements from the clinical laboratory to optimise patient outcomes for these patients.

Other subjects include the latest developments in our understanding of the clinical usefulness of bone turnover markers for evaluating and following treatment of the osteoporotic patient as well as biomarkers for osteoarthritis and rare bone diseases. From the clinical laboratory, experts will address the role of the latest generation of parathyroid hormone assays, the clinical impact of standardization of 25-hydroxyvitamin D assays and interpretation of their concentrations for the individual patient.

This satellite meeting will provide the opportunity for delegates to network with the international faculty and other specialists both clinical and from the laboratory. Being held in conjunction with EuroMedlab Athens 2017 registrants have the opportunity to attend the Satellite Meeting only or to combine your experience with the most important congress in Laboratory Medicine in Europe. EuroMedlab 2017 provides information on the state of the art and latest innovations of Laboratory Medicine for the 21st century.

Don't miss this important event in historic Athens. Book the dates and keep an eye on our website. We look forward to seeing you in Athens in June 2017!

Professor Howard Morris

Faculty

Body Jean-Jacques

Professor Jean-Jacques Body received his training at the "Université Libre de Bruxelles" (ULB, Free University of Brussels) and at the Mayo Clinic (Rochester, Mn, USA). He is an internist, an endocrinologist and a medical oncologist. He is now Professor Emeritus since March 2017. He was until then Full Professor of Internal Medicine at ULB and Head of the Department of Medicine at University Hospital Brugmann in Brussels.

He has been Head of the Internal Medicine Clinic at Institute J. Bordet, the Cancer Center of ULB. He developed the Supportive Care Department at the same Institute. During this period, he created the first National Course on Supportive and Palliative Care. He also created the "Groupe Européen francophone d'étude des Métastases Osseuses (GEMO)" of which he was the first President. He is also President of the "Belgian Bone Club" and is a member of the "Committee of Scientific Advisors" of "International Osteoporosis Foundation (IOF)". He is a member of several professional organisations, including ASBMR, ECTS, IBMS, ASCO, ESMO, SIOG, MASCC, Endo Soc.

His particular research interests are tumor bone disease, osteoporosis, and markers of bone turnover. He was involved in numerous trials in cancer patients with all bisphosphonates available in Europe and with denosumab from phase I to phase IV. More recently, he became interested in risk factors for osteoporotic fractures in postmenopausal women.

He has authored or co-authored more than 260 international peer-reviewed papers and more than 60 book chapters or proceedings and he counts more than 200 invited lectures for international meetings.

Cavalier Etienne

Cavalier Etienne is Professor of Clinical Chemistry at the University of Liège and Head of the Department of Clinical chemistry at the CHU de Liège. He graduated in pharmaceutical sciences, in laboratory medicine and received his PhD in 2010. His main current research concerns bones markers, vitamin D, PTH, vascular calcification markers, markers of acute kidney diseases, glomerular filtration rate (estimation, biomarkers), markers of frailty and sarcopenia and LCMS/MS methods for steroids and peptides quantification. He is member of 14 scientific societies and has published 184 papers and 4 chapter books.

Cristol Jean-Paul

Jean-Paul Cristol is Biochemist at the Montpellier Medical School. Since 2013, Jean-Paul Cristol is Head of the Federation of Biology and Pathology and coordinator of the Department of Biochemistry and Hormonology at the Montpellier University Hospital. Resident then fellow in Nephrology department, he obtained his MD (1989) and his PhD (1990) in Montpellier. The research group, belonging to "Physiologie et Médecine Experimentale INSERM U1046, CNRS UMR9214", has a long-standing research interest in chronic and acute kidney disease, especially in monitoring of renal function and non-traditional cardiovascular risk factor linked to renal disease such as inflammation, malnutrition and vascular calcifications. He is responsible for the working group "Biomarkers of vascular calcifications" on the behalf of "Société de Biologie Clinique" and "Société Française de Néphrologie Dialyse et Transplantation".

Delanaye Pierre, MD, PhD

Dr. Delanaye is currently Nephrologist at the University Hospital of Liège (CHU Sart Tilman), Belgium. His daily practice is the care of hemodialysis patients. His clinical research interest is the estimation and measurement of glomerular filtration rate, the epidemiology of chronic kidney disease (CKD) and Mineral Bone Disease (MBD) in dialysis patients. In his research, he underlines the strong and necessary links between Nephrology and Clinical Chemistry. He has published extensively on the epidemiology of CKD, on the evaluation of eGFR formulas and CKD-MBD.

Herrmann Markus

Professor Markus Herrmann is a Chemical Pathologist. He studied medicine at the Universities of Regensburg and Würzburg in Germany, where he graduated in 2000. After internships at the Department of Dermatology at the Technical University of Munich (Germany) and the Institute of Sports Medicine at the University of Saarland (Germany) he started his training in Laboratory Medicine at the Institute of Clinical Chemistry and Laboratory Medicine at the University of Saarland (Germany). In 2007 he received a postdoctoral fellowship grant from the Leopoldina Academy and a went for two years to the ANZAC Research Institute in Sydney (Australia). Subsequently, he became a fellow of the Royal College of Pathologists Australasia and continued working as a chemical pathologist at the Royal Prince Alfred Hospital and Laverty Patholgy in Sydney. In 2008 he became an associate professor at the University of Saarland (Germany). The University of Sydney awarded him the title of a clinical associate professor in 2010. In 2012 Professor Herrmann moved to Italy, where he directs the Department of Clinical Pathology at the Bolzano hospital.

Professor Herrmann's research is focused on bone metabolism and vitamin D. As a collaborator of the FIELD Study he has shown that vitamin D is an independent predictor of vascular disease in diabetic patients. In addition, he has studied the role of homocysteine and B-vitamins in age related degenerative diseases, such as osteoporosis, heart failure and thrombosis. He has published about 100 peer-reviewed articles and book chapters. His current interest is the influence of vitamins on telomere biology. Professor Herrmann is a member of the scientific committee of the Italian Society of Laboratory Medicine and since 2015 he serves on the editorial board of Clinical Chemistry and Laboratory Medicine.

Lafage-Proust Marie-Helene

Pr MH Lafage-Proust, MD, PhD, was trained as a rheumatologist in Bordeaux University where she got interested in metabolic bone disease and bone histomorphometry. After a post doctoral fellowship at Merck Research Labs in the Bone Research department (USA), she was recruited at the University Jean Monnet of Saint-Etienne, now member of University of Lyon, where she has worked ever since. She is a physician at the University Hospital of Saint-Etienne where she takes care of patients, notably renal patients or with disorders of calcium and phosphate metabolism and bone fragility. She teaches Cell Biology at the Medical School of St-Etienne. She is a researcher at the INSERM Unit U1059 SAINBIOSE. She first worked on the bone response to mechanical strain and more recently focused on bone vascularisation and mineralization in animal models. Her clinical research mostly concerns mineral and bone metabolism disorders in patients with chronic kidney disease (CKD-MBD). She has published 130 papers referenced in Medline and has been invited for more than fifty scientific conferences worldwide.

