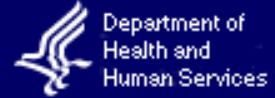




U.S. Food and Drug Administration

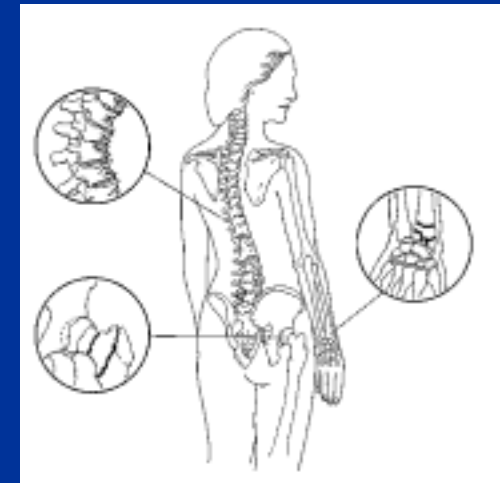


# Quantitative Ultrasound and the Management of Osteoporosis

**Keith A. Wear,  
FDA Center for Devices and  
Radiological Health**

# Osteoporosis

- Prevalence in USA: 10 million<sup>1</sup>
- Osteoporosis Drugs
  - Calcitonin (Miacalcin) 1991
  - Alendronate (Fosamax) 1995
  - Raloxifene (Evista) 1997
  - Risedronate (Actonel) 1998
  - Teriparatide (Forteo) 2002
  - Ibandronate (Boniva) 2005
  - Zoledronic acid (Reclast) 2007
  - Denosumab (Prolia, Xgeva) 2011
- High prevalence + multiple treatment options → high demand for diagnostic methods.
- Gold Standard: DXA (Dual Energy X-ray Absorptiometry)

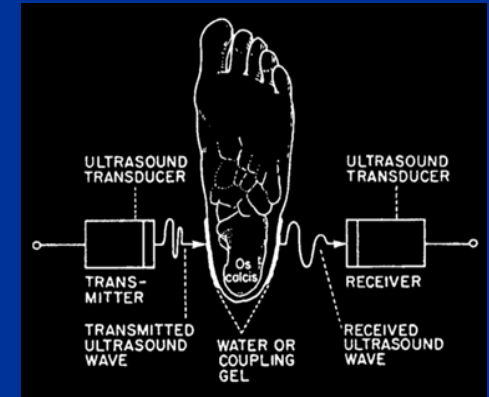


1. <http://www.nof.org>

# Quantitative Ultrasound (QUS)

- QUS devices transmit and monitor ultrasound waves in bone.
- Because osteoporosis is a systemic disorder, measurements at the heel can indicate fracture risk throughout the skeleton.
- QUS devices can measure ultrasound properties that correlate with material and micro-architectural properties of bone<sup>1</sup> and bone-mimicking phantoms.<sup>2,3</sup>

1. Wear *et al.*, *J. Acoust. Soc. Am.*, 131, 1605-1612, 2012.
2. Wear, *J. Acoust. Soc. Am.*, 118, 1186-1192, 2005.
3. Wear, *J. Acoust. Soc. Am.*, 124, 4042-4046, 2008.



Kaufman *et al.*, *J. Bone Miner. Res.*, 8, 517-525, 1993.



- “Heel QUS measures are related to global fracture risk with similar relative risk as other central bone density ROI for postmenopausal women.” – ISCD.<sup>1</sup>
- “Quantitative ultrasonography of the calcaneus predicts fractures of the femoral neck, hip, and spine as effectively as DXA.”<sup>2</sup>

1. Krieg *et al.*, *J. Clin. Dens.* 11, 163-187, 2008.
2. U.S. Preventive Services Task Force. *Ann. Int. Med.* 154, 356-365, 2011.

