Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders

December 4─5, 2006
Crystal Gateway Marriott
Arlington, Virginia, USA

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Welcome!

CONTENTS

On behalf of the organizers of this ASBMR-sponsored meeting, **Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders**, we welcome you and thank you for your participation.

Over the last several years, scientists from multiple disciplines have contributed to an astonishing increase in both our knowledge of vitamin D–related diseases and the appropriate treatment strategies for these diseases. However, there exist considerable and seemingly unresolved conflicts regarding appropriate diagnostic criteria and treatment for skeletal and non-skeletal vitamin D–related diseases. As a consequence, transmission of this increase in knowledge to the clinical arena has been considerably restricted. Therefore, we believe that it is critical to bring together both clinical and basic investigators working in this field to encourage open discussion regarding the conflicts and goals of the vitamin D field, to develop scientific approaches to resolve these conflicts, and to facilitate development of a reliable knowledge base. We believe that these discussions will facilitate translational research and transfer of information to the clinical arena.

This symposium will focus on identification, diagnosis, and management of vitamin D–related disorders. Our goal is to provide an opportunity for the participants in the field—researchers, clinicians, health policy personnel, regulatory personnel, marketing personnel, and others—to interact, to think collegially, to hypothesize, to argue constructively, and to plan together the future of appropriate treatment strategies for vitamin D–related disorders.

The organizers wish to thank the following U.S. National Institutes of Health Institutes for providing funding for this meeting through an R13 grant: the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute on Aging, (NIA), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the Office of Dietary Supplements (ODS).

We are grateful for the co-sponsorship of the American Association of Orthopaedic Surgeons (AAOS), the American Society for Nutrition (ASN), The Endocrine Society (ENDO), the International Society for Clinical Densitometry (ISCD), the National Osteoporosis Foundation (NOF), the Orthopaedic Research Society (ORS), the Osteogenesis Imperfecta Foundation (OIF), and The Paget Foundation for Paget's Disease of Bone and Related Disorders. We extend a special thanks to our colleagues (too many to name) for ideas, recommendations, and guidance along the way. We also want to thank the companies that have helped to support this meeting. Finally, we wish to thank the ASBMR staff who provided continuous organizational support.

Sincerely,

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*Funding for this conference was made possible in part by **AR055036** from the National Institutes of Health. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services, nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.*

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National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
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American Society for Bone and Mineral Research

Contemporary Diagnosis and Treatment of Vitamin D-Related Disorders

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ASBMR Young Investigator Award Recipients

Co-supported by educational grants from Immunodiagnostic Systems

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American Society for Bone and Mineral Research
Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders

Schedule-at-a-Glance

Monday, December 4, 2006

Time	Session
7:00 a.m. – 8:00 a.m.	Breakfast
8:00 a.m. – 8:15 a.m.	Introductions
8:15 a.m. – 10:35 a.m.	Session 1: Assessment of Vitamin D Status
10:35 a.m. – 10:55 a.m.	Break
10:55 a.m. – 12:55 p.m.	Session 2: Vitamin D Physiology
12:55 p.m. – 1:25 p.m.	Lunch and Poster Viewing
1:25 a.m. – 2:05 p.m.	Poster Session 1
2:05 p.m. – 3:50 p.m.	Session 3: Traditional Abnormalities of Vitamin D
3:50 p.m. – 4:10 p.m.	Break
4:10 p.m. – 5:55 p.m.	Session 4: Vitamin D and Population Health
5:55 p.m.	Adjourn
5:55 p.m. – 7:00 p.m.	Poster Viewing

Tuesday, December 5, 2006

Time	Session
7:00 a.m. – 8:00 a.m.	Breakfast
8:05 a.m. – 10:05 a.m.	Session 5: Non-Traditional Roles of Vitamin D
10:05 a.m. – 10:25 a.m.	Break
10:25 a.m. – 12:10 p.m.	Session 6: Vitamin D and Kidney Disease
12:10 p.m. – 12:40 p.m.	Lunch and Poster Viewing
12:40 p.m. – 1:20 p.m.	Poster Session 2
1:20 p.m. – 2:45 p.m.	Session 7: Vitamin D and Other Metabolic Bone Diseases
2:45 p.m. – 3:05 p.m.	Break
3:05 p.m. – 4:05 p.m.	Session 8: Final Comments
4:05 p.m.	Meeting Adjourns
4:05 p.m. – 5:00 p.m.	Poster Viewing Optional

American Society for Bone and Mineral Research
Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders

Monday, December 4, 2006

BREAKFAST
7:00 a.m. – 8:00 a.m.

INTRODUCTION
8:00 a.m. – 8:15 a.m.

8:00 a.m. **Opening Comments on Behalf of ASBMR**
Elizabeth Shane, M.D., Past-President, American Society for Bone and Mineral Research, Columbia University College of Physicians & Surgeons, New York, New York, USA

8:05 a.m. **Opening Comments on Behalf of NIDDK**
Ronald N. Margolis, Ph.D., National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA

8:10 a.m. **Opening Comments on Behalf of NIAMS**
Stephen I. Katz, M.D., Ph.D., Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA

SESSION 1
Assessment of Vitamin D Status

Moderator: Anthony W. Norman, Ph.D., University of California, Riverside, California, USA

8:15 a.m. – 10:35 a.m.

Presentation Number

8:15 a.m. **Molecular Action of 1,25$(OH)_2$D** **1**
Mark R. Haussler, Ph.D., University of Arizona College of Medicine, Phoenix, Arizona, USA

8:35 a.m. **Measurement of 25(OH)D (RIA, HPLC, LC/MS/MS)** **2**
Glenville Jones, Ph.D., Queen's University, Kingston, Ontario, Canada

8:55 a.m. **The Relative Value of 25(OH)D and 1,25$(OH)_2$D Measurements** **3**
Paul Lips, M.D., Ph.D., VU University Medical Center, Amsterdam, Netherlands

9:15 a.m. **Activation of Gene Expression by 1,25-Dihydroxyvitamin D_3: Delineating Intracellular Mechanisms and Extracellular Influences Both *In Vitro and In Vivo*** **4**
J. Wesley Pike, Ph.D., University of Wisconsin, Madison, Wisconsin, USA

9:35 a.m. **Substrate and Enzyme Trafficking as a Means of Regulating 1,25-Dihydroxyvitamin D D Synthesis in Action** **5**
John S. Adams, M.D., Cedars-Sinai Medical Center, Los Angeles, California, USA

9:55 a.m. **YOUNG INVESTIGATOR AWARD** **6**
Prevalence of Vitamin D Insufficiency and Relationship with Peak Bone Mass in Young Men, Results from the Odense Androgen Study
Morten F. Nielsen, Odense University Hospital, Odense, Denmark

10:10 a.m. **Question and Answer Period**

BREAK

10:35 a.m. – 10:55 a.m.

SESSION 2
Vitamin D Physiology

Moderator: Hector F. DeLuca, Ph.D., University of Wisconsin, Madison, Wisconsin, USA

10:55 a.m. – 12:55 p.m.

		Presentation Number
10:55 a.m.	**Normal/Abnormal Vitamin D Physiology** Robert P. Heaney, M.D., Creighton University Osteoporosis Research Center, Omaha, Nebraska, USA	**7**
11:15 a.m.	**Vitamin D Skin Physiology** Michael F. Holick, M.D., Ph.D., Boston University School of Medicine, Boston, Massachusetts, USA	**8**
11:35 a.m.	**Vitamin D Economy in African Americans** Felicia Cosman, M.D., Helen Hayes Hospital, West Haverstraw, New York, USA	**9**
11:55 a.m.	**Vitamin D Requirements in Pregnancy/Lactation** Bruce W. Hollis, Ph.D., Medical University of South Carolina, Charleston, South Carolina, USA	**10**
12:15 a.m.	**YOUNG INVESTIGATOR AWARD** **Studies Using Nullmutant Mice Reveal Active Intestinal Calcium Transport in the Absence of Calbindin-D 9k or TRPV6** Bryan S. Benn, New Jersey Medical School, Newark, New Jersey, USA	**11**
12:30 a.m.	**Question and Answer Period**	

LUNCH AND POSTER VIEWING

12:55 p.m. – 1:25 p.m.

POSTER SESSION 1

1:25 p.m. – 2:05 p.m.

SESSION 3
Traditional Abnormalities of Vitamin D

Moderator: Murray J. Favus, M.D., University of Chicago, Chicago, Illinois, USA

2:05 p.m. – 3:50 p.m.

		Presentation Number
2:05 p.m.	**Skeletal Consequences of Vitamin D Insufficiency/Deficiency (Calcium Homeostasis and Growth/Development)** Connie Weaver, Ph.D., Purdue University, West Lafayette, Indiana, USA	12
2:25 p.m.	**Treatment Strategies for Vitamin D (D_3 vs. D_2) Insufficiency/Deficiency in Diseases Including GI Disorders** Daniel D. Bikle, M.D., Ph.D., University of California Veterans Affairs Medical Center, San Francisco, California, USA	13
2:45 p.m.	**Vitamin D Insufficiency/Deficiency Contributions to the Morbidity of Patients With Osteoporosis** Neil Binkley, M.D., University of Wisconsin, Madison, Wisconsin, USA	14
3:05 p.m.	**Evidence Report on Vitamin D** Ann B. Cranney, MD, MSc, Ottawa Health Research Institute, Ottawa, Ontario, Canada	15
3:25 p.m.	**Question and Answer Period**	

BREAK

3:50 p.m. – 4:10 p.m.

SESSION 4
Vitamin D and Population Health

Moderator: Lawrence G. Raisz, M.D., University of Connecticut Health Center, Farmington, Connecticut, USA

4:10 p.m. – 5:55 p.m.

		Presentation Number
4:10 p.m.	**Therapy of Osteoporosis with Calcium and Vitamin D** Bess Dawson-Hughes, M.D., Tufts University School of Medicine, Boston, Massachusetts, USA	16
4:30 p.m.	**NIH Women's Health Initiative** Rebecca Jackson, M.D., Ohio State University, Columbus, Ohio, USA	17
4:50 p.m.	**Vitamin D Toxicity, Policy, and Science** Reinhold Vieth, Ph.D., Mount Sinai Hospital, Toronto, Ontario, Canada	18
5:10 p.m.	**Establishing Guidelines for Vitamin D Intake** Elizabeth A. Yetley, Ph.D., Office of Dietary Supplements, National Institute of Health, Bethesda, Maryland, USA	19
5:30 p.m.	**Question and Answer Period**	

ADJOURN

5:55 p.m.

Tuesday, December 5, 2006

BREAKFAST
7:00 a.m. – 8:00 a.m.

SESSION 5
Non-Traditional Roles of Vitamin D

Moderator: Roger A. Bouillon, M.D., Ph.D., Katholieke Universiteit, Leuven, Belgium

8:00 a.m. – 10:00 a.m.

		Presentation Number
8:00 a.m.	**Vitamin D Receptor Agonists in the Treatment of Autoimmune Diseases** Luciano Adorini, M.D., BioXell, Milan, Italy	**20**
8:20 a.m.	**Role of Vitamin D Regulation in Prostate Cell Growth** David Feldman, M.D., Stanford University School of Medicine, Stanford, California, USA	**21**
8:40 a.m.	**Epidemiological Role of Vitamin D in Cancer** Edward Giovannucci, M.D., Sc.D., Harvard School of Public Health, Boston, Massachusetts, USA	**22**
9:00 a.m.	**Vitamin D and Breast Cancer** JoEllen Welsh, Ph.D., University of Notre Dame, Notre Dame, Indiana, USA	**23**
9:20 a.m.	**YOUNG INVESTIGATOR AWARD** **Maternal Vitamin D Insufficiency and the Risk of Preeclampsia, an Adverse Pregnancy Outcome** Lisa M. Bodner, University of Pittsburgh, Pittsburgh, Pennsylvania, USA	**24**
9:35 a.m.	**Question and Answer Period**	

BREAK

10:00 a.m. – 10:25 a.m.

SESSION 6
Vitamin D and Kidney Disease

Moderator: Craig B. Langman, M.D., Feinberg School of Medicine, Northwestern University Chicago, Illinois, USA

10:25 a.m. – 12:10 p.m.

		Presentation Number
10:25 a.m.	**Role of Vitamin D Deficiency in Chronic Kidney Disease** Stuart Sprague, D.O., Northwestern University, Evanston, Illinois, USA	**25**
10:45 a.m.	**Paradoxical Effects of Active Vitamin D Analogue Agents in CKD/End Stage Kidney Disease** L. Darryl Quarles, M.D., University of Kansas Medical Center, Kansas City, Kansas, USA	**26**

11:05 a.m. **Effects of Vitamin D and Analogues on Cardiovascular Events and Life Expectancy in Patients with CRF** **27**
Sharon M. Moe, M.D., Indiana University School of Medicine, Indianapolis, Indiana, USA

11:25 a.m. **Management of Renal Osteodystrophy in Childhood** **28**
Mary B. Leonard, M.D., MSCE, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

11:45 a.m. **Question and Answer Period**

LUNCH AND POSTER VIEWING

12:10 p.m. – 12:40 p.m.

POSTER SESSION 2

12:40 p.m. – 1:20 p.m.

SESSION 7
Vitamin D and Other Metabolic Bone Diseases

Moderator: David Goltzman, M.D., McGill University, Montreal, Quebec, Canada

1:20 p.m. – 2:45 p.m.

Presentation Number

1:20 p.m. **Primary Hyperparathyroidism and Vitamin D Deficiency** **29**
Shonni J. Silverberg, M.D., Columbia University College of Physicians & Surgeons, New York, New York, USA

1:40 p.m. **FGF-23/MEPE/TIO/XLH and Vitamin D Metabolism** **30**
Marc K. Drezner, M.D., University of Wisconsin, Madison, Wisconsin, USA

2:00 p.m. **Vitamin D–Resistant Diseases** **31**
Uri A. Liberman, M.D., Ph.D., Tel Aviv University, Tel Aviv, Israel

2:20 p.m. **Question and Answer Period**

BREAK

2:45 p.m. – 3:05 p.m.

SESSION 8
Final Comments

Moderators: All Session Moderators

3:05 p.m. – 4:05 p.m.

3:05 p.m. **Summary and Conclusion**
Session Moderators

3:35 p.m. **Future Directions in Vitamin D Research**
Open Discussion

MEETING ADJOURNS

4:05 p.m.

General Information

VENUE

This meeting will take place in the Grand Ballroom, Salons B-J of the Crystal Gateway Marriot located at 1700 Jefferson Davis Highway, Arlington, Virginia, USA.

REGISTRATION

All registration services will take place in the Grand Ballroom Foyer of the Crystal Gateway Marriot.

Registration Hours

Sunday, December 3, 2006	4:00 p.m. – 7:00 p.m.
Monday, December 4, 2006	7:00 a.m. – 2:00 p.m.
Tuesday, December 5, 2006	7:00 a.m. – 11:00 a.m.

SPEAKER READY ROOM

All speakers must check into the Speaker Ready Room, preferably 24 hours prior to presentation. At that time, you are encouraged to review your slides to ensure all Greek characters and graphs transferred successfully. The Speaker Ready Room is located in the McLean Room of the Crystal Gateway Marriott.

Speaker Ready Room Hours

Sunday, December 3, 2006	4:30 p.m. – 9:00 p.m.
Monday, December 4, 2006	7:00 a.m. – 8:00 p.m.
Tuesday, December 5, 2006	7:00 a.m. – 4:00 p.m.

POSTER INFORMATION

Poster presentation time is scheduled during the two Poster Sessions and during breaks on both days of the Meeting. Posters will be displayed in the Arlington Ballroom, Salons 1-3 of the Crystal Gateway Marriot. Presenters must be at their posters during their allocated time periods to be available to answer questions.

	Monday, December 4, 2006	**Tuesday, December 5, 2006**
Poster Set-Up	7:00 a.m. – 8:00 a.m.	
Presentation Time	Poster Session 1 (M1-M77) 1:25 p.m. – 2:05 p.m.	Poster Session 2 (T4-T79) 12:40 p.m. – 1:20 p.m.
Poster Dismantle		5:00 p.m. – 5:15 p.m.
Poster Viewing Schedule		
Morning Break	10:35 a.m. – 10:55 a.m.	10:05 a.m. – 10: 25 a.m.
Lunch Break	12:55 p.m. – 1:25 p.m.	12:10 p.m. – 12:40 p.m.
Afternoon Break	3:50 p.m. – 4:10 p.m.	2:45 p.m. – 3:05 p.m.
Post-Meeting	5:55 p.m. – 7:00 p.m.	4:05 p.m. – 5:00 p.m.

MEETING MEALS

Your registration for the meeting includes a continental breakfast and boxed lunch on Monday, December 4th and Tuesday, December 5th. The meals will be served in the Arlington Ballroom, Salons 5 and 6, at the Crystal Gateway Marriot.

EXPECTATION OF PRESENTERS

Through ASBMR meetings, the Society promotes excellence in bone and mineral research. Toward that end, ASBMR expects that all authors and presenters affiliated with the ASBMR Meeting on Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders will provide informative and fully accurate content that reflects the highest level of scientific rigor and integrity.

Furthermore, the ASBMR expects that authors and presenters will disclose any conflicts of interest, real or perceived; authors and presenters describing a study funded by an organization with a proprietary or financial interest must affirm that they had full access to all the data in the study. By so doing, they accept complete responsibility for the integrity of the data and the accuracy of the data analysis; the content of abstracts, presentations, slides, and reference materials must remain the ultimate responsibility of the authors and presenters; the planning, content, and execution of abstracts, speaker presentations, slides, abstracts, and reference materials should be free from corporate influence, bias, or control; and all authors and presenters (invited and abstracts-based oral and poster presenters) should give a balanced view of therapeutic options by providing several treatment options, whenever possible, and by citing the best available evidence.

CONTINUING MEDICAL EDUCATION (CME) CREDITS

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for CME through the joint sponsorship of The Federation of American Societies for Experimental Biology (FASEB) and the ASBMR. FASEB is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

Category I Continuing Medical Education (CME) credits toward the American Medical Association's (AMA) Physician Recognition Award will be offered at this meeting. FASEB designates this educational activity for a maximum of 14.25 category 1 credits. Each physician should claim only those credits that he or she actually spent in the activity. CME application forms are included in the Program and Abstracts book that will be distributed at the meeting. CME forms should be sent to:

FASEB Office of Scientific Meetings and Conferences
9650 Rockville Pike
Bethesda, Maryland 20814
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Tel: (301) 634-7013
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MEETING OBJECTIVE

The ASBMR Meeting on Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders is designed to allow members and attendees to present new developments in education, research, and clinical practice focused on the identification, diagnosis, and treatment of vitamin D–related disorders. The program objectives include updating attendees on new scientific advances that have highlighted the need to redefine the role of vitamin D in a vast array of diseases and refine treatment strategies for vitamin D–related disorders. The principle topics to be discussed include assessment of vitamin D status, vitamin D physiology, traditional abnormalities of vitamin D, vitamin D and population health, non-traditional roles of vitamin D, vitamin D and kidney disease, and vitamin D and other metabolic bone diseases.

As a result of their attendance, participants should have enhanced their knowledge of vitamin D–related diseases and the appropriate treatment strategy for these diseases. Attendees should have developed a clearer relationship among basic research, clinical research, and patient care through the discussions that are expected to take place. The meeting program should produce and enhance appreciation of the investigative, diagnostic, and therapeutic aspects of vitamin D–related disorders.

TARGET AUDIENCE

The program is designed for researchers, physicians, clinicians, and allied health professionals with interests in endocrinology, physiology, cell biology, pathology, molecular biology, nutrition, epidemiology, internal medicine, rheumatology, orthopedics, dentistry, and pharmacology.

DISCLOSURE/CONFLICT OF INTEREST

ASBMR is committed to ensuring balance, independence, objectivity, and scientific rigor in all education activities. ASBMR requires that their presenters inform the audience of the presenters' (speakers', faculties', authors', and contributors') academic and profession affiliations and disclose the existence of any financial interest or other relationships a presenter has with the manufacturer(s) discussed in an educational presentation.

For full-time employees of industry or government, the affiliation listed in the program will constitute full disclosure.

Disclosure should include any relationship that may bias a presentation or that, if known, could give the perception of bias. These situations may include, but are not limited to:
1) Stock options or bond holdings in a for-profit corporation or self-directed pension plan
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4) Ownership or partnership
5) Consulting fees or other remuneration
6) Non-remunerative positions of influence such as officer, board member, trustee, spokesperson
7) Receipt of royalties
8) Speakers bureau

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AUDIO- AND VIDEOTAPING

ASBMR expects that attendees will respect presenter's willingness to provide free exchange of scientific information without the abridgement of his or her rights or privacy and without the unauthorized copying and use of the scientific data shared during his or her presentation. The use of cameras, audiotaping devices, and videotaping equipment is strictly prohibited within all Oral Scientific Sessions and the Poster Sessions without the express written permission of the ASBMR Convention Management. Unauthorized use of this taping equipment may result in the confiscation of the equipment or the individual may be asked to leave the Scientific Session. These rules will be strictly enforced.

MEETING WEBCAST

Supported by an Educational Grant from Eli Lilly and Company

A webcast of many of the presentations from the Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders Meeting will be available through the ASBMR website at www.asbmr.org after the meeting. We are pleased to be able to provide this added benefit and educational opportunity.

PRESS ROOM

A Press Room will be in operation to facilitate media–related activities during the Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders Meeting. The Press Room will be located in the Mount Vernon Room of the Crystal Gateway Marriot.

ASBMR MEMBERSHIP

The ASBMR Membership Booth will be located in the Grand Ballroom Foyer of the Crystal Gateway Marriot. Stop by and meet the ASBMR staff and pick up information about the Society, the high-ranking *Journal of Bone and Mineral Research (JBMR),* and the upcoming 29th Annual Meeting in Honolulu, Hawaii, USA, September 16–19, 2007.

MEETING EVALUATION

An online evaluation form for the ASBMR Meeting on Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders will be available on the ASBMR Website at www.asbmr.org following the meeting. Your participation in this evaluation is extremely important to us. Please take a moment to complete the evaluation of this meeting to aid in planning future meetings. Thank you in advance for your feedback.

USE OF ASBMR NAME AND LOGO

ASBMR reserves the right to approve use of its name in all material disseminated to the media, public, and professionals. ASBMR's name, meeting name, logo, and meeting logo may not be used without permission. Use of the ASBMR logo is prohibited without the express written permission of the ASBMR Executive Director Ann Elderkin. All corporate supporters should share their media outreach plans with the ASBMR Executive Director before any release.

No abstract presented at the ASBMR Meeting on Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders may be released to the press before its official presentation date and time. Press releases must be embargoed until 1 hour after the presentation.

FUTURE ASBMR MEETING DATES

ASBMR 29th Annual Meeting
September 16–19, 2007
Hawaii Convention Center
Honolulu, Hawaii, USA

ASBMR Meeting on Targeting Bone Remodeling for the Treatment of Osteoporosis
December 6–7, 2007
Omni Shoreham Hotel
Washington, DC, USA

ASBMR 30th Annual Meeting
September 12–16, 2008
Palais Des Congres
Montreal, Quebec, Canada

ASBMR 31st Annual Meeting
September 11–15, 2009
Colorado Convention Center
Denver, Colorado, USA

Apply Today!

Members at all career stages are encouraged to enroll in the ASBMR Mentorship Matching Program. This program allows members at any career level to search for, or volunteer to become, mentors to other ASBMR members online. There are numerous ways for you to volunteer to mentor individuals, most ways require very little time.

If you would like to participate as a mentor in this exciting new program, please visit the ASBMR website at **www.asbmr.org**, log in to the site using your membership username and password, click on "Become A Mentor," and sign up today!

The American Society for Bone and Mineral Research

Contemporary Diagnosis and Treatment of Vitamin D–Related Disorders

REQUEST FOR CME CREDITS

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		SESSION TITLE	NO. HOURS ATTENDED	EVALUATION
Monday, December 4, 2006	8:15 am – 10:35 am	Assessment of Vitamin D Status		
	10:55 am – 12:55 am	Vitamin D Physiology		
	2:05 pm – 3:50 pm	Traditional Abnormalities of Vitamin D		
	4:10 pm – 5:55 pm	Vitamin D and Population Health		
Tuesday, December 5, 2006	8:00 am – 10:00 am	Non-Traditional Roles of Vitamin D		
	10:25 am – 12:10 pm	Vitamin D and Kidney Disease		
	1:20 pm – 2:45 pm	Vitamin D and Other Metabolic Bone Diseases		

TOTAL HOURS:_____

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This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Federation of American Societies for Experimental Biology (FASEB) and The American Society for Bone and Mineral Research (ASBMR). FASEB is accredited by the ACCME to provide continuing medical education for physicians. The Federation designates this educational activity for up to 14.25 credit hours in Category I credit towards the AMA Physician's Recognition Award.

I certify that I have attended the above CME activity and claimed only those hours of credit that I actually spent in the activity.

Name: _____

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1

Molecular Action of 1,25(OH)2D.

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The renal vitamin D hormone, 1,25-dihydroxyvitamin D_3 (1,25D), regulates bone mineral ions to prevent diseases such as rickets/osteomalacia and osteoporosis. 1,25D exerts its actions to support the mineralized skeleton via liganding of the nuclear vitamin D receptor (VDR), which then recruits its retinoid X receptor (RXR) heterodimeric partner to recognize vitamin D responsive elements in target genes, with 1,25D-VDR-RXR attracting comodulator protein/enzyme complexes that either repress or induce DNA transcription by chromatin remodeling and linkage to RNA polymerase II. 1,25D is known primarily as a regulator of calcium, but it also promotes phosphate absorption from the intestine, reabsorption from the kidney, and bone mineral resorption. FGF23 is a phosphaturic hormone that, like PTH, lowers serum phosphate (Pi) by inhibiting renal reabsorption via Npt2a/Npt2c. FGF23 occurs in excess in X-linked hypophosphatemia (XLH) and autosomal dominant hypophosphatemic rickets, as well as in oncogenic osteomalacia. In addition to causing phosphaturia, FGF23 inhibits the renal 1α-OHase that generates 1,25D and appears to be an anti-mineralization factor, perhaps explaining why the rachitic bone phenotype in XLH is dissociable from the hypophosphatemia. The major, if not sole, source of circulating FGF23 is the osteoblast, rendering FGF23 a novel bone hormone that communicates with mineral transporting tissues such as the kidney. Moreover, 1,25D induces FGF23 synthesis in isolated rat osteoblast-like cells and raises circulating FGF23 by 80-fold in mice, in vivo. This response to 1,25D is likely transcriptional as evidenced by $\geq$ 50-fold increases in FGF23 mRNA expression in osteoblasts/calvaria measured by real time PCR. Because 1,25D induces FGF23, and FGF23 in turn represses 1,25D synthesis, a reciprocal relationship is established with FGF23 indirectly curtailing 1,25D-mediated intestinal absorption and counterbalancing renal reabsorption of phosphate, thereby reversing hyperphosphatemia and preventing ectopic calcification. This newly revealed FGF23/1,25D/Pi axis is comparable in significance to phosphate and bone metabolism as the PTH/1,25D/Ca axis is to calcium homeostasis. Finally, we also report that LRP5, Runx2, TRPV6, and Npt2c, all anabolic toward mineralized bone, and RANKL, which is catabolic, are transcriptionally regulated by 1,25D. This coordinated regulation, together with that of FGF23 and PTH, allows 1,25D to play a central role in maintaining calcium and phosphate homeostasis, while acting either anabolically or catabolically on bone.

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*Disclosures: **M.R. Haussler**, None.*

2

Measurement of 25-OH-D (RIA, HPLC, LC-MS/MS).

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The assay of plasma 25-OH-D has assumed paramount importance with the realization that vitamin D deficiency and insufficiency underlie a variety of clinical conditions, in addition to disturbances of calcium and phosphate homeostasis. In particular, an appreciation of the wide distribution of the extra-renal 1a-hydroxylase (CYP27B1) has emphasized the key role of plasma 25-OH-D as a precursor to both circulating, renally-synthesized & locally-produced target cell calcitriol. Currently-available 25-OH-D assays include a spectrum of competitive protein binding assay (CPBA), radioimmunoassay (RIA), high pressure liquid chromatography (HPLC) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) and combinations thereof. Some of these are sold as commercial kits or offered as services. The majority of analysts still feel that the gold standard for benchmarking 25-OH-D assays remains GC-MS, but this technique is performed by few laboratories forcing laboratories to accept surrogates for quality assessment. All current assays have the potential to measure 25-OH-D accurately and precisely, but all have documented advantages and disadvantages. Some of the current controversies regarding 25-OH-D assay to be discussed include (a) what is the correct normal range?; (b) over-estimation problems of some commercial kits for total 25-OH-D; (c) the performance of such assays to measure 25-OH-D in samples containing significant 25-OH-D_2; (d) the presence of LC-MS/MS interferences which cause over-estimation of 25-OH-D_2 in pediatric samples; (e) whether 25-OH-D_2 and 25-OH-D_3 are biologically equivalent and whether separate assay is clinically useful; and (f) the need for routine external performance testing of analytical laboratories performing 25-OH-D assays and certification by an international, independent body (eg DEQAS). These 25-OH-D quality control assessment panels have concluded that there still a wide variability in these assays, particularly for 25-OH-D_2 measurement. Furthermore, the healthy discussion of current technical problems encountered in the literature, is evidence that 25-OH-D kit providers and analysts are attempting to address problems. Nevertheless, given the increased clinical profile attached to the assay of 25-OH-D, a prudent approach might be to expect clinical chemists/commercial laboratories involved in 25-OH-D assay, using their chosen method, to be required to pass frequent external performance tests and this information be disclosed when publications include 25-OH-D data. Finally, it is essential that experts in the vitamin D field, including nutrition review panels, be aware of the type of systematic errors that exist in published data for 25-OH-D, when using such data or reviewing recommendations for vitamin D intake.

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Disclosures: ***G. Jones,*** *Cytochroma Inc, Markham, Ontario 1, 5.*

3

The Relative Value of 25(OH)D and 1,25(OH)$_2$D Measurements.

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The major circulating vitamin D metabolite is 25(OH)D. The serum 25(OH)D concentration is the measurement of choice to assess the nutritional vitamin D status. It is relatively stable and not directly influenced by dietary factors (calcium) or mobility. The half life of serum 25(OH)D is around 25 days. Serum 25(OH)D should be assessed in patients suspected of vitamin D deficiency or insufficiency, including nutritional causes, malabsorption and nephrotic syndrome. It should also be measured in case of suspected vitamin D intoxication. The active metabolite, 1,25(OH)2D should be measured in case of disorders of 1alpha-hydroxylation of 25(OH)D, existing in renal failure, vitamin D dependent rickets type 1 and hypophosphatemic rickets (decreased levels), or vitamin D receptor (VDR) defects as in vitamin D dependent rickets type 2 (increased levels). Serum 1,25(OH)2D is under negative feedback control by serum calcium and phosphate. Its formation in the kidney is stimulated by parathyroid hormone (PTH). A high calcium diet or calcium supplements will decrease serum 1,25(OH)2D and immobilisation has similar effects. The half life of serum 1,25(OH)2D is around 7 hours. While the renal hydroxylation of 25(OH)D is tightly regulated, the extrarenal hydroxylation in activated macrophages is not. Extrarenal formation of 1,25(OH)2D occurs in granulomatous diseases such as sarcoidosis, tuberculosis and inflammatory bowel disease, reumatoid arthritis, and lymphoproliferative diseases. In these disorders, serum 1,25(OH)2D may be elevated resulting in hypercalcemia and hypercalciuria. The measurement of serum 1,25(OH)2D in case of nutritional vitamin D deficiency is not of much value. It stays within the normal reference range and may even be relatively high because the increase of serum PTH stimulates the renal hydroxylation of 25(OH)D. However, serum 1,25(OH)2D may fall to subnormal levels in case of severe vitamin D deficiency, where the synthesis of 1,25(OH)2D becomes substrate dependent. When comparing groups of severely vitamin D deficient and replete patients, mean serum 1,25(OH)2D usually is lower in the former than in the latter group, but this is more important for research than for individual patient care. In conclusion, the measurement of serum 25(OH)D is important to assess nutritional vitamin D status and to exclude vitamin D deficiency or insufficiency, while serum 1,25(OH)2D should only be measured in disorders of 1alpha-hydroxylation in the kidney or in extrarenal tissues, or in genetic defects of the VDR.

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Disclosures: ***P. Lips****, Merck and Co 2, 5; Procter and Gamble 2; Wyeth 2; Servier 5.*

4

Activation of Gene Expression by 1,25-Dihydroxyvitamin D$_3$: Delineating Intracellular Mechanisms and Extracellular Influences Both *in Vitro* and *in Vivo.*

J. W. Pike. Biochemistry, University of Wisconsin, Madison, WI, USA.

1,25-Dihydroxyvitamin D_3 (1,25(OH)$_2$D$_3$) functions in vertebrate organisms as a primary regulator of calcium and phosphorus homeostasis, an activity that is achieved through direct actions on gene expression in intestine, kidney and bone. Important targets whose products are intimately involved in directing these homeostatic events include the renal and intestinal ion channel genes TRPV5 and TRPV6 and the osteoclastogenic regulatory factor gene RankL. 1,25(OH)$_2$D$_3$ is also a potent regulator of cellular proliferation and differentiation, and is capable of modulating the expression of unique subsets of genes involved in highly tissue-specific cell functions. These widespread pleiotropic actions have prompted speculation that 1,25(OH)$_2$D$_3$ or its analogues might be therapeutically useful for a wide range of clinical indications including those of hyper-proliferation (cancer), altered immune function and dermatologic dysfunction. While the potential for these applications is high, this potential has yet to be fully realized due primarily to the tendency for many of these ligands to trigger exaggerated calcemic responses. Interestingly, a subset of vitamin D analogues fails to induce these responses, thereby manifesting a specific level of tissue selectivity when evaluated *in vivo*. Our recent efforts have therefore focused on delineating the intracellular processes that underlie the regulation of these genes, with a view towards clarifying the mechanisms responsible for this selectivity. Accordingly, we have used chromatin immunoprecipitation and tiled DNA microarray analyses together with more traditional approaches to define regions within the TRPV6 and RankL genes that mediate the actions of 1,25(OH)$_2$D$_3$ in intestine and bone. Current studies now focus on determining the function of these regulatory regions both *in vitro* and *in vivo*. In a related vein, we have also explored the role of vitamin D binding protein (DBP) in modulating the biological potency and the efficacy of 1,25(OH)$_2$D$_3$. DBP is viewed as an important serum protein carrier, and has been suggested to participate in 1,25(OH)$_2$D$_3$ uptake into tissue targets. Our work demonstrates that this protein is not required for either the transport of 1,25(OH)$_2$D$_3$ or its uptake into tissues either *in vitro* or *in vivo*. Surprisingly, DBP has an enormous impact on the potency of ligands with which it interacts, although this action is restricted to studies carried out *in vitro*. Collectively, our findings begin to address both the intracellular mechanisms and extracellular influences that are integral to vitamin D ligand action, and could potentially identify mechanisms inherent to vitamin D analog selectivity *in vivo*.

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Disclosures: ***J.W. Pike****, None.*

5

Substrate and Enzyme Trafficking as a Means of Regulating 1,25-Dihydroxyvitamin D Synthesis in Action.

J. S. Adams, R. Chun, H. Chen, M. Hewison. Division of Endocrinology, Diabetes, and Metabolism, Cedars-Sinai Medical Center, Los Angeles, CA, USA.

Production of the active vitamin D metabolite, 1,25-dihydroxyvitamin D (1,25D) is regulated by concerted action of the synthetic CYP27b1-hydroxylase and catabolic CYP24-hydroxylase. Enzymatic activity, in turn, is controlled by the 1] availability of substrate and cofactors to the enzymes, 2] proper positioning of the hydroxylases and the inner mitochondrial membrane space, as well as 3] relative amount of hydroxylase gene product expressed. In recent years, it has become clear that directed trafficking of substrate and enzyme are part of the regulated process of hormone synthesis by both renal and extra-renal tissues which express the CYP-hydroxylase genes. Regulatory trafficking events currently under study are depicted in the schematic fashion in **Figure 1**.