Lotz Martin

Martin Lotz received his MD degree from the University of Heidelberg in 1981. He completed clinical training in internal medicine and rheumatology. Since 1983 he performed arthritis research at The Scripps Research Institute and the University of California, San Diego. His studies on joint aging and osteoarthritis aim at identifying aging-related changes in cartilage and other tissues that determine risk for osteoarthritis. Recent findings concern cellular homeostasis mechanisms, such as autophagy that are compromised in aging. A new direction of research is to establish gene and epigenetic networks that are dysregulated in OA. This led to the discovery of several differentially expressed transcription factors which are currently being pursued as new targets for the prevention and treatment of OA.

Morris Howard

Professor Howard Morris is Professor of Medical Sciences at the University of South Australia and a Clinical Scientist in Chemical Pathology at SA Pathology, Adelaide, South Australia.

He has over 30 years' experience in Laboratory Medicine largely managing the Endocrinology laboratory of a large public pathology service. His research investigates the pathophysiology of osteoporosis and the effects of vitamin D and dietary calcium.

Professor Morris is currently the President-Elect of the IFCC; he has served as Chair of the IFCC – International Osteoporosis Foundation Joint Working Group on Standardization of Bone Marker Assays. Vice-President of the IFCC between 2012 and 2014, and Secretary of the Scientific Division of the IFCC.

Papapoulos Socrates

Socrates E. Papapoulos is Professor of Medicine (Diseases of Calcium and Bone Metabolism) and senior medical specialist/advisor at the Leiden Center for Bone Quality, the Netherlands. He received his MD from the University of Athens, Greece and he was trained in Internal Medicine and Endocrinology in Athens, GR and in London, UK. In 1984 he joined the Department of Endocrinology and Metabolic Diseases of the Leiden University Medical Center where he was Director of Bone and Mineral Research between 1989 and 2012. Since 1974 he has been continuously engaged in basic and clinical research, patient care and teaching of disorders of calcium and bone metabolism. Dr Papapoulos is recipient, among other, of the Boy Frame Memorial Award and the Frederic C Bartter Award of the ASBMR, the John Haddad Jr Award of the IBMS, the JB Johnson Award of the Paget's Foundation, USA, the Steven Boonen Award of ECTS and The Pierre Delmas Award of the IOF and he is Doctor Honoris Causa of the Universities of Athens and Thessaloniki. He has served on numerous boards and committees including the Board and the Scientific Advisory Board of the IOF, the Board of Directors of the IBMS and of the ECTS, the European Union committee for the prevention of osteoporosis, a WHO task force for the development of a world wide strategy for the prevention and treatment of osteoporosis and he is senior scientific advisor of the European Union project Osteoporosis in Europe.

Rye Jorgensen Niklas

Niklas Rye Jørgensen is professor of Clinical Biochemistry at University of Southern Denmark and head of the Section of Clinical Biochemistry at Copenhagen University Hospital, Glostrup, Denmark. He graduated as Medical Doctor from the University of Copenhagen in 1992. His primary field of research is translational bone biology in which he has worked for more than 20 years. Also, he has a great interest in research in the clinical use of biochemical markers of bone turnover.

Terpos Evangellos

Evangelos Terpos, MD, PhD is an Associate Professor of Hematology in the National and Kapodistrian University of Athens, School of Medicine, Athens, Greece (since 2009). He has also been appointed as Honorary Senior Lecturer in the Department of Hematology, Faculty of Medicine Imperial College London, London, UK (since 2003).

His main research interest is the biology of bone disease in hematological disorders, including multiple myeloma and thalassemia. In more than 380 papers in peer-reviewed journals, Dr Terpos has reported the significant role of receptor activator of nuclear factor-kappa B ligand (RANKL) and osteoprotegerin axis, macrophage inflammatory protein-1alpha (CCL3, MIP-1), Wnt signaling (dickkopf-1 protein, Dkk-1; sclerostin) and activin-A antagonists in myeloma bone disease and thalassemia bone loss. He has studied the predictive value of markers of bone remodeling and osteoclast function in both myeloma and thalassemia-associated osteoporosis. He has studied the effect of bisphosphonates, mainly of pamidronate and zoledronic acid, on myeloma bone disease, solid tumors with bone metastases, thalassemia and hemophilia-related osteoporosis.

Dr Terpos is chairing the Bone Subgroup of the International Myeloma Working Group (IMWG) and is co-chairing the Guideline subgroup of the European Myeloma Network (EMN). He has given lectures in the European Hematology Association (EHA), American Society of Hematology (ASH) and American Society for Medical Oncology (ASCO) meetings, Thalassemia International Federation (TIF) meetings, International Myeloma Workshops, International Meetings on Cancer-Induced Bone Disease, and several National meetings. He is reviewer of scientific papers in more than 50 medical journals including the Lancet, Lancet Oncology, Journal of Clinical Oncology, Blood and Leukemia and he has reviewed abstracts for EHA, EBMT and ASH meetings. He is also a member of the Editorial Board of Haematologica.

Evangelos Terpos can be reached via e-mail at eterpos@med.uoa.gr and

Tournis Symeon

Symeon Tournis MD, PhD. is a Clinical Endocrinologist and Senior Research Fellow at the Laboratory for the Research of the Musculoskeletal System of the University of Athens, KAT Hospital.

He graduated from the medical school of the University of Thessaloniki and received his PhD degree from the University of Ioannina.

He has published more than 70 papers in peer-reviewed journal, has over 900 citations and an H-index of 15.

Vasikaran Samuel

Dr Samuel Vasikaran is a Chemical Pathologist based in Perth, Western Australia. He was previously Clinical Professor, Pathology and Laboratory Medicine, University of Western Australia until 2016. He has extensive clinical experience in treating patients with osteoporosis and research experience and publications on the use of bone turnover markers in the management of osteoporosis. He was Chair of the IOF-IFCC Working Group on Bone Marker Standards in Osteoporosis, which formulated position paper on reference bone turnover markers.

SCIENTIFIC PROGRAM

08:55 **Welcome**

Professor George P. Lyritis

Chair Organizing Committee and Professor

Professor Howard Morris

Chair Scientific Committee

Session 1
Bone Turnover Markers in Osteoporosis

Chair: Prof. George P. Lyritis

09:00 **The clinical usefulness of bone turnover assays**

Professor Samuel Vasikaran

Royal Perth Hospital, Perth, Australia

09:30 **Analytical requirements for bone marker assays**

Professor Niklas Rye Jørgensen

Research Centre for Aging and Osteoporosis,
Copenhagen University Hospital, Glostrup, Denmark

10:00 **Clinical requirements for new biomarkers of bone metabolism**

Dr. Marie-Hélène Lafage-Proust

University Hospital Saint-Etienne,
Université de Lyon, FRANCE

10:30 **Morning Break**

Plenary Lecture 1

Chair: Dr. Symeon Tournis

11:00 **New Therapeutics for Osteoporosis**

Prof. Socrates Papapoulos

Center for Bone Quality, Leiden University Medical Center, Leiden, Netherlands.