**Position Statement**

**Quantitative Ultrasound in the Management of Osteoporosis:  
 The 2007 ISCD Official Positions**

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**Abstract**

Dual-energy X-ray absorptiometry (DXA) is commonly used in the care of patients for diagnostic classification of osteoporosis, low bone mass (osteopenia), or normal bone density; assessment of fracture risk; and monitoring changes in bone density over time. The development of other technologies for the evaluation of skeletal health has been associated with uncertainties regarding their applications in clinical practice. Quantitative ultrasound (QUS), a technology for measuring properties of bone at peripheral skeletal sites, is more portable and less expensive than DXA, without the use of ionizing radiation. The proliferation of QUS devices that are technologically diverse, measuring and reporting variable bone parameters in different ways, examining different skeletal sites, and having differing levels of validating data for association with DXA-measured bone density and fracture risk, has created many challenges in applying QUS for use in clinical practice. The International Society for Clinical Densitometry (ISCD) 2007 Position Development Conference (PDC) addressed clinical applications of QUS for fracture risk assessment, diagnosis of osteoporosis, treatment initiation, monitoring of treatment, and quality assurance/quality control. The ISCD Official Positions on QUS resulting from this PDC, the rationale for their establishment, and recommendations for further study are presented here.

**Key Words:** Diagnosis; fracture; guidelines; osteoporosis; QUS; recommendations; standards; treatment; ultrasound.

**Introduction**

Osteoporosis is defined as a “disease characterized by low bone mass and microarchitectural deterioration of bone tissue

leading to enhanced bone fragility and a consequent increase in fracture risk” (1). This definition does not provide explicit diagnostic criteria that allow one to determine whether an individual is osteoporotic or not. As there is no available clinical tool to assess bone microarchitecture or directly measure bone fragility, measurement of bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) is used to diagnose osteoporosis (2). The World Health Organization (WHO) proposed a set of operational criteria to define osteoporosis in postmenopausal Caucasian women (3). The BMD value of an individual patient is expressed in terms of

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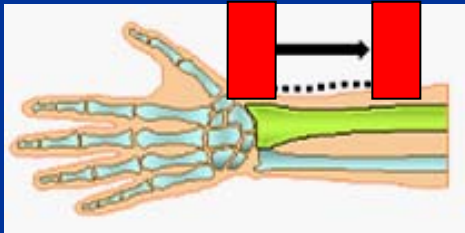
<sup>b</sup>Task Force Chair.

<sup>c</sup>Task Force Member.

<sup>d</sup>Task Force Liaison.

# Non-Calcaneal Methods of QUS

Transmitter Receiver

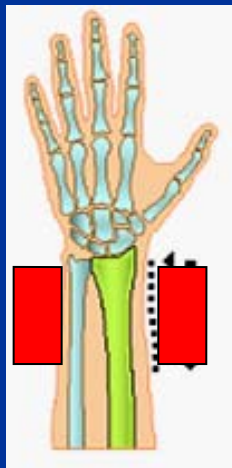


<http://www.beammed.com/>



<http://www.artannlabs.com/>

Transmitter



Receiver



Yamamoto *et al.*, *Osteo. Int.*, 20, 1215-1224, 2009



Stein *et al.*, *Ultrasound in Med. & Biol.*, 39, 388-395, 2013

# Backscatter Method of QUS



Garra, Locher, Felker, Wear,  
*Ultrasound in Med. & Biol.*,  
35, 165-168, 2009.



Wear et al., *Ultrasound in Med.  
& Biol.*, 24, 689-695, 1998



<http://www.boneindex.fi/en/page/2>

# Expansion of Bone Testing

- Ultrasound devices have benefits over DXA with regard to expansion of screening / diagnostic testing to a much wider population:
  - Less expensive
  - More compact
  - More portable
  - No ionizing radiation
- Unlike DXA, ultrasound devices are practical for primary care settings.