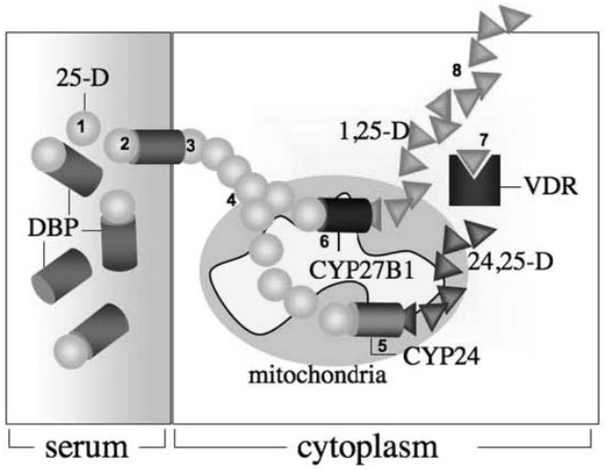

Figure 1. Steps (1-8) regulating the fate of circulating 25-hydroxyvitamin D (25-D) and synthesized 1,25-dihydroxyvitamin D (1,25-D)

Steps 1 and **2** are determined by the quantity of substrate 25-hydroxyvitamin D (25D) entering the circulatory pool and by affinity of the serum vitamin D binding protein (DBP) for substrate. A practical example is the failure of 25D-deficient, African-American serum to provide sufficient substrate to the human macrophage CYP27b1-hydroxylase in order to adequately promote expression of the host innate immune response to kill bacterial invaders[1]. In the kidney, **step 3** embodies the necessity of 25D-bound DBP to be recognized, internalized and released intracellularly by LDL receptor family molecules[2,3]. The "released" intracellular substrate is then moved to specific intracellular destinations (i.e., the hydroxylases and the vitamin D receptor [VDR]; **step 4**) by the hsc70 and BAG-1 family of chaperone and co-chaperone molecules[4]. The 1-hydroxylase reaction can be enhanced and inhibited by alternative splicing of the CYP24 (**step 5**) and CYP27b1 gene (**step 6**), respectively, the former by translation of an N-terminally-truncated CYP24 gene product lacking its mitochondrial targeting sequence and the latter by generation of untranslatable splice variants that compete with the holo gene product for the cell's translation machinery[5,6]. Finally, initiation of transcription of 1,25D-regulated genes, like the CYP24, require movement of the CYP27b1 product, 1,25D, to the VDR in the same cell (**step 7**) or export to another cell (**step 8**)[7]. In either case, the 1,25D ligand is required for the VDR to heterodimerize with the retinoid x receptor (RXR) and compete away the dominant-negative acting, hnRNP-related, promoter-based vitamin D response element binding proteins which constitutively inhibit hormone-directed transactivation of genes[8].

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Disclosures: ***J.S. Adams****, None.*

6

ASBMR YOUNG INVESTIGATOR AWARD Prevalence of Vitamin-D Insufficiency and Relationship with Peak Bone Mass in Young Men. Results from the Odense Androgen Study.

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Vitamin-D (25-OH-D) insufficiency is prevalent in elderly in Scandinavia. Thus, 25-OH-D insufficiency (serum 25-OH-D from 25 to 50 nM) and deficiency (serum 25-OH-D<25 nM) affect bone mineral density (BMD) and increase the risk of osteoporotic fractures. Seasonal variation in 25-OH-D has previously been verified and an impact on peak bone mass has been suggested. The aim of this study was to elucidate the prevalence of 25-OH-D insufficiency, the seasonal variation in serum 25-OH-D, and the relationship between 25-OH-D levels and BMD in young males.

The Odense Androgen Study is a population-based, prospective, observational study regarding the inter-relationship between endocrine status, body composition, muscle function, and bone metabolism in young men. In brief, 3000 males aged 20-30 years were randomly selected from the civil registration database in Funen County, Denmark, and invited by mail to participate in the study. Response rate was 73%. 783 gave written informed consent to participate in the study. The participants were equivalent to the background population on socio-economic status, BMI, and educational level. They received no 25-OH-D fortified food. In Marts-April, 10.6 % were insufficient and 0.2% deficient on 25-OH-D. In July, the corresponding figures were 0.01% and nil. Serum PTH and bone specific alkaline phosphatase (BAP), smoking, and truncal fat (r=0.22, 0.11, 0.12 and 0.21, p<0.01, 0.01 and 0.01) were negatively associated with serum 25-OH-D. Positive correlation existed with sporting activities (r=0.19, p<0.01). We found no interaction between tobacco consumption and sports in relation to serum 25-OH-D, but a significant interaction was seen between sports and truncal fat in relation to serum 25-OH-D (p<0.01). PTH was negatively associated with serum 25-OH-D, but no cases of sec. hyperparathyroidism were found. 25-OH-D insufficient participants had lower BMD in both total hip and lumbar spine (p<0.01 and p<0.01). The effect remained after correction for PTH and BAP in separate models. In conclusion, 25-OH-D insufficiency was prevalent during winter, a significant seasonal variation in 25-OH-D was found, and 25-OH-D status was associated with BMD in young Danish men.

Disclosures: ***M.F. Nielsen****, None.*

7

Normal/Abnormal Vitamin D Physiology.

R. P. Heaney. Creighton University, Omaha, NE, USA.

Serum 25OHD is the functional indicator of vitamin D status, both because it reflects the size of the vitamin D reserve and because 25OHD is the precursor of $1,25(OH)_2D$ (1,25D) and 25OHD concentration limits 1,25D synthesis in its multiple intracellular (autocrine) roles.

The canonical function of vitamin D is an endocrine effect, the facilitation of intestinal Ca absorption by active transport across the intestinal mucosa, a function due mainly to genomic induction by 1,25D of a Ca-binding protein in the mucosal cell. Without active transport, and at prevailing Ca intakes, the gut becomes a net excreter of Ca, not a net absorber. Multiple lines of evidence show that Ca absorption efficiency in adults rises with serum 25OHD up to ~80 nmol/L, above which physiological controls take over. While 1,25D is the form of the vitamin responsible for its genomic effects, both 1,25D and 25OHD are necessary for Ca absorption, as is shown by the subnormal Ca absorption in patients with osteomalacia, despite normal or high 1,25D levels.

Vitamin D status is the resultant of inputs from skin and oral sources, offset by metabolic utilization and degradation. On average, an adult requires a combined input from both sources of ~4000 IU/d to maintain serum 25OHD of 80 nmol/L.[1] Serum 25OHD half-time is inversely related to PTH and 1,25D concentrations,[2] as well as to drugs that upregulate 24-hydroxylation. High PTH levels can shorten 25OHD half-time (and lower serum 25OHD) by 50% or more.

Because Ca absorption efficiency drops as serum 25OHD falls, PTH typically rises in vitamin D deficient individuals. However, about half of the elderly with low 25OHD levels show little or no rise in PTH. It has recently been shown that such individuals have subclinical magnesium deficiency.[3]

Because cutaneous synthesis accounts for the majority of vitamin D input, it is important to quantify skin response to UV-B radiation. 40 mJ of UV-B to the whole body (equivalent to 30 minutes outdoors in July), 3×/wk, raises serum 25OHD by ~30 nmol/L in light-skinned individuals; the effect decreases as melanin pigmentation rises. Typically, in blacks, response to the same dosing regimen is 20 nmol/L or less.

Serum 25OHD is also the measure of vitamin D toxicity. While vitamin D is a highly potent molecule, there are no evidences of toxicity in adults at serum 25OHD levels below 400 nmol/L (or oral doses of up to 10,000 IU/d).[4]

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Disclosures: ***R.P. Heaney****, None.*

8

Vitamin D Skin Physiology.

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Vitamin D is the sunshine vitamin D. Sunlight has been the driver for life on earth and has been especially important for the evolution of land vertebrates. Solar ultraviolet B (UVB) radiation is absorbed by 7-dehydrocholesterol in the skin transforming it to previtamin D3. Previtamin D3 exists as two conformers. Because previtamin D3 is sterically entrapped within the lipid membrane in only the cis,cis conformation it efficiently is converted by a novel nonenzymatic process to vitamin D3. Season, latitude, time of day, skin pigmentation, aging, glass and clothing influence the number of UVB photons entering the skin, and, thus, dramatically affect vitamin D synthesis. Inadequate sun exposure and living at higher latitudes is associated with vitamin D deficiency and many chronic diseases including common cancers, autoimmune diseases, cardiovascular disease and increased risk of infectious diseases. Vitamin D deficiency is a global health problem in part due to a misinformed public that all exposure to direct sunlight should be avoided. More than 90% of human being?s vitamin D requirement comes from exposure to sunlight. Without adequate sun exposure, 1,000 IU of vitamin D3/d is needed to sustain blood levels of 25(OH)D > 30 ng/ml. Although it is not known what the adequate intake of vitamin D3 is for children, a recent study conducted by my group revealed that the recommended adequate intake of 200 IU of vitamin D/d is not adequate to raise blood levels of 25(OH)D into the healthful range above 30 ng/ml. It is well documented that skin pigmentation can greatly diminish the cutaneous production of vitamin D3. Healthy adults with skin types 2, 3, 4 and 5 were exposed to UVB radiation from a tanning bed along the guidelines recommended by the tanning bed manufacturers and sanctioned by the FDA. Circulating concentrations of 25(OH)D were measured weekly for three months. The average increase in circulating concentrations of 25(OH)D was 120%, 80%, 78% and 50% for skin types 2, 3, 4 and 5. At the beginning of the study, all subjects were asked about what they thought their skin type was and their historical recounting of their sensitivity to burning from sun exposure which is typically used to identify skin type. It was observed that the circulating concentrations of 25(OH)D was a more sensitive indicator for skin type than the subject?s historical recounting of their skin sensitivity to sun exposure. There needs to be a reevaluation of the beneficial effect of sensible exposure to sunlight and to increase health care professionals and the public awareness about the insidious detrimental health consequences of vitamin D deficiency.

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Disclosures: ***M.F. Holick****, Merck 8; P & G 8; Lilly 8.*

9

Vitamin D Economy in African Americans.

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African Americans have lower gender-specific rates of hip and other osteoporosis-related fractures compared to Caucasians. These differences are explained in part by differences in skeletal geometry and bone density at all ages. Peak bone mass is higher in young black individuals suggesting genetic racial differences and bone loss may be slower in black women after menopause. Some, but not all of the racial disparity in bone mass, can be explained by racial differences in body composition.

These findings are surprising in light of what is known about vitamin D status in African Americans. Mean 25OHD levels are lower in blacks vs. whites at all stages of life and a greater proportion of blacks meet criteria for vitamin D deficiency. The racial difference in serum 25OHD level is primarily due to increased pigmentation reducing vitamin D production in the skin. Seasonal differences in 25OHD levels are correspondingly blunted in blacks. Vitamin D intakes are also lower in blacks than those in whites, in part related to reduced consumption of milk, milk products and cereals.

Consistent with the lower 25OHD levels, black women have higher levels of PTH and 1,25(OH)2D. Despite the relative secondary hyperparathyroidism, measurements of bone turnover levels are lower in black vs. white women suggesting that the skeleton is relatively protected as a means of maintaining calcium homeostasis. Histomorphometric assessments comparing black and white premenopausal women indicate that while black women have a lower mineral apposition rate they have a longer total bone formation period, primarily within the phase of secondary mineralization, allowing greater accumulation of mineral in bone. . Furthermore, dynamic studies of the PTH/Vitamin D axis indicate that black women do not manifest as large an increase in bone resorption to PTH infusion as do whites. In contrast, premenopausal black women demonstrate superior renal calcium conservation compared to premenopasual white women in the face of PTH infusion. Furthermore, in response to 1,25(OH)2D administration, black women exhibit a slightly greater increase in serum calcium, greater decline in serum PTH, lesser increase in urine calcium and more robust increase in biochemical indices of bone formation. These dynamic studies suggest that renal calcium conservation, skeletal resistance to PTH, and greater bone formation response to 1,25(OH)2D might be adaptations in response to lower serum 25(OH)D, allowing blacks to maintain higher bone mass throughout life and protecting the black skeleton against fracture despite vitamin D deficiency.

Although there appears to be a weak relationship between 25OHD levels and BMD in blacks, studies of vitamin D supplementation have so far shown inconsistent results on serum PTH, bone turnover, and bone density. This may be a function of vitamin D dose, calcium supplementation in both active and control groups obfuscating treatment effects of vitamin D, or genetic variability of response in subgroups of black women. Continued studies to determine the effect of vitamin D supplementation on the skeleton and on other organ systems are definitely warranted in African Americans.

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*Disclosures: **F. Cosman** , Lilly 2, 5, 8; Merck 5, 8; Procter & Gamble 5; Pfizer 5; GSK/Roche 8; Novartis 5.*

10

Vitamin D Requirements in Pregnancy/Lactation.

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While Vitamin D is undoubtedly important for fetal development and in childhood for bone development, it also plays a much wider role in health and disease. Vitamin D is needed not only for bone metabolism, but also for other systems such as cardiovascular health, neurodevelopment, immunomodulation, and regulation of cell growth. Knowledge is emerging of the importance 25(OH)D in various tissues such as macrophages, monocytes and prostate tissue, which utilize 25(OH)D to produce $1,25(OH)_2D$ for tissue-specific use in a paracrine/intracrine fashion. As the role vitamin D during fetal and early childhood is less clear, vitamin D requiremenhts are not well defined for either mother or fetus during pregnancy, nor for maternal requirements during lactation to provide for the infant. A study published by the Centers for Disease Control (CDC) and our laboratory using the NHANE III database reveals a serious public health matter: 42% of African-American women in their childbearing years (15-49) yrs) exhibited significant vitamin D deficiency. Of concern is that fetuses of mothers with hypovitaminosis D are maturing in a hypovitaminosis D environment that could potentially be detrimental to aspects of their development. In our ongoing, NIH-sponsored study at latitude 32^o, of the 277 women thus far enrolled, 102 women had a baselline 25(OH)D <20 ng/mL: 43/57 (75%) Aftrican-American, 45/134 (34%) Hispanic, and 14/103 (14%) Caucasian mothers were significantly vitamin D deficent at presentation into the study. 218 women had a baseline 25(OH)D <32 ng/mL, and thus, were either deficient or with marginal vitamin D status: 1/1 Asian, 51/57 (89%) African-American, 102/134 (76%) Hispanic, and 64/103 (62%) Caucasian women. Thus far, 78.7% of women in this cohort enrolled since January 2004 are vitamin D deficient (25(OH)D <20 ng/mL) or have marginal vitamin D status (25(OH)D <32 ng/mL), indicating a widespread problem. Vitamin D status during pregnancy has implications for lactating women and their infants, especially in light of the significant rise in nutritional rickets in breastfed infants, mainly in the African-American population. The transfer of vitamin D in mother's milk is identified as the cause of hypovitaminosis in such infants. The deficiency state is created by limited sun exposure in mother and infant and the minimal contribution of dietary supplementation at the current adequate intake of 200 IU vitamin D/day in the mother. With respect to lactation, only three prospective studies have been performed to evaluate vitamin D dosing in lactating women. In Finland, supplementation of lactating mothers with either 1,000 or 2,000 IU vitamin D/day for a period of 15 weeks led to a rise in circulating 25(OH)D during supplementation to 16 and 23 ng/mL for the 1,000 and 2,000 IU dose groups, respectively. A recent study performed at MUSC involved supplementaing lactating mothers with 2,000 and 4,000 IU vitamin D^2/day for a period of three months demonstrated a rise in circulating maternal 25(OH)D. In our recent pilot study, 400 IU/day maternal supplement will do little to sustain the nutritional vitamin D status of the mother or her nursing infant. Conversely, mothers given 6,400 IU vitamin D_3/day had increased circulating 25(OH)D and a 10-fold increase in milk levels which supplied the nursing infant with ample vitamin D to increase and sustain circulating 25(OH)D. While the safety and efficacy of

high-dose maternal supplementation during pregnancy and lactation is not confirmed, screening for vitamin D deficiency especially in high risk groups is advised, with recommendations for oral supplementation of vitamin D_3, when indicated. The oral doses required to meet these demands are a magnitude higher than current recommendations.

Disclosures: ***B.W. Hollis****, DiaSorin 5.*

11

ASBMR YOUNG INVESTIGATOR AWARD
Studies Using Nullmutant Mice Reveal Active Intestinal Calcium Transport in the Absence of Calbindin-D_{9k} or TRPV6.

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To study the role of calbindin-D_{9k} and TRPV6 in intestinal calcium absorption, calbindin-D_{9k} and TRPV6 nullmutant mice were generated. To verify nullmutation various tissues including intestine were analyzed by RT-PCR and Western blotting. No signals (TRPV6 or calbindin-D_{9k}) were detected in mice homologous for the targeted mutation. Although, when fed a regular diet, TRPV6 knock out (KO) mice and calbindin-D_{9k} KO mice have serum calcium levels similar to those of wild type (WT) mice (~ 9 mg Ca^{++}/dl), in the TRPV6 KO mice there is a 3 fold increase in serum PTH and a 2.4 fold increase in serum $1,25(OH)_2D_3$ levels. Under low dietary calcium conditions, serum $1,25(OH)_2D_3$ and PTH levels in the TRPV6 KO mice were not further increased but were similar to high levels observed in WT mice fed diets low in calcium. Active intestinal calcium absorption was measured using the everted gut sac method and the first 5 cm of the duodenum of WT, calbindin-D_{9k} KO, TRPV6 KO and calbindin-D_{9k}/TRPV6 double KO mice. Under low dietary calcium conditions [mice were fed a low calcium (0.02%) from weaning for 4 weeks] there was a 4.2, 3.3 and 2.9 fold increase in calcium absorption in the duodenum of WT, calbindin-D_{9k} and TRPV6 KO mice respectively [n=5-12/group; $p>0.1$ among all groups on the low calcium diet; $p<0.05$ compared to mice fed a high calcium diet (1.0%)]. Duodenal calcium absorption was increased 2.6 fold in the calbindin-D_{9k}/TRPV6 double knock out mice fed the low calcium diet. Calcium uptake was not stimulated by low dietary calcium in the ileum of the WT or null mutant mice. In addition to low dietary calcium, $1,25(OH)_2D_3$ administration (three injections of $1,25(OH)_2D_3$ 100ng/100g body weight; 48, 24 and 12h prior to sacrifice) to vitamin D deficient mice also resulted in a significant increase in duodenal calcium uptake (1.7 - 2.0 fold; $p<0.05$ compared to vitamin D deficient mice) in WT, calbindin-D_{9k} and TRPV6 KO mice. This study provides evidence for the first time using nullmutant mice for calbindin-D_{9k} and TRPV6 independent regulation of active intestinal calcium absorption, thus challenging the dogma for the need for calbindin-D_{9k} and TRPV6 for vitamin D induced active intestinal calcium transport.

Disclosures: ***B.S. Benn****, None.*

12

Skeletal Consequences of Vitamin D Insufficiency/ Deficiency (Calcium Homeostasis and Growth/ Development).

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Overt vitamin D deficiency early in life has classically been associated with the etiology of rickets. Recent interest has focused on vitamin D insufficiency and calcium homeostasis and bone health. A review of the literature suggests that the relationship between vitamin D status and calcium utilization has some important differences with life stage and race. For example, the relationship between serum and vitamin D metabolites and calcium absorption varies with age. Serum 25-hydroxyvitamin D positively predicts calcium absorption is adults. Serum 1,25-dihydroxyvitamin D, but not serum 25-hydroxyvitamin D, predicts calcium absorption in growing children. PTH suppression with increasing serum 25-hydroxyvitamin D varies with race, at least in adolescents. A limitation of our understanding of vitamin D status on calcium homeostasis in children relates to the cross-sectional nature of the evidence and interventions that typically employ too little vitamin D supplementation to affect status. Vitamin D status has predicted changes in bone mineral density during growth and higher doses have been associated with increased bone mineral content of the hip in isolated studies. The impact of treatment with vitamin D is undoubtedly related to calcium status, age, race and genetics.

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Disclosures: ***C.M. Weaver****, Wyeth Global Nutrition 2, 6; Pharmavite 6; Delavau 2; Dairy Management Inc. 2.*

13

Treatment Strategies for Vitamin D (D_3 vs D_2) Insufficiency/ Deficiency in Diseases Including GI Disorders.

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The intestine provides the route for all calcium and all dietary vitamin D entering the body. Vitamin D via its active metabolite $1,25(OH)_2D$ stimulates active calcium absorption principally in the duodenum, but calcium can also be absorbed by the paracellular pathway. The liver via its production of bile and the pancreas via its production of digestive enzymes affect the intestinal absorption of calcium and vitamin D. Disorders of these organs are often associated with reductions in calcium and vitamin D absorption. Disorders of these organs are also associated with decreased BMD. However, the link

between vitamin D and calcium malabsorption and decreased BMD is not straight forward. Inflammatory bone disease (IBD) such as Crohn's and ulcerative colitis can lead to bone loss not only by malabsorption of calcium and vitamin D (less common in ulcerative colitis) but also by the chronic inflammatory process itself and treatment with glucocorticoids to control the inflammatory process. Increased $1,25(OH)_2D_3$ levels in a substantial number of subjects with IBD were found that appeared to originate from $1,25(OH)_2D_3$ production within the inflamed bowel, which the authors suggested contributed to the bone loss. Under these circumstances overzealous use of vitamin D and calcium supplementation may result in hypercalciuria and increased risk of nephrolithiasis. Liver disease, often accompanied by decreased BMD, is frequently associated with reduced 25OHD levels, but this may reflect the reduction in the vitamin D binding proteins (DBP and albumin) in blood rather than inadequate hepatic 25OHD production or intestinal vitamin D absorption. Bariatric surgery with diversion procedures that result in malabsorption can lead to profound deficiencies in vitamin D and calcium with loss of bone. But vertical banded gastroplasty, which is not expected to result in malabsorption, can also lead to bone loss. Therapeutic recommendations in these disorders tend to be empiric based on recommendations derived from the management of other forms of osteoporosis, with limited data from large prospective randomized placebo controlled trials. In most studies, bone biopsies were not performed, so the distinction between osteoporosis and osteomalacia cannot be made. That said, it is reasonable to ensure that patients with these disorders obtain enough vitamin D, whether by sunlight, UVB, or dietary supplementation, to maintain serum 25OHD and calcium levels sufficient to prevent secondary hyperparathyroidism. Numerous studies suggest a target 25OHD of 30ng/ml. This target may be different in patients with reduced DBP and albumin levels due to hepatic disease or protein losing enteropathies. Urine calcium levels need to be monitored to avoid hypercalciuria, and can also be used to monitor adequacy of intestinal calcium absorption.

Disclosures: ***D.D. Bikle****, None.*

14

Vitamin D Insufficiency/Deficiency Contributions to the Morbidity of Patients with Osteoporosis.

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It is becoming appreciated that vitamin D (D) involvement extends beyond the musculoskeletal system. As such, it is plausible that endemic vitamin D inadequacy contributes to much morbidity that adversely affects quality of life with advancing age in patients with osteoporosis and older adults in general. For example, D insufficiency increases osteoporotic fracture risk, but additionally is linked to other common geriatric syndromes including sarcopenia with associated gait disturbance and falls, incontinence, respiratory disease and neurologic impairment.

As vitamin D receptors are present in myocytes, a direct effect is probable. Vitamin D inadequacy has long been associated with impaired muscle strength and also is associated with loss of muscle mass.1 Not surprisingly, low D status is associated with an increased falls risk2 and, in older women, D reduces falls risk by approximately 20%.3 As D is essential for normal muscle calcium homeostasis and contractility, it is plausible that D inadequacy could contribute to muscular dysfunction associated with other geriatric syndromes, for example, respiratory decline, urinary incontinence and swallowing dysfunction, however these possible associations remain largely unexplored. It is reported that D inadequacy is associated with impaired pulmonary function4 and that higher D intakes are associated with lower risk of bladder dysfunction. The possibility that D inadequacy contributes to swallowing impairment with advancing age has yet to be evaluated.

Additionally, non-muscular effects of D inadequacy could contribute to morbidities associated with aging. For example, low D status has been associated with chronic pain. Similarly, D inadequacy has been associated with impaired neurologic function and depression; common morbidities associated with aging.

It is attractive to speculate that D inadequacy contributes to the development of multiple common geriatric syndromes. However, the observations that relationships exist between syndromes of aging and D status do not establish that D inadequacy contributes to the development of these syndromes. Further evaluation of the possibility that D may prevent and/or be an effective therapy for common geriatric morbidities is indicated.

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Disclosures: ***N. Binkley****, None.*

15

Evidence Report on Vitamin D.

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There is conflicting evidence on: a) the consequences of low 25(OH)D on bone health outcomes and b) the efficacy of supplemental vitamin D for the prevention of falls and fractures. Our objectives were to systematically review the evidence on: (1) the effect of vitamin D (D2 or D3) on: (a) falls and fractures and (b) serum 25(OH) D concentrations and; (2) to determine if specific 25(OH)D concentrations are associated with bone health outcomes in postmenopausal women and older men. An electronic search of the following databases: MEDLINE (1966 to June Week 3 2006); Embase (2002 to 2006 Week 25); CINAHL (1982 to June Week 4, 2006); AMED (1985 to June 2006); Biological Abstracts (1990 to February 2005); and Cochrane Central Register of Controlled Trials (CENTRAL; 2nd Quarter 2006) was conducted. Two reviewers independently assessed study eligibility, trial quality and extracted relevant data. Where possible, meta-analysis of RCTs was conducted using a random effects model, with an evaluation of heterogeneity. A total of 6564 potentially relevant records were identified and 675 met the inclusion criteria after full text screening. Of these, 141 studies were selected according to level of evidence. Fifteen RCTs evaluated the effect of supplemental vitamin D2 or D3 on fractures and fourteen RCTs evaluated the effect on falls in postmenopausal women and older men. In most trials, vitamin D3 was used and the study quality was ≥ 3

(Jadad scale). Pooled results of 12 RCTs (vitamin D3 +/- calcium) demonstrated a small reduction in total fractures (N = 54,995, OR 0.89, 95% CI 0.80-0.99, p=0.03). However, in a subgroup analysis stratifying trials by residential status, there was a significant reduction in pooled trials of elderly living in institutions (N=3998, OR 0.73; 95% CI 0.61-0.88) vs. a non-significant effect from pooled trials of community-dwelling elderly (N=50,997, OR 0.95, 95% CI 0.86-1.05). Pooled results of 12 RCTs that evaluated the effect of vitamin D2/3 (+/-) calcium on falls, demonstrated a 16 % reduction in fall risk (N = 14,101, OR 0.89, 95% CI 0.80-0.99), however pooled results of trials of vitamin D3 alone vs. placebo were not consistent with a significant reduction in falls. 73 RCTs evaluated the effect of vitamin D2 or D3 on 25(OH)D concentrations and the pooled results were heterogeneous. Review of the observational studies found that the majority reported an inverse relationship between [25(OH)D] and fractures.

Disclosures: ***A. Cranney****, None.*

16

Therapy of Osteoporosis with Calcium and Vitamin D.

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Inadequate intakes of vitamin D and calcium lead to reduced calcium absorption, higher bone-remodeling rates and increased bone loss. Vitamin D has also been linked to muscle function and risk of falling. Muscle tissue contains vitamin D receptors that, when activated, promote protein synthesis and muscle cell growth. In a random sample of men and women, age 60 and older, higher blood levels of 25-hydroxyvitamin D [25(OH)D] were associated with faster speeds on sit-to-stand and walking tests. Better performance was observed as levels rose into the reference range and from the lower to the upper end of the reference range. A recent meta-analysis of randomized, controlled vitamin D intervention studies revealed that supplementation with vitamin D, with or without calcium, lowered risk of falling by an average of 22%. In the elderly, falls are a major cause of fractures and other injuries.

A meta-analysis of randomized, controlled supplement trials indicated that vitamin D with or without calcium lowers risk of hip and all non-vertebral fractures in older adults by 26 and 23%, respectively. A mean serum 25(OH)D level of 75 to 80 nmol/L or higher appears to be needed in order to lower fracture risk. Three large trials have been published since that analysis. Two trials found no reduction in fracture rates with use of 800 IU/d of vitamin D3 and 1000 mg/d of calcium, perhaps because serum 25(OH)D levels in the treated subjects did not reach the needed level. The third trial, the Women's health Initiative, identified no significant fracture risk reduction in the group as a whole with use of 400 IU/d of vitamin D3 and 1000 mg of calcium compared with placebo in over 3,600 postmenopausal women. This finding needs to be interpreted with caution in view of the low dose of vitamin D given and of selected characteristics of the study population. Trials examining the effect of calcium alone on fracture incidence have had mixed results. In several randomized, controlled trials examining calcium and vitamin D both alone, and in combination, subset analyses have revealed that the more compliant subjects had greater benefit. In general, compliance with supplements tends to be even poorer than compliance with osteoporosis prescription medications.

The National Academy of Sciences recommends 400 IU/d of vitamin D for men and women age 51-70 yrs and 600 IU/d for those over age 70, together with 1,200 mg/d of calcium. Low calcium intakes are prevalent worldwide. There is increasing recognition that 400 to 600 IU/d of vitamin D3 will not raise mean 25(OH)D levels to 75 nmol/L and that intakes of 800 to 1000 IU/d or more are needed by the average older man and woman to accomplish this. Over half of older adults worldwide consume far less than these amounts, have 25(OH)D levels below 75 nmol/L, and therefore stand to benefit from additional vitamin D.

Disclosures: ***B. Dawson-Hughes****, None.*

17

NIH Women's Health Initiative.

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The efficacy of calcium plus vitamin D supplements for the prevention of bone loss and reduction of fracture in community-dwelling women not chosen for risk of osteoporosis remains unclear. The purpose of the Women's Health Initiative calcium plus vitamin D controlled randomized trial was to determine whether the addition of 1000 mg/day of elemental calcium (as carbonate) and 400 IU of Vitamin D_3 would significantly reduce the risk of hip and total fracture among women with ad lib calcium intake from diet and/or supplements. Postmenopausal women ages 50-79 were recruited from individuals already enrolled in the WHI Dietary Modification or Hormone Trials or both. Fracture incidence was assessed by semiannual questionnaire and verified by adjudication of radiology reports over an average of 7 years follow up. BMD was measured in a subset of women at baseline, year 3 and 6. At enrollment, these 36,282 women had an average calcium intake of 1100 mg/day. Overall, active supplementation in the trial produced a small but significant increase in total hip and femoral neck BMD and a non-significant reduction in risk of hip fracture with a hazard ratio of 0.88 (95% CI, 0.72-1.08). The effects of calcium-Vitamin D supplementation were greater among women with >80% adherence (HR=0.71, 95% CI, 0.52-0.97), women ages >60 at enrollment (HR=0.79, 95% CI, 0.64-0.98), and those not taking personal calcium supplements during the trial (HR=0.70, 95% CI, 0.51-0.98). There was no interaction between CaD and age on BMD change. There was a trend toward an effect of CaD on hip fracture reduction in older women with calcium intakes less than 1200 mg, with no benefit noted in older women taking more than 1200 mg or in younger women irrespective of calcium intake. In conclusion, although the intention-to-treat analyses do not confirm that CaD significantly reduces the risk of fracture in calcium-replete postmenopausal women, in older women, particularly those with a calcium intake less than 1200 mg daily, CaD appears to have an important effect on bone health.

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Disclosures: ***R.D. Jackson*** *, Procter & Gamble Pharmaceuticals 2, 8.*

18

Vitamin D Toxicity, Policy and Science.

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An optimal circulating concentration of 25-hydroxyvitamin D [25(OH)D] has never been established. A major reason for this is concern over vitamin D toxicity. Clinical trials tended focus on no more than 800 IU/day vitamin D, with no preliminary effort to establish what an appropriate dose might be. Cross-sectional data are limited to endemic vitamin D supplies, but they suggest that benefits progressively increase as serum 25(OH)D concentrations continue to rise (1). The serum 25(OH)D concentration that is the threshold for vitamin D toxicity remains unknown. For healthy individuals, the mechanisms that limit vitamin D safety are the capacity of circulating vitamin D-binding protein to sequester vitamin D and its metabolites, and the ability to suppress 25(OH)D-1 alpha-hydroxylase.

Toxicity occurs when there is a high "free" concentration of 1,25-dihydroxyvitamin D hormone despite what may be a normal total concentration (2). People with primary hyperparathyroidism or certain granulomatous disease are particularly susceptible to vitamin D toxicity.

Policy of the Food and Nutrition Board sets the Tolerable Upper-Intake Level (UL) for vitamin D at 50 mcg (2000 IU)/day, defining this as "the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population" (3). However, sunshine can safely provide an adult with vitamin D in an amount equivalent to daily oral consumption of 250 mcg/day. The incremental consumption of 1 mcg/day of vitamin D_3 raises serum 25(OH)D by about 1 nmol/L (0.4 ng/mL). Therefore, if sun-deprived adults should maintain serum 25(OH)D concentrations higher than 75 nmol/L (30 ng/mL) they will require vitamin D in excess of the UL.

For vitamin D, the most recent risk assessment of the Food and Nutrition Board in 1997 focused its considerations on the hazard of hypercalcemia. A recent effort to apply Food and Nutrition Board criteria to newer evidence now available concludes there is no convincing evidence that hypercalcemia occurs in adults with long-term vitamin D intakes of 250 mcg/day (10,000 IU/day) (4).

Inappropriately low UL values or guidance values for vitamin D have hindered objective clinical research into vitamin D nutrition; they have hindered our understanding of its role in disease prevention, and restricted the amount of vitamin D in multivitamins and foods to doses too low to benefit public health.

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Disclosures: ***R. Vieth****, None.*

19

Establishing Guidelines for Vitamin D Intakes.

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Population-based guidelines for vitamin D intakes include the Dietary Reference Intakes (DRIs) developed by the Institute of Medicine (IOM) (1) and the *Dietary Guidelines for Americans* (DGs) developed jointly by the Departments of Health and Human Services (2) with input from an Advisory Committee (3). The 1997 DRIs for vitamin D included an Adequate Intake reference value (AI) for persons ≤ 50 yr of 5 µg (200 IU)/d, with an AI of 10 µg/d (400 IU)/d for persons 51-70 y, and 15 µg (600 IU)/d for persons >70 y. The Tolerable Upper Intake Level (UL) is 25 µg (1000 IU)/d for 0 - 12 months and 50 µg (2000 IU)/d for persons ≥ 1 year. More recently, the 2005 *Dietary Guidelines for Americans* identified vitamin D as warranting special attention for groups at high risk of inadequacy (ie, the elderly, individuals with dark skin, and individuals with insufficient exposure to sunlight). They recommended daily intakes of 25 µg (1,000 IUs) of vitamin D per day for high-risk groups to reach and maintain serum 25-hydroxyvitamin D values at 80 nmol/L

The processes involved in setting nutrient guidelines began in the 1940s for the DRIs and in 1980 for the DGs. These processes evolved significantly over time as the science matured, as expert panels gained experience in translating the available science to population-based values, and as users identified challenges in incorporating the guidelines into wide-ranging applications. As updates to the current DRIs and DGs are anticipated, we wish to continue the tradition of improving these processes through constructive evaluations of 'lessons learned'. This aim is informed not only by the results of the most recent DRI and DG experiences but also by a recent joint WHO/FAO evaluation of the processes used to set nutrient ULs (4). Issues for which further discussion is warranted include questions as to how to: a) improve the transparency and systematic nature of the scientific reviews, b) clarify the nature of and the rationale used for the series of decisions made in deriving reference values, and c) improve the nature of the information presented so that users will have the tools they need to apply the reference values in a variety of contexts. Additionally, a long-standing and continuing challenge is the question of whether we can improve the processes of generalizing from the available scientific evidence that is almost always designed for purposes other than support of reference values to answer the series of questions needed for deriving DRIs and DGs for the general, healthy population. Finally, the question of stimulating research needs and gaps in the available evidence base will be informed by the pending availability of a DRI Research Synthesis workshop report from the IOM (5).

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Disclosures: ***E.A. Yetley****, None.*

20

Vitamin D Receptor Agonists in the Treatment of Autoimmune Diseases.

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$1,25(OH)_2D_3$, the activated form of vitamin D, is a secosteroid hormone that has, in addition to its central function in calcium and bone metabolism, important effects on the growth and differentiation of many cell types, and pronounced immunoregulatory properties (1, 2). The biological effects of $1,25(OH)_2D_3$ are mediated by the vitamin D receptor (VDR), a member of the superfamily of nuclear hormone receptors, which is expressed in most cell types of the immune system, including macrophages, dendritic cells (DCs), and T lymphocytes. In addition to exerting direct effects on T cell activation, VDR agonists markedly modulate the phenotype and function of DCs, promoting tolerogenic properties that favor the induction of regulatory rather than effector T cells (3). These intriguing actions of VDR agonists have been demonstrated in several experimental models and could be exploited, in principle, to treat a variety of human autoimmune diseases. Notably, VDR agonists can prevent systemic lupus erythematosus in $MRL^{lpr/lpr}$ mice, experimental allergic encephalomyelitis (EAE), collagen-induced arthritis, Lyme arthritis, inflammatory bowel disease, autoimmune diabetes and experimental autoimmune prostatitis in non-obese diabetic (NOD) mice (4). VDR agonists are able not only to prevent but also to treat ongoing autoimmune diseases, as demonstrated by their ability to inhibit type 1 diabetes development in adult NOD mice and the recurrence of autoimmune disease after islet transplantation in the NOD mouse, or to ameliorate significantly chronic-relapsing EAE. An important property of VDR agonists is their capacity to modulate both DCs and T cells. The induction of tolerogenic DCs, which leads to an enhanced number of $CD4^+CD25^+$ regulatory T cells renders them appealing for clinical use, especially for the prevention and treatment of autoimmune diseases (5). In addition, it is conceivable that $1,25(OH)_2D_3$, which is produced by macrophages, DCs and T cells, could physiologically contribute to regulate innate and adaptive immune responses.