Session 2
Clinical impact of assay standardization for Metabolic Bone Disease

Chair: Prof. Niklas Rye Jørgensen

11:45 **Practical considerations in parathyroid hormone testing**

Prof. Etienne Cavalier

University of Liège, Belgium

12:15 **Suggestion of vitamin D status – a changing landscape**

Professor Markus Herrmann

Zentrallabor für Klinische Pathologie / Laboratorio Centrale di Patologia Clinica Bozen (Italien)

12:45 **Emerging biochemical markers of osteoarthritis**
Professor Martin Lotz
Head of Arthritis Research. The Scripps Research Institute, CA

13:15 **Lunch break**

Session 3
Rare diseases of bone metabolism
Chair: Prof. Samuel Vasikaran

14:30 **Hypophosphatasia**
Dr Symeon Tournis
Laboratory for Research of Musculoskeletal System, University of Athens, KAT Hospital, Athens, Greece

15:00 **Bone markers in thalassemia major**
Professor Evangellos Terpos
University of Athens, Greece

15:30 **Inhibitors of bone resorption: from the treatment of cancer hypercalcemia to the prevention of metastases**
Professor Jean-Jacques Body
University Hospital Brugmann, Dept. of Medicine, Head Université Libre de Bruxelles, Brussels, Belgium

16:00 **Afternoon Break**

Session 4
Chronic Kidney Disease
Chair: Prof. Jean-Jacques Body

16:30 **CKD-MBD – Input from the clinical laboratory**
Professor Jean-Paul Cristol
University of Montpellier, Montpellier,France

17:00 **Bone markers and vascular calcification in CKD-MBD**
Dr. Pierre Delanaye
University of Liège, Liège, Belgium

Plenary Lecture 2
Chair: Prof. Jean-Jacques Body

17:30 **The Clinical Impact of Standardisation of 25-Hydroxyvitamin D Assays**
Professor Howard Morris

Closing remarks
Professor Howard Morris

18:00 **Farewell Cocktail**

General information

VENUE AND DATES

The **Metabolic Bone Disease**, will take place in Athens, on **June 10, 2017** at the **Athens War Museum - Annex "Saroglio Mansion"**

(Address: 1, Rigillis & Vas. Sofias Avenue Athens, Greece 106 75, website: www.laed.gr, Tel.: 0030 210 7212496).

LANGUAGE

The official language of the Meeting will be English.

SHOPPING IN ATHENS

In Athens the usual opening hours for shops are:

- Monday, Wednesday & Saturday from 09.30 - 14.30 hours

- Tuesday, Thursday & Friday from 09.30 - 14.30 hours and from 17.30 - 20.30 hours

These times are not always strictly adhered to. Many shops in tourist resorts are open seven days a week.

Department's stores and supermarkets are open from 09.00 - 20.00 hours (Monday-Friday) and from 08.00 - 15.00 hrs (Saturday) and are closed on Sunday.

Post offices are open from 07.30 - 14:00 hours (Monday-Friday)

WEATHER

Typically mediterranean climate. Athens enjoys relatively mild winters and lovely, temperate autumns and springs. The climate is pleasant, and sunshine is plentiful. June is warm without being stifling, the swimming is excellent and the temperature ranges from 25°C to 35°C.

TRANSPORTATION

Athens Airport

The Athens International Airport is located in Spata, 27 Kms north-east of Athens and handles all international and domestic flights.

For more information please visit the Eleftherios Venizelos website: http://www.aia.gr

A special feature of this web site is that on the home page you can link to live arrival and departure information by clicking on the link Real Time Flight Information

The Athens International Airport "Eleftherios Venizelos" is linked to the Athens city center by:

From Airport by Bus (www.oasa.gr):

Three express lines serve the Athens International Airport to Athens City Center on a 24 hours basis.

The bus line E95 (Direction Syntagma) serves Athens City center (Syntagma, Constitution Square)

The following timetable is applicable:

From Airport to Syntagma area	From Syntagma area to Airport
Every 25' from 06.30 to 21.20	Every 25' from 06.00 to 20.40
Every 25'-35' from 21.20 to 06.30	Every 25'-35' from 20.40 to 06.00

Current ticket price for the airport express line is € 6.

FROM AIRPORT BY TAXI

An average journey by taxi from Eleftherios Venizelos Airport to City Centre should take approximately 30- 45 minutes, depending on the traffic. The cost of the ride should be around € 38 per way.

FROM AIRPORT BY METRO

The metro (Lines 2 and 3) run from about 05.00 am until 2.00 am, every 10 minutes, the trip takes approximately 30 minutes. For further information contact Attiko Metro or through the Internet www.ametro.gr Current ticket price for the metro is € 10.

WEB SITE

Up-to-date information regarding the Meeting will be available at the Euromedlab web site: www. Athens2017.org Participants will be able to register and book hotel accommodation on line.

FULL REGISTRATION	**€200**
YOUNG REGISTRATION	**€60**
EUROMEDLAB REGISTRANT FULL REGISTRATION	**€140**
EUROMEDLAB REGISTRANT YOUNG REGISTRATION	**€40**

The registration fee includes:

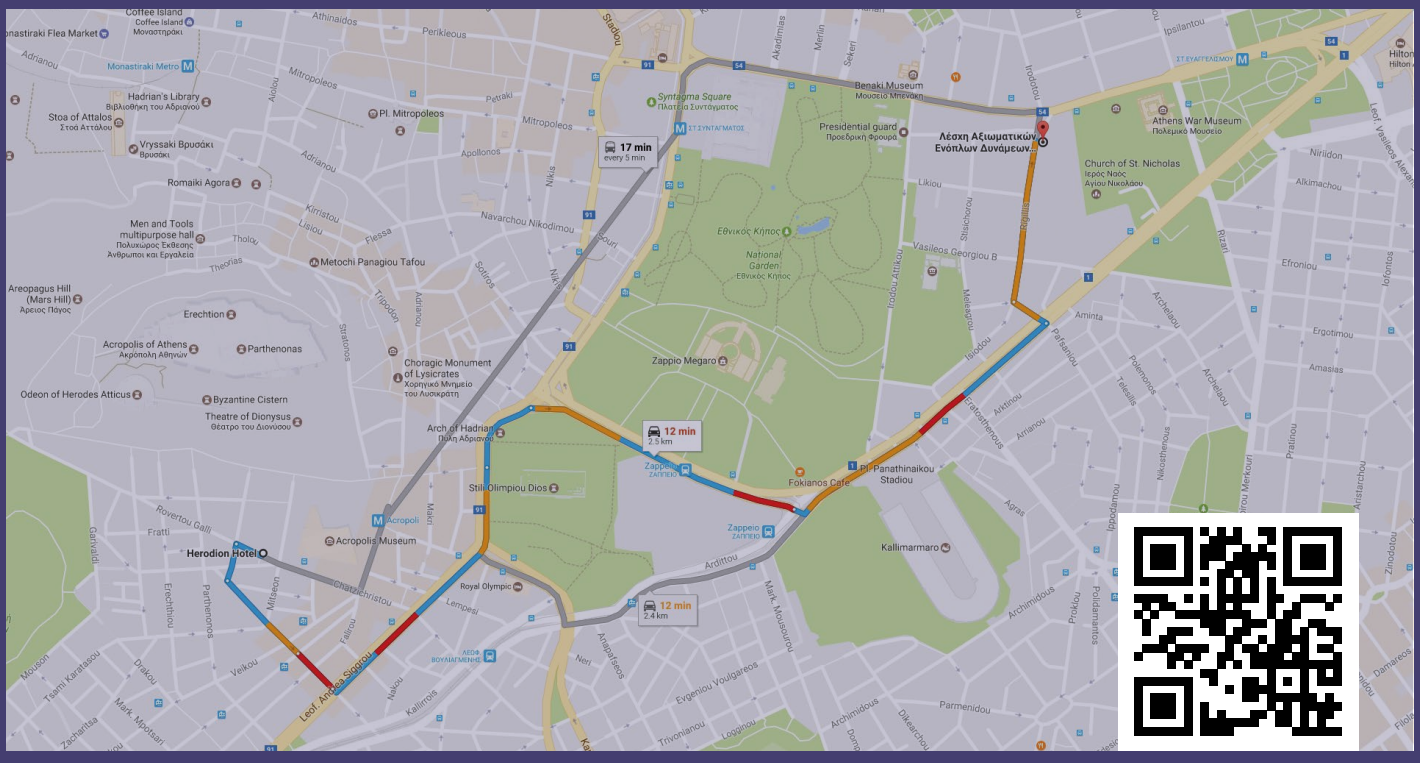
- Access to the conference hall
- Coffee and lunch break
- Certification of Attendance

MEETING SECRETARIAT & OFFICIAL TRAVEL AGENCY

For any information regarding Registration, Accommodation, Travel or Sponsoring please contact the Meeting Secretariat & official Travel agency:

ERA LTD 17, Asklipiou Str., 10680 Athens-Greece
Tel.: +30 210 3634944, Fax: +30 210 3631690 E-mail: info@era.gr, website: www.era.gr

The Registration Secretariat and Hospitality desk will operate at the Saroglio Mansion during meeting hours.



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Abstract Book

Session 1:
Bone Turnover Markers in Osteoporosis

The clinical usefulness of bone turnover assays

Samuel D Vasikaran
Department of Clinical Biochemistry, PathWest Laboratory Medicine WA, Perth, Australia

Osteoporosis is diagnosed by bone mineral density (BMD) measurement, which by itself is insensitive for identifying patients at the highest fracture risk. The calculation of absolute fracture risk by including clinical risk factors for fracture improves the accuracy with which patients at high risk can be identified. Bone turnover markers (BTMs) predict fracture risk independently of BMD; however, their relationship to other clinical risk factors needs to be determined before they are included in fracture risk calculators. The recent consensus on reference BTMs in osteoporosis (s-PINP for bone formation and s-CTX for resorption) should help focus future studies and accumulate adequate data for this purpose.
BTMs reflect the effect of drugs on bone turnover, predict treatment-related reduction in fracture risk, and are useful in dose finding studies. Changes in BTM during osteoporotic therapy depend on the mechanism of action of the drug and route of administration. Treatment-related changes in BTM are more rapid and of greater magnitude compared with change in BMD. Since early changes in BTM following initiation of treatment predict treatment response, BTM may be useful for monitoring therapy, predicting response and potentially improving adherence to therapy. More evidence is needed for utilizing BTMs in assisting with decisions to cease medication and in managing 'drug holidays'.

Analytical requirements for bone turnover marker assays

Jørgensen NR.
Research Center for Ageing and Osteoporosis, Dept. of Clinical Biochemisty, Copenhagen University Hospital, Glostrup, Denmark, and OPEN, Odense Patient data Explorative Network, Odense University Hospital/Institute of Clinical Research, University of Southern Denmark, Odense, Denmark

Bone turnover markers (BTM) have been used for more than three decades to determine effects of bone-active treatments in clinical studies and are now also widely used in clinical practice to monitor effect of anti-osteoporotic treatment in patients. Many different BTM are available for measurement of both bone resorption and bone formation. However, the clinical usefulness of BTM may be hampered by lack of attention to sources of variation. BTM have a relatively high biological variation; a number of factors contribute to this such as diurnal variation, effect of food intake, effect of medications, different diseases affecting bone metabolism etc. Also, the analytical variability is significant and can be caused by both pre-analytical issues such as type of sample material (serum vs. plasma), storage time, time-to-centrifugation as well as analytical issues like lack of comparability between assays for the individual BTM. Finally, previous clinical trials have used a range of different BTM, which hampers the comparability of effects of medications on the markers. Therefore, a working group established by the International Osteoporosis Foundation and the International Federation of Clinical Chemistry proposed two reference markers to use in future clinical trials and identified a list of pre-analytical and analytical issues to be solved in order to improve the clinical usefulness of BTM. This talk will focus on the analytical requirements that needs attention in order to best use the BTM in the clinical setting.

Clinical requirements for new biomarkers of bone metabolism

Dr. Marie-Hélène Lafage-Proust
MH Lafage Proust. INSERMU 1059, Université de Lyon, 42000, FRANCE