# Current BMD Testing Guidelines<sup>1,2</sup>

- BMD testing is recommended for
  - all women  $\geq$  65 years old (NOF, WHO, ACOG, ISCD, USPSTF)
  - postmenopausal women with risk factors (e.g. low body weight, prior fracture, high-risk medication use) (NOF, ACOG, ISCD, USPSTF)

1. U.S. Preventive Services Task Force. *Ann. Int. Med.* 154, 356-365, 2011.

2. <http://www.iscd.org/official-positions/2007-iscd-official-positions-adult/>

NOF: National Osteoporosis Foundation

WHO: World Health Organization

ACOG: American College of Obstetricians and Gynecologists

ISCD: International Society of Clinical Densitometry

USPSTF: United States Preventive Services Task Force



# Bone Mass in Girls

- Osteoporosis in the elderly woman is determined by <sup>1</sup>
  - Amount of peak bone mass in adolescence,
  - Premenopausal maintenance of such peak bone mass
  - Rate of postmenopausal bone mass loss
- “For the prevention of osteoporosis, the importance of bone gain early in life, i.e., during a period of relatively high plasticity of the skeleton to physical forces, has become an accepted axiom.”<sup>2</sup>

## Panel Session: Nutrition/Exercise

### Is Osteoporosis a Pediatric Disease?

### Peak Bone Mass Attainment in the Adolescent Female

CHARLES H. CHESNUT, III, MD

Dr. Chesnut is Professor of Medicine and Radiology, and Director, Osteoporosis Research Center, University of Washington Medical School, Seattle, WA. This article is based on his presentation at the FDA Special Topic Conference on Osteoporosis, sponsored by the Food and Drug Administration, held at Bethesda, MD, October 30, 1987.

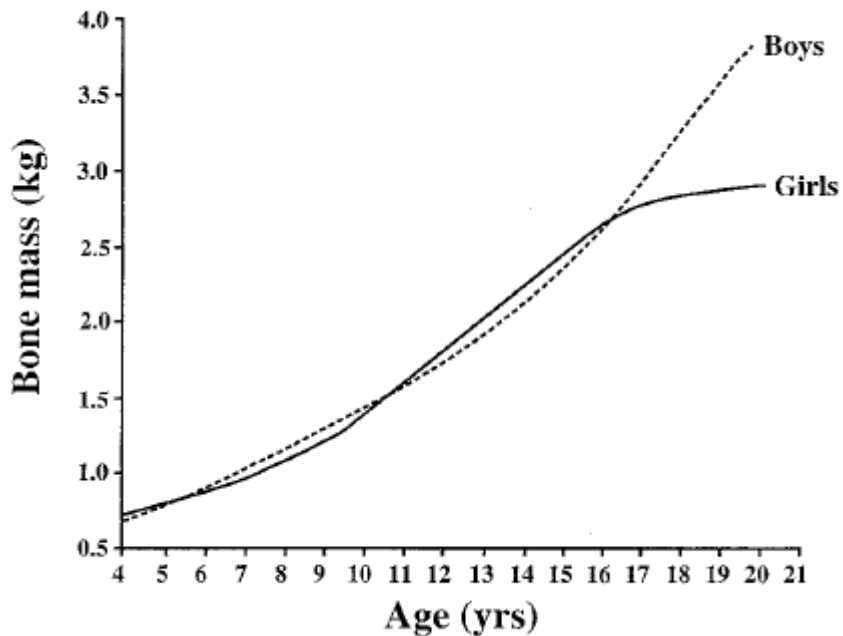
#### Synopsis . . . . .

*Osteoporosis in the elderly woman is determined by the amount of peak bone mass in adolescence, the*