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Disclosures: ***L. Adorini****, BioXell 1, 3.*

21

Role of Vitamin D Regulation in Prostate Cell Growth.

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Calcitriol, the active form of vitamin D, acts like a steroid hormone to regulate target gene expression by binding to intranuclear vitamin D receptors in most tissues in the body including normal prostate, BPH and prostate cancer (PCa). The actions of calcitriol are pleiotropic involving the stimulation or suppression of a number of genes that inhibit proliferation, advance differentiation and promote apoptosis. These findings have led to a multiple studies to ascertain whether therapy with calcitriol would be useful in the prevention and/or treatment of PCa. Recent studies from our lab have revealed new actions of calcitriol that include inhibition of the prostaglandin (PG) pathway by inhibiting COX-2 expression, stimulating 15-PGDH expression and decreasing PG receptors. Calcitriol also induces the expression of MAP kinase phosphatase 5 (MKP5) resulting in the inactivation of p38 stress kinase and reduction in the level of inflammatory cytokines such as IL-6. Since inflammation has been identified as an important carcinogenic stimulus involved in promoting the growth, progression and resistance to apoptosis of many cancers including PCa, these actions of calcitriol to inhibit important pro-inflammatory pathways provide a new rationale for its therapeutic use in cancer. Recent studies have shown some benefit of calcitriol to prevent or delay PCa development and/or progression in various animal models. Currently calcitriol is being evaluated in several clinical studies of men with PCa and the findings indicate some benefit including stabilization of disease progression in advanced PCa. When calcitriol was used in combination with the chemotherapy drug docetaxol to treat men with advanced PCa, a significant prolongation of survival as well as a reduction of side-effects from the chemotherapy was observed. Since calcitriol can be administerd orally, appears to be safe, is economical and has a very useful anti-cancer profile of actions, further study to evaluate its value in the chemoprevention or therapy of PCa are warranted.

Disclosures: ***D. Feldman****, Cytochroma 5; Sapphire 5; Novacea 2; Abbott 2.*

22

The Epidemiology of Vitamin D and Cancer Incidence and Mortality.

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In vitro and animal studies indicate that vitamin D may have anti-cancer benefits against a wide spectrum of cancers, including against progression and metastasis (*1*). Supporting an anti-cancer effect of vitamin D is the ability of many cells to convert 25(OH)vitamin D, the primary circulating form of vitamin D, into the biologically active $1,25(OH)_2$vitamin D. From an epidemiologic perspective, most evidence has focused on solar UV-B radiation, which is required to form vitamin D in the skin. In geographic regions with less solar UV-B radiation, higher rates of total cancer mortality are observed (*2*). In particular, cancers of the digestive tract system seem to be most affected (esophagus, stomach, colon, rectum, pancreas, and gallbladder and bile ducts) (*3*).

Studies directly linking pre-diagnostic serum levels of 25(OH)vitamin D and cancer risk are sparse, but several studies support an inverse association for colorectal cancer, and possibly prostate cancer. Increased cancer mortality among African-Americans and overweight/obese people, each associated with lower circulating vitamin D, is also compatible with a benefit of vitamin D on cancer mortality (*1*). Recent evidence also indicates that higher circulating levels of 25(OH)vitamin

D may improve survival in patients diagnosed with several cancer types (*4*).

The available data on vitamin D and cancer incidence or mortality are intriguing but are not definitive, and the following important questions remain: 1) do higher vitamin D levels lower cancer risk in humans; 2) what cancer sites are affected; 3) what stage in the natural history is vitamin D most important, and is the influence primarily on incidence or mortality; and 4) if beneficial, what is the optimal intake and circulating concentration. Nonetheless, confirming that vitamin D indeed accounts for these associations is critical because current health recommendations typically discourage high intakes of vitamin D as well as sun exposure, at least without the use of sunscreen, which effectively blocks vitamin D production.

Achieving a 25 nmol/L increment of 25(OH) vitamin D, which was shown to be associated with a substantially lower cancer rate in one study (*5*), may require about 1500-2000 IU/day of vitamin D, a level which is safe but not generally encouraged. A glass of milk, though perceived as being a good source of vitamin D when fortified as in the United States (100 IU/glass), would raise 25(OH) vitamin D by about 2-3 nmol/L. Adult sun exposure, discouraged because of risk of skin damage and cancer, is by far the most abundant source of vitamin D currently. For example, a person can potentially make 10,000 IU or more with 20 minutes of sun exposure. The potential benefits of substantially increasing the recommended level of vitamin D intake need to be evaluated.

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Disclosures: ***E. Giovannucci****, None.*

23

Vitamin D and Breast Cancer.

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Since the discovery of the vitamin D receptor (VDR) in mammary cells, the role of the vitamin D signaling pathway in normal glandular function and in breast cancer has been extensively explored. *In vitro* studies have demonstrated that the VDR ligand, 1,25-dihydroxyvitamin D, modulates key proteins involved in signaling proliferation, differentiation and survival of normal mammary epithelial cells. These findings suggest a potential role for the vitamin D pathway in mammary gland function during the reproductive cycle. Furthermore, similar anti-proliferative and pro-differentiating effects of 1,25-dihydroxyvitamin D have been observed in VDR positive breast cancer cells, indicating that transformation *per se* does not abolish vitamin D signaling. However, many transformed breast cancer cell lines are less sensitive to 1,25-dihydroxyvitamin D than normal mammary epithelial cells. Reduced sensitivity to 1,25-dihydroxyvitamin D has been linked to alterations in vitamin D metabolizing enzymes as well as down regulation of VDR expression or function. Over the years, our lab has focused in three general areas: 1) defining mechanisms of vitamin D mediated apoptosis in breast cancer cells, 2) examining changes in the vitamin D signaling pathway during transformation, including the development of vitamin D resistance, and 3) using mouse models to study the impact of the VDR on growth regulatory pathways in the context of development and tumorigenesis *in vivo*. We have also developed model systems, such as human breast cancer cells selected for resistance to 1,25-dihydroxyvitamin D and mammary tumor cell lines generated from VDR null mice, which represent unique tools to define mechanisms of vitamin D signaling in breast cells in vitro and in vivo. Recent developments include detection of megalin-mediated endocytosis of DBP and identification of CYP27B1 and CYP24 vitamin D metabolizing enzymes in mammary cells, demonstration of precocious mammary gland development in VDR null mice, and characterization of novel pathways triggered by 1,25-dihydroxyvitamin D during apoptosis. Our pre-clinical studies have been complemented by emerging data from other groups suggesting that human breast cancer may be influenced by VDR genotype and vitamin D status. Collectively, these studies have reinforced the need to further define the regulation and function of the vitamin D pathway in cells in relation to prevention and treatment of breast cancer.

Disclosures: ***J. Welsh****, None.*

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ASBMR YOUNG INVESTIGATOR AWARD
Maternal Vitamin D Insufficiency and the Risk of Preeclampsia, an Adverse Pregnancy Outcome.

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Preeclampsia, a pregnancy-specific disorder diagnosed by new-onset hypertension and proteinuria, is a leading cause of maternal and infant morbidity and mortality worldwide. Preeclampsia exhibits seasonal patterns that implicate vitamin D and sunlight exposure in its pathophysiology. Vitamin D has been proposed to regulate human placental implantation and cardiovascular function, processes key to the genesis of preeclampsia. Our objectives were to assess the independent effect of maternal vitamin D status on the risk of preeclampsia and to assess the likelihood of vitamin D insufficiency in preeclamptic mothers' offspring. We conducted a nested case-control study of 69 cases of preeclampsia and 394 women with normal pregnancy outcome and their newborns. Serum 25-hydroxyvitamin D [25(OH)D] was measured in maternal samples collected at <21 weeks' gestation and in cord blood samples. Multiple logistic regression was used to adjust for race/ethnicity, prepregnancy body mass index, prenatal vitamin use, and season. The adjusted mean serum 25(OH)D concentrations at <21 weeks were significantly lower among women who subsequently developed preeclampsia than women with a normal pregnancy outcome (geometric mean (95% confidence interval) 46.9 (41.2, 53.4) nmol/l vs. 52.5 (48.1, 57.3) nmol/l, $p<0.05$). There was a curvilinear relation between 25(OH)D at <21 weeks and the risk of preeclampsia. After adjusting for confounders, the risk of preeclampsia significantly decreased as 25(OH)D concentration increased from 0 to 80 nmol/l. Compared with a serum 25(OH)D concentration of 80 nmol/l, 25(OH)D concentrations of 25 and 50 nmol/l were associated with 3.2-fold (95% CI: 1.2, 8.7) and 1.7-fold (1.1, 2.8) increases in risk, respectively. There was no association

between serum 25(OH)D concentrations and preeclampsia risk beyond a 25(OH)D concentration of 80 nmol/l. Neonates of preeclamptic mothers had lower adjusted mean cord serum 25(OH)D than neonates of controls (46.6 (40.0, 54.2) vs. 53.5 (48.7, 58.7) $p<0.05$) and were 2.5 times as likely to have serum 25(OH)D <50 nmol/l (prevalence odds ratio: 2.5 (95% CI: 1.1, 5.6)). Our results suggest that maternal vitamin D insufficiency is an independent risk factor for preeclampsia and may contribute to the known racial/ethnic disparity in preeclampsia rates. Furthermore, these findings imply that the offspring of preeclamptic mothers may have poor vitamin D status and may be at risk for vitamin-D related morbidities later in life.

Disclosures: ***L.M. Bodnar,*** *None.*

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Role of Vitamin D Deficiency in Chronic Kidney Disease.

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Chronic kidney disease (CKD) has been recognized as a significant public health problem with approximately 20 million Americans, or about 11% of the adult population, currently living with CKD . A significant source of morbidity associated with CKD is the development of disturbances of mineral metabolism, which occurs in virtually all patients during the progression of their disease, and is associated with bone loss and fractures, cardiovascular disease, immune suppression, and increased mortality. As kidney disease develops, there is decreased functional renal mass and a tendency to retain phosphorus. The reduction in functional renal mass and the retained phosphorus act to reduce the renal 1α-hydroxylase activity and thus the renal production of calcitriol (1,25-dihydroxycholecalciferol). Further compensation to maintain normal serum calcium and phosphorus homeostasis includes increased production and release of parathyroid hormone (PTH) and potentially other phosphaturic factors, such as fibroblast growth factor-23 (FGF-23).[30] This increase in FGF-23 contributes to maintain normal serum phosphate independent of PTH, but may actually worsens calcitriol deficiency by also inhibiting renal 1α-hydroxylase activity. The decrease in calcitriol also results in promoting further hyperparathyroidism and parathyroid gland hyperplasia, as calcitriol normally inhibits the production of pre-pro-PTH and parathyroid cell proliferation.

Deficiency in vitamin D is not limited to the active hormone, calcitriol, but calcidiol (25-hydroxycholecalciferol), is also deficient in most patients with CKD, independent of their underlying renal function. Decreases in calcitriol occur relatively early in the progression of kidney disease and may predate the increase in PTH. These changes in calcitriol and PTH contribute to the maintenance of relatively normal serum and calcium concentrations until the GFR decreases to less than 20-25 %, however the result is the potential development of bone and vascular disease. In addition to the direct disturbances in bone and mineral metabolism associated with calcitriol deficiency, there are increasing epidemiologic data suggesting that vitamin D deficiency may play a role in overall morbidity and mortality associated with CKD.

Disclosures: ***S.M. Sprague****, Abbott 2, 5, 8; Amgen 2, 5, 8; Genzyme 2, 8; Shire 2, 5, 8.*

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Paradoxical Effects of Active Vitamin D Analogue Agents in CKD/End Stage Kidney Disease.

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CKD is associated with high mortality rates attributed to cardiovascular disease that includes a high prevalence of left ventricular hypertrophy, accelerated atherosclerosis and vascular calcifications. Although co-morbid factors such as diabetes mellitus, hypertension and vascular disease contribute to the development of chronic kidney disease as well as cardiovascular disease, the high mortality rate in CKD is not fully explained by these factors. Rather, the presence of uremic specific risk factors, such as disordered mineral metabolism and its treatment, appear to supersede the role of traditional risk factors in modifying cardiovascular mortality in CKD. Epidemiological studies identify hyperphosphatemia, hypercalcemia and elevated PTH as important risk factors for increased mortality in end stage renal disease (ESRD). Since phosphate is a key regulator of extracellular matrix mineralization and serum levels of phosphate >5.5 mg/dl is associated with vascular calcification and mortality, calcification ("phosification") of blood vessels is postulated to be the link between hyperphosphatemia and increased mortality in CKD. $1,25(OH)_2$ D production of ~1 μg of per day is lost in ESRD and nutritional vitamin D deficiency is prevalent in CKD. The intravenous administration of high dose vitamin D analogues is the current standard of care to suppress PTH in ESRD, but this therapy is associated with increased serum calcium and phosphate concentrations, which should promote vascular calcifications. Epidemiological studies, however, demonstrate that treatment with vitamin D analogues in incident patients on hemodialysis is paradoxically associated with a significant reduction in mortality, purportedly due to the salutary effect of vitamin D on immune and cardiovascular function. At present, the relative risk of concurrent hyperphosphatemia and high dose vitamin D therapy are uncertain due to the absence of prospective trials comparing different treatment regimens. The recent introduction of calcimimetics provide an alternative therapy for reducing PTH in ESRD without exacerbating hyperphosphatemia or use of high dose active vitamin D analogues. Prospective trials are needed to separately assess the impact of therapy with active vitamin D analogues, more effective control of hyperphosphatemia, and the use of calcimimetics on vascular calcifications and mortality in ESRD.

Disclosures: ***L.D. Quarles****, Amgen 2, 5, 8.*

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Effects of Vitamin D and Analogues on Cardiovascular Events and Life Expectancy in Patients with CRF.

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Vitamin D deficiency is common at all stages of chronic kidney disease (CKD) and the administration of active vitamin D sterols or analogues to treat secondary hyperparathyroidism is common. Recent retrospective cohort studies have demonstrated that the administration of active vitamin D sterols (paricalcitol more so than calcitriol) to patients on dialysis results in a reduction in mortality that appears independent of calcium, phosphorus, and PTH[1, 2]. These results have now been confirmed in several other retrospective studies around the world. However, given these data remain unconfirmed in prospective randomized clinical trials; one must look for biologic plausibility.

The VDR is located throughout the cardiovascular and immune system. The administration of calcitriol or paricalcitol decreases inflammation, dendritic cell maturation, and modulates matrix metalloproteinase-9, all of which may serve to reduce intimal atherosclerosis. Low vitamin D levels are associated with congestive heart failure in the general population, and the administration of calcitriol reduces left ventricular hypertrophy in the CKD population. Animal studies confirm these latter effects and demonstrate a reduction in cardiomyocyte hypertrophy in animals treated with calcitriol. Lastly, vitamin D treatment reduces blood pressure and proteinuria, perhaps mediated by the renin-angiotensin system as calcitriol suppresses renin gene expression in the kidney[3].

In contrast to these protective effects of calcitriol, many studies have demonstrated that calcitriol can lead to arterial calcification. However, the results of in vitro studies are somewhat conflicting. Animal studies traditionally use high dose vitamin D that is uniformly associated with hypercalcemia and hyperphosphatemia and suppression of bone turnover. Similarly, human studies cannot completely separate the direct effects of vitamin D on vascular calcification from its indirect effects on raising the calcium x phosphorus product and inducing low turnover bone which is known to be associated with arterial calcification[4].

Thus, it is likely that all patients need some vitamin D, but that it must be administered with care to avoid hypercalcemia and hyperphosphatemia with resultant vascular calcification. In addition, it is unknown if patients with CKD require activated sterols such as calcitriol or if nutritional D supplements may be adequate.

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Disclosures: ***S.M. Moe****, Genzyme 2, 5, 8; Amgen 2, 5, 8; Abbott 2, 5; Shire 2, 5.*

28

Management of Renal Osteodystrophy in Childhood.

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Children with chronic kidney disease (CKD) have multiple risk factors for impaired bone accrual, including vitamin D deficiency. While numerous studies have reported inadequate 25(OH) vitamin D levels in adults with CKD, none have included concurrent controls and few data are available in children. We recently assessed vitamin D status in 152 children with CKD Stages 2 - 5 and 207 healthy controls. CKD stages 4 and 5 were associated with significantly greater odds of vitamin D deficiency [serum 25(OH) vitamin D < 10 ng/mL] compared with controls, adjusted for season, race, and age; odds ratio = 6.1 (95% C.I. 3.0 - 12.5). Among the 69 Caucasian children with CKD stages 4-5, 25(OH) vitamin D levels were < 30 ng/mL in 87% and < 10 ng/mL in 29%. Among the 27 African American children, 25(OH) vitamin D levels were < 30 ng/mL in 100% and < 10 ng/mL in 52%. Log PTH levels were inversely associated with 25(OH)D levels ($r = -0.30$, $p = 0.03$).

The majority of studies of bone mass in children with CKD have been conducted using Dual Energy X-ray Absorptiometry (DXA). However, DXA measures of bone mineral density (BMD) are derived from the total bone mass within the projected bone area (g/cm^2), concealing distinct disease effects in trabecular and cortical bone. In contrast, quantitative CT (QCT) estimates volumetric BMD (vBMD, g/cm^3) and distinguishes between cortical and trabecular bone. Recent data have confirmed that QCT measures of cortical vBMD provide substantially better fracture discrimination in adult dialysis patients, compared with hip or spine DXA. We are currently conducting a prospective tibia QCT study in children with CKD. Preliminary data in 44 transplant recipients demonstrated that trabecular vBMD z-scores were significantly elevated at the time of transplant, compared with controls ($p<0.0001$) consistent with osteitis fibrosa. Following transplantation, trabecular vBMD z-scores decreased significantly; however, the vBMD did not fall below the 10th percentile in any subjects. Cortical vBMD was significantly decreased at the time of transplantation ($p<0.001$) and increased over the subsequent year ($p<0.0001$). Log PTH was inversely correlated with cortical vBMD ($p<0.0001$), positively correlated with trabecular vBMD ($p=0.04$), and decreased following transplantaton. Intervention studies with 25(OH) vitamin D supplementation are needed to determine effects on secondary hyperparathyroidism, bone mass and structure in children with CKD.

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Disclosures: ***M.B. Leonard****, None.*

29

Primary Hyperparathyroidism and Vitamin D Deficiency.

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Temporally associated with the improvement in vitamin D nutrition in many Western countries in the mid- 20th century, there was a change in many characteristics of primary hyperparathyroidism. With the evolution of the clinical profile of primary hyperparathyroidism, osteitis fibrosa cystica has become a rare manifestation of what is now frequently an asymptomatic disease. At the same time, levels of parathyroid hormone in the disease and parathyroid adenoma weights have fallen dramatically. In view of these observations, and supported by recent epidemiologic data from around the world, some have proposed an association between vitamin D deficiency and severity of primary hyperparathyroidism. A global view of the association of vitamin D deficiency and primary hyperparathyroidism will be reviewed. Data will be presented on the persistence of “classical” symptomatic primary hyperparathyroidism in regions where vitamin D deficiency is endemic. Vitamin D insufficiency is common in patients with mild primary hyperparathyroidism as well, and potential implications of vitamin D status for skeletal involvement in primary hyperparathyroidism will be discussed. The limited data on management of vitamin D deficiency in primary hyperparathyroidism will be examined. There are preliminary data on vitamin D repletion in mild primary hyperparathyroidism patients, which suggest that in some cases correction of vitamin D deficiency may be accomplished without worsening hypercalcemia. There are also data supporting an increased risk of postoperative hypocalcemia in vitamin D deficient

patients undergoing parathyroidectomy, which underscores the importance of preoperative assessment of vitamin D status in all patients with primary hyperparathyroidism.

Disclosures: ***S.J. Silverberg****, Merck & Co. 2.*

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FGF-23/MEPE/TIO/XLH and Vitamin D Metabolism.

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The discovery of the phosphatonins (or minhibins), a family of hormones which regulate bone mineralization and renal phosphate handling, has brought new perspective to the pathophysiology of the hypophosphatemic rachitic/osteomalcic diseases in man. These hormones are seemingly involved in regulatory loops with counter-regulation provided by serum phosphate and/or 1,25-dihydroxyvitamin D levels. Most recently, however, studies of vitamin D metabolism in murine homologues of X-linked hypophosphatemia, Tumor-induced osteomalacia, and autosomal recessive hypophosphatemia have challenged the regulatory effects of phosphatonins on renal 25(OH)D-1α-hydroxylase activity. In this regard, several groups have repeatedly documented in *in vitro* studies that FGF-23 and MEPE, classic phosphatonins, inhibit renal 25(OH)D-1α-hydroxylase mRNA. Such studies have led to the widely held belief that such inhibitory activity causes the classic relative deficiency of $1,25(OH)_2D$ observed in virtually all renal phosphate wasting disorders. However, contrary to this hypothesis, murine models of the human diseases, the *hyp*-, transgenic FGF-23 and $DMP1^{-/-}$-mouse, while exhibiting decreased serum $1,25(OH)_2D$ levels, manifest appropriately elevated 25(OH)D-1α-hydroxylase mRNA transcripts, relative to their characteristic hypophosphatemia. Unexpectedly, further studies revealed in each case that the defective regulation of vitamin D metabolism in these animal models is due to ineffective mRNA translation and a consequent relative deficiency of the 25(OH)D-1α-hydroxylase protein. The cause of this defect has been determined in transgenic Npt2-hyp mice, in which normal serum phosphorus levels are maintained by over-expression of Npt2 exclusively in the kidney. In this murine model, normal regulation of 25(OH)D-1α-hydroxylase mRNA production and translation is evident, eliminating the defect in vitamin D metabolism, despite continued elevation of serum FGF-23 levels. These observations suggest that abnormal renal phosphate handling and/or hypophosphatemia are critical factors in the genesis of $1,25(OH)_2D$ deficiency in renal phosphate wasting disorders. While these studies provide new insight to the regulatory mechanisms for vitamin D metabolism, they do not ascertain the role that the $1,25(OH)_2D$ deficiency plays in creation of the hypophosphatemic disease phenotype. However, a review of critical studies indicates that, whereas treatment with vitamin D (in pharmacological amounts) and phosphate does not heal the osteomalacia in patients with X-linked hypophosphatemia, prolonged high-dose $1,25(OH)_2D$ and phosphate therapy does effect normal bone mineralization in patients with this disorder. These data indicate that the unique abnormality in vitamin D metabolism, apparently manifest in the hypophosphatemic osteomalacic disorders, may have a pivotal role in the phenotype of the diseases.

Disclosures: ***M.K. Drezner****, Roche Pharmaceuticals 1; Eli Lilly and Company 1; Novartis 1; Merck Company 1.*

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Vitamin D Resistant Diseases.

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Hereditary vitamin D receptor defects (HVDRD) will be a more appropriate and precise title for the topic to be discussed. As many inborn errors of metabolism, it is a rare disorder, about 65 kindreds were described, but its main importance is elucidating the physiology of vitamin D and calcium homeostasis in humans.

It is an autosomal recessive disease, with frequent consanguinity and a high concentration in a region centered around the Mediterranean.

An unusual feature is total alopecia documented in about half of the patients. Patients develop usually the clinical and biochemical aberrations, identical to vitamin D deficiency, but with high serum levels of calcitriol, within the first year of life, *i.e.,* muscle weakness, bone pain, deformities and fractures. Defective calcium gut absorption leads to hypocalcemia, secondary hyperparathyroidism, hypophosphatemia and defective mineralization of newly-formed bone matrix.

The disease is not cured by vitamin D replacement therapy, though some patients respond to very high doses of vitamin D or its metabolites.

Cells derived from patients, mainly cultured skin fibroblasts were used to assess steps in calcitriol action from cellular uptake to bioresponse and to elucidate the molecular aberrations in the VDR. Transcriptional activity of patient's DNA and artificially recreated mutants were tested *in vitro*. Point mutations in the VDR gene were identified in every patient examined and the same defect observed in the obligatory hetrozygots. The functional characterization of the patient's VDR reflected the localization of the mutation, 18 different ones described up to now, thus providing vital information about structure-function relationship in human VDR.

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Disclosures: U.A. Liberman , None.

Posters

Assessment of Vitamin D I

M1

Safety of Vitamin D_3 8400 IU Once Weekly in Elderly Subjects with Vitamin D Insufficiency.

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Vitamin D deficiency is common in older adults. However, concerns about the safety of vitamin D treatment may result in under-replacement of patients with vitamin D insufficiency. This study examined the safety and efficacy of treatment with vitamin D_3 (D_3) 8400 IU once weekly for 16 weeks in subjects 70 years or older who had vitamin D insufficiency (25OHD ≥6 but ≤ 20 ng/mL). The study recruited 226 generally healthy subjects [mean age ± SD: 78.0 ± 6.4] from 5 countries during the fall and winter. Subjects were randomly allocated in a 1:1 ratio to receive either D_3 8400 IU once weekly or placebo; 25OHD serum levels were analyzed at a central laboratory by HPLC. Serum calcium, phosphate, creatinine and urine calcium were monitored for safety. Baseline serum 25OHD levels were similar in the 2 treatment groups [Mean ± SD: Vitamin D 14.3 ± 3.9; Placebo =14.4 ±4.3]. The percentage of subjects with abnormal laboratory values was comparable between the two treatment groups at baseline and at week 16. The incidence of hypercalcemia, hypercalciuria, or elevated creatinine in the D_3-treated group was not different from the placebo-treated group after 16 weeks of treatment. No kidney stones were reported in any subjects. A non-significant between-group difference ($p = 0.08$) was observed in 24-hour urinary calcium excretion, with the D_3-treated group increasing from 79.1 to 95.7 mg/day and the placebo-treated group decreasing from 108.2 to 103.3 mg/day. Following 16 weeks, 25OHD levels increased from baseline by 11.9 ± 0.6 ng/mL in the D_3 group and decreased from baseline by -1.1± 0.4 ng/mL in the placebo group ($p<0.001$). The between-group difference was 13.0 ng/ml (95% CI, 11.6; 14.4). At 16 weeks 90% of D_3-treated subjects reached 25OHD levels ≥20 ng/mL *vs*. 8% of subjects on placebo; none of the D_3-treated subjects had 25OHD levels < 9 ng/mL *vs*. 14% of subjects on placebo. No subject reached 25OHD levels > 60 ng/mL during the study. PTH levels decreased by 7.5 % in the D_3 group and increased by 9.2% in the placebo group (significant between-group difference of -16.8%, $p = 0.003$). In conclusion, treatment with vitamin D_3 8400 IU was safe, well-tolerated and efficacious at increasing 25OHD levels in this subject population.

Disclosures: ***N. Binkley****, None.*

M3

Factors Associated with Elevated or Blunted PTH Response to Serum 25(OH)-Vitamin D Levels.

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Vitamin D status is one of the major determinants of parathyroid function and the relationship between serum levels of PTH and 25(OH)-vitamin D has been well characterized. The purpose of this study was to examine factors associated with elevated or blunted PTH levels in relationship to vitamin D status.

A random sample of Caucasian men and women aged 30-85 took part. They completed a health- and diet-questionnaire, height and weight, and various factors affecting bone metabolism were measured. Participants with diseases or taking drugs affecting bone metabolism were excluded from current analysis. We defined elevated or blunted PTH response as PTH levels above or below the regression-line between serum PTH and 25(OH)D levels, dividing the sample into two groups, who were subsequently compared using ANCOVA, controlling for age and also BMI for BMD analysis. Men and women were analyzed separately.

Of 1630 participants, 490 healthy men (58.2±14.6 years) and 517 women (55.2±16.4 years) remained for analysis. Men with a blunted PTH response had a significantly ($p<0.05$) higher ionized calcium and IGF-1, but lower cystatin C, BMI, fat-mass, lean-mass and P1NP. There were no significant differences for sunshine exposure, vitamin D, calcium or energy intake, phosphate ($p=0.076$), 25(OH)D, free-testosterone, magnesium, osteocalcin, total alkaline phosphatase (ALP), collagen crosslaps or BMD at any site, Women with a blunted PTH response had a significantly higher phosphate and smoking percentage, but lower ALP, vitamin D binding globulin, 1.25(OH_2)D, magnesium and BMI. There were no significant differences for sunshine exposure, vitamin D, calcium or energy intake, ionized calcium, 25(OH)D, free-estrogen, cystatin-C, U-calcium/creatinine ratio ($p=0.05$), IGF-1, osteocalcin, collagen crosslaps, P1NP or BMD at any site.

The factors associated with PTH response to 25(OH)D seem to be gender dependent. Men with blunted PTH response seem to be more likely to smoke, have better kidney function and lower BMI with no effect on BMD. Women with blunted PTH response seem to be more likely to smoke, have lower BMI and lower magnesium levels with no effect on BMD. More detailed analysis is needed, especially at sub-optimal vitamin D levels. Better knowledge on these associated factors may help in determining optimal vitamin D requirements for different population groups.

Disclosures: ***G. Sigurdsson****, None.*

M5

Vitamin D ($25OHD_3$) Status and the *Cdx-2* Polymorphism of the Vitamin D Receptor Gene Are Determining Factors of Bone Mineral Density.

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Postmenopausal women with osteoporosis have an increased risk of future fractures and should be treated to reduce this risk. However, bone mass measurement is not generally available due to the lack of access to DXA (dual-energy X-ray absorptiometry). We developed a test to predict the risk of osteoporosis in young postmenopausal women that includes clinical risk factors, biochemical and genetic markers for disease screening.

A cross-sectional study in 229 healthy postmenopausal women. Participants were administered a questionnaire on clinical risk factors for low bone mass. Serum concentrations of PTH, $25OHD_3$, $1,25(OH)_2D_3$ and markers of bone turnover were measured. The *BsmI*, *FokI* and *Cdx-2* polymorphisms of the VDR gene, *Sp1* polymorphism of the COLIA1 gene and *PvuII* polymorphism of the ER gene were determined. DXA was performed (Hologic QDR 1000) applying the WHO criteria for diagnosis of osteoporosis (T-score < -2.5) in spine and/or hip. Multivariate logistic regression analysis was performed and the Receiver Operating Characteristic (ROC) curve was plotted to determine the optimum cutoff for the model.

Age increased the risk of osteoporosis (OR: 1.10; 95% CI: 1.00-1.10), while BMI (OR: 0.94; 95% CI: 0.88-0.99), number of reproductive years (OR: 0.94; 95% CI: 0.89-0.99), $25OHD_3$ level (OR: 0.96; 95% CI: 0.92-0.99) and the *Cdx-2* polymorphism in the VRD gene (having allele A: OR: 0.50;. 95% CI: 0.30-0.90) were protective. BAP was included as a variable in the model as a confounding factor.

Use of our model, which includes the *Cdx-2* polymorphism in the vitamin D gene, $25OHD_3$ levels, age, BMI and number of reproductive years, allows healthy postmenopausal women at increased risk of osteoporosis to be selected for DXA testing to confirm the diagnosis. Markers of bone turnover are not useful for assessment of bone mass. In our population of healthy postmenopausal women, the prevalence of insufficiency ($25OHD_3$ <30 ng/ml) was 80% hypovitaminosis D ($25OHD_3$<20 ng/ml) was over 50%. Diagnostic and therapeutic strategies need to be developed for prevention of vitamin D deficiency due to its association with low bone mass and fractures.

Disclosures: ***J.M. Quesada Gomez****, None.*

M7

ASBMR YOUNG INVESTIGATOR AWARD Retrospective Analysis of Vitamin D Levels among Orthopedic In-Patients on the Trauma Service.

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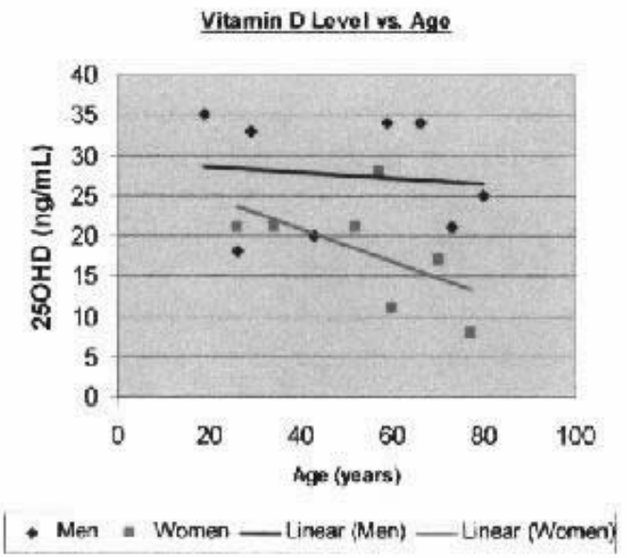
Vitamin D insufficiency is an under-recognized problem in adults in the United States. Vitamin D plays a significant role in Ca homeostasis and aids in the prevention of fractures by maintaining bone mineral density and muscle strength. Deficiency of vitamin D may contribute to the development of fractures and influence fracture healing. This retrospective study investigates the prevalence of vitamin D deficiency among in-patients on the trauma service. In-patients who sustained non-vertebral fractures were identified by the orthopedic trauma service at the Hospital for Special Surgery and evaluated by the metabolic bone disease team. While the investigation and treatments were tailored to each specific patient, common was the measurement of 25-hydroxyvitamin D, drawn after treatment in the hospital. The data revealed that 11 out of 15 patients with non-vertebral fractures were vitamin D-deficient, defined by a 25-hydroxyvitamin D (25OHD) level < 32 ng/mL. The only patients who had normal 25OHD levels were men. There was a significantly lower value of the 25OHD level in women, mean = 18.14 ng/mL, vs. men, mean = 27.50 ng/mL, ($p < 0.05$). This difference could not be attributed to varying ages between the men and women, as age was not significantly different between the sexes, nor was the difference in the number of men and women included in this study ($p > 0.05$). The correlation of age vs. 25OHD was 54.6% for women and 11.0% for men, indicating that age may be an important factor in determining women's, rather than men's, vitamin D level. This correlation suggests that women in the community who sustain non-vertebral fractures may be at a higher risk than men for vitamin D deficiency, and that the risk may increase with age for these women. This study tests the hypothesis that among patients who sustain non-vertebral fractures, there is a high prevalence of vitamin D deficiency which is more pronounced in women than in men. A larger study may have the power to further develop this hypothesis and determine if there is a significant correlation between the vitamin D level vs. age in women and men. The authors believe that orthopedic surgeons should consider vitamin D status as one of the 'vital signs' of the bone that should be measured and optimized in all orthopedic patients.



Disclosures: ***B. Schreck****, None.*

M9

Vitamin D Status and Sun Exposure in Ambulatory Elderly Women Living in the Tropics.

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Recent data suggest that vitamin D deficiency can occur even in sunny countries, especially in the Mediterranean region, where the solar irradiation absorption varies according to clothing determined by religious customs. Data from the tropics are limited. The aim of this study was to determine serum vitamin D concentrations in elderly ambulatory well-nourished women (seven of them with oral vitamin D

supplementation and four with morphometric vertebral fractures) living in Recife (10º S) and also correlate them with sun exposure scored by the Barger-Lux and Heaney method (sun index). We analyzed 50 postmenopausal women, of whom 32% had osteoporosis in the lumbar spine (LS) and 22% in the femoral neck (FN) with mean ± SD age 75.4 ± 3.4 years, BMI 27±5.3 kg/m2, calcium intake 530 ± 403 mg/day, serum calcium 9.6 ± 0.4 mg/dL, serum 25OHD 29 ± 7.5 ng/mL, LS BMD 0.900 ± 0.170 g/cm^2 (T score -2.38), FN BMD 0.750 ± 0.130 (T score-1.9) and sun index (hours of sun exposure per week x fraction of body surface area exposed to sunlight) 5.89 ± 5.63 (0.95 to 18.9). Prevalence of vitamin D deficiency varied according to different cut-off points of serum 25OHD: l0% for those with 25 OHD less than 20 ng/mL; 36% in those with less than 25ng/mL; 52% in those with less than 30ng/mL. In women with normal BMD 11.5% had 25OHD levels less than 30 ng/ml in contrast with women with low bone mass in whom 88.5% had vitamin D deficiency. There were no differences in 25 OH D levels among patients with low sun exposure (< 25 centile of sun index) compared with those with high exposure (> 75 centile): 28.1 *vs* 27.6 ng/mL; p= 0.8, nor the prevalence of vitamin D deficiency for the various cut points. Moreover, there were no differences in prevalence of vitamin D deficiency in those women with or without oral vitamin D supplementation. In conclusion, our data demonstrate that in this population of elderly women with a high prevalence of osteoporosis, sun exposure did not protect against vitamin D deficiency. High prevalence rates of vitamin D deficiency were observed even with, which is now considered, conservative cut-points for 25OHD levels.

