BIOGRAPHICAL SKETCH

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NAME: Hartmut H. Malluche, MD

eRA COMMONS USER NAME (credential, e.g., agency login): hartmut.malluche

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Phillips University, Marburg/L., Germany	BS	05/1965	Medicine
J.W. Goethe University, Frankfurt/M., Germany	MD	07/1970	Medicine
J.W. Goethe University, Frankfurt/M., Germany	MD	07/1973	Internal Medicine
J.W. Goethe University, Frankfurt/M., Germany	MD	07/1975	Nephrology

A. Personal Statement

I have trained over 90 students, residents, fellows and young faculty members for over 30 years. My particular focus is now on raising young faculty to become academically-oriented investigators rather than merely acquiring clinical knowledge that is applied to patients in a private practice setting. For decades, I have been conducting NIH-funded research in renal osteodystrophy. The following references highlight my experience and qualification for this project.

1. Malluche, H.H., Blomquist, G., Monier-Faugere, M.C., Cantor, T.L. & Davenport, D.L. (2015). High parathyroid hormone level and osteoporosis predict progression of coronary artery calcification in patients on dialysis. Journal of the American Society of Nephrology, 26(10), 2534-2544. PMID: 25838468
2. Malluche, H.H., Davenport, D.L., Cantor, T. & Monier-Faugere, M.C. (2014). Bone mineral density and serum biomechanical predictors of bone loss in patients with CKD on dialysis. Clinical Journal of the American Society of Nephrology, 9(7), 1254-1262. PMID: 24948144
3. Lima, F., El-Husseini, A., Monier-Faugere, M.C., David, V., Mawad, H., Quarles, D. & Malluche, H.H. (2014). FGF-23 serum levels and bone histomorphometric results in adult patients with chronic kidney disease on dialysis. Clinical Nephrology, 82(5), 287-295. PMID: 25208316
4. Haarhaus, M., Monier-Faugere, M.C., Magnusson, P. & Malluche, H.H. (2015). Bone alkaline phosphatase isoforms in hemodialysis patients with low versus non-low bone turnover: a diagnostic test study. American Journal of Kidney Disease, 66(1), 99-105. PMID: 25843703
5. Fang, Y., Ginsberg, C., Sugatani, T., Monier-Faugere, M.C., Malluche, H.H. & Hruska, K.A. (2014). Early chronic kidney disease-mineral bone disorder stimulates vascular calcification. Kidney International, 85(1), 142-150. PMID: 23884339

B. Positions and Honors

Positions and Employment

1969-1970 Residency, County Hospital Aichach, Germany
1970-1975 Fellowship and Faculty, Center of Internal Medicine, University Hospitals, J.W. Goethe University, Frankfurt/Main
1975-1981 Assistant and Associate Professor, LAC-USC Medicine Center, Department of Medicine, Division of Nephrology, Los Angeles, CA

1981- Professor and Chief, Division of Nephrology, Bone and Mineral Metabolism, Department of Internal Medicine, University of Kentucky Medical Center, Lexington, KY
2000- Robert G. "Robin" Luke Chair in Nephrology, Department of Internal Medicine, University of Kentucky Medical Center, Lexington, KY
2000-2005 Program Director, General Clinical Research Center, University of Kentucky, Lexington, KY
2013- Co-chair, Internal Advisory Board for the Center for Clinical and Translational Science, University of Kentucky, Lexington, KY