50 PUBLIC HEALTH REPORTS SUPPLEMENT

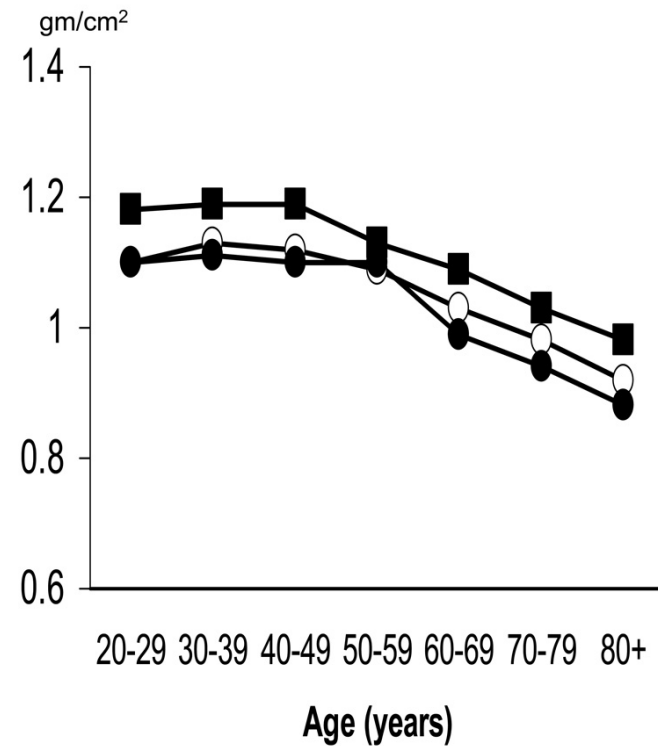
1. Chesnut, *Public Health Rep.* 104(suppl.), 50-54, 1989  
2. Anderson, *J. Amer. Coll. Nutrition*, 20, 186S-191S, 2001

# Bone Accrual vs. Age



## A. Women

○ NonHispanic white ■ NonHispanic black ● Mexican American



# Factors for Low Bone Mass in Adolescents

- Diet – e.g. low calcium intake<sup>1</sup>
- Physical Inactivity<sup>2</sup>
- Low Weight<sup>2</sup>
- Anorexia Nervosa<sup>3,4</sup>
- Athletic Energy Deficit<sup>5,6</sup>
- Smoking<sup>7</sup>
- Use of injectable contraceptive, DMPA<sup>8</sup>

1. Anderson, *J. Amer. Coll. Nutrition*, 20, 186S-191S, 2001

2. Boot *et al.*, *J. Clin. Endocrin. & Metab.*, 82, 57-62, 1997.

3. Bachrach *et al.* *Pediatrics* 86, 440-447, 1990.

4. Misra *et al.* *J. Clin Endocrinol Metab.* 93, 1292-1297, 2008.

5. Cobb *et al.* *Med & Sci in Sports & Exerc.*, 711-719, 2003.

6. [http://americanbonehealth.org/images/About\\_AED\\_Symposium\\_Press\\_Release\\_\\_FINAL.pdf](http://americanbonehealth.org/images/About_AED_Symposium_Press_Release__FINAL.pdf)

7. Dorn *et al.*, *J Adolescent Health* 52, 393-399, 2013.

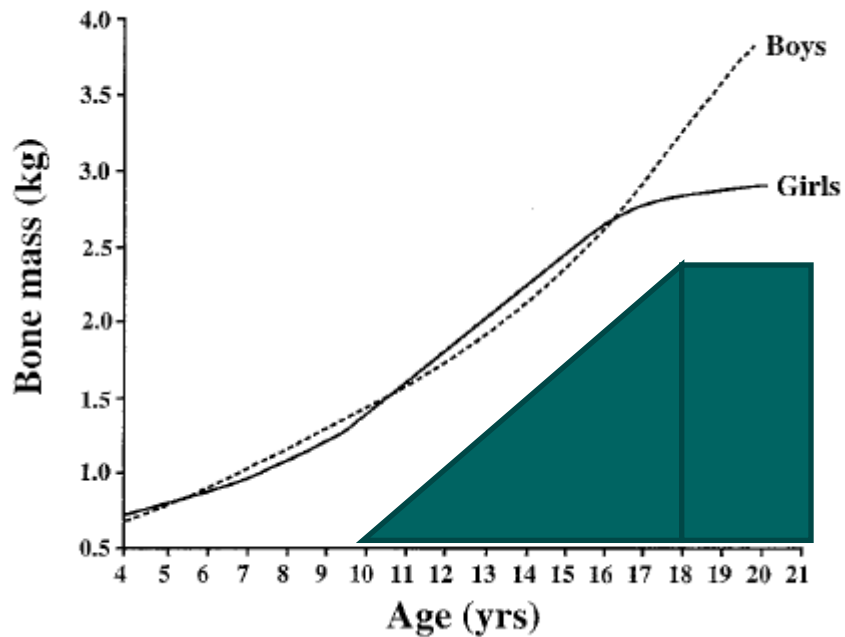
8. Scholes *et al.* *Arch Pediatr Adolesc Med.*, 159, 139-144, 2005.