Disclosures: ***P. Dreyer****, None.*

M11

High Dose Vitamin D Supplementation in Children with Cerebral Palsy or Neuromuscular Disorder.

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Adequate vitamin D levels are essential for normal skeletal development and mineralization. This is particularly important in children with cerebral palsy or other neuromuscular disorder who are at an increased risk for osteoporosis because of decreased weight-bearing and impaired muscle function.
The purpose of this study was to evaluate vitamin D status and the impact of high dose vitamin D supplementation on biochemical parameters in disabled children.
Vitamin D status was studied in a cohort of 44 disabled Finnish children and adolescents (25 males; median age 13 years) with cerebral palsy or other severe neuromuscular disorder attending a school for disabled children. Clinical and dietary histories were collected. Vitamin D was administered during school days (1000 IU vitamin D3 perorally five days per week for 10 weeks) by the school staff to half of the hildren (N=21) while the others (N=23) continued without supplementation. Blood samples were obtained at baseline (in the beginning of March) and at 10 weeks for serum concentrations of 25-hydroxyvitamin D (S-25-OHD), parathyroid hormone, calcium, phosphorus and parameters of bone turnover.
At baseline the median S-25-OHD was 44 nmol/L (range 26-82 nmol/L); it was below 38 nmol/L in 16 children (36%). The S-25-OHD increased significantly during the 10 weeks' intervention in the supplemented group (median 56 nmol/L, range 39-88 nmol/L; P=0.012 for the difference from baseline) and decreased in the control group (median 37 nmol/L, range 24-74 nmol/L; p=0.038). However, with the 10 weeks' high dose vitamin D supplementation only four out of 21 subjects (19%) attained a S-25-OHD concentration >80 nmo/L. No significant changes in any other measured parameters were observed. None of the patients developed hypercalcemia or other adverse effects.
Hypovitaminosis D is common in disabled children. Supplementation with a total weekly dose of 5000 IU results in a significant improvement in vitamin D status and is not associated with hypercalcemia or other adverse effects. However, even higher doses may be needed to attain optimal S-25-OHD concentration. The presently recommended daily allowance of vitamin D may be too low for optimal osteoporosis prevention in disabled children.

Disclosures: ***O. Mäkitie****, None.*

M13

Vitamin D and Pediatric Multiple Sclerosis.

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Sun exposure during childhood is associated with reduced risk of adult onset multiple sclerosis (MS). Studies showing insufficient vitamin D levels in MS adults raise concerns, given vitamin D's role in immune regulation. There are few vitamin D data in children with MS. The aims of this study was (a) to measure and compare 25 (OH) vitamin D levels (25OHD) in children with MS, healthy controls(C) and children attending a calcium bone clinic (CBC), (b) to determine the prevalence of vitamin D insufficiency/deficiency (D I/D) in these populations and (c) to evaluate the relationship of sunlight exposure or skin sensitivity to pediatric MS.
We recruited all pediatric MS patients (n=23) diagnosed between 1999 and 2005. Otherwise healthy children (n=40) with acute illness were recruited from the HSC ER as controls. Values of age and gender matched children (n=48) attending the CBC were used. Levels were taken between January and March 2005. D I/D was defined using serum 25OHD levels (table 1). Questionnaires detailing sun exposure and skin sensitivity to sunlight were completed. Inflection point for PTH vs 25OHD was calculated from nonlinear regression analysis. ANOVA was used for comparison of mean values.
Subjects were ethnically diverse. Mean age of the MS, C and CBC subjects were 14.7 $\pm$ 2.7 SDS, 13.3 $\pm$ 3.2 and 10.9 $\pm$ 5.5 respectively. Mean 25 OHD levels (nmol/L) (53.04 $\pm$ 22.3, 45.83 $\pm$ 18.7, 58.52 $\pm$ 23.4 respectively p =0.03) and urinary calcium/creatinine ratios (0.26$\pm$0.22, 0.18$\pm$ 0.15, 0.44$\pm$ 0.44 respectively, p=0.01) were significantly higher in CBC subjects. There were no significant differences in serum calcium, phosphate, alkaline phosphatase or PTH . Inflection point analysis showed a PTH plateau at a 25OHD level of 65 nmol/L. D supplementation was reported by 48% of MS and 28% of the C (400 IU/day). Sun exposure (summer/winter) was not associated with risk of MS. There was no association between skin sensitivity and risk of MS. The prevalence of D I/D using the defined cut offs are given in table 1

	MS) n, (%)	**Control)** n, (%)	**CBC** n, (%)
Vitamin D deficiency (25-(OH)D < 30)	2 (8)	10 (25)	6 (12)
Vitamin D insufficiency (25-(OH)D= 30-70)	17 (74)	26 (65)	27 (54)
Vitamin D insufficiency based on the inflection point (25-OHD < <65)	17 (74)	33 (83)	20 (40)

We report a high prevalence of D I/D in both pediatric MS and healthy patients in a northern climate. D I/D occurred in all groups. This suggests that current recommendations for vitamin D supplementation need revision. Further larger scale population-based studies are needed

Disclosures: ***R. Hung****, None.*

M15

Current Status of Clinical 25(OH)D Measurement.

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Measurement of circulating 25-hydroxyvitamin D (25(OH)D) is accepted as the clinical indicator of vitamin D status. However, the clinical measurement of 25(OH)D has been problematic. It might be assumed that the recent widespread clinical availability of liquid chromatography mass spectroscopy (LC-MS) and high pressure liquid chromatography (HPLC) technologies has improved performance of the 25(OH)D assays, and thereby clinical agreement between measurements obtained at different laboratories and by variable methods. However, a review of recent DEQAS (vitamin D External Quality Assessment Scheme) data revealed substantial variability in measurements of 25(OH)D between laboratories using LCMS and HPLC technology, despite good agreement of mean values. We hypothesized that this between laboratory variability reflects differences in assay calibration. To evaluate the current clinical status in the US, and investigate the possibility that assay calibration would improve between laboratory agreement, serum specimens and a calibrator were analyzed in one research and four clinical laboratories in the US.

Serum specimens were obtained from six generally healthy volunteers (age 29-53 years), aliquots prepared and frozen at -80°C. 25(OH)D measurements were performed in the usual manner at five laboratories, defined here as laboratories A through E. The methodology utilized for 25(OH)D measurement was as follows: Labs A and B HPLC, C and D LCMS and E RIA. Results from laboratory A were arbitrarily assigned as the reference values to which the others were compared utilizing linear regression and Bland-Altman analysis.

Excellent correlation was observed between Lab A and the other four laboratories; r2 = 0.962-0.997. Modest between laboratory variation was noted; the mean bias ranged from -6.1 ng/ml to + 4.2 ng/ml. Systematic bias between laboratories was suggested; for example, each individual value in laboratory C was from 82% to 87% of the corresponding value in laboratory A. This systematic bias ranged from 16% lower than, to 7% higher than, laboratory A. As it could be hypothesized that standard calibration would reduce the systematic bias between laboratories, 25(OH)D results from labs B - E were corrected by their respective calculated mean percent difference from laboratory A. When adjusted in this fashion, the between laboratory bias was reduced to a range from -0.3 ng/ml to +1.4 ng/ml.

In conclusion, excellent 25(OH)D correlation between some clinical laboratories in the US currently exists. However, modest between laboratory variability persists. It appears likely that availability and utilization of standard calibrators would/will substantially enhance between-laboratory agreement of 25(OH)D results from labs using HPLC, LC-MS and RIA methodology.

Disclosures: ***N. Binkley****, None.*

M17

Serum 25-Hydroxyvitamin D Response to Supplementation with 800 IU Vitamin D_3 in Premenopausal Women.

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The purpose of this research was to measure the serum 25-hydroxyvitamin D [25(OH)D] response to daily supplementation with 800 IU vitamin D_3 in premenopausal women living in Maine and to examine the effects of body composition and oral contraceptive use on serum 25(OH)D levels and the response to supplementation. 112 women, aged 19 to 35 years, received placebo from March 2005 until September 2005 when they were randomized to receive either placebo or 800 IU vitamin D_3 through February 2006. Serum 25(OH)D and parathyroid hormone (PTH) levels were measured in February 2005, September 2005, and February 2006. Body composition was measured by dual-energy x-ray absorptiometry in March 2005 and 2006.

In February 2005 the mean ± SD serum 25(OH)D was 61.1 ± 25.7 nmol/L in all subjects; 49.1 ± 17.7 nmol/L in the 50 subjects who did not use oral contraceptives (OCP-); and 70.9 ± 27.1 nmol/L in the 62 subjects who used oral contraceptives (OCP+). There were no significant differences in baseline BMI, body fat, PTH, calcium intake, or vitamin D intake between OCP- and OCP+ groups or between placebo and treatment groups. Serum 25(OH)D levels were significantly higher (p<.001) in the OCP+ group, but did not differ between placebo and treatment groups. There was a significant inverse correlation between 25(OH)D and PTH levels (r=-.25, p<.01).

In September 2005 (n=102), mean 25(OH)D levels were 101.5 ± 31.8 nmol/L. The levels in OCP- (91.0 ± 23.9) were significantly lower than OCP+ (109.7 ± 34.9, p<.001). The seasonal increase in 25(OH)D levels was not significantly different between OCP+ and OCP-.

In February 2006 (n=98), after five months of supplementation, the seasonal decrease in 25(OH)D was significantly (p<0.001) less in the treatment group (-6.1 ± 27.4) compared to the placebo group (-26.7 ± 23.1). In the treatment group, 25(OH)D levels increased by 36.1 ± 27.2 nmol/L from February 2005 to February 2006 compared to 11.4 ± 17.3 nmol/L in the placebo group. The seasonal and annual changes in 25(OH)D levels did not differ between OCP- and OCP+. There was a significant inverse correlation between 25(OH)D levels and bodyfat and BMI at all time points (r=-.29 - .35, p<.01), but there was no correlation between response to supplementation and bodyfat or BMI.

Daily supplementation with 800 IU vitamin D_3 during winter maintained optimal 25(OH)D levels (>80 nmol/L) in 73% of subjects, indicating that this dose is too low to meet the needs of the population as a whole. The research did not provide evidence that use of oral contraceptives or amount of body fat influences the serum 25(OH)D response to a given oral dose in the practical setting.

Disclosures: ***M. Nelson****, None.*

M19

The Relationship of Vitamin D Levels, BMI, Vitamin Intake and LDL Cholesterol with Bone Density in Patients of an Endocrine Practice.

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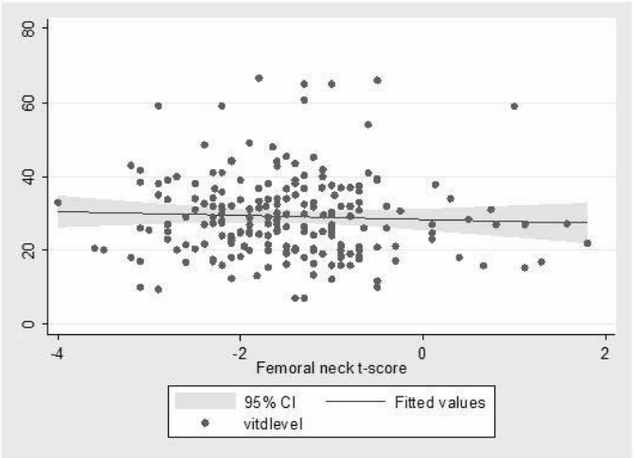
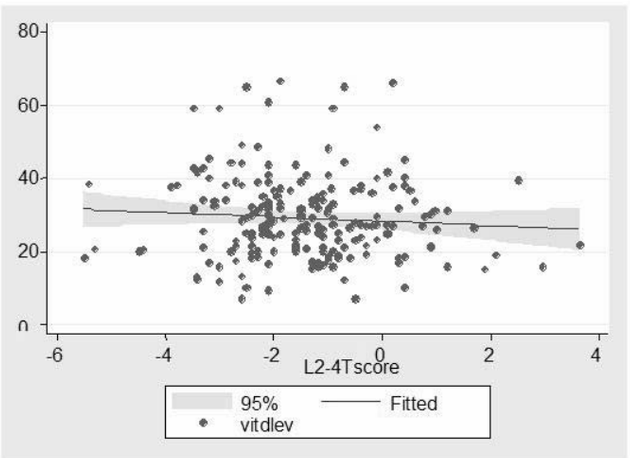
Low Vitamin D levels, as measured in blood by 25 OH vitamin D (OHVD) have been correlated with bone density (BD) and fracture risk, as well as muscle strength and a variety of cancers (Holick. AMJ Clin Nutr 2004;79:362) Obesity and dark skin have been shown to reduce blood levels of OHVD (Looker. J Clin Endocrinol Metab 2005;90:635.)
228 peri- or postmenopausal women in an endocrine practice had BD, OHVD and lipid profiles measured. OHVD was measured by the DiaSorin RIA.History of calcium and vitamin intake was recorded.

Results OHVD,BD

variable	No.	Mean(SD)	Min	Max
Age	228	60.07 (11.88)	20	95
OHVD	227	28.68(11.01)	7	66.5
FN Tsc	210	-1.49(.98)	-4	1.8
SP Tsc	211	-1.43(1.42)	-5.5	3.64

Neither statin use nor LDL levels correlate to OHVD levels.
Calcium and Vit D intake were significantly related with low BD.This likely reflects increased intake in people who have low BD. High BMI was related to low OHVD. We conclude that in this population there was no association between vitamin D intake, OHVD and BD.





Disclosures: ***R. Freeman****, None.*

M21

A Dynamic Algorithm for Optimizing Vitamin D Status.

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PURPOSE: There is increasing evidence that optimal levels of 25 hydroxy vitamin D (25-OHD) exceed 75-80 nmol/L. The goal of the study is to test an algorithm to optimize 25-OHD levels with vitamin D supplementation, and to assess the ethnic differences in response to vitamin D supplementation between African Americans and Caucasians.
METHODS: Based on prior studies, we developed an algorithm for achieving optimal levels of 25-OHD, starting with 50 mcg/d of vitamin D3 for individuals with 25-OHD levels between 50 and 80 nmol/L and 100 mcg/d for those with 25-OHD levels below 50 nmol/L. Doses were subsequently adjusted in 20, 30, and 50 mcg/d increments or decrements based on 25-OHD serum levels. 25-OHD was measured by RIA using the DiaSorin assay. The study was initiated in the winter (November-March) and continued for 27 weeks. 138 subjects entered the study, 62 African Americans and 76 Caucasians. Those with chronic medical conditions, morbid obesity, disorders of bone metabolism, or those taking medications known to interfere with bone or vitamin D metabolism were excluded. A double-dummy design was used to preserve the double-design.
RESULTS: We are reporting data on 50 black (22 active, 28 placebo) and 64 white (33 active, 31 placebo) subjects enrolled in the ongoing study and who have completed at least eighteen weeks. Their characteristics are summarized in the table below. By week 18, 90% of black and white subjects in the active group achieved 25-OHD levels $\geq$ 80 nmol/L. At that point, 18% (10/55) of individuals in the active group required a reduction in vitamin D3 dose, and 16% (9/55) required an increment in vitamin D3 dose. The mean dose of vitamin D given to active subjects at week 18 was 102.7$\pm$ 33.8 mcg/d for Blacks and 77.9 $\pm$ 37.0 for Whites. The Blacks required significantly higher doses due to their lower baseline 25-OHD levels. The 25-OHD response to 1 mcg of vitamin D per day was similar in both black and white subjects, and was 0.76 $\pm$ 0.53 nmol/L/mcg/d. Serum calcium and fasting urine Ca/Cr did not change significantly from baseline. No adverse events were noted.
CONCLUSION: The amount of vitamin D supplementation needed to achieve "optimal" 25-OHD level is greater than the current recommended adequate intake. To achieve 25-OHD level of $\geq$ 80 nmol/L, black subjects needed 30% higher doses of vitamin D supplementation than Whites. The 25-OHD response to 1 mcg of vitamin D per day was similar in black and white subjects.

Response to vitamin D3 supplementation

Parameter	Blacks n=50 Mean (SD)	Whites n=64 Mean (SD)	P value (blacks vs. whites)
Age (years)	45.8 (12.1)	49.0 (9.4)	0.09
BMI (kg/m2)	27.0 (3.5)	25.5 (4.3)	0.03
Basal 25OHD (nmol/L)	39.8 (14.8)	57.8 (14.2)	0.0001
18 wk 25OHD			
Active	121.7 (38.3)	117 (33.4)	NS
Placebo	58.4 (22.8)	70.2 (20.9)	
Change in 25OHD			
Active	85.2 (39.7)	59.8 (39.3)	<0.001
Placebo	13.9 (15.1)	10.3 (16.9)	NS

Disclosures: ***M. Mikhail****, None.*

M23

ASBMR YOUNG INVESTIGATOR AWARD
Prevalence of Profound Vitamin D Deficiency and Hypogonadism in Individuals Being Evaluated for Liver Transplant.

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Osteoporosis with fracture is a common complication of advanced liver disease. Although the same risk factors as those commonly associated with postmenopausal osteoporosis,(age, gonadal status, and vitamin D deficiency) apply, cirrhosis is an independent risk factor for osteoporosis.
The exact prevalence of vitamin D deficiency, hypogonadism, and osteoporosis in patients with liver disease is unknown.
Methods: We conducted a retrospective chart review of adult patients awaiting orthotopic liver transplant at KUMC. Data was collected from April 2000 through April, 2006.
Data included: Age, sex, DEXA scores, serum NTX, osteocalcin, calcium, 25OHD, PTH, & free testosterone levels, Model for End stage Liver Disease (MELD) & etiology of liver disease.
Results: A total of 179 subjects were analyzed, 103 males and 76 females.
1. Prevalence of Vitamin D insufficiency (25OHD<30ng/dl) was 89% and of deficiency (25OHD<17 ng/dl) was 52%.
2. Prevalence of hypogonadism in men (free testosterone <1.0 ng/dl) was 90.2%.
3. The prevalence of osteopenia was 48.6% & osteoporosis 37.4%.
4. Significant correlations were found between MELD score and 1,25 Vit D (r= -0.39963, p<.0001), & MELD score and 25 OH Vit D (r= -0.23269, p=0.0042) using Pearson correlation coefficients
5. Those with MELD score 15 or greater signifying worse liver disease were found to have a significantly lower 1,25 Vit D value than those with MELD score lower than 15 using Satterthwaite's t-test.
6. Using analysis of variance for comparison of patients having osteoporosis, osteopenia, and normal bone mineral density no significance was found for PTH, 1,25 Vit D, 25OH Vit D, MELD scores, and testosterone (in males). Thus there is no clear evidence that any of these single parameters had a dominant effect on bone loss in this population.
Conclusions: To our knowledge, this is the largest published study of subjects awaiting liver transplantation. Low vitamin D correlates with the severity of liver disease (MELD score). The high prevalence of vitamin D insufficiency (89%) and deficiency (52%), and male hypogonadism (89%), osteopenia (49 %) and osteoporosis (37%) mandates evaluation of these parameters in all patients with chronic liver disease.

Disclosures: ***R. Bhattacharya****, GSK/Roche 8; Proctor and Gamble 2, 8.*

Vitamin D Physiology I

M25

Time Course of Serum Calcidiol, Calcitriol and PTH Following a Single Massive Dose of Ergocalciferol or Cholecalciferol.

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The potencies of vitamin D_2 and D_3 were evaluated by administering a single dose of 300,000 IU of the respective calciferols by mouth (os) or by intramuscular (im) route to 4 groups of elderly nursing home female patients (D_3 os: n=8, age= 78.5±7.5 yrs mean ± SD; D_3 im: n=5, 85.2±6.8 yrs; D_2 os: n=6, 79.8±5.5 yrs; D_2 im= n= 4, 74.0 ± 7.1 yrs). The time course of serum calcidiol [25(OH)D], calcitriol [$1,25(OH)_2D$], Ca^{++} and PTH was followed at 0 and at 3, 7 and 30 days. Serum calcidiol and calcitriol were determined by RIA and PTH levels by IRMA (N-tact PTHSP) (DiaSorin Inc., Stillwater, MN, USA).
Basal calcidiol levels were: D_3 os: 13.3±9.9 ng/ml; D_3 im: 8.2±4.4; D_2 os: 11.9±10.3; D_2 im: 8.7±1.7. We observed a brisk increase of 25(OH)D levels at 3 day only when vitamins were given by mouth; furthermore, the 30 day-basal difference of serum calcidiol was significantly greater after D_3 oral administration (47.3±7.3 ng/ml) with respect to other forms (D_3 im: 15.1±9.6; D_2 os:17.9±5.4; D_2 im: 5.8±4.0; all $p<0.001$).
Concerning serum levels of $1,25(OH)_2D$, there was a brisk increase at 3 days, only after oral administration. The oral 3 day-basal difference of $1,25(OH)_2D$ following both D_3 (40.2±39.8 pg/ml, $p<0.001$) and D_2 (85.6±21.5, $p<0.03$) was significantly greater than the levels obtained by similar amounts of vitamin given by im. Furthermore, following im administration there was a slow continuous gradual $1,25(OH)_2D$ increase throughout the entire period of observation.
A general linear model has been therefore applied to study the influences of Ca^{++}, calcidiol, calcitriol and route of administration on PTH changes at 3, 7 and 30 days. The influence on PTH variations has been considered using a stepwise procedure introducing in the model first Ca^{++}, calcidiol, calcitriol and then the way of vitamin administration. The influence of calcidiol on PTH levels has been studied on the residual part of variation not explained by Ca^{++}. Calcidiol had a significant role in influencing PTH levels both at 3 ($p<0.038$), 7 ($p<0.054$) and 30 days ($p<0.003$). Our data demonstrate that, based on the 30 day values, vitamin D_3 is almost 2.5 times more potent than vitamin D_2 in raising serum calcidiol, when administered both by mouth or im; a different pharmacokinetic profile of both calcidiol and calcitriol after oral or im injection of a massive vitamin dose; a role of calcidiol in modulating serum PTH, possibly via a residential parathyroid 1-alphahydroxylase.

Disclosures: ***S. Minisola****, None.*

M27

Stimulation of Osteoblast Differentiation in Human Bone Marrow Stromal Cells by 1,25 Dihydroxyvitamin D_3 Declines with Age.

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In vivo and *in vitro* studies indicate that a sub-population of bone marrow stromal cells (MSCs) has the potential to differentiate into osteoblasts, identifiable by alkaline phosphatase (AlkP) activity and osteoblast gene expression. In this study, we tested two hypotheses: 1) that 1,25-dihydroxyvitamin D_3 [1,25OHD_3] stimulates human MSCs to differentiate to osteoblasts and 2) that responsiveness to 1,25OHD_3 depends on the age of the subject.

Age-related declines in osteoblast potential were found from 3 studies with marrow from subjects undergoing total hip replacement. Low-density mononuclear cells were isolated by Ficoll Histopaque 1077 and selected for adherence. First, there was an age-related decline ($r=-0.81$, $p=0.010$) with hMSCs from 8 women (17-90 years) after 14 days with osteogenic supplements (10 nM dexamethasone, 5 mM β-glycerophosphate, 50 μg/ml ascorbate-2-phosphate). Second, there was an age-related decline in osteoblast differentiation ($r=-0.79$, $p=0.025$) for hMSCs from 3 women and 4 men (48-79 years) after 7 days with osteogenic supplements. Third, there was an age-related decline in AlkP ($r=-0.661$, $p=0.014$) for hMSCs from 13 men (27-79 years). Treatment of the latter with 10 nM 1,25OHD_3 and Dex stimulated AlkP activity (mean 457%) with an even stronger negative correlation with age ($r=-0.712$, $p=0.006$).

Vitamin D receptor (VDR) mRNA was present in hMSCs (17-70 years;2 women, 3 men). For assessment of molecular actions of 1,25OHD_3, hMSCs (n=9, 17-76 years) were cultured in MEM-α, 10% or 1% FBS-HI with osteogenic supplements for 2 or 14 days ± 10 nM 1,25OHD_3. At 14 days, 1,25OHD stimulated osteocalcin (OC) gene expression (494% ± 415). Consistent with effects on AlkP (above), upregulation of OC by 1,25OHD_3 tended to decrease with age. Assessment of effects on gene expression prior to osteoblast maturation (day 2) shows that 1,25OHD_3 upregulated osterix (OS, 62% ± 137), IGF-I (60% ± 90), and IGFBP3 (37% ± 32) gene expression. Stimulation in young subjects was dramatic, e.g. by quantitative cRT-PCR, 1,25OHD_3 produced a 7.8-fold increase of IGF-I gene expression in hMSCs from a 34-year-old. Cells from older subjects (55-73 years) showed variable gene responses to 1,25OHD_3, with a tendency to an age-related decline. In sum, these results show that 1,25OHD_3 stimulates osteoblast differentiation in hMSCs, and suggest an age-related decrease in several responses to 1,25OHD_3. The osteoblastogenic effects of 1,25OHD_3 on human marrow-derived cells may be mediated through the skeletal IGF-I system.

Disclosures: ***S. Zhou****, None.*

M29

Does Treatment of Vitamin D Insufficiency Increase True Fractional Calcium Absorption?

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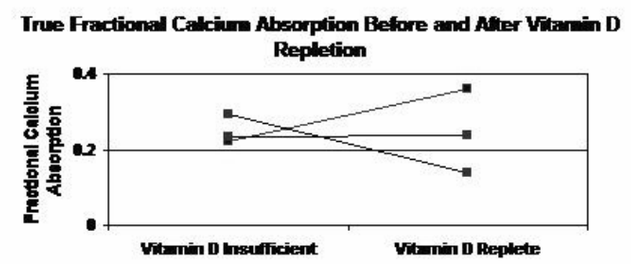
Vitamin D insufficiency is widespread and repletion in individuals with the condition is believed to increase intestinal calcium absorption. However, only 1 of 3 people with insufficiency has secondary hyperparathyroidism, suggesting that the subset of people with normal parathyroid function maintain neutral calcium balance despite such "insufficiency." We initiated a study to determine the impact of vitamin D repletion on calcium homeostasis in postmenopausal women with vitamin D insufficiency.

Eligible women were ≥ 5 years postmenopausal with a serum 25(OH)D of 16-24 ng/ml by HPLC assay and an estimated calcium intake ≤ 1,100 mg daily. Exclusion criteria included hypercalcemia, hypercalciuria, renal insufficiency, nephrolithiasis, chronic intestinal disorders and use of medications known to interfere with vitamin D or calcium metabolism. Women with osteomalacia, prior adult clinical fragility fracture or a T-score < -3.0 at the lumbar spine or femur were also excluded.

Following informed consent, each woman underwent two inpatient dual calcium isotope studies, initially when vitamin D insufficient and then later when vitamin D replete, defined as a serum 25(OH)D > 35 ng/ml by HPLC after ergocalciferol 50,000 IU/day x 15 days. Typical diet was replicated during each study using 7-day diet records and Food Processor software. In each woman, we collected blood (8 hours) and urine (6 days) and analyzed its calcium isotope content (^{42}Ca and ^{44}Ca) by mass spectrometry. We calculated intestinal calcium absorption using the formula by Eastell, which accounts for urine calcium loss and renal and intestinal calcium re-absorption.

Thus far, three women have participated in the study; all had normal parathyroid hormone levels at baseline (50 ± 13 pg/ml). Basal serum 25(OH)D was 19.9 ± 1.9 ng/ml, increasing to 69.9 ± 13.6 ng/ml with ergocalciferol. True fractional calcium absorption was 24% ± 5% initially and 28% ± 13% following vitamin D repletion ($p>0.05$).

Preliminary study results suggest that calcium absorption may not improve in women with vitamin D insufficiency and normal parathyroid function following vitamin D repletion. Additional research is needed to elucidate the clinical effects of correcting "vitamin D insufficiency," particularly in patients with normal parathyroid hormone levels.



Disclosures: ***K.E. Hansen****, None.*

Vitamin D and Population Health I

M33

ASBMR YOUNG INVESTIGATOR AWARD
Prevalence of Vitamin D Insufficiency in Brazilian Adolescents.

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Vitamin D is an important determinant of bone development, however there is no common definition of optimal vitamin D status, mainly in adolescents. The purpose of this study was to evaluate the nutritional status of vitamin D in Brazilian adolescents, and compare the prevalence of vitamin D insufficiency according to the serum $25(OH)D_3$ optimal levels proposed by several investigators. One hundred forty-five (143) adolescents, 68 boys and 75 girls, mean age 18.2 (0.9) years old, were selected from public school in autumn 2006. Information on dietary intake was obtained by a tree day dietary records. Serum levels of $25(OH)D_3$ was measured by radioimmunoassay kit DiaSorin (Stillwater, MN). Height and weight was measured in order to evaluate BMI. Underweight was observed in 1.4% of adolescents, normal weight in 81.1%, overweight in 14.0% and 3.5% presented obesity, according to National Center for Health Statistics growth charts (CDC, 2000). Mean dietary vitamin D intake was 3.6 (0.3) μg/day, only 16.5% of the students met the adequate intake (AI) recommendation of vitamin D/day (5.0 μg/day). The mean serum levels of $25(OH)D_3$ was 74.6 (28.7) nmol/l. The prevalence of vitamin D insufficiency is presented in Table 1.

Table 1 - Prevalence of vitamin D insufficiency in Brazilian adolescents according to serum $25(OH)D_3$ proposed optimal levels

Cut-off	Boys n=68		Girls n=75		Total n=143	
	Insufficiency	Optimal levels	Insufficiency	Optimal levels	Insufficiency	Optimal levels
50 nmol/l[a]	4.5%	95.5%	2.7%	97.3%	3.5%	96.5%
70 nmol/l[b]	52.2%	47.8%	51.4%	48.6%	51.8%	48.2%
75 nmol/l[c]	62,7%	37.3%	59.5%	40.5%	61.0%	39.0%
80 nmol/l[d]	71.6%	28.4%	70.3%	29.7%	70.9%	29.1%

a Lips et al. 1996; b Vieth et al. 2004; c Holick et al. 2003, Meunier et al. 2002; d Heaney et al. 2003, Dawson-Hughes et al. 1997.

The present study demonstrated that hypovitaminosis D is presented in healthy Brazilian adolescents. Dietary vitamin D is insufficient, since a minority of adolescents reached the AI for vitamin D. Furthermore, considering the 75 nmol/l cut-off for $25(OH)D_3$ as optimal levels, more than 50% of our adolescents presented insufficiency. Our findings suggest that nutritional strategies are necessary to guarantee vitamin D sufficiency.

Disclosures: ***B.S.E. Peters****, None.*

M35

ASBMR YOUNG INVESTIGATOR AWARD
Vitamin D Deficiency in Southern Arizona.

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In addition to classically defined vitamin D deficiency diseases, vitamin D insufficiency has been linked to cardiovascular disease, cancer, diabetes, and arthritis. Because UV irradiation is an efficient way to increase the concentration of the circulating vitamin D metabolite 25(OH)D, a risk for vitamin D deficiency due to the lack of adequate UV exposure has been demonstrated among populations living in northern latitudes. However, the prevalence of vitamin D deficiency in areas of high-sun exposure such as Arizona has been less commonly studied. To address the question of whether circulating 25(OH)D levels are adequate in southern Arizona, we conducted a cross-sectional analysis of participants in a colorectal adenoma prevention study, and assessed the rates of vitamin D deficiency in this population. Participants were categorized into three groups based on their serum 25(OH)D concentrations: extreme deficiency if 25(OH)D levels were less than 10 ng/ml, deficiency if levels were less than 20 ng/ml, and suboptimal if levels were less than 32 ng/ml. The mean serum 25(OH)D level was 26.3 ng/ml, with a range of 5.5 ng/ml-66.1 ng/ml. Out of 567 participants, approximately 77% of the population had suboptimal levels of vitamin D, 24.0% were found to be vitamin D deficient, and 1.9% were extremely deficient. Those participants who reported African American, Hispanic, or Native American ethnicity were more prone to vitamin D deficiency as compared to Caucasians, with mean 25(OH)D levels of 20.1 ± 8.7 vs. 26.6 ± 9.1 for Caucasians. In addition, women were at higher risk for vitamin D deficiency than men ($p<0.01$). Out of the 200 female participants, 3.0% were extremely deficient and 35.0% were deficient, with approximately 80% at suboptimal levels. Among the 367 male participants 1.4% were extremely deficient, 18.4% were deficient, and 75% were at suboptimal levels, which are significantly lower rates than were observed for women ($p<0.001$). In conclusion, vitamin D deficiency exists in southern Arizona, despite the relatively high sun exposure in this region, and is more common in women, African-Americans, Hispanics, and Native Americans. Improvement of vitamin D status in these groups might aid in prevention of cancer and other diseases potentially related to vitamin D deficiency.

Disclosures: ***E.T. Jacobs****, None.*

M37

Cholecalciferol Supplementation Reverts 25-Hydroxyvitamin D Insufficiency and Improves Lower Limb Muscle Strength in Institutionalized Elderly People of São Paulo City - Brazil.

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This study aimed to evaluate the effects of cholecalciferol supplementation on 25OHD and PTH serum levels, and on lower limb muscle strength (LLMS) of institutionalized elderly. In a double-blind prospective trial, 56 elderly (77.6; 62-94 years) were randomized into G1 for placebo and G2 for cholecalciferol. Both groups received 1000 mg/day of elemental calcium. Serum levels of 25OHD, PTH and calcium were measured at the beginning of the study (M1- January), 2 months (M2) and 6 months (M3) after the intervention. G2 received 150,000 IU/month during the first 2 months and 90,000 IU/month in the 4 subsequent months. A muscle strength index, including hip flexors and knee extensors, was used to assess the LLMS measured by a hand-held dynamometer at M1 and M3. The statistical analysis was done using panel data for gamma and binomial distribution and Chi-square test. Level of significance was set at 0.05. Results showed that serum levels of 25OHD improved at M2 and decreased at M3 in both groups; however, cholecalciferol supplementation was related to higher concentrations of 25OHD at M2 (G2/G1:OR=1.4, 95%IC=1.17-1.6) and also at M3(G2/G1:OR=1.52, 95%IC=1.3-1.8) (Table 1 - Figure 1a). At M3, 40% of G1 patients still presented insufficient levels (<50nmol/L) of serum 25OHD, whereas in G2 no patient did so. Also after treatment, G1 had no patient with ideal levels (over 100 nmol/L) of 250HD whereas in G2 50% were in this stage. PTH levels declined at M2 and increased at M3 equally in both groups (Table 1). Though, cases of secondary hyperparathyroidism reduced in 5% in G2, increasing in 10% in G1. LLMS enhanced only in G2 (20%) at M3 (OR=1.20,95%IC=1.12-1.29) (Figure 1b). The intervention proposed in this study was efficient and safe in elevating low levels of serum 25OHD and increasing muscle strength of lower limb in institutionalized elderly.

Table 1: Median and limits of serum biochemical concentration in G1 and G2 at the three assessed moments.

Variables	Groups	M1	M2	M3	p-value M1 xM2	M1xM3	M2xM3
25OHD nmol/L	G1	39,5 (20,3 - 68,8)	73,9 (27,5 - 167)	51,8 (23,5 - 107,8)	<0,001	0,002	0,001
	G2	45,9 (20,3 - 84,8)	99,8 (62,0 - 146,3)	86,6 (52,3 - 106,5)	<0,001	<0,001	<0,001
PTH Pg/mL	G1	45,0 (20,7 -162,7)	35,6 (8,03 - 66,49)	47,47 (6,6 - 101,50	<0,001	0,574	<0,001
	G2	48,5 (24,3 - 158,1)	30,1 (2,0 - 101,6)	41,42 (21,6 - 151,6)			
Total Calcium mg/dL	G1	9,0 (7,4-9,4)	9,7 (8,9 - 10,6)	8,9 (7,3 - 10,0)	<0,001	0,008	<0,001
	G2	8,9 (7,9 - 9,9)	9,8 (8,9 - 10,5)	9,1 (8,3 - 9,8)			

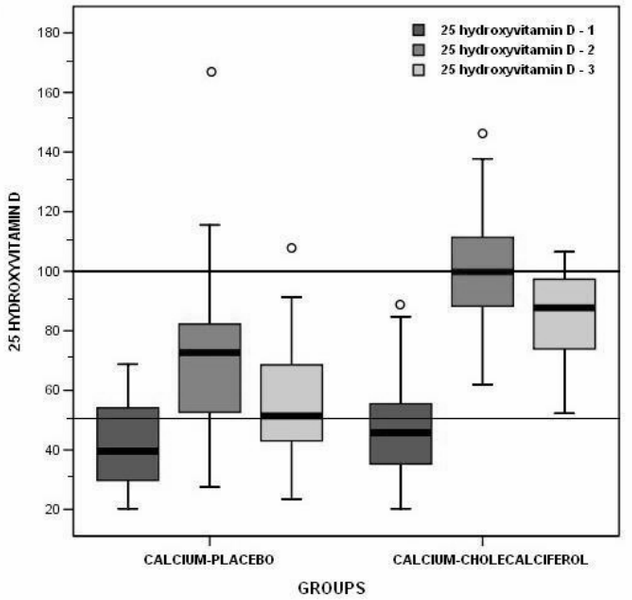

Figure 1a: Variation in 25(OH)D serum concentration (nmol/L) between the three assessed moments in both groups.