Biochemical markers are broadly used for the diagnosis and follow-up of metabolic bone diseases. A first set of currently measured markers consist in molecules released into the blood circulation during bone remodeling; they characterize the osteoclastic resorption and osteoblastic formation processes. Among these, the various carboxylated forms of osteocalcin display a specific potential which has not yet been clinically validated. Indeed, osteocalcin is produced by osteoblasts and can also be released from bone during resorption Extensive data in mice and an increasing body of evidence in humans suggest that osteocalcin is also involved in insulin sensitivity and fertility in men. Of note, despite the wide range of markers that can be potentially utilized, some clinical needs have not yet been met. Indeed, some bone formation markers may give indications on bone primary mineralisation, however, their interpretation remains difficult when both remodeling and mineralization are affected concomitantly as in mixed uremic bone disease. Post-fracture modeling may also strongly impact bone biochemical marker serum levels for several weeks and thus become useless at a time when precisely they are critically needed. A number of the bone turnover markers depend on Glomerular Filtration Rate (Collagen-derived markers) or liver function (Bone alkaline phosphatase) making their use problematic when dealing with patients with chronic kidney (CKD) or liver diseases. Finally, current bone biomarkers remain not sensitive enough to detect early bone metastases. A second set of markers including parathyroid hormone and the various forms of circulating Vitamin D are also commonly used to manage disorders of calcium and phosphate metabolism. In the CKD context, convincing work showed that combination of markers from these two sets may help clinicians to better discriminate between the various bone lesions. However, while the diagnosis is fairly accurate with markers for very low or very high turnover there is a wide window of diagnosis uncertainty for milder bone disorders. Fibroblast growth factor 23, an osteocyte-derived hormone, regulates phosphate and vitamin D metabolism. FGF-23 serum level predicts poor cardiac outcomes in CKD patients. In contrast, its role for assessing bone mineralization is still a matter of research. A third set of newer markers are currently being developed. They include matricellular proteins such as periostin or peptides from the SIBLINGs family, (bone sialoprotein, ASARM), enzymes (cathepsin K), inhibitors of the wnt pathway (Dickkopf-1, sclerostin), and the lipid mediator sphingosine-1-phosphate. For some of them, serum levels are associated with vascular calcifications and may reflect the pathophysiological relationships between bone and vascular diseases. Finally, more recently, the assay of micro RNAs which modulate the expression of several genes at one time, or circulating exosomes emerged as potential research opportunities. This field opens promising prospects for better management of many clinical conditions related to bone diseases.

Plenary Lecture 1

New Therapies for Osteoporosis

Socrates E Papapoulos
Center for Bone Quality, Leiden University Medical Center, Leiden, The Netherlands

The aim of pharmacological management of osteoporosis is the reduction of the risk of fractures and associated clinical consequences. Most currently available agents do not stimulate the formation of new bone which is essential for the management of patients with severe disease and only modestly reduce the risk of nonvertebral fractures. For such patients agents capable of stimulating new bone formation are required. Teriparatide, the only available bone-forming treatment, binds to the PTH/PTHrP type 1 receptor and activates several signaling pathways, including the canonical Wnt-signalling pathway, having both anabolic and catabolic effects on bone that are probably exerted via signaling in osteocytes. Teriparatide, given by daily subcutaneous injections, increases cancellous and endocortical bone formation, mainly at sites undergoing active bone remodeling, but has limited effect on periosteal bone formation and increases cortical porosity. PTHrP and its analog abaloparatide, which also bind to the PTH/PTHrP 1 receptor, increase bone formation and bone resorption markers, but to a lesser extent than teriparatide, and improve hip BMD significantly more than teriparatide. The antifracture efficacy of abaloparatide, given by daily sc injections for 18 months, on vertebral and nonvertebral fractures was demonstrated in a phase 3 clinical trial (ACTIVE trial). Concurrent treatment of women with osteoporosis with teriparatide and the RANKL inhibitor denosumab increased BMD at all skeletal sites considerably more than either monotherapy alone after two years (DATA trial). In addition to illustrating the feasibility of an efficacious combination therapy for patients with osteoporosis, these results reinforce the hypothesis that for optimal therapeutic outcome, bone formation and bone resorption should be modulated in different directions. The latter can be achieved by treatment with inhibitors of sclerostin, a natural inhibitor of the Wnt signaling pathway, which in animal models stimulated trabecular and cortical bone formation and increased bone mass and strength. The majority of bone formation was modelling-based and was not associated with increased bone resorption. Instead, a decrease of osteoclast surface was observed suggesting a functional uncoupling of bone formation and resorption with treatment. The restricted expression of sclerostin in the skeleton, the markedly increased bone mass and bone strength in patients and mice with sclerostin deficiency, and the lack of extraskeletal complications made sclerostin an attractive therapeutic target in osteoporosis. These actions of sclerostin inhibitors were confirmed in phase I and II clinical studies by measuring the levels of biochemical markers of bone turnover. In a phase III clinical study the sclerostin inhibitor romosozumab, given sc twice monthly, reduced the risk of vertebral and clinical fractures and increased spine and hip BMD to levels higher than any single agent tested so far after one year (FRAME study). These new developments will provide a wider choice of treatments allowing a more rational management of the individual patient with osteoporosis.

Session 2: Clinical impact of assay standardization for Metabolic Bone Disease

Practical considerations in parathyroid hormone testing

Prof. Etienne Cavalier
University of Liege, Belgium

Parathyroid hormone (PTH) is an 84 amino acid that plays a key role in phosphocalcic metabolism. Its measurement is essential to diagnose and treat primary hyperparathyroidism and to evaluate chronic kidney disease-mineral and bone disorders (CKD-MBD). PTH determination is not an easy task, because of the many similar fragments that circulate in our blood. Among these fragments are a group commonly called (7-84) PTH, which are truncated in the amino-terminal part of the peptide. These fragments are quite low in normal healthy subjects; they accumulate in patients with chronic kidney diseases (CKD) and can be up to 50% of the (1-84) PTH in hemodialyzed patients (HD).
Clinical laboratories are often using "intact" PTH assays. These assays detect the (1-84) peptide and the (7-84) PTH fragments. Because these fragments are recognized differently by the various assays, the values obtained are often very

different between "intact" kits. 3rd generation PTH assays, are specific for the (1-84) PTH and do not cross-react with the (7-84) fragments, resulting in less variability. There is a huge problem regarding the standardization of PTH assays. Indeed, results obtained in the same patients, notably CKD patients, can vary up to a 4 times factor. Also, reference ranges are totally different among the assays and results cannot be interchanged between laboratories. Hence, a IFCC working group on PTH standardization has been launched to improve this important point. A WHO reference material and described LCMS/MS method already exist and can be used for this outcome (even if some problems still need to be fixed). Nevertheless, if standardization of the PTH assays is theoretically possible, it can only be achieved in healthy individuals. Indeed, as soon as GFR decreases, PTH fragments tend to accumulate and these fragments cross-react with the antibodies used in the "intact" assays with cross-reactivities that can range from 50 to 150%. Hence, in the patients for whom PTH determination is mandatory, standardization will be lost, unless 3rd PTH assays, that do not cross-react with the fragments, are used. PTH can be oxidized on two methionines, in position 8 and 18. Oxidized PTH is inactive but can be recognized by PTH assays. Some papers have shown that non-oxidized PTH is associated with mortality in hemodialyzed patients, but it still remains unclear whether PTH oxidation occurs in vitro or in vivo.
It is important to carefully select the "normal" subjects to establish reference ranges that allow the proper interpretation of the patient's PTH results. These "normals" should not have secondary hyperparathyroidism and should have eGFR, 25(OH)D, calcium and phosphorus levels within a normal range. Unfortunately, manufacturers have not judiciously selected their "normals", leading to falsely elevated PTH reference ranges. Using correctly established PTH reference ranges will assist physicians in correctly classifying HD patients in the appropriate bone turnover category.