# Promotion of Bone Mass in Adolescents

- Diet – e.g., calcium intake<sup>1-3</sup>
- Physical Activity<sup>1,4</sup>
- Estrogen (girls with anorexia nervosa)<sup>5</sup>
- Discouraging smoking<sup>6</sup>
- Discontinue use of contraceptive DMPA<sup>7</sup>

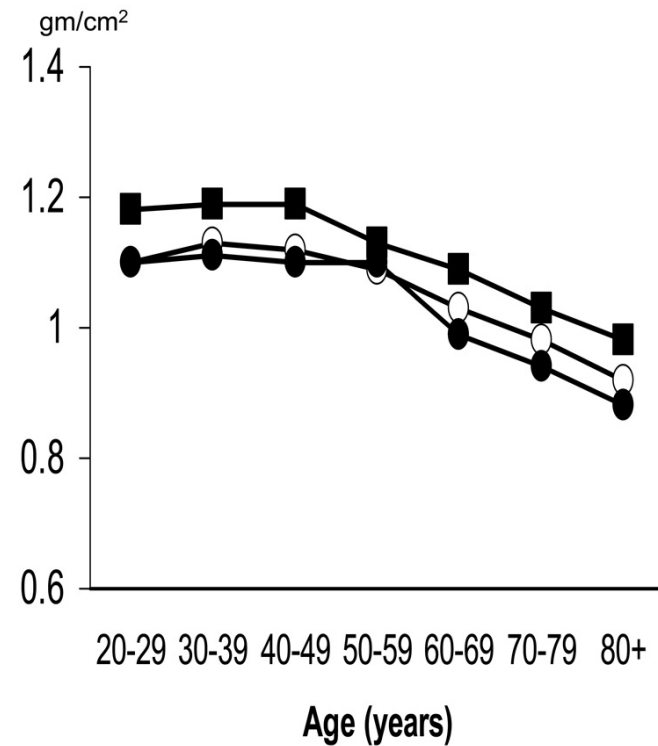
1. Anderson, *J. Amer. Coll. Nutrition*, 20, 186S-191S, 2001.
2. Johnson *et al.*, *N Engl J. Med.*, 327, 82-87, 1992.
3. Loud *et al.*, *Arch Pediatr Adolesc Med.*, 160, 1026-1032, 2006.
4. Belew & Gehrig, *Pediatr. Phys. Ther* 18, 19-22, 2006.
5. Misra *et al.*, *J Bone & Miner Res.*, 26, 2430-2438, 2011
6. Dorn *et al.*, *J Adolescent Health* 52, 393-399, 2013.
7. Scholes *et al.* *Arch Pediatr Adolesc Med.*, 159, 139-144, 2005.

# Bone Mass vs. Age



## A. Women

○ NonHispanic white ■ NonHispanic black ● Mexican American



# Challenges for QUS

- QUS devices should implement standardization methods to reduce variability of measurements.<sup>1,2</sup>
- Most criteria for osteoporosis drug therapies use DXA measurements as a standard. Equivalent criteria must be developed for QUS.
- Appropriate methods for interpreting QUS measurements on girls before they have attained peak bone mass must be developed.
- Not all QUS devices are appropriately sized for use in younger adolescents.

1. Wear, *J. Acoust. Soc. Am.*, 122, 636-644, 2007.

2. Wear, *IEEE Trans Ultrason., Ferro., Freq. Contr.*, 55, 1473-1479, 2008.

# Summary

- QUS on the calcaneus is effective for prediction of osteoporotic fractures.
- Because ultrasound devices are smaller, lighter, and less expensive than x-ray devices, they offer potential to expand bone testing to a much wider population.

# Disclaimer

- The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the FDA.