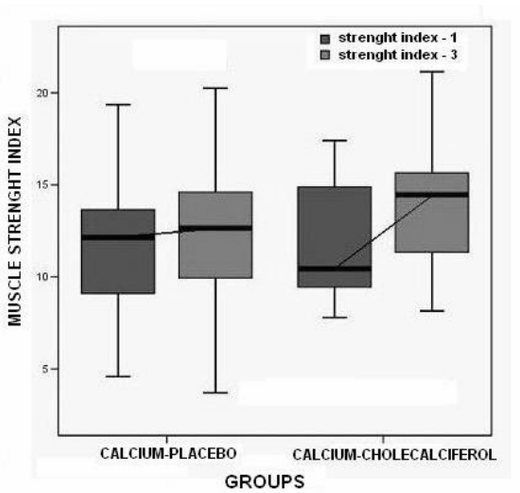

Figure 1b: Variation of muscle strength index from M1 to M2 (six months) according to treatment groups.

Disclosures: ***L.D.F. Moreira-Pfrimer,*** *None.*

M39

Vitamin D Deficiency in Oncologic Patients - an Ignored and Potentially Life Threatening Condition.

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The aim of this work was to assess vitamin D status in oncologic patients and its impact on the risk of hypocalcemia.
Inadequate vitamin D levels are frequently observed in all age groups. Patients receiving vitamin supplements often do not achieve vitamin D adequacy.
An 18 ng/ml $25(OH)D_3$ serum level is needed for effective calcium absorption
Monthly administration of bisphosphonates to oncologic patients with skeletal involvement, decreases bone turnover and in combination with poor vitamin D status may lead to life threatening hypocalcemia.
Three patients -one man and two women, aged 53.33±17.7 were hospitalized for severe symptomatic hypocalcemia. The patients were treated with intravenous bisphosphonates due to metastatic bone disease; none of them underwent vitamin D status evaluation nor received calcium and vitamin D supplements. Renal function was normal in all patients. Serum calcium levels corrected for albumin were 6.5-7 mg/dl, $25(OH)D_3$ levels were 2.4-12 ng/ml, serum PTH - 73-275 pg/l.(normal 11-65)
We were informed that routine or sporadic (based on medical history) evaluation of vitamin D status and vitamin D supplementation is not included in the national or international guidelines for bisphosphonate treatment for metastatic bone diseases.
Following these findings, after IRB approval, we have assessed serum calcium, phosphate, albumin, $25(OH)D_3$, and PTH in 11 consecutive, active and ambulant patients, aged 71.73 ± 8.86 years, with metastatic bone disease due to carcinoma of prostate, before initiation of intravenous treatment with zoledronate.
Results: $25(OH)D_3$ serum level was 23.63±10.24 (mean ± SD). Three patients (25%) had $25(OH)D_3$ levels < 18 ng/ml (9.6;14.9;16.3). The patients were treated with calcium and vitamin D_3 supplements with dose adjustment according to the initial $25(OH)D_3$ serum level. The patients were treated with zoledronate (4 mg/4 weeks) for 2-8 months with no evidence of hypocalcemia on quarterly laboratory evaluation. Currently, after IRB approval, all patients treated with IV bisphosphonates for metastatic bone disease undergo the $25(OH)D_3$ serum assessment.
We conclude that inadequate 25(OH)D3 serum levels are not uncommon in oncologic patients; they are prone to hypocalcemia due to bisphosphonate treatment and absence of supplementation with calcium and vitamin D. Hypocalcemia and vitamin D deficiency are a preventable conditions; evaluation of vitamin D status and adequate calcium and vitamin D supplementation should be a part of management of oncologic patients.

Disclosures: ***E. Segal****, None.*

M41

Utilization of Vitamin D, Calcium and Antiresorptives in a Long Term Care Population.

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The purpose of this study is to explore the utilization of osteoporosis related medications, particularly Vitamin D, in a Long Term Care (LTC) population. Osteoporosis is highly prevalent in LTC residents. Vitamin D supplementation in the LTC setting has been shown to reduce fracture rate (Chapuy et al. NEJM 327:1637-1642, 1992) and perhaps also falling (Flicker et al. JAGS 53:1881-1888, 2005). The dose required is probably 800IU or more. Patients with osteoporosis should be receiving a bisphosphonate, the medications shown to prevent hip fracture. In 1998 (Crilly et al. Can J Geriatr Soc. 6(1):16-20, 2003) we explored through a National Pharmacy database the prevalence of treatment that could reduce or prevent fractures. This showed a very low rate of vitamin D supplementation (including multivitamins), a low rate of calcium supplementation and a very low rate of bisphosphonate use (20%, 9% and 6.5% respectively). With the growing awareness of the importance of vitamin D in particular and in preparation for an intervention designed to improve the prevention and management of osteoporosis in LTC, we have re-visited this issue in 12 local LTC establishments.
The study involves 12 LTC homes with a population of 1512 residents mean age, 83+/- 10.2 yrs, 75.3% female. The medications and vitamin and calcium supplements are all supplied by a single commercial pharmacy. The pharmacy database was analysed to determine the proportion of residents on various doses of calcium, vitamin D (including all supplementary sources) and bisphosphonates, the mainstay of osteoporosis treatment, and other antiresorptive agents.
Overall, 28% were receiving vitamin D in any dose and form, 14.1% were on 400IU per day, 5% on 800IU and 8.4% on 1000IU or more. Only 11.2% received 1000mg calcium or more, and 10.5% a lower dose, usually 500mg per day. Very few (16.7%) were receiving antiresorptive medication. Almost all of these, 16.5% of all patients, were on a bisphosphonate but one third of these were on etidronate. Only 10.3% were on either alendronate or risedronate, the antiresorptives shown to prevent hip fractures.
In conclusion, these data show a small improvement over those of 1998 but still show considerable room for improvement both in terms of the prevalence of treatment and, in the case of Vitamin D, in the doses employed. Over one third of those treated with specific osteoporosis medications were on antiresorptives not shown to prevent hip fractures.

Disclosures: ***R. Crilly****, The Alliance for Better Bone Health 2.*

M43

Vitamin D Status among American Indians in the Great Lakes Region.

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Vitamin D deficiency affects many populations around the world, yet very little is known about vitamin D status among American Indians (AI) in the Great Lakes region. We hypothesized that vitamin D inadequacy would be common in this population due to northern latitude of residence (46-48°) and skin pigmentation. Therefore, in collaboration with a tribal clinic in northern Minnesota, we evaluated serum 25-hydroxyvitamin D (25OHD) in a convenience sample of 78 AI women. In March 2006, information on medical history and UV exposure was obtained by a questionnaire, height and weight were measured and serum obtained for 25OHD, PTH, calcium, BSAP, and NTx measurement.

Participants' mean age was 50.2 years (range 32-75) and 37 (54%) were postmenopausal. There were no statistically significant differences between pre- and postmenopausal women for self-reported prevalence of diseases and conditions known to affect vitamin D metabolism, or blood biochemistry. Self-reported summertime sun exposure was 19.9±14.5 hours/week in this sample. 87% reported spending 6 or more hours per week outside and 74% reported 20% or more skin surface exposure without sunscreen (equivalent to face and arms) while outside.

Serum 25OHD concentrations were low and ranged between 5 and 46 ng/ml. Moreover, 80% of the study population had 25OHD concentrations below 30 ng/ml and 42% were below 15 ng/ml. There was no statistically significant association between 25OHD and iPTH or BMI in this sample. As expected, markers of bone turnover were elevated in postmenopausal women ($p<.01$), but were not correlated with serum 25OHD concentration.

These preliminary data suggest that vitamin D inadequacy is common among American Indians in the Great Lakes region. Additional studies using a population-based approach are needed to document the extent, and health consequences of vitamin D deficiency in this population. Such studies must evaluate culturally appropriate methods to optimize vitamin D status thereby improving health across the lifespan.

	Premenopausal (n=36)	*Postmenopausal (n=42)*
25OHD (ng/ml)	16.42±6.60	19.50±10.28
Calcium (mg/dL)	9.36±0.34	9.47±0.33
Serum BSAP (U/L)	21.78±6.49	27.13±8.31
Serum NTx (nm BCE)	14.40±3.14	18.11±5.31
iPTH (pg/ml)	40.09±15.12	44.57±29.06
BMI (kg/m^2)	32.41±7.83	32.08±5.43

Disclosures: ***I.V. Haller,*** *None.*

M45

High Prevalence of and Preventable Risk Factors for Vitamin D Deficiency in Non-Western Immigrants.

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Low sunlight exposure, a darker skin, covering of the skin and a diet low in vitamin D may contribute to lower vitamin D concentrations in non-Western immigrants. The purpose of this study was to assess the prevalence of vitamin D deficiency and its determinants in various ethnic groups living in the Netherlands.

We performed a cross-sectional study. A random sample was drawn from general practitioners' patient-files (18-64 years), stratified by gender and ethnicity. General characteristics, sunlight exposure and diet were assessed using questionnaires. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D (25(OH)D) < 25 nmol/L.

Data of 613 respondents was used for analyses. Prevalence of vitamin D deficiency was significantly higher in Turkish (41.3%), Moroccans (36.5%), Surinam South Asians (51.4%), Surinam Creoles (45.3%) and sub-Sahara Africans (19.3%) compared to the indigenous Dutch (5.9%). Ethnic group remained significantly associated to ln-transformed serum 25(OH)D after adjustment for various determinants. Other, modifiable, significant determinants were consumption of fatty fish and margarine, use of vitamin D supplements, area of uncovered skin, use of tanning bed and use of sun cream (potential measure sunlight behaviour).

Prevalence of vitamin D deficiency is considerably higher in the non-Western groups compared to the indigenous Dutch. Further study is needed to find ways to stimulate consumption of vitamin D-containing foods, suppements and exposure to sunshine in various non-Western groups.

Disclosures: ***I.M. van der Meer,*** *None.*

M47

Dietary Vitamin D in Brazilian Population.

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Dietary vitamin D is an important component of vitamin D status. Several studies reported low vitamin D intake, mainly in elderly and in countries were vitamin D fortification is not mandatory. The Food and Nutrition Board in 1997 established the level of Adequate Intake (AI) for men and women at 5 µg/d for < 50y , from 51 to 70 y at 10µg/d and from 71y and older at 15 µg/d. Furthermore, they recommended that vitamin D intake should be evaluated throughout lifespan by geographical and racial variables. The purpose of the present study was to evaluate vitamin D intake in a representative sample of Brazilian men and women, older than 40 y. This study was part of the BRAZilian Osteoporosis Study (BRAZOS), undertaken in 120 cities across the 5 regions (North, Northeast, Central, Southeast and South) of the country, and enrolled people from 5 categories of economical level. A total of 2400 people were enrolled in the study. Dietary intake of 1000 (one hundred) men and women, 70% women and 30% men, were evaluated by one 24 h dietary record. For the nutrient analysis the Nutrition Data System software (Minneapolis, MN 2005) was used. The dietary records were calculated by a trained dietitian. The use of supplements was not considered in the present analysis. The mean dietary vitamin D intake in all participants was 2.2 ± 1,2 µg/d. No differences were observed considering gender and age. People from North region presented significantly higher mean vitamin D - 2.8 ± 2.5 µg/d, compared to the all other regions (2.1 ± 1.8µg/d in South; 1.8 ± 1.7µg/d in Southeast, 2.2 ± 1.8 µg/d in Central, 2.2 ± 1.8µg/d in Northeast, $p<0.05$). This observation could be explained by the higher fish consumption presented by the people from North region. A positive correlation was observed between dietary vitamin D and calcium ($r=0.53$ $P<0.0001$). Mean calcium intake was 404 ± 263 mg/d. Although not significant, Central and Southeast regions presented higher mean calcium intakes (458 ± 289 mg/d and 418 ± 264 mg/d, respectively). The present study demonstrated an important dietary inadequacy in our population. Dietary vitamin D was under recommended values for age in all regions and economical levels. Also, calcium intake above the preconized value by the Food and Nutrition Board (1200 mg/d). Consequently, our observations suggests that an improvement in vitamin D and calcium intake should be recommended routinely for people older than 40 y.

Disclosures: ***L.A. Martini****, None.*

M49

Vitamin D Status Is Associated with Baseline and Recovery of Bone Density in Recently Diagnosed Inflammatory Bowel Disease: The Manitoba IBD Cohort Study.

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Bone mineral density (BMD) is usually normal at the time of IBD diagnosis, but some patients show accelerated BMD loss and increased fracture rates. The role of abnormal vitamin D metabolism in IBD-related bone disease is uncertain. The Manitoba IBD Cohort Study is a population-based prospective cohort study of recently diagnosed IBD. Adult subjects (age 18 y or older) with recently diagnosed IBD (median 4 y) were recruited from the University of Manitoba IBD Epidemiology Database, the largest population-based database of IBD in North America. Baseline DXA (Hologic QDR-4500) and serological measurements (including 25-hydroxy vitamin D [25OHD, Diasorin] done in non-winter months) were obtained in a nested subgroup (101 subjects, 59 female and 42 male, age 47±15 y) of whom 94 (53 female and 41 male) returned for repeat BMD measurements 2.3 ± 0.3 y later. Mean baseline sex-and age-matched Z-scores were near-normal (L1-L4 -0.14, total hip +0.08, total body [females only] -0.03). Serum 25OHD was unrelated to age, gender, weight or BMI (all $p>.2$) but was inversely related to serum markers of bone turnover (bone-specific alkaline phosphatase $r=-0.20$, $p<0.05$; N-telopeptide $r=-0.18$, $p=0.07$). 25OHD was positively correlated with baseline BMD at all sites (all $p<0.05$). Vitamin D status was categorized according to serum 25OHD quartile (see Table) and MANOVA confirmed significant between-group differences in T-scores ($p<0.05$). Gain in total body BMD between the baseline and follow up DXA scans was positively correlated with 25OHD ($r=0.20$, $p=0.05$), but no correlation was seen between 25OHD and BMD change for L1-L4 or total hip. In conclusion, only a minority of recently diagnosed IBD participants have optimal 25OHD levels (> 70-75 nmol/L). Poorer vitamin D status correlates with lower baseline BMD and better vitamin D status is correlated with a gain in total body BMD. Early optimization of vitamin D may play an important role in preventing IBD-related bone disease.

Table: Correlation between baseline T-scores (±SE) and 25OHD.

	Serum 25OHD quartile *				Pearson Correlation Coefficient
	<41 nmol/L	41-53 nmol/L	54-72 nmol/L	>72 nmol/L	
Lumbar L1-L4	-0.85±0.20	-0.90±0.21	-0.27±0.22	-0.11±0.21	r=0.28 **
Total hip	-0.46±0.20	-0.01±0.21	0.27±0.22	0.09±0.21	r=0.21 *
Total body	-0.07±0.24	0.20±0.25	0.85±0.25	0.46±0.25	r=0.21 *

* $p<0.05$, ** $p<0.01$

Disclosures: ***W.D. Leslie****, Merck Frosst Canada 2, 8; Sanofi-Aventis and Proctor & Gamble Pharmaceuticals Canada 2, 5.*

M51

Relationship between Serum 25-hydroxyvitamin D Levels and Health-Related Quality of Life in Postmenopausal Women with Osteopenia.

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Recent evidence suggests that vitamin D may affect wellbeing and mood. The objective of this study is to examine whether serum levels of 25-hydroxyvitamin D are associated with health-related quality of life in postmenopausal women with osteopenia.

We examined the baseline data obtained from the ECKO trial: a 2-year single-centre double-blind placebo-controlled randomized trial investigating the effect of vitamin K supplementation on bone mineral density. Four hundred and forty-four postmenopausal women with osteopenia (defined as lowest T-score between -1 and -2 in the lumbar spine (L1-L4), total hip, or femoral neck) completed the screening visit. Serum 25-hydroxyvitamin D levels were measured at the screening visit when each participant also completed a Medical Outcomes Study 36-item short form questionnaire on health-related

quality of life (SF-36). The SF-36 assesses nine health domains: physical functioning, role functioning - physical, bodily pain, general health, vitality, social functioning, role functioning - emotional, mental health, and reported health transition. We performed regression analyses of serum 25-hydroxyvitamin D levels versus the various domains of the SF36. The mean serum 25-hydroxyvitamin D level is 76.7 nmol/L (SD 25.2 nmol/L). The mean scores for all domains of the SF-36 are approximately 100% of age-adjusted predicted mean scores in the general population. After adjusting for age and seasonal variation, we found that higher serum 25-hydroxyvitamin D levels are associated with higher scores for physical function (r2=0.03, p=0.001), mental health (r2=0.03, p=0.036) and social function (r2=0.03, p=0.004), although the effects are small. For an increase of 10 nmol/L of serum 25-hydroxyvitamin D level, there is a 1 point, 0.5 point and 1 point increase in score in physical function, mental health and social function, respectively.

Our results showed that higher 25-hydroxyvitamin D levels may be beneficial to health-related quality of life in postmenopausal women with osteopenia.

Disclosures: ***A.M. Cheung****, None.*

M53

Hypovitaminosis D and Environmental Related Factors in Healthy Elderly People Living in Different Geographical Regions in Argentina.

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We have previously reported insufficiency/deficiency of vitamin D status in a community dwelling elderly people.The aim of this study was to investigate 25 OH D serum levels in winter in elderly ambulatory people living in different latitudes in Argentina (26° - 55° SL) and the related environmental factors.

A total of 339 people, 226 women and 113 men (mean age 71.3 ± 5.2 yr) were studied at the end of the winter. None of them was taking vitamin D supplements. Sunlight exposure, housing, type of clothing worn in summer, vitamin D fortified food intake (D food),co-morbility and socioeconomic status were assessed using specific questionnaires. The serum levels of 25OHD was measured by specific radioimmunoassay.

The mean 25 OHD level of the whole population was 17.5 ± 7.8 ng/ml.Serum levels of 25OHD were higher in men (18.7 ± 8.5 vs 16.8 ± 7.2 ng/ml $p < 0.03$) , in subjects who had more than 3.0 hrs /week of sun exposure (21.1 ±9.6 vs 16.8 ± 7.1 ng/ml; $p < 0.001$), ate D food three times /week or more (18.8 ± 8.1 vs 16.8 ± 7.5 ng/ml; $p < 0.03$), wore light clothes in summer (20.3 ± 8.7 vs 14.6 ± 6.3 ng/ml; $p< 0.001$) and lived at lower latitudes (North 20.7± 7.3 , Mid 17.8±8.2 and South regions: 14.4 ± 5.6 , $p < 0.00001$). Subjects with lower incomes had worse vitamin D status (low, middle and high incomes had 25OHD levels 17.0± 6.7; 17.3± 8.7 and 21.1±8.9 ng/ml respectively; $p < 0.02$).

Elderly subjetcs presenting 25OHD vitamin D above 30 ng/ml, had greater exposure to sunlight, ate natural vitamin D rich foods, lived in central and north geographycal region and had less co-morbility (Table).

A multivariable regression linear analysis showed that gender ($p<0.03$) sunlight exposure ($p<0.000$), latitude ($p<0.0001$) and D food intake ($p<0.001$) were predictors of 25OHD serum levels (adjusted R squared 0.20; $p<0.0001$).

Hypovitaminosis D in Argentina is a common finding in elderly otherwise healthy people. Contributing environmental factors include: poor sunlight exposure in winter and summer time, low intake of vitamin D fortified foods and higher latitude. Subjects with low income are most vulnerable.

25OHD ng/ml	<10 (34)	10-19.9 (193)	20-30 (83)	>30 (35)
Calcium intake mg/day	416.6± 256.2	507.1± 307	561.7±319.3	531.2±315.4
D food time /wk*	1.5±0.7	2.1± 1.0	1.9±0.95	2.3±1.0
Sunshine expos/h. wk**	2.08±2.4	2.68±3.5	3.25±4.1	5.05±6.9
Female %*	74	69	60	60
Latitude S/C/N %**	29.4/67.6/2.9	32.1/53/14.8	13.2/62.6/24.1	11.1/61.1/27.7
Co-morbility no/ yes %**	47.1 / 52.9	68.6 / 31.4	54.2 / 45.8	77.1 / 22.9

$p<0.05$,**$p<0.01$

Disclosures: ***L.C. Plantalech****, None.*

M55

Differences in Calcium/Vitamin D Prescriptions among Women with Osteoporosis,Osteopenia and Fragility Fracture by Ambulatory Care Setting.

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A cross-sectional study using National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) data from 1997-2004 was done to evaluate differences in calcium/vitamin D prescriptions by U.S. ambulatory care setting. A total of 712 and 659 ambulatory care patient visits of women over the age of 40 were identified with at least one diagnosis of osteoporosis, osteopenia or fragility fracture, representing 37.1±2.3 and 2.6±4.0 million national visits in the private and hospital ambulatory care settings, respectively. From the private care setting, 83.8% of the visits were associated with osteoporosis or fragility fracture while 16.9% had at least one osteopenia diagnosis. In NHAMCS 86.1% of visits had osteoporosis or fragility fracture and 14.7% were associated with an osteopenia diagnosis. Prevalence of calcium/vitamin D prescriptions was low in both settings (NAMCS: 20.1% vs. NHAMCS: 33.1%). In the private setting, 20.4% and 17.5% of visits with osteoporosis or fragility fracture and osteopenia respectively, were associated with calcium/vitamin D. In the hospital setting 35.6% and 20.1% of the visits with osteoporosis or fragility fracture and osteopenia respectively had a calcium/vitamin D prescription. Multivariate logistic regression was used to assess factors associated with a calcium/vitamin D prescription in each care setting. Of the covariates, including age, race, insurance type, metropolitan area status, region, physician specialty and use of anti-osteoporosis medications (AOM) in the models, insurance, race and AOM use were statistically significant predictors of calcium/vitamin D in the private setting. Visits made by women with AOM prescriptions were more likely to be associated with calcium/vitamin D (OR=2.41(1.56-3.72). Additionally visits from White and Black women were more likely to be associated with calcium/vitamin D compared to other races. Similar associations between AOM and calcium/vitamin D were observed in the hospital setting. Visits from women older than 60 were more likely to be associated with calcium/vitamin D and those with Medicare were less likely to have calcium/vitamin D compared to those of private insurance holders. In conclusion, the overall study findings indicate low rates of calcium/vitamin D prescribing among visits recorded with osteoporosis or fragility fracture and osteopenia. Additionally, management of these conditions with calcium/vitamin D showed some disparities by insurance type in both care settings and by race for ambulatory visits to private physician offices.

Disclosures: ***M.K. Maneno****, None.*

M57

ASBMR YOUNG INVESTIGATOR AWARD - PLENARY POSTER
Rapid Correction of Vitamin D Inadequacy in Nursing Home Residents.

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Approximately 1.6 million Americans currently reside in nursing homes (NH); a number expected to triple by 2030. Osteoporosis and vitamin D inadequacy are epidemic in this population. Vitamin D deficiency is associated with bone loss, muscle weakness and increased falls risk, contributing to a fracture incidence of approximately 10% annually among NH residents. However, approaches to rapidly correct vitamin D inadequacy among NH residents have received limited attention. In this study of 63 nursing home residents, the effect of oral high dose vitamin D2 (ergocalciferol) on serum 25-hydroxyvitamin D (25OHD) status, markers of skeletal health and gait speed was evaluated.

Individuals with vitamin D inadequacy (defined as a 25OHD < 25 ng/ml) received vitamin D2 50,000 IU, 3 times weekly for 4 weeks (N=25); the others received no change to their routine care. The investigative staff were blinded to treatment group assignment. Measurements of serum calcium, 25OHD (by liquid chromatography mass spectroscopy), bone specific alkaline phosphatase (BSAP), n-telopeptide of type 1 collagen (NTx) and parathyroid hormone (PTH) were performed at baseline and at 4 weeks. Timed 4-meter walk tests were performed at baseline and at 4 weeks. Average subject age was 86.8 (range 42 to 99) years. There were no between group differences in age, serum calcium, BSAP, NTx or gait speed at baseline. Mean (SEM) total 25OHD concentration increased ($p < 0.0001$) from 17.3 (1.2) to 63.8 (3.3) ng/ml in the D2 treated group and remained unchanged in the control group at 35.2 ng/ml. The maximum 25OHD value observed was 102 ng/ml. Serum 25OHD3 remained stable in the control group, but declined ($p < 0.0001$) with D2 treatment from 15.6 (1.2) to 9.1 (0.8) ng/ml over the 4 weeks of study. Mean serum calcium was 9.4 (0.1) and 9.5 (0.1) mg/dl at baseline and after 1 month of vitamin D2, respectively. Hypercalcemia was not observed in the treatment group. However, 3 individuals in the control group developed hypercalcemia during the month of this study, reflecting the frailty of this study population. No treatment-induced changes in BSAP, NTx or gait speed were observed.

In conclusion, 4 weeks of high-dose oral vitamin D2 supplementation safely increases serum 25OHD. The absence of changes in bone turnover markers and gait speed probably reflects short study duration, small sample size and heterogeneity of the NH population. It seems likely that rapid vitamin D repletion of NH residents would reduce fracture risk, however this supposition requires prospective study confirmation. As vitamin D3 has recently been reported to be more potent than D2, the observed reduction in 25OHD3 following D2 treatment is interesting and merits further evaluation.

Disclosures: ***S. Agrawal****, None.*

Non-Traditional Roles of Vitamin D I

M59

Insufficient Circulating 25 OH-Vitamin D Levels and Accelerated Conversion to Inactive D-Metabolites Are Clinically Associated with Non-Tubercular Mycobacterial Infection of the Lung.

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Activation of the Toll-Like Receptor pathway in monocytes results in the induction of the P450 isoenzyme (CYP27B1) vitamin D-1 hydroxylase leading to increased conversion of 25 to 1,25 OH Vit D_3. This intracellular synthesis of active vitamin D metabolites induces bacteriocidal proteins such as cathelicidin and/or agents such as nitric oxide, compounds that are essential for innate-immunity mediated killing of mycobacteria. Adequate levels of circulating 25 OH Vit D are necessary to provide sufficient substrate for intracellular conversion to 1,25 OH Vit D. Therapeutic agents used to treat Non-Tubercular Mycobacterial infection (NTM) can induce 24-hydroxylase yielding inactive D metabolites and hence impair intracellular killing of mycobacteria.

The first case illustrates the possible detrimental effect of vitamin D insufficiency. Metabolic evaluation in a healthy 75 yo male found a serum calcium of 9.3, 25 OH VitD of 17.3ng/ml and an iPTH of 204pg/ml, 1,25 OH Vit D was 27pg/ml. In spite of correction of the 25OH Vit D to 39ng/ml, the iPTH remained elevated. Imaging studies identified a single enlarged (90-133mg) parathyroid adenoma and a 2cm RUL lung nodule. FNA of the lung nodule identified m. avium complex.

The next case illustrates the potential clinical dilemma of iatrogenic vitamin D deficiency in a patient with NTM. After a five year history of recurrent pulmonary infections, increasing hemoptysis and disability the patient was diagnosed with m. avium in 1999. Since 1999, she has received continuous therapy with rifampin, ethambutol and claithromycin. In 2001, after recurrent episodes of respiratory distress, superinfection with m. abscessus was noted, and she received multiple supplemental courses of moxifloxacin, linezolid and fluconazole. Now at age 66, she presented for endocrine consultation for failing thyroid function. She had been started on thyroid hormone replacement since February 2005 and has recently had a dose adjustment to 0.1 mg of L-thyroxine/day. Additional testing revealed a normal BMD at hip and spine, serum calcium of 9.3 mg/dl, iPTH of 43 pg/ml (nl), 25 OH Vit D of 28ng/ml (nl 20-100nl/ml) and a 1,25 OH Vit D of 14 pg/ml (nl 19-67pg/ml). The patient was started on cholecalciferol, 800 IU/day and 0.25 mcg of 1,25 OH Vit D three days/week.

Conclusion: These cases raise concern that basal vitamin D deficiency, with “insufficient” circulating levels of 25 OH Vit D3 along with increased 25 and 1,25 Vitamin D conversion to inactive 24,25 and 1,24,25 Vitamin D metabolites by rifampin induction of vitamin D-24 hydroxylase (a CYP24 isoenzyme) results in severe vitamin D deficiency impairing innate immunity responsible for bacteriocidal activity against mycobacteria.

Disclosures: ***R.S. Bockman****, None.*

M61

Pathophysiology of Disease as Influenced by Vitamin D.

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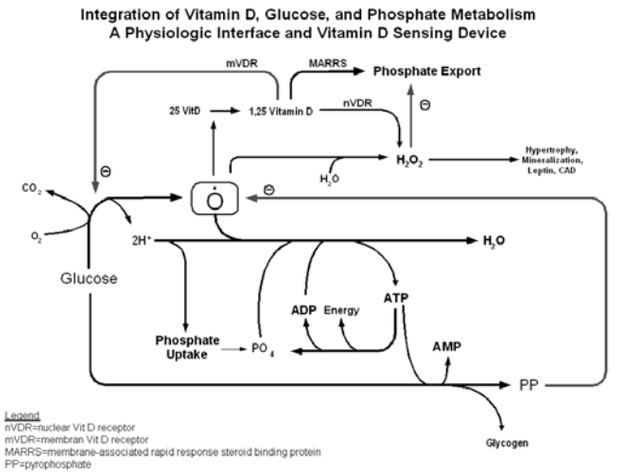
Vitamin D's endocrine, paracrine and intracrine effects focus our strategy for the understanding of bone mineral density as a record of metabolic health. Patients are given 1000 mg of oral calcium, with measurement of physiologic parameters before and after calcium. Evaluation of the data has required the development of integrated models in the context of complex dynamic systems to guide the intervention. Available analogues of Vitamin D probe the nature of integrated physiologic-metabolic function clarifying human variance, avoiding the ecologic fallacy which compromises conclusions from data obtained across levels of systemic organization. Intracellular metabolism of phosphate, glucose and vitamin D interface with physiologic signals, making vitamin D both a physiologic and cellular signal; creating a vitamin D sensing device. This has been demonstrated in our work with adipocytes.



Recent findings in the FGF23/Klotho signals suggests that this device is applicable to renal tubular function and can be integrated in a manner consistent with informative cases as involved in a balance of aging and fatigue. Evaluation of patients recognizing variance in renal tubular function will be useful for the individualized treatment of stage 3 chronic kidney disease. We find our approach applicable to therapy of fluid and electrolytes, disorders of energy metabolism, bone phenotypes, and subjective symptoms. In the tradition of Selye, stress responses are influenced by exposure to calcium, allowing for the evaluation of individual predisposition to stress induced metabolic disease as expressed on the background of aging. The calcium sensing receptor is a target of both the calcium challenge and therapeutic intervention. Calcium acts as a danger signal threatening the integrity of energized phosphate. The vitamin D sensing device interfaces systemic and intracellular signals allowing for the translation of physiologic signals to metabolic work; organizing adaptive strategies to environmental change. We have obtained average increases in femoral neck BMD of 8.4% over 4 years, approximately double that seen in follow up of single agent randomized control studies which ignore the ecologic fallacy. While the number of cases in this cohort is small (39), they demonstrate that with appropriate individualization, the skeleton can be understood as a complexly organized structure, recording individual predisposition to metabolic disease as strongly influenced by vitamin D.

Disclosures: ***R.S. Fredericks****, None.*

Vitamin D and Kidney Disease I

M63

ASBMR YOUNG INVESTIGATOR AWARD
25(OH)D Deficiency in Ambulatory Pediatric Patients with Chronic Kidney Disease: Uncovering an Epidemic.

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Background: Vitamin D deficiency (D-) in children adversely affects bone development by reducing mineralization. Children with chronic kidney disease (CKD) are at risk for altered bone development from renal osteodystrophy and concomitant D-. The pediatric NKF-KDOQI guidelines suggest measuring serum 25(OH)D levels if serum PTH levels are above the target range for CKD stages 2 and beyond, but the magnitude of D- in children with CKD is not well-studied. *Objective:* The purpose of this study was to determine whether children with CKD had D-, to evaluate whether the prevalence of D- was changing over time, and to determine the relationship between secondary hyperparathyroidism and 25(OH)D levels. *Methods:* Incident levels of 25(OH)D in ambulatory pediatric patients with CKD, stages 1-5, were measured over a 10-year period from 1987-1996. Simultaneous measurements of iPTH and 25(OH)D were evaluated over the 5 year period from 1992-1996. *Results:* Yearly mean incident 25(OH)D levels during the 10 year period ranged from 11.6 to 30.2 ng/mL (n=79-336 per year), and there were differences between the yearly mean values over the decade ($F=25.75$; $p<0.001$). The prevalence of D-, defined as a 25(OH)D level <15 ng/mL, ranged from 20% to 75% in the decade studied, and there were differences between the yearly values ($F=311.59$; $p<0.001$). Additionally, we observed a trend ($p<0.001$) of increasing prevalence of 25(OH)D levels <15 over the decade studied. When we assigned a 25(OH)D level of 32 ng/mL as the lower limit of "normal", we found a negative correlation with iPTH values at no greater than 2x the upper limit of the assay (n=1492 paired observations; p=4.9E-015). *Conclusions:* Children with CKD have great risk for vitamin D deficiency, and its prevalence was increasing yearly in the decade from 1987-1996. Further, we found that in children with CKD, secondary hyperparathyroidism increased as levels of 25(OH)D fell below 32 ng/mL. Our data support the recent pediatric KDOQI guidelines for measurement of 25(OH)D levels in children with CKD and secondary hyperparathyroidism, in order to reduce the effects of D- as an important component of their renal osteodystrophy.

Disclosures: ***F.N. Ali****, None.*

Vitamin D and Other Metabolic Bone Diseases I

M65

Synergy Between 1,25(OH)$_2$D$_3$ and Genistein: A Novel Approach for the Treatment of Obesity and Osteoporosis.

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Increased numbers of adipocytes in bone marrow can be a risk factor for aging-related bone loss by inhibiting osteoblast proliferation, by stimulating the differentiation of osteoclasts and by disrupting the normal blood supply to bone tissue. A reciprocal relationship was shown to exist between the osteoblast and adipocyte differentiation and hence treatments that specifically target reduction of adiposity could greatly improve bone health. In this study, we investigated the ability of 1,25(OH)$_2$D$_3$ and genistein, an isoflavone, singly and in combination, to inhibit adipogenesis and induce apoptosis in 3T3-L1 adipocytes. 1,25-dihydroxyvitamin D$_3$ [1,25(OH)$_2$D$_3$] has been shown to regulate adipogenesis by acting on multiple targets to block differentiation. 1,25(OH)$_2$D$_3$ was also shown to induce apoptosis in 3T3-L1 cells at high doses. Preconfluent preadipocytes and mature adipocytes were incubated with 0.1,1,10 and 100 nM 1,25(OH)$_2$D$_3$ alone and in combination with 100 and 200 μM genistein. DMSO and ethanol at 0.1% each were used as carrier controls and MTS assay was used as an overall measure of cell proliferation. No synergistic effect on cell viability in either preadipocytes or mature adipocytes was observed at these concentrations. Maturing preadipocytes were treated with 0.1 and 0.5 nM 1,25(OH)$_2$D$_3$ in combination with 12.5, 25 and 50 μM genistein for 6 days during the differentiation stage. The lipid content was visualized with Oil Red O staining and quantified by using a hydrophilic Nile Red stain. Single stranded DNA (ssDNA) was measured by ELISA and served as a determinant for apoptosis. 1,25(OH)$_2$D$_3$ and genistein as single compounds inhibited lipid accumulation by 20% (P=0.4348) and 10% (P=0.299), respectively and each increased apoptosis by 50% (P<0.001). However, 1,25(OH)$_2$D$_3$ and genistein in combination synergistically inhibited lipid accumulation by 80% (P<0.0001) and increased apoptosis by 200% (P<0.0001). These findings suggest that 1,25(OH)$_2$D$_3$ and genistein synergistically inhibit lipid accumulation and induce apoptosis in maturing 3T3-L1 preadipocytes and hence may lead to development of novel treatments for the prevention and treatment of obesity and osteoporosis.

Disclosures: ***S. Rayalam****, AptoTec, Inc 1, 2, 4.*

M67

Burn-Associated Vitamin D Deficiency Does Not Improve with Standard Supplementation.