Other Experience and Professional Memberships

1983-1986 NIH Special Study Section, member
1984-1987 NIH Program Projects Site Visit, consultant
1985 NIH, General Medicine B Study Section, member
1985-1986 NIMH Study Section, member
1985-1992 NIH, Orthopedic Study Section, member
1990 NIH/NCI Site Visit Team, member
1992 NIH, Orthopedics and Musculoskeletal Study Section, member
1992 Food and Drug Administration, grant reviewer
1993 NIH/NIEHS Lead Bone Metabolism Workshop, consultant
1993 NIH, Conference on Morbidity and Mortality in Dialysis Patients, consultant
1994 Food and Drug Administration Metabolism Renal Panel, member
1994 NIH, Nephrology, Bone and Mineral Metabolism, consultant
1996 Food and Drug Administration Arthritis Advisory Committee, consultant
1996- Honorary Member, Australian and New Zealand Society of Nephrology
1998-2006 NIH/NCRR GCRC, Clinical Research Review Committee and Site Visits, chairman/member
2000 Food and Drug Administration Division of Cardio-Renal Drug Products, advisor
2003-2005 NIH/NIAMS Special Emphasis Panel, members
2004-2009 NIH/NCRR Special Emphasis Panel, members
2005 NIH Special Emphasis Panel, members
2006- Honorary Member, South African Renal Association
2007-2009 NIH/CSR Special Emphasis Panel, members
2009-2013 NIH/NIDDK Special Emphasis Panel, chairman/members
2010-2012 NIH/NIDDK Studies Review Panel, members
2013-2014 NIH/NIDDK Ancillary Studies, members
2013 Medicare End Stage Renal Disease Technical Expert Panel, advisor
2013 NIH/NIAID Special Emphasis Panel, member
2015 NIH/NCATS Special Emphasis Panel, member
2015-2016 NIH/SBDD Study Section, member
2016 NIH/NIDDK Study Section (Biomarker R01), chairman

Honors

1987- Who's Who in the World
1992 Distinguished Lecturer Award, Chinese Society of Nephrology, Taiwan
1996- 100 Best Doctors in America
2003 National Leadership Award, Honorary Chairman, Physicians' Advisory Board
2003 Appreciation for Valuable Contributions, Swedish Society of Medicine
2006 Clinical and Translational Science Mentor Recognition Award, University of Kentucky
2014 The Rogosin Visiting Professor, University of Cornell

C. Contribution to Science

1. Renal osteodystrophy: The pathogenesis and treatment of renal osteodystrophy represented a very early focus in my academic career. In 1976, I have published that bone abnormalities begin with CKD stage 2-3. Starting in the late 70s, I was also involved in the evaluation of effects of management of renal osteodystrophy on clinical radiographic, biochemical and histologic abnormalities of bone. In collaboration with colleagues from the U.S. and abroad, I was able to demonstrate that cardiovascular morbidity and mortality in CKD 2-4 can be predicted by markers of bone formation and resorption. Most recently, I was able to identify blood levels of sclerostin and TRAP-5B as predictors for bone loss and high parathyroid

hormone levels and osteoporosis as predictors for progression of coronary artery calcification in CKD-5D patients.

a. Malluche, H.H., Ritz, E., Lange, H.P., Kutschera, J., Hodgson, M., Seiffert, U. & Schoeppe, W. (1976). Bone histology in incipient and advanced renal failure. Kidney International, 9(4), 355-362. PMID: 940274

b. Goldstein, D.A., Malluche, H.H. & Massry, S.G. (1979). Management of renal osteodystrophy with $1,25(OH)_2D_3$. Mineral and Electrolyte Metabolism, 2, 35-47.

c. Fahrleitner-Pammer, A., Herberth, J., Browning, S.R., Obermayer-Pietsch, B., Wirnsberger, G., Holzer, H., Dobnig, H. & Malluche, H.H. (2008). Bone markers predict cardiovascular events in chronic kidney disease. Journal of Bone and Mineral Research, 23(11), 1850-1858. PMID: 18597636

d. Malluche, H.H., Mawad, H.W. & Monier-Faugere, M.C. (2011). Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. Journal of Bone and Mineral Research, 26(6), 1368-1376. PMID: 21611975

e. Malluche, H.H., Blomquist, G., Monier-Faugere, M.C., Cantor, T.L. & Davenport, D.L. (2015). High parathyroid hormone level and osteoporosis predict progression of coronary artery calcification in patients on dialysis. Journal of the American Society of Nephrology, 26(10), 2534-2544. PMID: 25838468