Vitamin D status – a changing landscape

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Vitamin D deficiency is associated with an increased incidence as well as the progression of a broad range of diseases including osteoporosis, rickets, cardiovascular disease, autoimmune disease, multiple sclerosis and cancer. In recent years requests for the assessment of vitamin D status have increased exponentially. Despite significant progress in the analysis of vitamin D metabolites and an expansion of our pathophysiological knowledge of vitamin D, the assessment of vitamin D status remains a challenging and partially unresolved issue. Scientific bodies around the globe recommend the measurement of serum 25-hydroxy vitamin D (25-OHD) as the preferred test. However, numerous studies show significant limitations of this test, including analytical aspects and interpretation of results. The relationships between 25-OHD and various clinical indices, such as bone mineral density and fracture risk, are rather weak and not consistent across races. Recent studies have systematically investigated new markers of vitamin D status including the vitamin D metabolite ratio (VMR) (ratio between 25-OHD and 24,25-dihydroxy vitamin D), bioavailable 25-OHD [25-OHD not bound to vitamin D binding protein (DBP)], and free 25-OHD [circulating 25-OHD bound to neither DBP nor albumin (ALB)]. These parameters have expanded our knowledge about vitamin D metabolism and may potentially change our approach for assessing an individual's vitamin D status in the future. However, a range of unresolved issues regarding their measurement and the interpretation of results prevent their use in daily practice. It can be expected that some of these issues will be overcome in the near future so that they may be considered for routine use (at least in specialized centers). Until then, 25-OHD remains the analyte of choice for the assessment of vitamin D status in clinical practice. However, the concept of a universal 25-OHD cut-off for vitamin D deficiency/insufficiency needs to be reviewed. Mounting evidence shows that the amount of 25-OHD required for an adequate calcium metabolism varies with age and ethnic background. Therefore, age and ethnicity specific ranges or cut-offs are required to avoid misinterpretation of results. In addition, reference ranges/cut-offs should be established with LC-MS/MS methods that are traceable to international reference methods and materials.

Emerging Biochemical Markers of Osteoarthritis

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Osteoarthritis affects the whole joint structure with progressive changes in cartilage, menisci, ligaments, and subchondral bone, and synovial inflammation. Biomarkers are being developed to quantify joint remodelling and disease progression. The best candidates are generally molecules or molecular fragments present in cartilage, bone, or synovium, and may be specific to one type of joint tissue or common to them all. Many currently investigated biomarkers are associated with collagen metabolism in cartilage or bone, or aggrecan metabolism in cartilage. Other biomarkers are related to non-collagenous proteins, inflammation, and/or fibrosis. Biomarkers in osteoarthritis can be categorized using the BIPEDS classification (burden of disease, investigative, prognostic, efficacy of intervention, diagnostic, and safety). There are a number of promising candidates, notably urinary CTX-II and serum COMP, though none is sufficiently discriminating to differentiate between individual patients and controls (diagnostic) or between patients with different disease severity (burden of disease), predict prognosis in individuals with or without osteoarthritis (prognostic), or perform so consistently that it could function as a surrogate outcome in clinical trials (efficacy of intervention). Future avenues for research include exploration of underlying mechanisms of disease and development of new biomarkers; technological development; the "omics" (genomics, metabolomics, proteomics, lipidomics); and design of aggregate scores combining a panel of biomarkers and/or imaging markers into single diagnostic algorithms; and investigation into the relationship between biomarkers and prognosis.

Session 3: Rare diseases of bone metabolism

Hypophosphatasia

SymeonTournis MD, PhD

Hypophosphatasia (HPP) is a rare inherited metabolic disorder, caused by loss-of function mutations within the gene that encodes the tissue non-specific isoenzyme of alkaline phosphatase (TNSALP). TNSALP is cell-surface enzyme expressed in several tissues, especially in the skeleton, liver, kidney and developing teeth. Loss of function of TNSALP leads to extracellular accumulation of its substrates, namely PPi, an inhibitor of mineralization that explains the cardinal manifestations of the disease including rickets or osteomalacia, premature tooth loss and arthropathies. The clinical expression in highly variable, ranging from intrauterine death to asymptomatic carrier state. Prevalence of severe HPP is estimated to be about 1/100,000 to 1/300,000 live births in Canada and Europe respectively, while in adults the estimated prevalence is 1 per 6370.There are seven recognized forms of HPP based on age at onset, with younger age associated with more severe disease: "adult" HPP, "mild childhood" HPP, "severe childhood" HPP, "infantile" HPP, and "perinatal" HPP, the rare "benign prenatal" and the odonto-HPP, the most common and mild form, with only dental manifestations. Other features of early-onset severe disease include pyridoxine-dependent seizures, hypercalciuria, hypercalcemia, muscle weakness and craniosynostosis leading to elevated intracranial pressure. In late-onset HPP common features include non-healing metatarsal "stress" fractures, femoral pseudofractures resembling AFF, chondrocalcinosis and PPi arthropathy. Finally there are "carriers" of the disease, meaning subjects' heterozygotes for one abnormal TNSALP allele but in general good health. Laboratory findings include persistently low alkaline phosphatase activity, elevated phosphoethanolamine level and elevated serum pyridoxal 5 phosphate, which seems to be the most sensitive and specific marker of HPP. Low alkaline phosphatase levels must be differentially diagnosed from other inherited bone diseases (severe osteogenesis imperfecta, cleidocranial dysplasia) or acquired disease (multiple myeloma, glucocorticoids, bisphosphonates, denosumab treatment, hypothyroidism, vitamin D intoxication, milk-alkali syndrome, etc). Positive family history or low alkaline phosphatase levels in first degree relatives might facilitate the correct diagnosis. Finally genetic testing confirms the diagnosis (more than 300 mutations, mainly missense) and the pattern of inheritance (autosomal dominant or recessive). Prognosis was poor, especially for the "infantile" and "perinatal" HPP. Treatment includes supportive measures, such as extended mechanical ventilation, low calcium diet, loop diuretics, craniotomy for elevated intracranial pressure, or a course of teriparatide in adults for non-healing fractures. Treatment with asfotase alfa (recombinant TNSALP targeted to hydroxyapatite) approved since 2015 for severe paediatric onset HPP has dramatically improved survival and quality of life.
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Bone Markers in Thalassemia Major