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Burn injury exceeding 40% total body surface area (TBSA) is followed by progressive vitamin D (vitD) deficiency (J Trauma 2002; 52:346-50). Two contributing factors are failure of skin to synthesize normal quantities of vitD on UV light exposure (Lancet 2004; 363: 291-2) and failure to supplement patients on discharge. Our aim was to provide a standard vitamin supplement to correct biochemical vitD deficiency. 8 patients aged 5-18 yr, discharged from hospital after treatment for burns >40% TBSA were given a standard chewable multi-vitamin tablet containing vitD 400 IU after having received this same supplement during in-patient therapy.A research nurse witnessed daily intake of the tablet for 6 mo during outpatient rehabilitation. Serum was analyzed for 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D (1,25(OH)2D) and intact PTH at 6 mo post-burn. Lumbar spine (LS) BMC and BMD and total body (T) BMC were analyzed by DXA at discharge and 6 mo post-burn. Serum 25(OH)D was 21+/-11(SD)ng/ml, range 9-46, median 20 (normal range 20-100 ng/ml) with 7 of the 8 values below the desired value of 30 ng/ml. Serum 1,25(OH)2D levels were 23 +/- 12 pg/ml (normal range 15-60). IPTH levels were 25 +/-15 pg/ml (normal 15-60). LS BMD was 98.6 +/- 5.5% of discharge values, LS BMC was 100+/-9.4% discharge values, and TBMC was 94.4 +/- 9.2% discharge values at 6 mo. None of these changes were significant. Serum levels of total protein and albumn were normal in all patients by 6 mo post-burn. These data suggest that 400 IU/day of vitD may not be adequate to preserve nutritional status following severe acute burn injury. The cause of the initial vitD deficiency is unknown and failure of standard supplementation to maintain desired levels of 25(OH)D suggests that maintenance doses of vit D may be substantially higher following burn injury.

Disclosures: ***G.L. Klein****, None.*

M69

Effects of Vitamin D Supplementation on Calcium Metabolism and Bone Growth in Young Rats.

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Objectives: Vitamin D inadequacy is a common problem worldwide. Majority of the population during adolescence do not receive adequate calcium and vitamin D intake. While vitamin D supplementation has been recommended in many nations, whether vitamin D supplementation can improve the pick bone mass during growth is not known. The purpose of this study was to evaluate the effect of vitamin D supplementation on bone growth in young rats fed a normal or low calcium diet. **Materials and Methods:** Fifty female Sprague-Dawley rats, 6 weeks of age, were randomized into five groups with 10 rats in each group: baseline control, and 0.5% (normal) or 0.1% (low) calcium diet, either alone, or with vitamin D (25 ug/100 g, food intake), Duration of the experiment was 10 weeks. **Results:** Vitamin D supplementation stimulated intestinal calcium absorption and increased urinary calcium excretion in rats fed a low or normal calcium diet. Vitamin D supplementation reduced the maturation-related cancellous bone gain, prevented the reduction in periosteal bone gain, and enhanced the enlargement of the marrow cavity, with no significant effect on the reduction in the maturation-related cortical bone gain in rats fed a low calcium diet, and increased the maturation-related cancellous and cortical bone gains with increased periosteal bone gain in rats fed a normal calcium diet. **Conclusion:** This study shows the differential effects of vitamin D supplementation on cancellous and cortical bone mass in young growing rats fed a normal or low calcium diet. Under normal calcium intake, vitamin D supplementation has beneficial effect on bone growth, whereas under calcium deficiency, the supplementation will have a detrimental effect on bone growth.

Disclosures: ***J.K. Yeh****, None.*

M71

Vitamin D Metabolites and Skeletal Consequences in Primary Hyperparathyroidism.

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Background: Plasma 25-hydroxyvitamin D (25OHD) levels are typically reduced and plasma 1.25-dihydroxyvitamin D ($1.25(OH)_2D$) slightly increased in primary hyperparathyroidism (PHPT). PHPT is associated with reduced bone mineral density (BMD) mainly at sites rich in cortical bone, whereas successful parathyroidectomy causes an increase in BMD especially at sites rich in trabecular bone.
Aim: To investigate relations between preoperative vitamin D metabolites and skeletal consequences in patients with untreated PHPT and to appraise the influence of preoperative vitamin D metabolites on postoperative changes in BMD.
Design: Cross-sectional and cohort study.
Materials: 246 consecutive Caucasian PHPT patients aged 19 - 91 yrs. (median 63, 87% females).
Methods: Plasma intact PTH was measured by IMMULITE® automated analyzer (Diagnostic Products Corporation, Los Angeles, CA, USA), plasma 25-OHD by enzyme-immunoassay (IDS, Phoenix, Arizona, USA), and plasma $1,25(OH)_2D$ radioimmunoassay (IDS, Phoenix, Arizona, USA).
Results: BMD was reduced at the femoral neck ($p < 0.001$) and forearm ($p < 0.001$) but normal at the lumbar spine ($p = 0.11$). Levels of biochemical bone markers were associated with high plasma PTH, high plasma $1,25(OH)_2D$ and low plasma levels of 25OHD. Moreover, low plasma 25OHD was associated with low levels of BMD at the femoral neck ($r_p = 0.23$), the forearm ($r_p = 0.19$), and the whole body ($r_p = 0.30$) whereas plasma $1,25(OH)_2D$ was inversely associated with BMD at all regional sites and the whole body. Plasma PTH only showed an inverse association with BMD at the forearm($r_p = -0.21$). No association was observed between biochemical variables and prevalent spinal fractures. The annual increase in BMD after surgery at the spine was positively associated with preoperative plasma PTH ($r_p = 0.40$) whereas the annual increase in whole body BMD was inversely associated with plasma 25OHD ($r_p = -0.32$). No change in BMD at the femoral neck and forearm was observed one year after surgery.
Conclusion: Low vitamin D status and high plasma $1,25(OH)_2D$ are associated with increased bone turnover and decreased bone mineral density in patients with primary hyperparathyroidism.

Disclosures: ***L. Mosekilde****, None.*

M73

ASBMR YOUNG INVESTIGATOR AWARD
Vitamin D Nutritional Status and Its Relationship with Nutrient Intakes in Postmenopausal Osteoporotic Women.

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Vitamin D is essential for maintaining calcium homeostasis and optimizing bone health. Its inadequacy has been related to many factors including dietary intake. The aim of the present study was to evaluate serum $25(OH)D_3$ and its relationship with nutrient intakes in postmenopausal Brazilian women with osteoporosis. This cross-sectional study comprised 45 free-living elderly, mean age 63.32 (8.2), assisted at São Paulo Hospital. Dietary intakes were assessed by a three day dietary records. The Nutrition Data System software (Minneapolis, MN) was used to evaluate nutrient intakes. Bone mineral density was measured with dual-energy X-ray absorptiometer (DXA) by Lunar Radiation Corporation, Madison, WI, USA. Blood sample were collected after 12h fasting, in order to analyze biochemical markers of bone and mineral metabolism. Serum calcium and ionized calcium were measured by colorimetry and ion selective electrode respectively, $25(OH)D_3$, $1,25(OH)_2D_3$, were measured by radioimmunoassay kit DiaSorin (Stilwater, MN) and intact parathyroid hormone-iPTH concentrations was measured utilizing the Nichols Advantage® Chemiluminescence Intact Immunoassay. Urinary sample were collected to analyze calcium, sodium and creatinine and was measured by standards laboratory methods. The optimal levels for serum vitamin D adopted was 50 - 80 nmol/l (Dawson-Hughes, 2005). The loss of bone mass evaluated by T-score and was predominat in lumbar spine (t-score = - 3.0) and was observed presence of insufficiency of vitamin D in 24.4% of the women and optimal levels in 75.6%. Mean serum calcium, ionized calcium and $1,25(OH)_2D_3$ were in accordance to the reference values, however iPTH was above reference in 51% of the participants. The mean calcium (723.8 mg/d) and vitamin D (4.2 mcg/d) intakes were lower (137.96 mEq/24h) than the proposed values by The Food and Nutrition Board and sodium intake was more than two fold above the recommendation. Serum $25(OH)D_3$ was inversely associated with sodium intake ($r= -0.414$; $p=0.029$) and a significant positive correlation was observed between calcium intake and serum vitamin D ($r=0.405$; $p=0.006$) as well as serum $25(OH)D_3$ and vitamin D intake ($r=0.433$; $p=0.003$). In conclusion dietary strategies to prevent and treat inadequate levels of serum $25(OH)D_3$ must focus on increase intake of calcium and vitamin D through dairy products and fortified foods. Reduction in sodium intake should be considered to optimize bone health.

Disclosures: ***P.S. Genaro****, None.*

Other I

M75

ASBMR YOUNG INVESTIGATOR AWARD
Potential for Vitamin D Production in an Urban Environment.

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Exposure to ultraviolet radiation (UV) results in both damaging and beneficial health outcomes. Excessive UV exposure has been linked to many skin and eye problems, but moderate exposure induces vitamin D production. It has been reported that humans receive 90-95% of their vitamin D from production that starts after UV exposure, and that although it is possible to acquire vitamin D through dietary supplementation, the average person receives very little in this manner. Therefore, since most people acquire their vitamin D from synthesis after exposure to UV, it is very important to understand the different environments in which people encounter UV.

This project focused on UV and the resultant potential for vitamin D production in the 'urban canyon' - an environment consisting of tall buildings and tropospheric air pollution, which both have an attenuating effect on UV. Most UV measurements are taken in areas outside the 'urban canyon', meaning that at times this data may not accurately represent the amount of UV reaching street-level in highly urbanized areas. Therefore, if sun-exposure guidelines are developed using data collected in non-'urban canyon' locations it may be the case that they are underestimating exposure times for people who receive their UV inside the 'canyon'. A study in Lodz, Poland found, that with building height only 1.1-1.5 times greater that street width, both total solar radiation and UV levels were significantly lower in the 'canyon' than outside of it. This becomes increasingly important as the number of people working and living in 'urban canyons' steadily increases.

This study was conducted in the central business district (CBD) of Brisbane, Australia, which models the CBDs of large cities around the world in that it boasts a great number of tall buildings, including many skyscrapers, meaning that most areas only see a small amount of direct sunlight each day.

During this study minimum erythemal dose (MED) data was collected at five locations in Brisbane's CBD - on either side of two streets running perpendicular to one another (4 sites) and in a public square. Results were compared to guidelines for exposure times determined in a recent study by Samanek et. al., which used previously collected UV data to calculate healthy exposure times for each month of the year in major Australian population centres and to data collected on the same day at QUT's Australian Sun and Health Research Laboratory (ASHRL), which is located 2.5 kilometres outside Brisbane's CBD. Each site received varying amounts of UV throughout the day, but measured MED levels were nearly always lower than those predicted for August in Brisbane, and never reached those received at the ASHRL lab.

Disclosures: ***A. McKinley****, None.*

M77

Primary Hyperparathyroidism and Hypovitaminosis D.

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Hypovitaminosis D including vitamin D deficiency (25-OHD ≤ 10 ng/ml) and insufficiency (>10-30 ng/ml) appears to be epidemic in all age groups in the general population and is seen frequently in a number of clinical situations including patients with primary hyperparathyroidism (PHP). Treatment with 50,000 units of vitamin D weekly has been shown to restore serum 25-OHD levels to normal. However, in patients with PHP and hypovitaminosis D there has been great reluctance to treat with vitamin D with comments in the literature that such therapy is dangerous and should be avoided. To evaluate the effect of vitamin D therapy in patients with PHP, studies were carried out in 54 patients with PHP. There were 36 females and 18 males, mean age 63±14.7 yrs. Eight patients had serum 25-0HD levels of ≤ 10 ng/ml, 46 had levels ranging from 11-24 ng/ml. Patients were treated with 50,000 units of vitamin D weekly for 8 weeks. Serum Ca, PO4, and 25-OHD levels were measured before therapy and at 5 and 10 weeks and serum intact PTH levels and urine Ca/Cr were measured before therapy and at 10 weeks. Twelve weeks later on subsequent maintenance with 800 units of vitamin D daily, serum 25-OHD levels were again measured and if subnormal patients were then treated with 50,000 units twice monthly and serum 25-OHD levels were measured 12 weeks later. Results:

	Pre Rx	5 Weeks	10 Weeks 800D/day	34 Weeks 100,000D/month
Ca	10.8±0.6	10.6±0.7	10.7±0.7	10.6±0.4
PO4	3.0±0.6	3.2±0.7	3.0±0.6	
Cr	1.0±0.3			
25-OHD	14.4±4.0	33.6±9.8	35.1±12.2	34.4±4.9
PTHR*	1.9±1.2	1.7±1.3		
Urine Ca/Cr	0.18±0.1	0.17±0.1		

*PTH/ULN

With vitamin D therapy there was a significant increase in serum 25-OHD levels versus baseline at 5 and 10 weeks ($p<.0001$). There were no significant changes in serum Ca, PO4, or PTH levels or in urinary Ca/Cr. During and after therapy there were no patients who reported any new complaints or problems. Conclusions: These data indicate that replenishment of body stores of vitamin D in patients with PHP and hypovitaminosis D is not associated with adverse effects. These findings do not support the generally accepted position that treatment with vitamin D is dangerous in PHP. Also, when one considers the potential deleterious skeletal and nonskeletal effects of untreated hypovitaminosis D particularly in patients with PHP such a position now seems untenable.

Disclosures: ***J.R. Tucci****, None.*

Assessment of Vitamin D Status II

T2

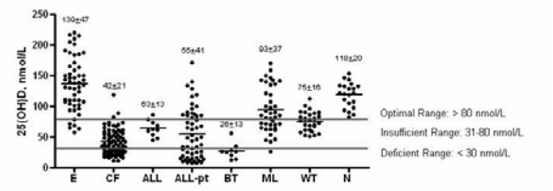
Withdrawn.

T4

Vitamin D Status in Pediatric Clinical Disorders in Children and Youth Living in Southern Ontario, Canada.

S. A. Atkinson*[1], S. Docherty-Skippen*[1], V. Grey*[1], R. Barr*[1], G. Ronen*[1], F. Yousif*[1], I. Odame*[1], K. Mandel*[2]. [1]Pediatrics, McMaster University, Hamilton, ON, Canada, [2]Pediatrics, CHEO, Ottawa, ON, Canada.

Aims: 1) To determine the vitamin D status of children and youth with various clinical disorders living in southern Ontario (latitude ~ 43ºN) in relation to the recent recommendations (Whiting and Calvo 2005) for cut-off values for plasma 25-hydroxyvitamin D (25OHD) to define deficiency (<30 nmol/L), insufficiency (30-80 nmol/L) and sufficiency (>80 nmol/L). 2) To determine the prevalence of vitamin D insufficiency/deficiency associated with various pediatric clinical disorders in which low bone mass often exists. Methods: Serum was obtained from 290 subjects (age = 2-18 yr.) as part of protocols to study bone and mineral metabolism in children and youth under treatment for epilepsy with valproate and/or lamotrigine (E n=53), cystic fibrosis (CF n=75), or acute lymphoblastic leukemia with chemotherapy (ALL n=10); and survivors post-therapy of ALL (ALL-pt n=55), brain tumour (BT n=9), malignant lymphoma (ML n=40) or Wilm's tumour (WT n=27); and a comparison group of healthy children at pre-pubertal age (N n=21). Serum was assayed for 25OHD after acetonitrile extraction by RIA (Diasorin) or Nichols Advantage (for CF only with adjustment to Diasorin values) and intact PTH by IRMA (Nichols).
Results: Mean serum 25OHD was similar between winter (Nov-Mar) and summer (Apr-Oct) samples within disease groups but was lower in winter for all groups combined (57±45 vs. 77±33 nmol/L, p<0.03). The figure presents individual subject and mean±SD values within disease group, with horizontal lines indicating lower cut-off values for deficiency and insufficiency. Insufficient and/or deficient status occurred in 11% of E, 96% of CF, 90% of ALL, 100% of BT, 43% of ML, 22% of WT, 73% of ALL-pt. Serum 25OHD was inversely weakly correlated with serum PTH (R = - 0.2, p = 0.005).
Conclusion: Vitamin D deficiency or insufficiency occurs frequently in pediatric clinical disorders and may be a factor in abnormal bone mass observed in these populations. The determinants of sub-optimal vitamin D status and associated health risks for those in the insufficient/deficient categories require further investigation.



Disclosures: ***S.A. Atkinson****, Amercian Society for Nutrition 6.*

T6

3-epi 25OHD in Infants - Further Evidence for Longitudinal Decline with Age.

R. J. Singh*, T. Robert*, S. K. Grebe*. Mayo Clinic, Rochester, MN, USA.

We have previously reported that 22.7% of children under the age of 1 have significant concentrations of circulating 3-epimers of 25OHD2 and D3 in addition to 25OHD2 and D3. We were able to detect and separate the epimers from 25OHD2 and D3 using liquid chromatography (with chiral columns), followed by detection by tandem mass spectrometry.
In children with detectable 3-epimers, up to 60% of apparent 25OHD2 and D3 can exist as 3-epimers, complicating measurement and interpretation of 25OHD testing, depending whether assays crossreact with these epimers or not. In the initial study there appeared to be an inverse relationship between 3-epimer percentage and age.
We have now extended the study to 286 children under the age of 1. The prevalence of detectable 3-epimers of 25OHD2 or D3 remained at 21.3% (61 children) with a similar distribution of 3-epi percentage ranging from 8.1% of total 25OHD to 60.1% of total 25OHD. The apparent rate of decline with age also remained similar: 0.068 percent per day with an intercept (=average value at birth) of 32.9%. In 3 children with detectable 3-epimers multiple measurements were available showing a longitudinal rate of decline of between 0.1 and 1.2% per day.
3-epimers of 25OHD in infants are present at birth and then gradually decline. There appears to be no ongoing productions. Possibly the 3-epimers are therefore of maternal or placental origin. Metabolic disposure of the 3-epimers is highly variable between individuals and might reflect variable degrees of maturity of metabolic enzyme systems in different children

Disclosures: ***R.J. Singh****, None.*

T8

ASBMR YOUNG INVESTIGATOR AWARD
High Risk of Vitamin D Deficiency in Children with Sickle Cell Disease.

A. Rovner[1], V. Stallings*[2], D. Kawchak*[2], J. Schall*[2], E. Richard*[2], K. Ohene-Frempong*[3], B. Zemel[2]. [1]Center for Human Nutrition, Johns Hopkins School of Public Health, Baltimore, MD, USA, [2]Division of GI, Hepatology and Nutrition, The Children's Hospital of Philadelphia, Philadelphia, PA, USA, [3]Division of Hematology, The Children's Hospital of Philadelphia, Philadelphia, PA, USA.

Sickle cell disease, a disorder affecting primarily African-Americans, is characterized by chronic hemolytic anemia and tissue infarction. Children with type SS (SCD-SS) are the most severely affected and exhibit poor growth and bone mineral deficits. These children have risk factors for hypovitaminosis D, including dark skin pigmentation, poor dietary intake and reduced levels of physical activity (which may result in less time outdoors and decreased sunlight exposure). The objective of this study was to determine vitamin D insufficiency [25(OH)D < 30 ng/mL] and deficiency [25(OH)D < 11 ng/mL] in children with SCD-SS compared to healthy African-American children in the same geographic area. 25(OH)D concentrations were measured using a radioimmunoassay, and serum iPTH was measured by immunochemiluminometric assay (Quest Diagnostics Nichols Research Institute, San Juan Capistrano, CA). Mean differences between subjects with SCD-SS and controls were determined using Student's t-test and the Wilcoxon rank-sum test. Proportions were compared by Fisher's exact test. Logistic regression analysis was used to determine the risk of vitamin D deficiency in subjects with SCD-SS compared to controls after adjusting for age and season. Sixty-one children (51% males) with SCD-SS and 89 healthy children (54% males) aged 5 to 18 years participated. The mean concentrations of 25(OH)D and iPTH and the prevalence of vitamin D deficiency and insufficiency are presented in Table 1. The odds of vitamin D deficiency among children with SCD-SS were 9.2 times greater than among healthy African-American subjects adjusted for age and season. Vitamin D deficiency is common in children with SCD-SS.

Table 1. 25(OH)D Status in SCD-SS and Healthy African-Americans

	25(OH)D Concentration Mean (SD)	PTH Concentration Median (Range)	25(OH)D < 11 ng/mL N (%)	25(OH)D < 30 ng/mL N (%)
SCD-SS	16.2 ± 7.7	35 (13, 185)	20 (33%)	56 (93%)
Controls	20.9 ± 8.0	37 (13, 94)	8 (9%)	78 (88%)
p-value	0.0005	NS	0.001	NS

Disclosures: ***A. Rovner****, None.*

T10

ASBMR YOUNG INVESTIGATOR AWARD
Vitamin D Status in the Skin Cancer Capital of the World.

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Queensland has the highest rates of skin cancer in the world and has invested in Sun-Smart public health campaigns for more than 25 years. Due to the high levels of solar UV in this region, it is assumed that incidental UV exposure should provide adequate vitamin D status for the population. This research was undertaken to test this assumption among healthy free-living adults aged 18 to 87 years, in south-east Queensland, Australia (27°S), at the end of winter. 126 adults (40 males, mean age 42±21 years) participated in this cross-sectional survey, by having a blood sample taken to assess serum 25(OH)D status and answering a self-reported questionnaire which sought demographic data and information about sun exposure. This research was approved by Queensland University of Technology Human Research Ethics Committee and conducted under the guidelines of the Declaration of Helsinki. 10.2% of the sample had serum vitamin D levels below 25nm/L (deficiency) and a further 32.3% had levels between 25nm/L and 50nm/L (insufficiency). Thus vitamin D deficiency and insufficiency can occur at the end of winter, even in sunny climates. No statistically significant associations were found between vitamin D status and age, gender, education level or BMI, however a non-significant trend was found with BMI and blood serum 25(OH)D status, showing a lower Vitamin D levels with increasing BMI. The wintertime UV levels in south-east Queensland (UV index 4-6) are equivalent to summertime UV levels in northern regions such as Boston. These ambient UV levels are sufficient to ensure synthesis of vitamin D requirements. However, increasing sun exposure to ensure adequate vitamin D status should be treated with caution in Queensland, which has such a high incidence of skin cancer. Clear public health messages are needed to balance these issues. Further research is needed to explore the interactions between the solar UV environment and vitamin D status, particularly in high UV environments, such as Queensland.

Disclosures: ***M.G. Kimlin****, Research Grant from Queensland Health 2.*

T12

Prevalence and Risks of Vitamin D Insufficiency in African-American Male Veterans.

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Prevalence and risks of vitamin D insufficiency are well studied in women; however there is a paucity of such data in men. In NHANES III study (Looker et al, Bone 30:771-77;2002), analysis of a subgroup of African-American (AA) men age greater than 60 years showed that prevalence of vitamin D insufficiency in this group was high. In that study, 1% of AA men had serum 25-hydroxyvitamin D (25-OHD) level < 8 ng/ml, 27% and 59% had levels below 15 ng/ml and 20 ng/ml, respectively. In the present study, we examined the prevalence and risks of vitamin D insufficiency in ambulatory African-American male veterans participating in diabetes mellitus trial. A questionnaire validated for evaluation of vitamin D insufficiency risks in women was used. Serum 25-OHD levels were measured by a radioimmunoassay kit (DiaSorin Inc., Stillwater, MN, normal range 15-80 ng/ml). The data for 43 subjects were available for preliminary analysis. Age range was 53-80 years, (Mean ± SD 66.7 ±7.7 years); with 72% older than 60 and 23% older than 75 years. Body mass index (BMI) range was 23-38 kg/m^2 (Mean ± SD 29.0+3.5 kg/m^2). Serum 25-OHD levels were between 5 and 41 ng/ml (Mean ± SD 17.6±7.3 ng/ml); and 7%, 19%, 49%, and 67% of men had levels below 8, 10, 15, and 20 ng/ml, respectively. Only 27% of men consumed any food containing vitamin D (milk, eggs, salmon and sardines) more than 7 times a week or were taking vitamin D supplements; 55% of men considered themselves exercising more than 5 times a week, predominantly walking; 92% were walking outside but only 26% spent more than an hour per day outside; 75% of men considered their health to be good. None of the men had renal insufficiency. There was a correlation between vitamin D levels and amount of vitamin D containing food ($r=0.3$, $p<0.05$). Dietary vitamin D consumption was higher in men with 25-OHD levels above 20 ng/ml than in men with 25-OHD below 10 ng/ml ($p=0.08$). A similar trend was observed for the level of education ($p=0.09$). The preliminary data indicates that vitamin D insufficiency is highly prevalent in African-American male veterans. This prevalence appears to be higher than that reported for non-institutionalized African-American men of similar age from the NHANES III study described above. Similar to the findings in women, dietary vitamin D consumption and level of education appear to be important determinants of vitamin D status. Evaluation of vitamin D deficiency risks in African-American male veterans and correlation of these risks with clinically important outcomes including bone density requires more research.

Disclosures: ***E.I. Barengolts****, None.*

T14

Automated Immunoassays for 1,25-Dihydroxyvitamin D and 25-Hydroxyvitamin D on the LIAISON® Chemiluminescence Analyzer.

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There is growing recognition that vitamin D sufficiency is required for optimal health and that insufficiency is common even within apparently healthy populations. The importance of the vitamin D endocrine system in mineral homeostasis and bone metabolism, cardiovascular health in chronic kidney disease, neuromuscular function, and the prevention of certain cancers has been demonstrated. 25-hydroxyvitamin D (25(OH)D) is the most abundant form of vitamin D in circulation, and measurement of serum 25(OH)D is used to assess nutritional status. 1α,25-dihydroxyvitamin D ($1,25(OH)_2D$) is the active hormonal form of vitamin D, primarily formed from 25(OH)D in the kidney under tight regulation by calcium, phosphorus and parathyroid hormone. Therefore, it is desirable to have a means of measuring both 25(OH)D and $1,25(OH)_2D$ with excellent sensitivity and precision and with the convenience of an automated system.

The purpose of this work is to develop high-quality automated immunoassays for $1,25(OH)_2D$ and 25(OH)D on the LIAISON® Chemiluminescence Analyzer. The assay for $1,25(OH)_2D$ is an indirect, competitive assay that uses the same polyclonal antiserum as the DiaSorin $1,25(OH)_2D$ RIA, with an improved offline sample extraction procedure similar to that used with the RIA. The LIAISON $1,25(OH)_2D$ assay measures up to 200 pg/mL $1,25(OH)_2D$ with analytical sensitivity of 3 pg/mL and inter-assay precision ≤16%. The assay demonstrates good correlation to the DiaSorin RIA: (LIAISON) = 1.03*(RIA) + 10.9, R = 0.95.

We have also developed an improved assay for 25(OH)D on the LIAISON Chmiluminescence Analyzer. The antiserum used in the new

assay is the same as that used for the current LIAISON assay and in the DiaSorin RIA; this antiserum has equal recognition of both the D_3 and D_2 forms of vitamin D, but does not react with the inactive 3-epi form. In the LIAISON 25(OH)D assay, analyte binds to antibody on paramagnetic beads in competition with a chemiluminescent tracer. The method does not require any off-line extraction or pretreatment of samples. The range of the assay is 4-150 ng/mL (10-375 nmol/L). Time to first result is about 35 min and throughput is about 90 results per hour. Analytical sensitivity is <1 ng/mL and functional sensitivity (LoQ) is <5 ng/mL. Inter-assay precision, measured in quadruplicate over 5 runs, is <10% for values >10 ng/mL. Comparison of results to the DiaSorin RIA gives linear regression of LIAISON = 0.98*(RIA) + 1.24 ng/mL, R = 0.93.
In conclusion, these assays are convenient tools for measuring clinically important forms of vitamin D to aid in the diagnosis of vitamin D related conditions.

Disclosures: ***G.T. Olson****, None.*

T16

Vitamin D Deficiency in Obese vs. Non-obese African American Children: Response to 400 IU Vitamin D_3 Supplementation.

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Background: Evidence suggests that serum 25-hydroxyvitamin D [25(OH)D], the measure of vitamin D (vit D) status, is low in obese adults.
Objective: To examine the differences in serum 25(OH)D in obese (Body Mass Index [BMI]: > 95th percentile for age) vs. non-obese (BMI: = 5th -75th percentile for age) 6-10 year old African American children and compare the differences in their therapeutic response to vit D_3 400 IU daily for 1-month in winter.
Study design: Serum 25(OH)D, 1, 25-dihydroxyvitamin D [$1,25(OH)_2D$], parathyroid hormone (PTH), and markers of bone turnover (serum bone-specific alkaline phosphatase, osteocalcin and urine n-telopeptide crosslinked collagen type 1) were measured. Vit D deficiency was defined as serum 25(OH)D ≤20 ng/mL and insufficiency as: > 20 ng/mL serum 25(OH)D < 30 ng/mL.
Results: 21: obese [OB] and 20: non-obese [non-OB] subjects matched for age, sex, skin color and pubertal maturation were compared. Vit D deficiency occurred in 12/21 OB vs. 8/20 non-OB at baseline (p = 0.374) and persisted in 5/21 OB vs. 2/18 non-OB (p = 0.414) after treatment. There were differential effects for treatment response. The therapeutic response seemed to depend on the value of basal 25(OH)D. When the cohort was stratified into 3 groups based on basal 25(OH)D (1: ≤20 ng/mL, 2: >20 ng/mL to <30 ng/mL, 3: ≥30 ng/mL), the differences in the change of 25(OH)D with treatment was significant between any 2 groups for the non-OB and was significant only between groups 1 and 2, and 1 and 3, and not 2 and 3 for the obese (see Table).

25(OH)D ng/mL	Obese (N=21)		Non-obese (N=20)	
	Pre (mean ± SD)	Post (mean ± SD)	Pre (mean ± SD)	Post (mean ± SD)
≤20	*(n=12)* **15.67 ± 3.28**	*(n=12)* **23 ± 7.34*** α	*(n=8)* **15.13 ± 3.13**	*(n=8)* **22 ± 5.39*** α
>20-<30	*(n=5)* **25.2 ± 2.38**	*(n=5)* **31 ± 8.86**	*(n=5)* **25.4 ± 2.30**	*(n=5)* **28.2 ± 1.78** α
≥30	*(n=4)* **38 ± 7.34**	*(n=4)* **30 ± 5.9**	*(n=7)* **38.57 ± 6.29**	*(n=7)* **35.57 ± 2.87**

**: Groups significantly different (p ≤0.05)*
α: the difference in the rate of change of 25(OH)D significantly different between groups (p ≤0.05)

Conclusions: Vit D deficiency was common among OB and non-OB preadolescent African American children. Vit D_3 400 IU daily for 1-month was inadequate to raise blood levels of 25(OH)D to ≥30 ng/mL in vit D deficient OB and non-OB children. Obesity may play a role in the response to oral vit D_3 in African American children.

Disclosures: ***K. Rajakumar,*** *None.*

T18

Season-Related Serum Concentrations of 25-OH Vitamin D_3 in Healthy Subjects Measured by a Highly Specific 25-OH Vitamin D3 ELISA .

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It is well recognized that vitamin D and its metabolites are important for human bone metabolism system to prevent rickets from children and osteomalacia from adults through their effects on the maintenance of calcium homeostasis and bone remodelling. Among vitamin D metabolites, 25-hydroxy vitamin D (25OHD) is considered as a reliable indicator of the nutritional vitamin D status, but there is no consensus on the optimal serum level of 25OHD and the relative potency of the vitamin D2 and D3 forms. Because of this, it is necessary and important to have highly specific measurements to detect different form of 25OHD.
The objective of the present study was to evaluate the technical performance of a recently developed enzyme immunoassay for measurement of 25-hydroxy vitamin D_3 ($25OHD_3$) in serum, and to investigate the influence of gender, menopausal status, and the seasonal variation on the level of $25OHD_3$ in healthy subjects. Serum samples obtained from healthy subjects aged 40-59 yrs, males (*n*=48), premenopausal women (*n*=41), and postmenopausal (*n*=39) were measured in the 25-OH Vitamin D3 ELISA (Nordic Bioscience A/S).
The 25-OH Vitamin D3 ELISA based on a polyclonal antibody was highly specific for $25OHD_3$ having less than 0.7% cross-rectivity towards $25OHD_2$ and 5-7% cross-reactivities towards $24,25(OH)_2D_3$ and $25,26(OH)_2D_3$. The detection limit of the assay was determined to 5 nmol/L, and intra- and interassay imprecision was <9% and <15%, respectively. Excellent agreement was observed between concentrations measured by the ELISA and by HPLC as assessed through the Vitamin D External Quality Assessment Scheme (DEQAS, UK) with mean values of 96% in the ELISA relative to HPLC, r = 0.93; n=20. Comparable serum levels of $25OHD_3$ were found in males (64 nmol/L), premenopausal women (69 nmol/L), and postmenopausal women (67 nmol/L). A marked seasonal variation in $25OHD_3$ concentration was observed with the mean value of 61 nmol/L in the samples obtained during November - April (n=84), as compared with the mean of 79 nmol/L in the samples obtained during August - October (n=44) (p<0.0001; t-test). The 30% higher values found in the samples from late summer can be explained by the synthesis of vitamin D in skin in response to exposure to ultraviolet light during summer, and lack of sunshine during the long winter in this area.
In summary, the clinical data with the seasonal variations and the data of technical performances support that the recently developed 25-OH Vitamin D3 ELISA provides a highly specific, accurate, and precise method for measurement of $25OHD_3$. The assay could be used as a reliable measure of the nutritional vitamin D_3 status in humans.

Disclosures: ***B. Li****, Bo Li 3; Per Qvist 3; Claus Christiansen 4; Inger Byrjalsen 3.*

T20

Vitamin D in Postmenopausal Women.

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Osteoporosis incidence increase in women after menopause. That can be prevented with oestrogens, but this treatment is associated with an increment of endometrium cancer risk that can persist in spite of combining its use with progestins. The problem include alternative methods as vitamin D. Bioactive vitamin D or calcitriol is a steroid hormone that has long been known for its important role in regulating body levels of calcium and phosphorus, and in mineralization of bone Objetive: to value the level of vitamin D in the menopausal women with osteoporosis. Material and method: on 150 women with osteoporosis we have studied the level o of 25OHD3. The women, who were 47 to 72 years old at base line, were within 3 and 18 years of menopause, and had bone mineral lumbar density at the spine between 150 mg/cc and 50 mg/cc measured by the QBMAP system with a spiral CT Picker PQ-s densitometer at L2, L3, L4 and L5. Results: in 98 % of all women the 25OHD3 level was below the normal level. Conclusions: approach of the osteoporosis in postmenopausal women would have to include determination of 25OHD3 and its suitable ingestion.

Disclosures: ***A. Bazarra-Fernandez,*** *None.*

T22

Risk Factors for Vitamin D Deficiency in Otherwise Healthy Children in the U.S.

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Hypovitaminosis D is a state of suboptimal vitamin D stores, as measured by the serum concentration of 25-hydroxyvitamin D [25(OH)D]. Prior studies have not examined vitamin D status in a multi-ethnic sample of U.S. children across a broad age range. To determine the prevalence of hypovitaminosis D and more severe deficits of 25(OH)D in children, as well as the factors associated with hypovitaminosis D, we measured 25(OH)D concentrations in 382 healthy children, ages 6 to 21 years of age, living in the northeastern U.S. Dietary vitamin D intake was assessed by three 24-hour recall interviews, and supplemental intake was assessed by interview. Sociodemographic information was elcited by questionnaire. Serum 25(OH)D was analyzed by ^{125}I-labeled radioimmunoassay (DiaSorin, Inc, Stillwater, MN). 1,25 dihydroxyvitamin D [1,25$(OH)_2$D] concentrations were determined by radioreceptor assay preceded by extraction and chromatography. Intact PTH concentrations were measured with the Nichols chemiluminescence assay. Correlation and logistic regression analyses were used to identify bivariate relationships between vitamin D status and related factors. The final model used multivariable ordinal logistic regression to determine the factors associated with decreased 25(OH)D. The median serum concentration of 25(OH)D was 28 ng/mL (interquartile range, 19 - 35 ng/mL). Fifty-five percent of subjects had hypovitaminosis D [25(OH)D <30 ng/mL]. 25(OH)D concentrations were inversely correlated with PTH concentrations but not correlated with 1,25$(OH)_2$D concentrations. Poor vitamin D status was more likely to occur in study participants who were: older, Black, members of households with lower annual incomes, members of households with lower caregiver education levels, evaluated during winter months, and had higher BMIZ. Poor vitamin D status was also associated with lower dietary, supplemental, and total daily intake of vitamin D. In the multivariable model, older age (P<0.001), Black race (odds ratio [OR] 14.2, 95% confidence interval [CI] 8.53 - 23.5), a study visit during winter (OR 3.55, 95% CI 2.29 - 5.50), and total daily vitamin D intake ≥200 IU (OR 0.63, 95% CI 0.41 - 0.98) were associated hypovitaminosis D. These results demonstrate that hypovitaminosis D is prevalent among otherwise healthy children in the northeastern U.S. and is related to race, vitamin D intake and season.

Disclosures: ***B.S. Zemel****, Quest Nichols Research Institue 2.*

T24

Is Skin Colour a Suitable Predictor for Estimating Vitamin D Status?

