Quantitative Ultrasound in Diagnosis of Metabolic Bone Diseases

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Abstract: Currently, the diagnosis of osteoporosis is based on bone mineral density measurements using Dual Energy X-ray Absorptiometry (DXA). DXA provides information about quantitative content of calcium hydroxyapatite in the skeleton. From about 20 years Quantitative Ultrasound (QUS) measurements are used. QUS reveals both quantitative and qualitative (elasticity and microstructure) features of bone tissue and was used in several pathologic and physiologic conditions.

The most important are results of prospective studies showing the ability of QUS measurements to predict osteoporotic fractures. QUS was used in monitoring skeletal changes during therapy on osteoporosis. In several studied QUS measurements showed an ability to detect skeletal changes in children and adolescents and involutional changes at the skeleton. QUS measurements were also used in order to follow bone changes during pregnancy and lactation, glucocorticosteroid therapy, renal osteodystrophy, oncologic and rheumatic diseases, and prolonged immobilization.

Advantages of QUS are: lack of ionizing radiation, portability of devices and their relatively low cost.

Disadvantages of QUS include the lack of precise determination of measured bone features, measurements limited to peripheral skeleton, relatively poor precision and the lack of unification of several devices.

Currently, despite these limitations QUS is a validated method in diagnostic armentarium in metabolic bone diseases.

Keywords: Metabolic bone diseases, quantitative ultrasound.

INTRODUCTION

Currently, densitometric methods are the most commonly used in order to assess skeletal status in metabolic bone diseases. Early investigations were performed using ionizing methods (single photon absorptiometry - SPA and dual photon absorptiometry - DPA), and last years were a period of the development of Dual Energy X-ray Absorptiometry (DXA). DXA provides information on quantitative content of hydroxyapatite calcium in measured bones. Thus, DXA widely used in a clinical practice does not provide any data on bone qualitative features. It is well known that biomechanic competence of the skeleton is dependent both on bone mineral density (BMD) measured by DXA and qualitative features of bone like elasticity or microarchitecture. The role of bone quality is currently widely accepted and there is urgent need to develop new methods able to assess not only bone quantity.

Commercially available QUS machines measure several peripheral skeletal sites: calcaneus, phalanges, patella, radius or tibia.

Some methods may give additional data on bone tissue and among them are quantitative ultrasound (QUS) and high resolution quantitative computed tomography. QUS used since mid eighties shows several important advantages**:** an ability to assess some qualitative features of bone tissue, the lack of ionizing radiation, relatively low costs and small sizes of equipment. QUS has also some disadvantages involving difficulty in precise determination of measured bone tissue features, skeletal sites limited only to peripheral skeleton and relatively poor precision.

In the review, current data on the use of QUS are shown. Commonly, in reviews concerning QUS [1,2] in the scope of interest were mainly osteoporotic populations. It's obvious that osteoporosis is the most common metabolic bone disease but there are several other areas where is a necessity to follow bone status. Skeletal status changes during the whole life in physiologic (growth, involution) or pathologic states (endocrine disorders, side effects of some medications etc.). In further part of the review, an ability of QUS to detect bone changes is discussed.

CLINICAL ULTRASOUND BONE MEASUREMENTS SYSTEMS

Commercially available ultrasound systems measure several skeletal sites like calcaneus, tibia, patella, forearm, phalanges. The calcaneus is the most popular measurement site for several reasons: calcaneus consisted of almost only active metabolically trabecular bone may early express skeletal changes, is weight-bearing bone and is easily accessible. Early devices as a coupling medium - in order to allow a penetration of ultrasound waves - used a water bath and currently a standard ultrasound gel is more popular. Some devices available use contact-free systems of measurements. Fig. **1** and **2** show schematic representation of some ultrasound systems.

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1573-4056/05 $50.00+.00

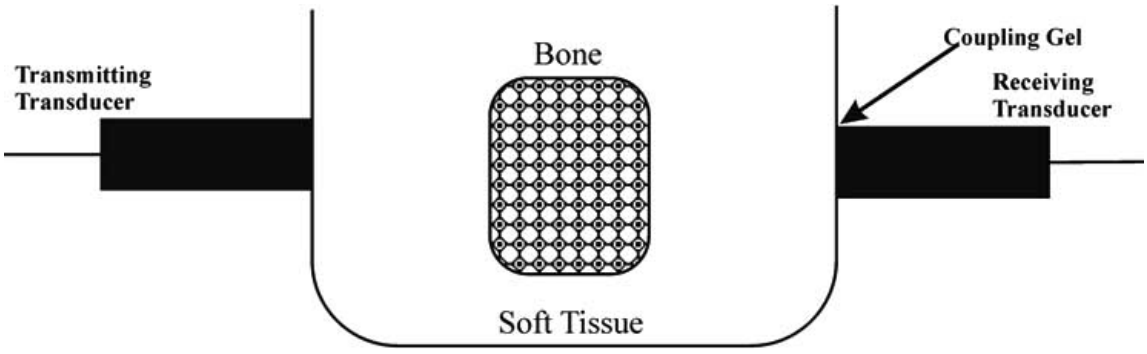

Fig. (1). Contact method of QUS measurement.