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Osteoporosis represents a prominent cause of morbidity in patients with thalassemia major (TM). The delay in sexual maturation, the presence of diabetes and hypothyroidism, the parathyroid gland dysfunction, the progressive marrow expansion, the iron toxicity on osteoblasts, the use of iron chelators, the deficiency of growth hormone (GH) or insulin growth factors (IGFs) have been identified as major causes of bone loss in TM. Dynamic bone formation histomorphometry studies established reduced bone formation rate in TM patients, which is thought to-date to be mainly the result of iron poisoning in osteoblasts and/or the result of reduced function of GH and IGF-1 axis. However, novel molecules seem to be implicated in osteoblast dysfunction in TM. Dickkopf-1 (Dkk-1) is a Wnt signaling inhibitor that inhibits the osteoblast differentiation and function. Sclerostin is another Wnt inhibitor which is produced by osteocytes and inhibits osteoblast-driven bone formation. Both Dkk-1 and sclerostin were found to be elevated in the serum of patients with TM and osteoporosis. Furthermore, recent data support that the reduced osteoblastic activity is accompanied by a comparable or even greater increase in osteoclast function in TM. Several biochemical markers that reflect bone resorption, such as the N- or C- cross-linking telopeptide of collagen type I (NTX or CTX, respectively) and the tartrate-resistant acid phosphatase type-5b (TRACP-5b) are elevated in the serum or urine of patients with TM and osteopenia or osteoporosis. These markers are reduced after administration of anti-resorptive agents, like bisphosphonates that are used for the management of osteoporosis in TM patients. The increased osteoclast activity, which is observed in TM, is due to an imbalance in the receptor-activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) system and the ratio of sRANKL/OPG is elevated in the serum of TM patients with bone loss. Moreover, the overproduction of cytokines that are involved in osteoclastogenesis, such as interleukin (IL)-1, IL-6, transforming growth factor-beta, activin-A and tumor necrosis factor-alpha is present in TM. These data suggest that in addition to our current management of osteoporosis in TM, novel drugs that target RANKL, such as denosumab, which has been licensed by FDA and EMA for the treatment of postmenopausal osteoporosis, and antibodies against Dkk-1 or against sclerostin (such as romosozumab) may be future agents for the effective control of bone

loss in thalassemia. Bone markers of bone resorption and formation along with bone mineral density measurements are useful tools for the follow-up of bone loss in TM patients under anti-osteoporotic treatment.

Inhibitors of bone resorption: from the treatment of cancer hypercalcemia to the prevention of metastases

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Tumor bone disease is most commonly seen in breast, prostate, lung and kidney cancer, as well as multiple myeloma. Bone metastases often lead to skeletal complications typically referred to as skeletal-related events (SREs). Bone destruction is mediated by the osteoclasts, the normal bone resorbing cells, whose activity and proliferation are increased in the presence of tumor cells. Inhibitors of bone resorption, first the bisphosphonates and, later, denosumab, have been shown to be effective to prevent SREs. Before the introduction of inhibitors of bone resorption, hypercalcemia was quite often the cause of death in patients with advanced breast cancer and bone metastases. It was in the early eighties that the bisphosphonate pamidronate was shown to correct cancer hypercalcemia in most cases. A single infusion of zoledronic acid was then shown to be effective in more than 90% of the cases. In the last two decades, the bisphosphonates and denosumab have become established as a valuable additional approach to the range of current treatments in patients with tumor bone disease. Multiple, randomized, controlled trials have clearly demonstrated that they are effective in reducing skeletal morbidity from metastatic cancer. Zoledronic acid has been shown to be more effective than pamidronate in breast cancer metastatic to bone and, compared to zoledronic acid, denosumab has been shown to further reduce the skeletal morbidity rate in patients with solid tumors and bone metastases.
Inhibitors of bone resorption have also been shown to counteract cancer treatment-induced bone loss (CTIBL). Androgen deprivation for prostate cancer and aromatase inhibitors in breast cancer accelerate age-related bone loss and increase fracture rates. Antiresorptive treatment has been shown to prevent CTIBL and denosumab reduces fracture rates in both disease settings. Recent data indicate that inhibitors of bone resorption also increase disease-free and overall survival in postmenopausal women with breast cancer when used in the adjuvant setting. Bone targeted agents may disrupt tumor cell / bone cell interactions, and thereby affect survival, dormancy and migration of tumor cells to other distant sites. The results of large adjuvant trials in breast cancer have demonstrated the ability of bisphosphonates to prevent metastases and improve disease outcomes in women with low levels of female hormones. The improvement in disease outcomes in both the zoledronic acid and oral clodronate trials were predominantly mediated by a reduction in bone metastases as the first distant metastatic site. A formal individual patient data meta-analysis of data from more than 18,000 women involved in 26 randomized trials of adjuvant bisphosphonates for early breast cancer showed that bisphosphonates not only improved time to first distant recurrence in bone but also overall breast cancer recurrence, distant recurrence and breast cancer mortality, at least in postmenopausal women. Bisphosphonates are likely to become part of routine clinical practice in the adjuvant management of CTIBL in 'at risk' patients and prevention of metastases in patients with low level of female hormones. Ongoing trials of denosumab will add interesting data to the new role of adjuvant anti-resorptives in CTIBL and metastases prevention.

Session 4: Chronic Kidney Disease

CKD-MBD – Input from the clinical laboratory

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Since 2005, the term 'Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD)' should be used to describe the broader clinical syndrome encompassing mineral abnormalities of calcium, phosphorus PTH and vitamin D metabolisms; or abnormalities in bone turnover, mineralization, volume, linear growth, or strength; or vascular or other soft-tissue calcification. The CKD-MBD guidelines were originally published in 2009 and a draft of a 2016 update has been released in August 2016.
The recommendations for biological parameters assessment are still based on regular monitoring of calcium, phosphorus, PTH, phosphatase alkaline (PAL) and vitamin D levels. Source of variations included physiologic parameters such as meal or sun exposure but also internal regulation by calcium and phosphate balance during dialysis session or PTH down regulation by vitamin D. Analytical variations, due to the lack of standardisation, remain the most important factor and should be taken into account specially, but not only, for PTH. In addition, the emergence of third generation assays will modify the classical cut-off of PTH values. The CKD-MBD range of 2 to 9-fold the upper limit of the laboratory requires that these normal values were defined rigorously with special attention of vitamin D levels. Interpretation of results should be based on serial assessments of phosphorus, calcium and PTH levels, considered together. In addition, it should be noted that modest increases in PTH may represent an appropriate adaptive response to declining kidney function. During the last decade, FGF-23 and its co-receptor Klotho, appear as a major regulator of Calcium / Phosphate / PTH balance. Beyond calcium and phosphate regulation, FGF-23 is recognized as a biomarker of cardiac disease, mainly heart failure and left ventricular hypertrophy. By contrast, soluble Klotho is thought to be a protective factor.
Emerging data strongly suggest that DEXA should be performed regularly, but bone turnover could be evaluated using the association of PTH and bone PAL. Exploration of collagen metabolism such as CTX, PINP, Trap5B remains not recommended neither to bone remodeling or vascular calcifications. The bioclinical interpretation should be based on risk factors for osteoporosis, DEXA and bone turnover biomarkers and could help to define bone biopsy indications which could in turn impact treatment decisions.
Exploring the two main pathways of bone and vascular remodeling, the OPG/RANKL/RANK system and the Wnt/betacatein/sclerostin pathway, could be a tempting option. During the course of CKD, the equilibrium between inhibitors or activators of bone resorption and bone formation could be modify and could be dramatically dependent of PTH levels. The involvement of these metabolic signaling in both bone and vessels are not completely understood. However, these metabolic pathways are therapeutic targets now available in osteoporosis and could be considered as helpful after a clear analysis and understanding of the type of osteodystrophy. Thus, combining risk factors, DEXA, mineral metabolism, bone remodeling biomarkers and eventually bone biopsy could help to define the indications or to the monitoring of activity of future treatments.