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The influence of sunlight exposure on Vitamin D status is an intriguing and complex question. Recent research suggests that latitude of residence is a major factor when estimating the potential for Vitamin D synthesis. Indeed, latitude strongly impacts the amount of UV radiation, however, an individual's characteristics, such as skin type may also contribute to the potential to synthesize Vitamin D, even in a sunny climate.

The aim of this research was to investigate the relationship between skin colour and the Vitamin D status of healthy adults in South East Queensland, Australia (27°S). A sample of blood was collected to assess 25(OH)D status. Subjective skin colour was recorded as well as objectively determined using a Minolta reflectance spectrophotometer that recorded spectral skin reflectance along with L*A*B measures of skin colour. Measurements occurred on the dorsum of the hand, forehead and upper inner arm and from these melanin density was calculated. This research was approved by Queensland University of Technology Human Research Ethics Committee and conducted under the guidelines of the Declaration of Helsinki.

126 people (40 males / 86 females) with a mean age 42 ± 21 years participated in this cross-sectional survey. 45% described themselves as having a fair complexion, 34% medium and 21% an olive/dark complexion. There were only 23% of the sample with an adequate Vitamin D (blood serum 25[OH]D) level, and 43% were Vitamin D deficient. There was a statistically significant association (p=0.019) between Vitamin D sufficiency/insufficiency and the melanin density of a high UV exposure site of the forehead (mean (SD) 2.60 (1.12) vs 3.17 (1.14)). However, no association was found between Vitamin D status and self-reported skin colour, or the melanin density on the dorsum of the hand (mean 3.90, SD, 0.72) which is a high UV exposure site, or the upper inner arm (mean 3.29, SD, 1.11), a low UV exposure site.

Our results indicate that this measure of skin colour may be a simple, non-invasive indicator for Vitamin D status. Further research is required into the interactions between the solar UV environment and Vitamin D synthesis, particular with respect to how skin colour may be a suitable predictor for Vitamin D status.

Disclosures: ***C.A. Lang****, None.*

Vitamin D Physiology II

T26

ASBMR YOUNG INVESTIGATOR AWARD
Markedly Elevated 25-OH Vitamin D Levels with No Associated Symptoms of Hypervitaminosis D Following Bariatric Surgery.

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The number of bariatric surgeries for morbid obesity is rapidly growing. These surgeries cause large amounts of weight loss by restrictive and malabsoprtive mechanisms. The rapid weight loss seen with these surgeries is associated with the development of deficiencies of fat soluble vitamins including vitamin D. Vitamin D and calcium deficiency in addition to elevated parathyroid hormone levels are common following these surgeries. The case below illustrates a patient with an anomalous response following bariatric surgery, markedly elevated levels of circulating 25-OH vitamin D following bariatric surgery.

FM is a 42 yo man with a history of morbid obesity who underwent a sleeve gastrectomy in 5/02 and a second stage gastric bypass in 7/05. His preoperative weight was 404 lbs. Intraoperatively a liver biopsy confirmed the presence of nonalcoholic fatty liver disease. There was 20% steatosis and no significant inflammation. In 10/05 he was first noted to have a markedly elevated 25-OH Vitamin D level of 162 ng/mL on no supplemental vitamin D. He has no history of hypercalcemia, fractures or kidney stones and no intake of supplements containing vitamin D. His sun exposure was less than 15 minutes/ week although he has spent his life in the Dominican Republic. His fish consumption is limited to one serving of red snapper per week. He does not consume mackerel, codfish or salmon. He had no symptoms of vitamin D toxicity including hypercalcemia, dehydration, irritability, vomiting, anorexia, fatigue, constipation, polyuria or polydipsia.

Relevant metabolic bone parameters are below:

Date	10/05	1/06	2/06	5/06
BMI(kg/m^2)	43.5	41.0		39.6
Calcium (8.5-10.1 mg/dL)		8.9	8.9	9.2
Albumin (3.0-5.0 g/dL)		3.6	3.9	3.8
Magnesium (1.7-2.4 mEq/L)		1.8	1.8	1.5
Phosphorus (2.5-4.5 mg/dL)		3.0	4.2	4.1
PTH-intact (9-44 pg/mL)		38	23	31
25-OHVitD (9-54 ng/mL)	162	218	177	154
1,25-OHVitD (15-75 pg/mL)		75		64
Alk phos (25-95 U/L)		73		60
Urine N-tx (nMBCE/mMCr)		87		52
24 hr urineCa (60-200 mg/dL)			499	232

A renal sonogram in 3/06 revealed microlithiasis in the bladder. A bone density revealed normal density at hip and spine. A Vitamin D level measured by HPLC confirmed an elevated D3 of >140 ng/mL. A restricted calcium diet of 1000 mg/day resulted in a reduction in hypercalciuria to 232 mg/day. This case illustrates markedly elevated levels of circulating 25-OH vitamin D following bariatric surgery. It raises the concern for rapid mobilization of vitamin D stores secondary to rapid fat loss or possible abnormalities in hepatic vitamin D-25-hydroxylase secondary to nonalcoholic fatty liver disease.

Disclosures: ***N. Sinha****, None.*

T28

Effects of Vitamin D Status on Osteoblast Differentiation in Human Marrow Stromal Cell Cultures: Preliminary Results.

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There is a worldwide pandemic of vitamin D-deficiency, which is associated with reduced bone strength, skeletal fragility, and fractures. We found variable responses of human marrow stromal cells (hMSCs) to $1,25D_3$. In a study with a similar pool of subjects, we found that 46% had serum 25-hydroxy-vitamin D (25OHD) levels below 20 ng/ml and only 13% were sufficient (>32 ng/ml) [J Bone Joint Surg 85A: 2371, 2003].

This study tests the hypotheses that vitamin D status of the subject *in vivo* influences *in vitro* marrow response to $1,25D_3$. Marrow was obtained as discarded tissue during orthopedic surgery. A set of subjects was enrolled and consented to provide blood for 25-hydroxyvitamin D (25OHD) measurement. Undifferentiated, low-density cells were separated by Ficoll Histopaque 1077 and adherence; hMSCs were cultured in αMEM, 1% FBS, and osteogenic supplements (10 nM dexamethasone, 5 mM β-glycerophosphate, 170 μM ascorbic phosphate). For some experiments, STRO-1$^+$ cells were isolated from the low-density preparations by magnetic selection; STRO-1$^+$ cells were cultured in gelatin-coated Terasaki plates at 10 cells/well in Iscove's medium supplemented with 1% BSA, 10 μg/ml insulin, 200 μg/ml transferrin, 0.1 mM 2-mercaptoethanol, 40 μg/ml low-density lipoproteins, GP&S, 20 ng/ml heparin sulfate, 10 nM dexamethasone, 10 ng/ml EGF and 10 ng/ml PDGF-BB. Alkaline phosphatase (AlkP), an index of osteoblast differentiation, was measured colorimetrically for activity or immunocytochemically for protein.

Dose-response studies showed that $1,25D_3$ stimulated AlkP activity in 7/10 samples from elders, with peak stimulation between 1 and 10 nM $1,25D_3$, but with different magnitudes (8-158%). Responsiveness of AlkP to 10 nM $1,25D_3$ was measured for a set of 10 different subjects with known 25OHD levels. All but one were significantly stimulated. Osteoblast differentiation was stimulated to a greater degree by $1,25D_3$ in hMSCs from 3 subjects with 25OHD < 25 ng/mL (2.4-fold ± 0.8) than in hMSCs from 7 subjects with 25OHD > 25 ng/mL (1.6 ± 0.3; p=0.048 by t-test; p=0.087 by Mann-Whitney test). In parallel experiments with STRO-1$^+$ low-density marrow cells cultured in miniwells at 10 cells/well, $1,25D_3$ increased AlkP immunoreactivity in cells from subjects with 25OHD < 25 ng/mL, but had no effect on cells from subjects with 25OHD > 25 ng/mL. These preliminary data indicate greater stimulation of osteoblast differentiation by $1,25D_3$ in cells from vitamin D-deficient elders. This may mean that repletion of vitamin D-deficient subjects may lead to more vigorous bone formation.

Disclosures: ***J. Glowacki****, None.*

T30

UVB Therapy Increases 25(OH) Vitamin D Syntheses in Postmenopausal Women with Psoriasis.

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Vitamin D3 is produced in epidermis by ultraviolet radiation (295-315 nm) of 7-dehydrocholesterol. The similar range 290-320 nm (broadband UVB) has been successfully used for years to treat psoriasis and other inflammatory skin disorders. The aim of the study was to examine if UVB therapy could influence D-vitamin production in the skin in psoriasis patients. 24 postmenopausal, Caucasian women, age 68.8 ±5.9 (SD) with active psoriasis were treated with broadband UVB 2-3 times/week during 8-12 weeks (mean number of treatments 23.3±5.5). The serum concentrations of calcidiol (25-hydroxyvitamin D [25(OH)D]), calcitriol (1,25-dihydroxyvitamin D [1,25(OH)2D]), intact parathyroid hormone (PTH), thyroid hormones, osteocalcin, calcium and creatinine were measured before the first, and 2 days after the last dose of radiation. All patients performed a DEXA (Dual-Energy X-ray Absorptiometry, Hologic Delphi A) at the hip and the lumbar spine after the study.

Mean serum levels of 25(OH) D before the UVB treatment was 36.6±16.7 ng/ml and after treatment 58.4±18.8 ng/ml ($p<0.001$). Serum PTH decreased from 62.8±25.7 ng/l to 48.2±17.4 ng/l ($p<0.001$). Secondary hyperparathyroidism (PTH>65ng/l) was found in 7 patients before treatment. PTH values were normalized by UVB treatment. The serum levels of calcitriol, calcium, osteocalcin, thyroid hormones and creatinine were unaltered. Mean value of Z score at the hip was +0.64 SD (±1.17) and at the lumbar spine +0.69 SD (±1.44). Mean T score at the hip was -0.79 SD (±1.28) and at the lumbar spine -1.27 SD (±1.51).

In conclusion, UVB therapy healed psoriasis, increased serum 25(OH) vitamin D and decreased serum PTH which may be beneficial for bone status.

Disclosures: ***A. Osmancevic****, None.*

T32

A Single Amino Acid Substitution Converts Human CYP24 from a 24-Hydroxylase into a 23-Hydroxylase Which Synthesizes the VDR Antagonist, 1,25-$(OH)_2D_3$-Lactone.

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It is well known that CYP24 from different species will catalyze either 24-hydroxylation or 23-hydroxylation of 1,25-$(OH)_2D_3$ to give the biliary excretory compound, calcitroic acid or the VDR antagonist, 1,25-$(OH)_2D_3$-26,23-lactone, respectively. We set out to identify the molecular determinants of the 23- and 24-hydroxylase activities in order to begin to understand the physiological roles of their major products. We compared CYP24 sequences from 16 species at the same time as measuring target cell hydroxylation activity in representative cell lines from the same species. We found that human CYP24 (in HPK1A-ras) predominantly 24-hydroxylates vitamin D substrates while a species such as opossum CYP24 (OK) 23-hydroxylates its vitamin D substrates. When we compared the amino acid sequences of human and opossum CYP24, we found 30 amino acid differences, most of which were expected to have minimal effect upon enzyme activity based upon a novel CYP24 homology model. We focused on three differences around the substrate binding domain of potential importance in determining 24- or 23-hydroxylase activity, namely residues Ala326, Asn448 and Gln471. Using site-directed mutagenesis, we substituted amino acids found in the 23-hydroxylating opossum CYP24 homolog to give three human CYP24 mutants with Ala326Gly, Asn448His or Gln471His. Mutant and wild-type human CYP24s were transiently transfected into Chinese hamster lung cells, V79, devoid of endogenous CYP24, and side chain hydroxylating activity was assessed by HPLC and LC-MS/MS methodology. We found that wild-type hCYP24 and mutants with Asn448His or Gln471His continued to primarily hydroxylate at C-24, while hCYP24 with a single substitution of Ala326Gly dramatically changed the hydroxylation site to C-23 with the predominant enzymatic products being 1,23,25-$(OH)_3D_3$ and 1,25-$(OH)_2D_3$-26,23-lactone, the pattern observed in opossum cells. We conclude that Ala326 is an important determinant of the docking of the vitamin D side chain and from modeling studies that Ala326Gly permits the side chain to occupy a deeper orientation thereby allowing preferred 23-hydroxylation of substrate. These studies also validate the current CYP24 model and allow us to more accurately design clinically-important CYP24 inhibitors. We hypothesize that 23-hydroxylating CYP24s allow certain species which have high vitamin D or calcium intakes to not only catabolize 1,25-$(OH)_2D_3$ but also antagonize the action of 1,25-$(OH)_2D_3$ at the level of the VDR; whereas 24-hydroxylating CYP24s, such as the human form are designed only to detoxify the hormonal form to biliary products.

Disclosures: ***D.E. Prosser****, None.*

Traditional Abnormalities of Vitamin D

T34

ASBMR YOUNG INVESTIGATOR AWARD
Bone Mineralization Correlates with Vitamin D Status in the Vitamin D Insufficient Range in Newborns.

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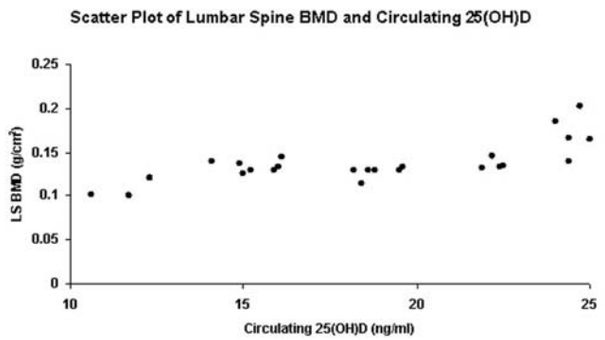
Background: Vitamin D deficiency rickets occurs when circulating 25-hydroxyvitamin D (25OHD) levels fall below 8-10 ng/ml. In adult studies, circulating 25OHD levels in the range 10-25 ng/ml denote vitamin D **insufficiency** and have a positive linear correlation with bone mineralization. The aim of this study was to evaluate in infants the relationship of circulating 25OHD levels 10-25 ng/ml and bone mineralization.
Methods: A cohort of neonates, enrolled in either a study of vitamin D supplementation in pregnancy or vitamin D supplementation during lactation, had 25OHD levels obtained from cord blood or venous sampling in the first 4 weeks after delivery measured by radioimmunoassay. Bone mineral content (BMC) (g) and bone mineral density (BMD) (g/cm^2) of the lumbar spine (LS) and right femur were measured by dual energy x-ray (DEXA) scan (Hologic Discovery A) at 2-4 weeks after delivery. An evaluation of the relationship between circulating 25OHD level and BMC and BMD of the 2 skeletal sites by Pearson's correlation was undertaken in a subset of infants with circulating 25OHD in the range of 10-25 ng/ml.
Results: Fifty-two infants had circulating 25OHD measurements and DEXA scans performed. Twenty-five of these infants had circulating 25OHD in the range of 10-25 ng/ml. For these 25 infants, LS BMC and BMD and right femur BMC and BMD had significant linear correlation with circulating 25(OH)D (**table**). The scatter plot of LS BMD and 25OHD is presented (**graph**).

Correlation of Vitamin D Insufficiency (10-25 ng/ml) and Bone Mineralization in Neonates

	Correlation Coefficient (r)	P-value
LS BMC	0.65	0.0005*
LS BMD	0.72	<0.0001*
Right Femur BMC	0.42	0.04*
Right Femur BMD	0.48	0.01*

* signifies significant p-value.



Conclusion: In the range of 10-25 ng/ml, circulating 25OHD is positively associated with bone mineralization in neonates. The goal of vitamin D intake should go beyond the prevention of rickets to the optimization of bone mineralization. Further study to define 1) the circulating 25OHD level that sustains optimal bone mineralization, and 2) the vitamin D dose required for all infants to achieve this 25OHD status is warranted.

Disclosures: ***S.N. Taylor,*** *None.*

T36

ASBMR YOUNG INVESTIGATOR AWARD - PLENARY POSTER
The Association of Vitamin 25OHD and Inflammation with the 6-Minute Walk and Frailty in Patients with Heart Failure.

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Older heart failure (HF) patients are at increased risk for frailty and decline in exercise capacity. Contributing factors to physical decline in HF patients are poorly understood. This cross-sectional study examines the hormones affecting muscle function and markers of inflammation in the context of aerobic capacity and frailty. The purpose of the study was to identify relationships of these hormones/ inflammatory markers with physical function.
The 6-Minute Walk Distance (6MW) and Frailty Phenotype (FP) (composite score of weight loss, grip strength, physical activity, reported exhaustion, and walk time) were measured in HF patients with and EF of ≤40%. The relationship of physical measures to hormonal levels included testosterone, DHEA, cortisol, 25OHD, PTH, and BNP as well as inflammatory markers CRP and IL6. Linear and ordinal logistic regression analysis was performed for the physical measures. Assessment of appendicular skeletal muscle mass was measured by dual-energy x-ray absorptiometry.
Sixty (43 m, age 77± 9 and 17 w, age 78±12) participated. NYHA class I, 1% (n=1); class II, 57% (n=34); class III, 37% (n= 22); class IV, 5% (n=3). The mean EF was 29±8. The frailty phenotype criteria 28.3% were not frail, 20.0% had 1/5 frailty characteristic. 25.0% had 2/5 frailty characteristics, and 25.0% had 3-5/5 characteristics. Mean 6MW was 308.7 ± 120.6 meters. Longer 6MW was correlated with a higher vitamin 25OHD level, and a shorter walk was correlated with higher cortisol/DHEA, CRP, IL6 and PTH, (each $p < 0.05$). Percent free testosterone, DHEA, and BNP did not correlate with the 6MW. The higher FP score (more frail) was correlated with higher CRP, higher IL6 and lower 25OHD levels (each $p < 0.05$).). Linear regression with the 6- minute walk distance as the dependant variable revealed age, male sex, vitamin D and CRP to be significant (R^2 = 53.5%). Ordinal logistic regression with the FP and hormonal levels revealed that age, vitamin 25OHD, and CRP also predicted frailty status. There was no correlation between appendicular skeletal muscle mass and any of the hormonal or inflammatory measures.
Vitamin 25OHD and CRP may be important factors in aerobic capacity and frailty in patients with HF. Longitudinal study is needed to further define the role of 25OHD and CRP on muscle health, and their role in functional decline.

Disclosures: ***R.S. Boxer,*** *None.*

Vitamin D and Population Health II

T38

ASBMR YOUNG INVESTIGATOR AWARD - PLENARY POSTER

A Randomized Comparison of Increase in Serum 25-Hydroxyvitamin D after Oral Intake of 10 µg Vitamin D3 from Multivitamin Tablets or Fish Oil Capsules in Healthy Young Adults.

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Many types of vitamin supplements are available on the market, but little is known about whether vitamin D3 obtained from fat-containing capsules differs in bioavailability from that of solid tablets. We performed a randomized trial in order to compare two common vitamin D supplements. Our objective was to test whether four weeks of daily supplementation with 10 µg vitamin D3 given as a fish oil capsule produces a larger increase in serum 25-hydroxyvitamin D levels compared with the same dose of vitamin D3 given as a multivitamin tablet.

A total of 55 healthy subjects aged 19-48 yr (mean 28.5 yr) completed the study during late winter 2005. After completing a self-administered questionnaire about diet and sun exposure and having a non-fasting venous blood sample drawn, participants were randomized to receive either multivitamin tablets of type Vitaplex ABCD, or fish oil capsules. A second blood sample was drawn after 28 days of supplementation. The vitamin D3 content of both supplements was assessed by an independent laboratory; mean (SD) 9.79 (1.51) µg and 9.99 (0.23) µg, respectively. Statistical analysis was performed using linear regression analysis with change in serum 25-hydroxyvitamin D as the dependent variable and intervention supplement as the independent variable, adjusted for serum 25-hydroxyvitamin D at baseline.

In the total sample, mean (95% CI) serum 25-hydroxyvitamin D was 44.3 (38.0, 50.7) nmol/l at baseline, and it increased by 34.1 (30.5, 37.6) nmol/l during the intervention. The increase in serum 25-hydroxyvitamin D was not significantly different between the two groups (p=0.33).

We conclude that fish oil capsules and multivitamin tablets containing 10 µg vitamin D3 produced a similar increase in serum 25-hydroxyvitamin D levels over a 4-week period.

Disclosures: ***K. Holvik****, None.*

T40

Global Serum 25-Hydroxy-Vitamin D Levels: A Meta-analysis.

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Aim: To study the levels of serum 25-hydroxy-vitamin D (25OHD) in native subjects in all countries of the world to assess if the serum levels varied by latitude.

Subjects and methods: A search was performed of the PubMed, Embase, and Web of Science using the search term: serum vitamin D. The search spanned the time interval January 1, 1970 to November 1, 2004 and resulted in 5,855 papers. Abstracts of all papers were screened and papers judged to be of interest were retrieved for further appraisal. Inclusion criteria were papers reporting original cross-sectional data on serum 25OHD levels in subjects who were native inhabitants of the area where the measurements were performed, i.e. immigrants were excluded. A meta-regression was performed.

Results: A total of 433 studies including 110,528 subjects from all over the world were included in the study. The mean serum 25OHD level was 54 nmol/l (SEM 1.3 nmol/l, 95% confidence intervals for the mean 51-57 nmol/l). The 25OHD levels tended to be log-normally distributed. Unadjusted, there was a trend towards lower serum 25OHD with increasing latitude (Fig 1, $p<0.05$) with large variations in mean values. The meta-regression showed that women tended to have a little higher mean serum 25OHD (56±1.6 nmol/l) than men (49±2.4 nmol/l, $p < 0.01$). People with white skin had significantly higher serum 25OHD levels than people with black skin (on average 29.6±7.2 nmol/l higher in white than in black subjects, $p<0.05$). However, there was a trend towards an interaction ($p=0.07$) between skin colour and latitude because in most areas except USA, people with different skin colour lived in different areas. The change in serum 25OHD levels with latitude was similar in people with white and black skin. There was a significant decrease in 25-OHD levels with age ($p< 0.01$) Subjects older than 65 years of age had a mean serum 25OHD level of 37±5.7 nmol/l compared with 56±1.7 nmol/l in subjects aged 15-64 years and 53±2.1 nmol/l in subjects <15 years. Upon adjustment for these factors, serum 25OHD did not depend on latitude ($p=0.23$ for latitude). *Conclusion:* Age and skin colour are major determinants for serum 25OHD levels. Upon adjustment for confounders no change in serum 25OHD was present with latitude. This may mean that the dressed human race has a "set point" for serum 25OHD at around 50 nmol/l, and that genetic and environmental factors, life-style and supplementation and fortification policy tend to maintain serum 25OHD levels at a certain level around the globe.

Disclosures: ***L. Mosekilde****, None.*

T42

Supplementation with 800 IU of Vitamin D3 Is Insufficient for Achievement of Vitamin D Adequacy in Elderly Hip Fracture Patients.

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Hip fracture rate increases yearly by 1-3% in the developed countries. Improvement of vitamin D status decreases hip fracture risk by 30%, bisphosphonates should be given to vitamin D replenished patients. Currently used vitamin D supplementation in the community in Israel ranges between 200 - 800 IU/day. Physicians often fear to use higher doses or other therapeutic regimens.

The purpose of this study was to assess the effect of 800 IU/day vitamin D_3 supplementation on vitamin D status and plasma PTH in elderly participants of Post-Surgical Treatment Program (PSTP), and long term adherence to this regimen

122 consecutive elderly patients after surgical hip fracture correction, aged 72.7±9.46; 32 (26.2%) men, 90 (73.8%) women, were enrolled in PSTP for 24 months. Laboratory evaluation (intact PTH, $25(OH)D_3$ and routine biochemical tests) was performed at baseline and during quarterly visits to the Metabolic Bone Diseases Clinic. All the patients received daily supplementation with 1500 mg of calcium carbonate and 800 IU of vitamin D.

Baseline $25(OH)D_3$ concentration was 2.4-20.7 ng/ml, mean 15.14±18.58: in 40 patients(pts): (32.8%) < 10; in 32 (26.2%) between10- 15.9 ; in 46 (38.5%) between 16- 29.9; in 4 (2.5%) > 30

ng/ml. Seventy six pts (62%) dropped out from the PSTP: at 6 mo 15 (38%) of pts with baseline $25(OH)D_3$ level < 10 ng/ml; 9 (28%) of pts with $25(OH)D_3$ 10-15; 8 (17%) of pts with baseline $25(OH)D_3$ level 15-30. Drop out at 12 mo: 24 (60%) pts with baseline $25(OH)D_3$ level < 10 ng/ml; 18 (56%) of pts with $25(OH)D_3$ 10-15; 26 (56%)of pts with baseline $25(OH)D_3$ level of 15-30.

Vitamin D concentration of 15-30 ng/ml at 6 mo had 8 (20%) pts with baseline $25(OH)D_3$ level < 10 ng/ml; 11 (34%) of pts with $25(OH)D_3$ 10-15; 23 (50%) of pts with baseline level of 15-30. Vitamin D concentration of 15-30 ng/ml at 12 mo had 11(28%) pts with baseline $25(OH)D_3$ level < 10 ng/ml; 13 (40%) pts with $25(OH)D_3$ 10-15; 15 (32%) of pts with baseline level of 15-30.

Pts with lowest $25(OH)D_3$ level had highest PTH, p= 0.042: $25(OH)D_3$ <10, mean PTH 48.5±29.8, $25(OH)D_3$ 16-30- mean PTH 36.38±16.58. Thirty four (27.8%) pts reached vitamin D level of 25 ng/ml at13.45±4.9 months.

Conclusion: The majority of elderly hip fracture patients had inadequate $25(OH)D_3$ serum levels and had not achieved adequate vitamin D status with daily vitamin D supplementation of 800 IU during a 24 month follow up period. Supplementation strategies using a periodic single high dose of vitamin D might be more appropriate and should be considered in these patients.

Disclosures: ***E. Segal****, None.*

T44

ASBMR YOUNG INVESTIGATOR AWARD
Vitamin D Deficiency in Traumatic Spinal Cord Injury: Seasonal and Geographic Comparisons.

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Osteoporosis is observed in the majority of patients who have experienced traumatic spinal cord injury (SCI). Vitamin D deficiency can raise the likelihood of osteoporosis and heighten its severity. The first objective of this study was to compare rates of vitamin D deficiency during winter months in different geographic latitudes for subjects with motor complete spinal cord injury (SCI). A second purpose was to explore seasonal and racial differences in vitamin D deficiency in similar SCI subjects living within the same geographic region.

A convenience sample design was chosen. All participants were ages 20-54 and gave informed consent. The study was approved by the institutional review boards of two major teaching hospitals.

Eighteen subjects in Alabama with motor complete SCI for minimum of 12 months (chronic) were tested for levels of 25-hydroxy vitamin D; 1,25-dihydroxy vitamin D, and parathyroid hormone during winter and were compared with 11 subjects with comparable injuries living in Chicago. These same markers, obtained in chronic SCI subjects from Alabama, were compared with 5 recently injured subjects during winter in Alabama. Next, 18 different chronically injured SCI patients during summer months in Alabama were compared to the previously described group from Chicago, obtained in winter. Differences between 18 chronic and 18 acutely-injured subjects during summer in Alabama were evaluated. Racial differences were examined within the same season and geographic location.

Results demonstrate significant differences in serum vitamin D-25 (OH) levels for winter chronic SCI subjects living in Alabama versus Chicago (p=0.02) and between winter chronic SCI subjects in Chicago and summer chronic subjects in Alabama (p=0.006). Significance was found between winter Caucasians and winter African-American subjects in chronic subjects only (p=0.039), and between chronic and acute subjects combined (p=0.036). Within Alabama, differences in summer Caucasian and African-American subjects approached significance (p=0.058).

Based on a desired minimum of 32 ng/ml for serum D-25 (OH) levels, we conclude that vitamin D deficiency is highly prevalent in spinal cord injury. Deficiencies are found in 100% of Chicago subjects in winter; 94% of chronic and 80% of acute patients living in Alabama in winter; 67% of chronic SCI subjects in Alabama in summer, and 53% of acute SCI subjects in Alabama in summer. Periodic surveillance of Vitamin D-25 (OH) during the first year post-injury is advisable, since early identification and treatment may prevent further losses. African-American SCI patients may be at particularly high risk of vitamin D deficiency.

Disclosures: ***C.V. Oleson****, None.*

T46

Importance of Vitamin D in the Design of Hospital Hip Fracture Care Pathways.

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Hip fractures are associated with significant morbidity and mortality, yet fewer than 30% of hip fracture patients worldwide receive osteoporosis evaluation and treatment. We had previously found that only 10% of hip fracture patients admitted to our hospital were vitamin D-sufficient [25-hydroxyvitamin D (25OHD) >32 ng/mL]. That motivated us to design, implement, and evaluate multidisciplinary, [hospital care pathways to improve vitamin D status and osteoporosis care, including computer-assisted admission and discharge components. The BWH Discharge Pathway was implemented in 2003; the Admission Pathway, in 2004 and amended in 2005. The Admission Pathway prompts the orthopedic housestaff surgeon to start daily calcium carbonate (600 mg elemental calcium/200 IU cholecalciferol, bid) and multivitamin (with 400 IU cholecalciferol), to obtain levels of serum calcium, albumin, and 25OHD (DiaSorin radioimmunoassay), and to order Endocrinology consult. The amended Admission Pathway includes administration of a single dose of ergocalciferol (50,000 IU) upon admission. The Discharge Pathway prompts the surgeon to prescribe daily calcium carbonate with vitamin D (500 mg elemental calcium/50 IU cholecalciferol, bid), additional vitamin D (400 IU cholecalciferol), a multivitamin (containing 400 IU cholecalciferol), and outpatient osteoporosis evaluation. For assessment of pathway effectiveness, we reviewed the medical records of two cohorts [from August through December in 2004 (n=57), and likewise in 2005 (n=41)] of consecutive patients ≥50 years of age who were admitted with a fragility hip or femur fracture. Effectiveness of Admission Pathway was defined as measurement of serum 25OHD during the hospital admission and effectiveness of Discharge Pathway, as a discharge prescription for calcium/vitamin D.

In adherence with the Admission Pathway, serum 25OHD was measured in 37% (36/98). Of those, 78% were vitamin D-insufficient (25OHD ≤32 ng/mL) and 58% were vitamin D-deficient (25OHD ≤20 ng/mL). As instructed by the 2005 amendment, 29% (12/41) received 50,000 IU ergocalciferol on admission. In adherence with the Discharge Pathway, 74% were discharged on calcium and vitamin D. The BWH Hip Fracture Discharge Pathway was older and was more effective than the newer Admission Pathway (p<0.001). The high prevalence of vitamin D insufficiency observed in this study corresponds with prior reports and reaffirms the importance of incorporating vitamin D recommendations in fracture care pathways. According to our ongoing analysis to increase effectiveness, computer reminders, multidisciplinary teams, and retraining are necessary to advance the care of fracture patients.

Disclosures: ***J. Glowacki****, None.*

T48

Rickets Identified among Children in Oakland, California: A Chart Review.

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Since rickets has been observed recently among children living in the United States, we undertook a review of all charts of children seen at our hospital between January, 2001, and July, 2006, to identify the incidence of rickets in our population and to summarize demographic, physical, and biochemical characteristics of the cases.
All charts with relevant diagnosis codes were pulled and reviewed using a systematic data collection form. Any questions regarding the interpretation of the clinical information were reviewed by the endocrinologist (SB). Care was taken to ensure confidentiality and the project was approved by the institutional review board at our hospital.
A total of 59 infants and children were treated for vitamin D deficient rickets during the 5.5 year period. Of the 59 cases, 66% identified as African-American or of African descent, 8% Latino, and 5 % either South Asian or Middle Eastern. Of those with information about infant feeding practice (42/59) 90% were breast-fed. Two thirds of the cases were identified in the winter and spring months (December-May) in our area. The age of onset was reported for 56 cases. Of those cases 29% were identified during the first six months of life; most presenting with hypocalcemic seizures, whereas those presenting after six months of age usually came to attention due to bony deformities. The laboratory values confirmed the diagnosis of vitamin D deficiency with serum 25-OH vitamin D less than 20 ng/ml (50 nmol/L) in practically all the cases (93%). Other biochemical characteristics included elevated alkaline phosphatase, intact parathyroid hormone, and 1,25-OH vitamin D as well as reductions in total and ionized calcium.
Vitamin D deficiency causing rickets is prevalent in the population served at our hospital at a rate of 59 cases in the past 5.5 years. The data show higher risk in African American and breast fed babies. We suspect that the children coming to attention were the most severe cases, but that many more cases escape detection. Marginal vitamin D deficiency has long term health consequences in developing children and in adults, including under-mineralization of bone. Extra-skeletal effects are not completely defined, but intriguing associations with autoimmune conditions, certain types of adult cancers, hypertension and schizoprenia have been reported. The American Association of Pediatrics recommends vitamin D supplementation in all breast fed infants at a dose of 200 IU daily, though higher doses are recommended in Canada and Europe. Actual implementation of these guidelines seems uncommon in our area. Further work is planned to reach and inform our community. Discussion with non-physician community breast feeding advocates is likely to be crucial.

Disclosures: ***S. Bhatia****, None.*

T50

Supplementation with Vitamin D and Calcium Reduces Cancer Risk.

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A large body of epidemiological evidence now links low vitamin D status to increased risk of cancer. However, no randomized clinical trials have been reported that used a vitamin D intervention sufficient to raise serum 25OHD to optimum levels and that targeted a cancer outcome. The purpose of this analysis was to determine the efficacy of both calcium and calcium plus vitamin D_3 in reducing incident cancer risk of all types.
We conducted a four-year, population-based, double-blind, randomized placebo-controlled trial in a nine-county largely rural area in eastern Nebraska. The subjects were a population-based sample of 1,179 healthy postmenopausal women aged 55 and older. Subjects were randomly assigned to one of three groups; 1) 1400-1500 mg/d supplemental calcium (Ca-only); 2) calcium plus 1100 IU/d vitamin D_3 (Ca+D) and 3) placebo for both Ca and D. The outcome variable was diagnosis of cancer.
When analyzed by intention-to-treat, cancer incidence was lower in the Ca+D women than in placebo controls ($P < 0.03$). Using logistic regression, the unadjusted relative risk (RR) of incident cancer in the Ca+D group was 0.402 ($P = 0.01$) and for the Ca-only group 0.532 ($P = 0.06$). When analysis was confined to cancers diagnosed after the first 12 months, RR for the Ca+D group fell to 0.232 (CI: 0.09 to 0.60; $P < 0.005$), but did not improve for the Ca-only group. In multiple logistic regression models, both treatment and serum 25OHD were significant predictors of cancer risk. We conclude that improving calcium and vitamin D nutritional status substantially reduces all-cancer risk in postmenopausal women.

Disclosures: ***J.M. Lappe****, None.*

T52

Attitudes, Beliefs, and Practices of Patients and Physicians with Regard to Vitamin D Use in Osteoporosis Management.

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Although osteoporosis treatment guidelines include recommendations for calcium and vitamin D intake, routine use of adequate supplementation of vitamin D is low. This study surveyed physicians and their patients to examine their knowledge and usage of vitamin D and calcium in the management of osteoporosis.
Approximately 50 physicians in the United Kingdom, Mexico, and Austria (as a special situation in which calcium and vitamin D are provided free of charge to patients being treated for osteoporosis) were randomly surveyed, as were the first 10 patients with osteoporosis from each of their practices. Physicians were asked to rate the importance of vitamin D, calcium and exercise in osteoporosis management on a scale of 1 to 10 (1=not important at all, 10=extremely important) and to estimate use of calcium and vitamin D supplements by their patients. Patients were asked about their own intake of vitamin D and calcium.
Altogether 151 physicians completed the telephone survey and 910 of their own patients (350 in Austria, 212 in UK and 348 in Mexico) with osteoporosis completed the telephone interviews. Approximately 86%,

28%, and 46% of physicians rated the importance of vitamin D and calcium as being 9 or 10 in Austria, UK, and Mexico, respectively. Around 34% of patients in Mexico and UK reported taking vitamin D supplements, while 90% of patients in Austria were doing so. However, only 20% of patients in Austria reported that they took the supplements daily.

In this survey, despite the recognition by both physicians and patients that vitamin D is important for bone health, only a low proportion of osteoporosis patients regularly take supplements containing vitamin D. This is the case even when vitamin D and calcium supplements are provided free with osteoporosis drug prescriptions.

Disclosures: ***L.E. Wehren****, Merck Research Laboratories 3.*

T54

Vitamin D Deficiency in Healthy Adolescent Girls in the UK.