2. Osteoporosis: A second major focus in my research is related to understanding pathogenesis, diagnosis and treatment of osteoporosis in patients with and without CKD. My group has established the model of ovariohysterectomy in animals for postmenopausal bone loss. We could demonstrate that bone formation is not decreased rather increased after loss of ovarian function, but bone resorption increases more than bone formation with explains bone loss. In the clinical setting, we found postmenopausal osteoporosis to present with distinct levels of bone turnover whereby high turnover is characterized by excessive resorption (requiring anti-resorptives) while low turnover presents with low bone formation and low resorption which slightly exceeds formation. The latter situation calls for anabolic therapy rather than anti-resorbers. Bone biopsies are required for diagnosis. Most recently, we established a bone matrix disorder in osteoporotic patients with fractures despite non-osteoporotic t scores.

   a. Faugere, M.C., Friedler, R.M., Fanti, P. & Malluche, H.H. (1990). Bone changes occurring early after cessation of ovarian function in beagle dogs: a histomorphometric study employing sequential biopsies. Journal of Bone and Mineral Research, 5(3), 263-272. PMID: 2333786

   b. Malluche, H.H., Mawad, H. & Monier-Faugere, M.C. (2007). Bone biopsy in patients with osteoporosis. Current Osteoporosis Reports, 5(4), 146-152. PMID: 18430388

   c. Malluche, H.H., Porter, D.S., Mawad, H., Monier-Faugere, M.C. & Pienkowski, D. (2013). Low-energy fractures without low t-scores characteristic of osteoporosis. Journal of Bone and Joint Surgery America, 95(19), e1391-e1396. PMID: 24088974

3. Aluminum: Presentation of renal osteodystrophy included for many years a component of osteomalacia. We were able to show that this is related to the use of aluminum containing phosphate binders. We could show that one-time infusion of deferoxamine can be used for diagnosis of aluminum overload and long-term deferoxamine therapy can reverse the osteomalacia and loss of bone resulting from aluminum intoxication. Importantly, we could identify aluminum toxicity of an infant formula as a cause of neonatal uremia resulting in death of most affected infants. Avoidance of aluminum did prevent this serious clinical entity.

   a. Malluche, H.H., Smith, A.J., Abreo, K. & Faugere, M.C. (1984). The use of deferoxamine in the management of aluminum accumulation in bone in patients with renal failure. New England Journal of Medicine, 311(3), 140-144. PMID: 6377067

   b. Freundlich, M., Zilleruelo, G., Abitbol, C., Strauss, J., Faugere, M.C. & Malluche, H.H. (1985). Infant formula as a cause of aluminum toxicity in neonatal uraemia. The Lancet, 2(8454), 527-529. PMID: 2863545

   c. Faugere, M.C., Arnala, I.O., Ritz, E. & Malluche, H.H. (1986). Loss of bone resulting from accumulation of aluminum in bone of patients undergoing dialysis. Journal of Laboratory and Clinical Medicine, 107(6), 481-487. PMID: 3486929

d. Malluche, H.H., Faugere, M.C., Friedler, R.M., Matthews, C. & Fanti, P. (1987). Calcitriol, parathyroid hormone, and accumulation of aluminum in bone in dogs with renal failure. Journal of Clinical Investigation, 79(3), 754-761. PMID: 3818947

4. Bone biopsy and histomorphometry: Early on in my career, it became clear to me that for thorough understanding of bone abnormalities in CKD one needs to look at the bone itself and not only at blood levels or at images obtained by x-ray, CT or similar. Only bone histology gives information on cellular number, activity, mineral and collagen quality. For this purpose, I developed a minimally bone biopsy technique. In addition, I developed a computerized system (without applying for a patent) to quantitatively assess bone changes because renal osteodystrophy does not present like cancer with clear qualitative cellular abnormalities rather mainly quantitative deviations from normal. I validated this system and collected a large number of normal bone samples to provide the basis for clinical studies addressing histomorphometric changes. This was complimented by my development of a bone biopsy technique and employment of bone biopsies in clinical practice and research of both osteoporosis and renal osteodystrophy. The computerized method has been adopted by three different companies that sell those instruments to laboratories across the globe involved in histomorphometry of bone.
    a. Manaka, R.C. & Malluche, H.H. (1981). A program package for quantitative analysis of histologic structure and remodeling dynamics of bone. Computer Programs in Biomedicine, 13(3-4), 191-201. PMID: 7032836
    b. Malluche, H.H., Sherman, D., Meyer, W. & Massry, S.G. (1982). A new semiautomatic method for quantitative static and dynamic bone histology. Calcified Tissue International, 34(5), 439-448. PMID: 6817891
    c. Malluche, H.H., Meyer, W., Sherman, D. & Massry, S.G. (1982). Quantitative bone histology in 84 normal American subjects: micromorphometric analysis and evaluation of variance in iliac bone. Calcified Tissue International, 34(5), 449-455. PMID: 6817892
    d. Malluche, H.H., Langub, M.C. & Monier-Faugere, M.C. (1999). The role of bone biopsy in clinical practice and research. Kidney International, 73, S20-S25. PMID: 10633459