Bone markers and vascular calcification in CKD-MBD

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Patients with chronic kidney disease (CKD), and still more, patients treated by dialysis, have an impressive higher risk of cardiovascular mortality. This over-mortality is explained, at least in part, by the presence of early, severe and very progressive vascular calcifications (VC). There is a strong link between calcium, phosphate and parathormone concentrations and cardiovascular mortality. Interestingly, both the abnormalities of bone turnover (high and low bone turnover) and bone volume (osteopenia or osteoporosis) are associated with the presence and progression of VC in dialysis patients. In this context, we will briefly review if bone biomarkers have a role in the diagnosis and management of these bone abnormalities. Basic researches have also focused on the active phenomena involved in the pathogenesis of VC. If phosphate level has a central role, several pro- and anti-calcification proteins have been described. Among these different proteins, some have been showed to be associated with VC in dialysis patients. We will review available data but we focus on two biomarkers, matrix Gla protein (MGP) and sclerostin. Indeed, these two proteins have a double interest: first, therapies are available (anti-sclerostin antibody and vitamin K) and could be useful in the near future to decrease VC (or, at least, decrease their development). Second, from a laboratory perspective, these two biomarkers are relatively difficult to interpret (and sometimes to measure) making the collaboration between labs and clinicians mandatory.
Sclerostin, a 22kDa protein secreted by osteocytes and chondrocytes, was originally described in humans with mutation of its producing gene (SOST), leading to a phenotype characterized by a high bone mass (sclerosteosis). Further researches suggested that sclerostin acts as a potent inhibitor of osteoblast activity and thus bone formation. Recent evidence points to sclerostin as the long missing link between osteocytes as mechanoreceptors, and bone formation. Sclerostin has been extensively studied in the context of chronic kidney disease (CKD), especially as a putative driver of the bone-vascular axis. Numerous correlates have been identified including age, glomerular filtration rate (GFR) and parathormone. Many investigators reported associations between circulating sclerostin levels and indices of bone and vascular health and mortality. However, the strength and even the direction of these associations showed important differences between studies. Besides case-mix, analytical issues may have contributed to the discrepant findings.
MGP is an 11 kDa protein secreted by vascular smooth muscle cells, acting as a potent local inhibitor of vascular calcification. In order to be fully active, MGP must be phosphorylated and carboxylated. This carboxylation is highly dependent on availability of vitamin K. Recent data have shown that dephosphorylated-uncarboxylated (dp-ucMGP) MGP concentrations, the inactive form of MGP, were higher in hemodialysis patients and that dp-ucMGP could be associated with vascular calcifications. Interestingly, dp-ucMGP is higher in dialysis patients treated by anti-vitamin K (but rapidly decreased after stopping anti-vitamin K). Moreover, dp-ucMGP concentrations decreased after vitamin K therapy. The impact of vitamin K on VC is currently investigated by several ongoing randomized controlled trials.

Plenary Lecture 2

The Clinical Impact of Standardisation of 25-Hydroxyvitamin D Assays

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A high prevalence of vitamin D deficiency continues to be reported internationally stimulating significant public health and individual patient concerns. Several factors contribute to variation in measurements of serum/plasma 25-hydroxyvitamin D, the biomarker of vitamin D status, confounding efforts to develop public health and clinical vitamin D guidelines. Analytical variation arising from lack of assay standardization is one of these factors as indicated by the Vitamin D External Quality Assurance Scheme (DEQAS) data. The Vitamin D Standardization Program (VDSP) has provided the resolution of this issue with development of a reference measurement procedure accepted by the Joint Committee for Standardization of Laboratory Medicine (JCTLM). Furthermore, the VDSP has verified protocols to retrospectively standardize assays from prior research including the US NHANES and German KIGGS surveys. Reanalysis of such standardized data have often indicated statistically significant changes to serum 25-hydroxyvitamin D levels initially collected in these surveys although clinical significance has varied. Perhaps the most clinically significant change from a retrospective standardization has been the loss of the so-called J-curve of the relationship between serum 25-hydroxyvitamin D and all-cause mortality. Unlike some original results, current data indicate increased all-cause mortality with levels less than 50 nmol/L (20 ng/mL) and no increase at levels greater than 100 nmol/L (40 ng/mL). The standardization of 25-hydroxyvitamin D levels is consolidating agreement of clinically significant cut points at 20 nmol/L for plasma mineral homeostasis and 50 nmol/L for other clinical outcomes including bone mineral homeostasis and all-cause mortality.

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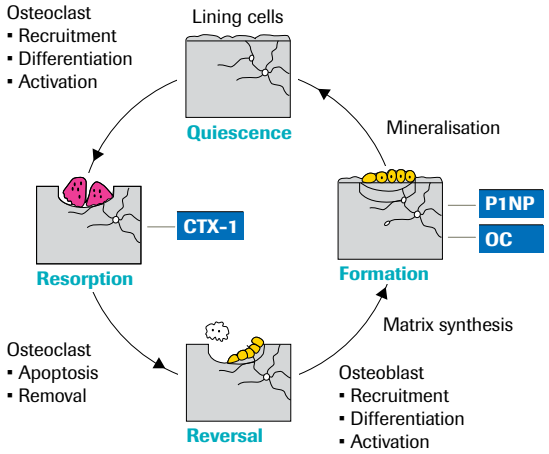
What does Roche offer?	What does it detect?	What is its intended use/clinical value?
Elecsys β-CrossLaps/ serum (CTx)	Degradation products of type I collagen during bone resorption	Aid in the assessment of bone resorption rate, monitoring anti-resorptive therapies such as bisphosphonates
Elecsys total P1NP* (Procollagen 1 N-terminal peptide)	Degradation products of type I collagen during bone formation	Aid in monitoring therapy of osteoporosis in post-menopausal women and in patients diagnosed with Paget's disease of the bone
Elecsys N-MID Osteocalcin	Non-collagenous protein in bone matrix, synthesized by osteoblasts during bone formation	Aid in the control of antiresorptives therapeutic efficiency, e.g. for patients with osteoporosis or hypercalcemia
Elecsys Vitamin D total II	Vitamin D3 (25-OH) and vitamin D2 (25-OH)	Aid in the assessment of vitamin D sufficiency
Elecsys PTH (Parathyroid hormone)	Parathyroid hormone secreted by parathyroid glands	Differential diagnosis of hypercalcemia and hypocalcemia and monitoring of parathyroid surgery

* Not available in the US

Bone remodelling cycle



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