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We have recently highlighted the problem of severe symptomatic vitamin D deficiency among some adolescents presenting with bony deformities, muscle weakness and skeletal pain. Prompted by these observations, in May 2003 we undertook a cross-sectional study to determine vitamin D status of healthy adolescent girls attending an inner city multiethnic girls' school. 73% of girls were found to be vitamin D deficient (25-hydroxyvitamin D (25OHD) <12 ng/ml [30 nmol/L]). We have now embarked on a pilot randomised controlled trial to determine if vitamin D treatment will result in a greater bone mass acquisition in pubertal girls. 100 post-menarchal girls aged 12-14 years were recruited from the same inner city multiethnic school and screened for vitamin D deficiency, in July 2006, prior to inclusion in the study. Serum 25OHD was assessed by HPLC.

The baseline data show that even during summer 69% of girls were vitamin D deficient (25OHD <12ng/ml). White girls had significantly higher median [range] 25OHD levels (24.8 [11.6-35.4] ng/ml; n=24) than black and Asian girls (6.9 [1.0-19.1] ng/ml, n=76) ($p<0.0001$) this was accompanied by a significantly lower serum PTH (white girls 2.7 [0.7-5.5] pmol/L; non-white girls 4.2 [0.5-26.2] pmol/L ($p<0.0004$) (Kit reference range 0.7-.3.9 pmol/L).

This study has confirmed in a further cohort that hypovitaminosis D is still common among healthy adolescent non-white girls, even in the summer months. It is not yet known if vitamin D status has any direct influence on the accelerated bone mineral acquisition that occurs during puberty. This study will find out if vitamin D supplements taken by mouth will result in a greater increase in the amount of minerals in bones of asymptomatic girls with low body stores of vitamin D.

Disclosures: ***J.L. Berry****, None.*

Non-Traditional Roles of Vitamin D II

T56

The Effect of Vitamin D_3 8400 IU Once Weekly on Body Sway in Elderly Subjects with Vitamin D Insufficiency.

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Vitamin D status has been shown to be related to body sway (a measure of neuromuscular stability) and the probability of falling in the elderly. A recent study showed that subjects with mediolateral body sway ≥0.46 cm have ~ 3-fold risk of recurrent falling over the next 12 months. This study examined the effects of treatment with vitamin D_3 8400 IU once weekly for 16 weeks on mediolateral body sway measured with eyes open in subjects 70 years or older who had vitamin D insufficiency (25OHD ≥6 but ≤20 ng/mL), but were not severely deficient. The study was conducted in 226 generally healthy subjects [mean age ± SD: 78.0 ± 6.4] recruited between October 2005 and February 2006. Subjects were randomly allocated in a 1:1 ratio to either vitamin D_3 8400 IU once weekly or placebo and were stratified in a 2:1 ratio based on baseline 25OHD levels (≤15 or >15 ng/mL). Mediolateral sway was assessed using the AccuSway platform which recorded mediolateral displacement from center of pressure. Baseline serum 25OHD levels were similar between groups. [Mean ±SD: vitamin D 14.3 ± 3.9; placebo =14.4 ±4.3], with about 2/3 of all subjects having 25OHD level ≤15 ng/ml. Baseline sway was similar across both treatments groups [Mean ±SD: vitamin D 0.311 ± 0.134 cm; placebo = 0.341 ± 0.151 cm]. Following 16 weeks a small decrease in mediolateral sway was seen in the vitamin D group (-0.003 cm) and a small increase in the placebo group (0.015 cm). However, the between-group difference of -0.021 (95% CI, -0.53,0.012) was not significant (p=0.208). Mean 25OHD levels were 26.2 ±5.6 ng/mL in the vitamin D group and 13.3 ± 5.1 ng/mL in the placebo group. Mean changes from baseline in body sway of treated patients *vs*. placebo were not significantly different in patients with 25OHD baseline levels ≤15 ng/ml (-0.017) vs. >15 ng/ml (-0.034). When subjects with higher baseline sway were analyzed separately, a significant decrease in sway was seen in subjects with baseline sway ≥0.460 cm treated with vitamin D3 *vs*. placebo (between-group difference -0.200, p = 0.008). However, as there were only ≈30 subjects in this subgroup, these results need to be confirmed in a larger population. In addition, severely vitamin D deficient subjects were excluded, and the effect may be larger in that group. In conclusion, treatment with vitamin D3 8400 IU qw reduced body sway in subjects with elevated basal mediolateral sway, but it had no effect on body sway in subjects with normal basal mediolateral sway. Baseline 25OHD status did not interact with the effectiveness of vitamin D_3 8400 IU qw on body sway.

Disclosures: ***P. Lips****, None.*

T58

A Positive Correlation Between the Mini-Mental State Examination Score and Serum 25-Hydroxyvitamin D Concentration in Geriatric Patients.

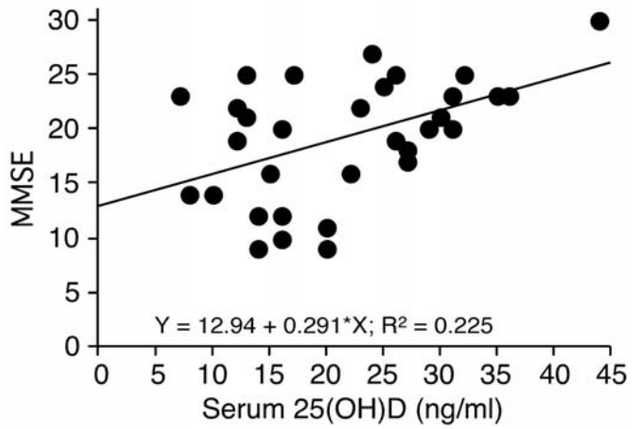
R. J. Przybelski*, N. Binkley. University of Wisconsin, Madison, WI, USA.

Clinical observations of improved cognitive function in memory-impaired geriatric patients receiving aggressive vitamin D supplementation prompted a chart review of data from patients presenting for memory assessment over a 34-month period. These patients were referred by their primary care provider to a community-based, university-affiliated monthly outreach clinic providing consultative assessments for older adults with memory problems. The objective of this study was to evaluate whether an association exists between cognitive performance and vitamin D status. The possibility that such a correlation might be explained by a concomitant vitamin B12 deficiency, as might occur with generalized malnutrition as opposed to a selective vitamin D insufficiency, was also assessed.

Data from all patients (n=80) presenting for initial visits to the memory assessment clinic were reviewed to identify those who had their serum 25-hydroxyvitamin D, serum vitamin B12, and mini-mental state examination score all obtained on the day of their first clinic assessment (n=32). Correlation analyses were performed between the patients' mini-mental state examination scores and their 25-hydroxyvitamin D levels, and between their mini-mental state examination scores and vitamin B12 levels; these analyses were planned prior to data review, and were the only analyses performed on the data other than descriptive statistics of patient demographics and test results.

The analyses showed a significant (p=0.006) positive correlation between these patients' serum 25-hydroxyvitamin D concentrations and mini-mental state examination scores (Figure). In contrast, no significant (p=0.875) correlation was observed between serum B12 concentration and mini-mental state examination score.

In conclusion, the positive, significant correlation between serum 25-hydroxyvitamin D concentration and mini-mental state examination score in this cohort of 32 geriatric patients presenting for memory assessment suggests a potential role for vitamin D in cognitive function of older adults.



Disclosures: ***R.J. Przybelski****, None.*

T60

Mechanistic Analysis of VDR-Mediated Renin Suppression.

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Recent studies have shown that VDR is involved in the regulation of renin expression. VDR knockout mice are hypertensive and exhibit an increase in the plasma renin level. In this study we first showed that vitamin D analogs down-regulated renin mRNA expression in As4.1 cells and the effect was blocked by cycloheximide, suggesting that de novo protein synthesis is involved. To further investigate the mechanism, DNA microarray was used to assess VDR-mediated gene expression profile in As4.1 cells treated with or without 100 nM paricalcitol. The microarray results revealed a number of major pathways, specific vitamin D-related genes (e.g. CYP24A1, VDR and renin), and many transcription factors such as CREM being affected by paricalcitol. Using the electrophoretic mobility shift assay, we found the nuclear protein binding to the CRE-like domain in the renin distal enhancer region, but not other domains such as E-Box, RAR/RXR binding site, which was reduced by paricalcitol treatment of As4.1 cells. VDR and CREB1 were identified in the complex binding to the CRE-like domain by Western blot, and paricalcitol treatment resulted in an increase in theVDR level and a decrease in CREB1 binding. These results suggest that VDR-mediated renin suppression likely acts through a transcription regulatory complex including CREB and VDR that binds to the CRE-like domain in the renin promoter.

Disclosures: ***M. Nakane****, Abbott Laboratories 3.*

Vitamin D and Kidney Disease II

T62

High Dietary Vitamin D Increases Plasma 25-Hydroxyvitamin D Concentration, but Does Not Attenuate the Hypertension and Exacerbates the Kidney Damage of Dahl Salt-Sensitive Rats Fed a High Salt Diet.

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The Dahl salt-sensitive rat, a model for salt-induced hypertension, develops hypovitaminosis D during high salt intake, which is caused by loss of protein-bound vitamin D metabolites into urine. We tested the hypothesis that high dietary vitamin D (5- and 10-fold standard) would increase plasma 25-hydroxyvitamin D (25-OHD) concentration (indicator of vitamin D status) of salt-sensitive rats during high salt intake. Salt-sensitive rats were fed 0.3% salt (low salt, LS), 3% salt (high salt, HS), 3% salt and 25 IU vitamin D_3/g food (HS-D25), or 3% salt and 50 IU vitamin D_3/g food (HS-D50) and sacrificed at week 4. Plasma 25-OHD concentrations of LS, HS, HS-D25, and HS-D50 rats were 41 ± 5, 26 ± 4, 60 ± 14, and 56 ± 11 nmol/L, respectively. Urinary vitamin D metabolite content was 12 ± 2, 22 ± 3, 175 ± 61, and 158 ± 29 pmol/24 h, respectively. Urinary calcium was significantly increased by both high salt and vitamin D intake (HS-D50>HS-D25>HS>LS rats). The mean systolic blood pressure of the hypertensive HS and HS-D rats did not significantly differ, but the mean kidney weight /body weight ratio of HS-D rats was higher than that of HS rats ($P < 0.01$). Histological examination indicated more widespread glomerulosclerosis, fibrinoid necrosis, and tubular protein casts in HS-D25, compared with HS rats. LS rats had significantly

higher plasma 25-OHD concentrations than HS rats and exhibited neither hypertension nor renal damage. We conclude that high dietary vitamin D increases plasma 25-OHD concentrations, but does not ameliorate the hypertension and exacerbates the renal damage of salt-sensitive rats during high salt intake. An implication of this study is that low salt intake is necessary to prevent hypertension and renal damage and maintain optimal vitamin D status in salt-sensitive individuals.

Disclosures: ***M. Thierry-Palmer****, None.*

Vitamin D and Other Metabolic Bone Diseases II

T64

Vitamin D Deficiency in Osteogenesis Imperfecta.

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Vitamin D Deficiency in Osteogenesis Imperfecta (OI): E.L.Martin, K BrinzenhofeSoc, J.R. Shapiro, Kennedy Krieger Institute, Johns Hopkins Medical Institutions, Baltimore MD, Catholic University of America, Washington DC.

The contribution of vitamin D deficiency to bone mineral density and fracture risk in OI is undefined. This report presents pre-treatment serum 25 (OH) D concentrations in 58 adults,18-65 years, with OI types I (n=27), III (n=25) and IV OI (n=6). Results were examined with respect to OI type, bone mineral density (BMD), serum PTH and urine NTx concentrations.

Table : Percentage of Patients Defined as Vitamin D Deficient Based on Serum25(OH) D. [++]

Serum 25(OH)D-	Type I OI[++]	Type III OI[++]	Type IV OI	Healthy Canadian Adults[1]	Healthy U.S. Adults age 18 to 29 and 49-83 yrs[2]	U.S. Adult Inpatients[3]
<10 ng/mL	7%	4%	17%	6%	N/a	22%
<20 ng/mL	56%	40%	50%	34%	36% and 41%	57%
<32ng/mL	79%	84%	100%	N/a	N/a	N/a

[++]p = > 0.05) . In a preliminary sampling of type I patients at baseline (n=9), BMD values measured by DXA trend to lower values in patients with lower serum 25(OH) D levels (p=ns), but not in type III patients. Serum PTH varied inversely to 25(OH) D in some, but not all, patients. There was no relation between serum 25(OH) D and urine NTx excretion.

Following supplementation with 400 IU D/day serum levels were measured at 6 month intervals: 42% Type I, 55% type III and 75% of type IV patients remained less than 32 ng/mL.[4] Thus, the RDA recommendation of 400-600 IU is not adequate to produce serum levels above 32 ng/mL (RDA,1989). We propose the following guidelines based on patient weight rather than age because of marked size variation within the OI population [5]. Adjustment for serum 25(OH) concentration is required for the individual patient.

Table 2: Recommended vitamin D daily intake

Age RDA		Weight Recommended[5]	
0-50 yrs	200 IU/day	50 lbs / 20 kg	600-800 IU/day
51-70 yrs	400 IU/day	90 lbs / 40 kg	1100-1600 IU/day
70+ yrs	600 IU/day	110 lbs / 50 kg	1200-2000 IU /day
		150 lbs / 70 kg +	2000-2800 IU /day

Conclusions: Vitamin D deficiency is a significant problem in the OI population. Evaluation of proposed increases in dietary vitamin D on metabolic parameters is required.

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[2]Holick MF. *Mayo Clin Proc* 2006 81:353-73

[3] Thomas MK, et al. *NEJM* 1998;338:777-783

[4]. Heaney RP. Am J Clin Nutr 2004; 80: 1076S

[5:] Shapiro, JR, Mc Mahon, E., Hollis BW. Recommended Vitamin D Intake for Adults with Osteogenesis Imperfecta., 2006

Disclosures: ***J.R. Shapiro****, None.*

T66

Lack of Correlation between 1,25-Dihydoxyvitamin D Concentrations and Changes in Serum or Urinary Calcium with Teriparatide Therapy.

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When teriparatide [TPTD, rhPTH(1-34)] at either 20 μg/day (TPTD20) or 40 μg/day (TPTD40) was given subcutaneously once daily to postmenopausal women with osteoporosis in the Fracture Prevention Trial [NEJM 344(19) 2001: 1434-41], serum calcium (sCa) concentrations were transiently increased (>10.6 mg/dL) at 4 to 6 hours after dosing and urinary calcium (uCa) excretion was elevated (>300 mg/24 hr) at 1 month in some women. Since 1,25-dihydroxyvitamin D (1,25-OHD) influences Ca metabolism, this analysis examines the relationships between 1,25-OHD concentrations and changes in sCa or uCa in a subgroup of 517 women with 1,25-OHD measurements from the Fracture Prevention Trial. Serum Ca and 1,25-OHD were measured at baseline, 1, 3, 6, and 12 months. Urine Ca was assessed in 24-hr urine collections at baseline, 1, 6, and 12 months. Pearson correlation analyses were performed to assess the relationship between baseline and post-baseline changes in 1,25-OHD concentrations with changes in sCa or uCa. Baseline 1,25-OHD concentrations were not significantly correlated with post-baseline changes in sCa at 4-6 hr post-dose (Table), except at 1 month in the TPTD20 group and at 12 months in placebo group. Baseline 1,25-OHD concentrations were not correlated with changes in uCa at any time point (Table).

Pearson Correlation Coefficients Between Baseline 1,25-OHD and Post-Baseline Changes in sCa and uCa

	Month	Placebo (n=173)	TPTD20 (n=170)	TPTD40 (n=174)
Changes in sCa	1	-0.10	-0.16*	0.01
	3	-0.14	-0.06	-0.06
	6	-0.08	-0.02	0.04
	12	-0.17*	0.03	-0.01
Changes in uCa	1	0.08	0.08	0.08
	6	0.10	-0.09	-0.08
	12	0.07	-0.03	-0.02

*P<0.05

Changes in 1,25-OHD were correlated with changes in sCa at 1 month (r=0.15, P<0.05) and 6 months (r=0.10, P<0.05) in the overall population; however, there were no significant correlations at any time point within each treatment group. Changes in 1,25-OHD were correlated with changes in uCa at 1 month in the overall population (r=0.17, P<0.05) and the TPTD40 group (r=-0.44, P<0.05). Some statistically significant correlations may have resulted due to the large numbers of women in the Fracture Prevention Trial. However, these correlations were very weak, as indicated by the low coefficients (Table) and do not imply any clinical significance. In conclusion, there is no clinically relevant correlation between 1,25-dihydroxyvitamin D concentrations and changes in serum or urine Ca with TPTD therapy.

Disclosures: ***P. Chen****, Eli Lilly and Company 1, 3.*

T68

Effect of Alfacalcidol on Bone Mineral Density Measured by DXA in Alendronate-Treated Postmenopausal Women with Osteopenia or Osteoporosis: 1 Year Interim Analysis of the ALFA Study.

O. Bock[1], H. Boerst*[1], M. Runge*[2], G. Armbrecht*[1], P. Martus*[3], E. Schacht[4], J. Hashimoto*[5], D. Felsenberg[1]. [1]Centre for Muscle and Bone Research, Charité - Campus Benjamin Franklin, Berlin, Germany, [2]Centre for Muscle and Bone Research, Aerpah Kliniken Esslingen-Kennenburg, Esslingen, Germany, [3]Institute of Biometrics and Clinical Epidemiology, Charité - Campus Benjamin Franklin, Berlin, Germany, [4]ZORG - Zurich Osteoporosis Research Group, Zurich, Switzerland, [5]Bone Disease Area Department, Chugai Pharmaceutical Co.Ltd., Tokyo, Japan.

The purpose of the ALFA (Alfacalcidol & Falls) study (three-year prospective, randomized, double-blind, placebo-controlled trial) is to evaluate the effect of alfacalcidol 1 µg daily on the number of falls in postmenopausal, alendronate-treated, osteopenic or osteoporotic women. A pre-planned one year interim analysis was performed to examine the effect of alfacalcidol on bone mineral density for safety reasons.
A total of 278 postmenopausal women (mean age 73.7 years, SD 4.8) received either alfacalcidol 1 µg or placebo daily, in addition to alendronate 70 mg weekly and calcium 500 mg daily. Lumbar spine and hip Bone Mineral Density (BMD) were measured by DXA at baseline and after 12 months of treatment.
Baseline characteristics of patients, including age, body mass index, biochemical markers of bone metabolism, lumbar spine BMD (mean T-Score -2.33 SD vs. -2.40 SD), and hip BMD (mean T-Score -1.40 vs. -1.45) were not significantly different between the two groups.

	BMD change from baseline after 1 year		
	alfacalcidol + alendronate	placebo + alendronate	t-test
Lumbar spine BMD	+ 5.02 % (n = 96)	+ 2.99 % (n = 95)	p < 0.001
Hip BMD	+ 2.03 % (n = 120)	+ 1.92 % (n = 117)	n.s.

The increase of lumbar spine BMD after one year was significantly more pronounced in alendronate-treated patients who additionally received alfacalcidol. It was not significantly different for hip BMD.
Our data showed an additional, potentially beneficial, effect of alfacalcidol 1 µg daily in alendronate-treated postmenopausal women on lumbar spine BMD measured by DXA.
Alfacalcidol in alendronate-treated patients is safe, since only one case of clinically relevant hypercalcaemia and no further statistically significant differences in other adverse events were observed.

Disclosures: ***O. Bock****, None.*

T70

Reduction of Falls and Osteoporotic Fractures - Plain Vitamin D or Active Vitamin D Analogues?

E. Schacht. ZORG, Zürich Osteoporosis Research Group, Zurich-Munich-Hong Kong, Switzerland.

Falling in old age has disastrous consequences. Falls break bone, fear of falling reduces self-esteem and physical activity, social contacts and quality of life. Fractures are also the relevant outcome of osteoporosis and most of the non-vertebral fractures are fall-related.
D-Hormone ($1,25(OH)_2D$; calcitriol), the active vitamin D metabolite, and its receptor (VDR) play an important role in muscle development and function. Older age is significantly associated with decreased VDR expression in human skeletal muscle tissue and femoral muscle power and function and D-Hormone serum levels in the elderly are positively correlated suggesting that the age-related increase of falls is partly explained by a decrease of VDR's and of D-Hormone.
A significant decrease in the fall rate after 3 years treatment with 0.5 µg calcitriol daily in osteopenic women without vitamin D deficiency has been described. Alfacalcidol (1 µg daily), an advantageous pro-drug of calcitriol, has demonstrated after 9 months the reduction of falls by 50-70% in elderly women and men with normal vitamin D levels and who have taken more than 500 mg of daily calcium from diet or had a creatinine clearance of less than 65 ml/min. A meta-analysis of the potential effects of plain vitamin D and active vitamin D analogues on falls concludes that both reduce the risk of falls among elderly and institutionalized older individuals, but subgroup analyses have proven the advantage of active vitamin D analogues.
Four recently published clinical studies in elderly with or without previous osteoporotic fractures cast doubt on the role of an annual injection of 300'000 IU of plain vitamin D and of the combination of daily orally given vitamin D (400-800 IU) with calcium (1g) in the prevention of falls or any kind of fractures. New meta-analyses have proven the reduction of vertebral and non-vertebral fractures by active vitamin D analogues in women with postmenopausal osteoporosis and the superiority of active vitamin D analogues in comparison to plain vitamin D. In one head-to-head study the superiority of alfacalcidol versus plain vitamin D has been shown in glucocorticoid-induced osteoporosis. The combination therapy with alendronate and alfacalcidol seemed to be superior in terms of BMD, rate of falls, overall fractures and back pain over alendronate combined with plain vitamin D.
The rationale of the advantage of active vitamin D analogues is that these drugs are acting without the physiologically controlled metabolic activation in the kidneys which results in higher concentrations at the target organs and in local expression of VDR's. Plain vitamin D seemed to be active only in vitamin D deficient patients with normal kidney function.

Disclosures: ***E. Schacht****, TEVA Pharmaceuticals Industries Ltd. 5.*

T72

Higher Serum 25(OH)D Concentrations Are Related to Larger BMD Increases with Alendronate Therapy for Osteoporosis.

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Bisphosphonate treatment studies included daily calcium supplements and corrected low serum 25(0H)D concentrations. However, the optimal serum 25(OH)D concentration required for bone health is unclear.
We therefore performed a prospective cohort study to examine the influence of baseline serum 25(OH)D concentrations on changes in BMD during alendronate therapy at the spine, total hip and femoral neck over 11 to 14 (median 12) months.
172 women and 11 men with osteoporosis aged 27-87 years who had already been treated with alendronate for 12 to 28 months were studied. The majority (96%) also received calcium (mean daily dose 667 mg), while 69% received vitamin D_2 (ergocalciferol) supplements (mean daily dose 1180 IU). All patients had baseline serum 25(OH)D concentrations between 50 and 120 nmol/L (mean 69 nmol/L). Baseline fracture prevalence was spine (82%); hip (29%); humerus (4%) and distal radius (2%). Baseline mean spinal, total hip and femoral neck T-scores were -1.9, -1.8, and -2.5, respectively.

Changes in spinal BMD ranged from -2% to +15% and were strongly positively related to baseline serum 25(OH)D concentrations ($r=0.80$, $p < 0.05$). No such relationship existed at the total hip. Changes in femoral neck BMD ranged from -8 to +16%, but were only positively related to baseline serum 25(OH)D concentrations in those patients with a baseline 25(OH)D > 80 nmol/L ($r=0.57$, $p < 0.05$).
Conclusion: Higher baseline serum 25(OH)D concentrations appear to improve spinal BMD responses to bisphosphonate therapy. This may relate to an improved calcium supply to bone, but further prospective, placebo controlled studies are required to determine possible mechanisms.

Disclosures: ***P.R. Ebeling****, Merck 5.*

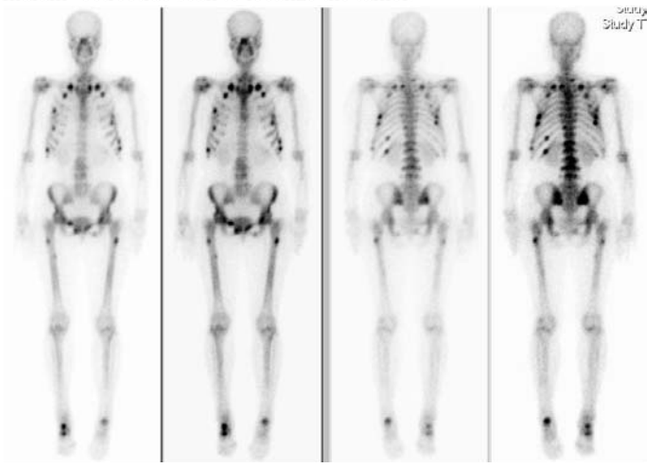
Other II

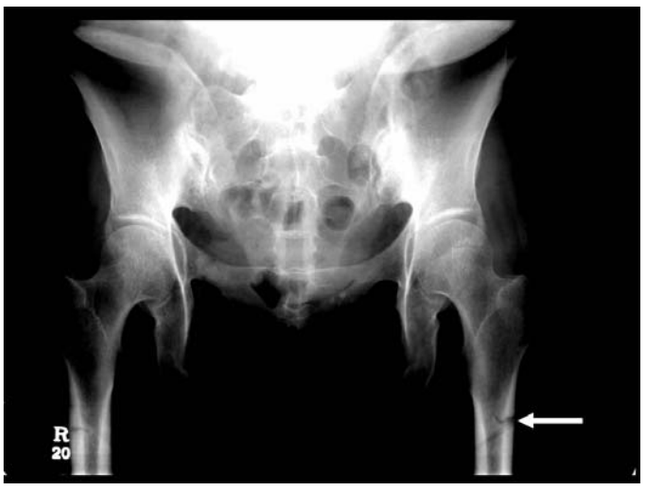
T74

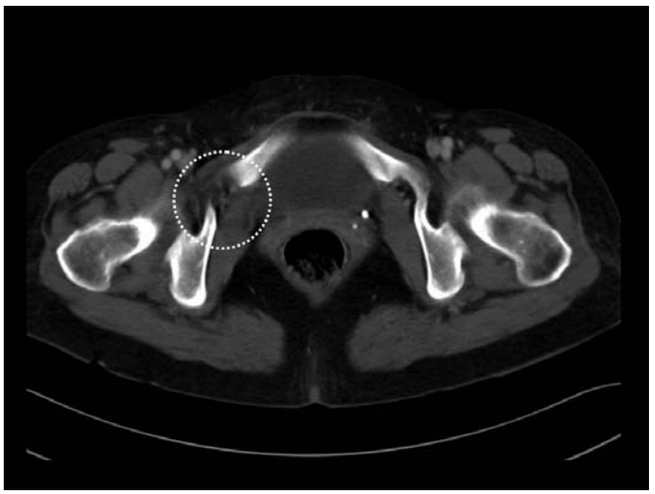
Multiple Pseudofractures Mimicking Metastatic Bone Tumor in Oncogenic Osteomalacia.

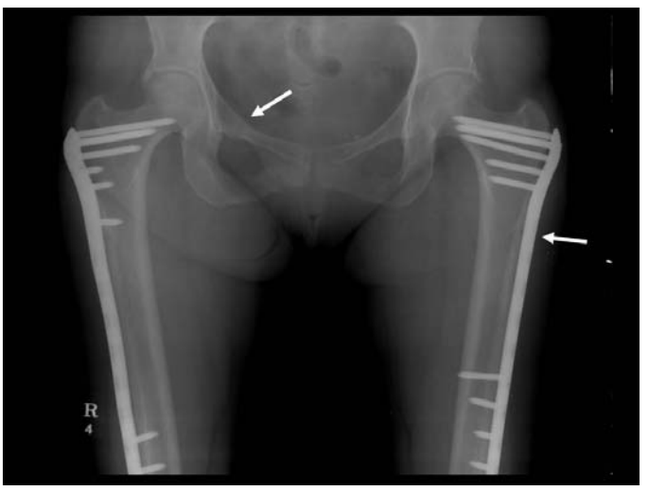
K. Yang*, J. Jahng, H. Yoon*. Orthopaedics, Yongdong Severance Hospital, Seoul, Republic of Korea.

A 52-year-old lady was admitted to the hospital because of low back pain and easy fatigability for 3 years. Laboratory tests were performed; calcium 9.9mg/dl (albumin 4.7g/dl), inorganic P 1.9mg/dl, tubular reabsorption of phosphorous 34% (85-95), alkaline phosphatase 251 IU/L (42-117), iPTH 69.4pg/ml (13-104), 25(OH) Vit D 21.9ng/ml (7.6-75) and $1,25(OH)_2$ Vit D 5pg/ml (20-60). A Whole body bone scan with ^{99m}Tc revealed multiple hot spots on spine, ribs, pelvis, both femora, both ankle (Figure 1). CT studies on the chest and abdomen was nonspecific except multiple skeletal defects on the ribs and superior pubic ramus (Figure 2). MRI and 18-FGF-PET scan didn't provide additional information. Pathologic fracture was imminent on left femoral shaft which required prophylactic internal fixation (Figure 3). Iliac bone biopsy shows widening of the unmineralized osteoid stream. 111- Indium- octreotide scan revealed focal area of moderately increased uptake on superior aspect of right maxillary sinus. Caltriol 1.0 microgram was prescribed and pseudofractures on the pelvis and both femora healed one year postoperatively (Figure 4). $1,25(OH)_2$ Vit D level was elevated to 19pg/ml. Patient is waiting for second 111-Indium- octreotide scan to localize the tumor.









Disclosures: ***K. Yang****, None.*

T76

Mechanisms of Anti-osteoclastogenic Action of Vitamin D and Synthesis of New Analogs.

H. Takasu[1], A. Sugita*[1], Y. Uchiyama*[1], M. Okazaki*[1], E. Ogata[2], K. Ikeda[3]. [1]Chugai Pharmaceutical Co. Ltd., Gotemba, Japan, [2]Cancer Institute Hospital, Tokyo, Japan, [3]National Institute for Geriatrics and Gerontology, Obu, Japan.

We have demonstrated in estrogen-deficient animals with accelerated bone resorption that active vitamin D drugs reduce the number of osteoclasts, thereby potently suppressing bone resorption in vivo (JBMR 2000). In order to define the molecular pathway(s) that VDR acts on, we employed OPG-KO mice that exhibit excessive bone resorption as a result of constitutive activation of RANKL/RANK signaling. Oral treatment of OPG-KO mice with $1\alpha,25(OH)_2D_3$ (0.1μg/kg BW) for 6 weeks caused a marked reduction in osteoclast number per surface and increases in BMD at the femur, without a change in the number of CD11b+ osteoclast precursors, suggesting that $1\alpha,25(OH)_2D_3$ inhibits bone resorption by interfering with osteoclastogenic signaling downstream of RANK. Based on these results, we examined the effect of $1\alpha,25(OH)_2D_3$ on RANKL-induced osteoclast development from M-CSF-dependent bone marrow monocyte/macrophage precursor cells (BMMs) in vitro. $1\alpha,25(OH)_2D_3$ markedly and dose-dependently inhibited RANKL-induced osteoclast formation, whereas it failed to do so in BMMs derived from VDR-KO mice. Western blot analyses revealed that among known molecules involved in RANK signaling, $1\alpha,25(OH)_2D_3$ markedly and dose-dependently suppressed c-Fos protein induced by RANKL. This effect was not seen in BMMs from VDR-KO mice. In order to prove that the suppression of c-Fos protein by $1\alpha,25(OH)_2D_3$ is responsible for the inhibition of RANKL-induced osteoclast development, we examined the effect of forced expression of c-Fos. Retroviral expression of c-Fos in BMMs completely blocked the inhibitory effect on osteoclast differentiation by $1\alpha,25(OH)_2D_3$ at 10^{-9} M and partially at higher doses. Interestingly, only modest change in c-fos mRNA level was observed after $1\alpha,25(OH)_2D_3$ treatment by real-time PCR analyses. Pulse-labeling experiments showed that the biosynthesis of c-Fos protein was inhibited by $1\alpha,25(OH)_2D_3$, implying that VDR may regulate translation of c-Fos protein in osteoclast precursor cells. By screening vitamin D analogs based on their c-Fos-suppressing activity, we identified a new analog, named DD281, that inhibited bone resorption and prevented bone loss in ovariectomized mice more potently than $1\alpha,25(OH)_2D_3$ with similar levels of calcium absorption. Thus, c-Fos protein is an important target of the skeletal action of VDR-based drugs, and screening by c-Fos-suppressing activity may be useful for determining bone-selective vitamin D analogs for the treatment of bone diseases with excessive osteoclastic activity.

Disclosures: ***H. Takasu****, Chugai Pharmaceutical Co. Ltd. 3.*

T78

ASBMR YOUNG INVESTIGATOR AWARD
Seasonal and Latitudinal Dependence of Vitamin D UV on the East Australian Coast.

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Australia does not widely practise fortification of foods with vitamin D. Hence the majority of the population rely on incidental sun exposure to maintain vitamin D sufficiency. However, recent studies have uncovered deficiency rates of up to 78% (at a threshold of 75 nmol/L of circulating 25-hydroxyvitamin D) in the southeast Queensland population, the world's capital of skin cancer. This paradox highlights the dual nature of UV exposure.

If we are to alleviate the worldwide burden of vitamin D deficiency by UV exposure, a more mature understanding of UV exposures in everyday life is required. Such exposures are strongly influenced by season/time of year, time of day, climate, location, pollution, ozone and other factors. In this work, we use the vitamin D action spectrum in conjunction with UV computer simulations to obtain daily totals of vitamin D producing UV during one year. Simulations are performed for many major centres of population along the eastern coast of Australia, ranging in latitude from 12°S to 43°S. We compare locations, highlight the seasonal dependence of vitamin D UV and discuss implications for population health.

We also explore the notion of latitude gradients of vitamin D producing UV in Australia. In particular, it is apparent that vitamin D levels do not follow a strong latitude gradient during warmer summer months of the year, but during colder winter months vitamin D UV gradients could greatly influence vitamin D status. Low latitude locations, it seems, do not exhibit a significant seasonal dependence. High latitude locations, on the other hand, may need to advocate extended UV exposure during some times of the year. Vitamin D UV levels will finally be contrasted with erythemal UV levels, highlighting the need for balanced message about UV exposure.

Disclosures: ***W.J. Olds****, None.*

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ASBMR YOUNG INVESTIGATOR AWARD - PLENARY POSTER

The Effect of Vitamin D on Osteoarthritic Bone and Cartilage in a Guinea Pig Model.

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The Framingham study showed that low intake and serum levels of vitamin D appeared to be associated with an increased risk of osteoarthritis (OA) progression of the knee. We want to determine if vitamin D intake has an effect on cartilage and bone in an OA model.
Male Dunkin-Hartley guinea pigs spontaneously develop OA. A menisectomy (MNX) accelerates and predicts this OA model. A MNX was performed on the left leg of 3 month old guinea pigs, the right leg acting as a control. Two time points (1, 3 months after MNX) were studied with three groups; no vitamin D (0 IU/day), control (153 IU/day) and high vitamin D (380 IU/day). Vitamin D treatment began on 2 month old guinea pigs. OA progression was determined using histological sections of the proximal tibia stained with Safranin-O and fast green and graded using a modified Mankin grading. Bone mineral density (BMD) was evaluated using DEXA on the distal femur. Bone histomorphometric parameters were evaluated on the distal femur and proximal tibia using parameters that comply with ASBMR guidelines. Blood serum vitamin D levels, Ca, P, Mg, ALP, ALT, GGT, creatinine, albumin and kidney tissue calcification were evaluated.
Blood serum vitamin D levels showed a 6 fold increase between no vitamin D (mean 10.1nmol/L) and control (59.8nmol/L) and a 4 fold increase between control and high vitamin D (245.8nmol/L) groups 1 month after MNX. At 3 months the same ratios were seen between no vitamin D (12.9nmol/L), control (79.4nmol/L) and high vitamin D (343nmol/L) groups. No differences were seen between the serum biochemistries. The liver function tests ALP and GGT showed no changes between the groups, but ALT showed a significant ($p<0.05$) increase between no and high vitamin D groups. The BMD of the distal femur showed a significant decrease in the MNX leg compared to the control in each group. Bone histomorphmetry showed an increase in bone volume, osteoid volume and trabecular number for both the proximal tibia and distal femur with increasing vitamin D treatment after1 month. At 3 months the MNX femur showed an increase in osteoid volume compared to the control in the no vitamin D group. At both 1 month and 3 months the MNX Mankin score of the high vitamin D group was significantly higher than the no vitamin D group indicating more severe OA. No differences were seen in the kidney tissue calcification between the groups.
The vitamin D treatment was effective at raising 25(OH)D without hypercalcemia at each time point. Vitamin D affected bone morphometric properties, which points to an increase in bone formation at 1 month. At 3 months the increase in osteoid volume in the MNX no vitamin D leg suggests impaired mineralization.

Disclosures: ***T.A. Hunt****, None.*

Notes