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41146530/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

R01 DK080770 — Malluche (PI) — 07/01/15-06/30/20
Renal Osteodystrophy: A Fresh Approach
The goal of this study is to test the concept that osteoporosis associated with chronic kidney disease can be successfully treated when treatment is individualized by patients' turnover status.
Role: PI

R01 AR061578 — Malluche (PI) — 07/01/12-06/30/16
Bisphosphonate Use and Bone Quality
The goal of this project is to determine the effect of long-term bisphosphonate treatment on the material, histomorphometric and nanomechanical properties of human bone.
Role: PI

R01 HL128592 — Vandsburger (PI) — 08/01/15-04/30/20
Novel MRI Techniques for Imaging Cardiac Fibrosis to Improve Clinical Practice in Patients with Renal Failure
The goal of this project is to seek to comprehensively validate a gadolinium free MRI technique for identification and quantification of cardiac fibrosis and probe its application in individuals with renal failure.
Role: Co-investigator

Center for Clinical and Translational Science, University of Kentucky — Mohamed (PI) — 01/29/15-07/31/16
Advancements in the understanding of chronic kidney disease-mineral and bone disorder (CKD-MBD)
The goal of this project is to study the pathogenesis of bone disease in diabetic CKD patients and to find early non-invasive parameters for bone disease in CKD patients.

Role: Mentor

American Heart Association Vandsburger (PI) 07/01/14-06/30/16
High-resolution magnetization transfer weighted cardiac magnet resonance imaging of myocardial fibrosis using endogenous contrast mechanisms
The goal of this study is to validate a 2-point MT-weighted MRI method against standard of care gadolinium enhanced MRI for diagnosis of cardiac fibrosis.
Role: Co-investigator

Keryx Pharmaceuticals, Inc. Malluche (PI) 05/01/15-01/31/16
Effects of ferric citrate hydrate on aortic calcification, bone, and FGF-23 in an animal model
The goal of this study is to investigate the effects of ferric citrate hydrate treatment on the development of renal osteodystrophy, serum and bone FGF-23, and aortic calcifications.
Role: PI

Completed Research Support

R01 DK080770 Malluche (PI) 03/01/09-02/28/14
Renal Osteodystrophy: A Fresh Approach
There were two major goals of this project:
1) Comparison of DXA and QCT for diagnosis of bone loss in CKD-5 patients and determination of the prevalence of low bone turnover in CKD-5 patients with bone loss.
2) Identification of the optimal combination of noninvasive tests for definition of the turnover component of renal osteodystrophy.

Role: PI

R01 AR061578 Malluche (PI) 07/01/13-06/30/14
Bisphosphonate Use and Bone Quality
The goal of this study was to determine the effect of varying duration bisphosphonate treatment on the calculated finite element analyses-derived stiffness and strength of human bone samples.

R01 DK069681 O'Neill (PI) 01/01/07-12/31/12
Effects of pyrophosphates, and 2 bisphosphonates on vascular calcifications and bone turnover in uremic rats
Role: Consultant

R01 DE019490 Lin (PI) 04/01/10-03/31/12
Is Mitf the Missing Puzzle Linking NFATc1 to Osteoclastogenesis?
Role: Consultant

Novartis Pharmaceuticals Gedaly (Co-PI) 12/16/11-12/31/13
Effects of zortress® (everolimus) versus standard immunosuppression therapy on progression of coronary artery calcifications in patients with renal transplantation
Role: Co-PI