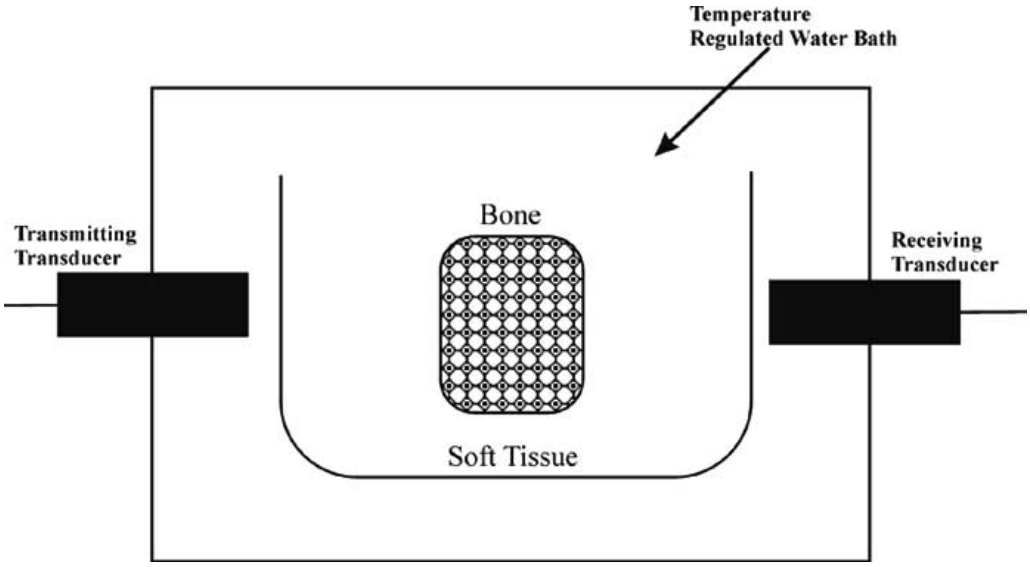

Fig. (2). Method of QUS measurement.

Ultrasound is a traveling mechanical vibration and the mechanical properties of the medium progressively alter the shape, intensity (energy per second per unit area) and speed of the propagation wave [1]. Therefore, the nature of the method being able to provide some qualitative bone features in addition to bone quantity seems to be especially promising.

One of the most important features of devices used in order to detect skeletal changes is their precision error. This aspect is especially important in longitudinal studies when small changes ought to be precisely assessed. CV (coefficient of variation) does not express range of QUS parameter. CV% values range from 0.3% to 4%, and standarized CV (SCV) defined as the percentage CV divided by the ratio of the range over the mean may be preferable. SCV values are almost 10%.

QUALITY OF BONE ASSESSED BY QUS

A potential of QUS to express qualitative features of bone seems to be one the most important advantages of the method. Bone diseases may affect both bone quantity and quality. It is well known that BMD is important but no sole determinant of biomechanical properties of skeleton [3]. Fundamental rules of biomechanics indicates that the strength depends not only on material quantity but also on its internal structure, size and biomechanical properties. It should be known that the risk of bone fracture depends on its density, internal structure (mainly trabecular anisotrophy, connectivity and porosity) and bone biomechanical properties.

QUS may provide some additional data on fracture risk because QUS parameters express both bone mass and bone quality. QUS measures two parameters: speed of sound (SOS) and broadband ultrasound attenuation (BUA). SOS is believed to express elasticity and bone mass, and higher SOS values are obtained in denser and more elastic bone tissue [4]. BUA is a function of absorption and dispersal of ultrasound wave, and is associated with density and structure of trabecular bone [4]. Studies *in vitro* confirm that SOS [5] and BUA [6] depend on biomechanical features of bone tissue expressed by Young modulus. Thus, QUS seems to be able to predict biomechanical properties of bone. In contrary

to DXA method, QUS expresses anisotropic properties of bone and internal structure of trabeculae [7]. Such data indicate that QUS may give some additional data to those given by densitometric evaluation of bone independent of BMD [6,8]. Some researchers consider that common use of QUS and BMD measurements may better express biomechanical competence of bone than BMD measurements alone [9], and others stated that QUS parameters are able to predict mechanical properties of bone independently of bone density [10].

It could be concluded that a potential of QUS to express some qualitative features of bones cannot be neglected. This ability of the method is the most promising area of future studies and a combination of data on qualitative bone features and bone quantity would lead to wider clinical applications in the future.

OSTEOPOROSIS

Assessment of fracture risk is a very important clinical problem, and comparisons of groups with and without fractures may show an ability to discriminate fractured and non-fractured subjects. QUS was used in several case-control studies (subjects with fractures versus subjects without fractures), and patients with past, low-energy fractures (due to minimal trauma caused by a fall from standing height or less) had significantly lower QUS values [11-18]. In these studies, fracture risk was assessed using Relative Risk (RR) in longitudinal studies or Odds Ratio (OR) in cross-sectional studies calculated as increasing risk per 1 standard deviation decrease in measured QUS parameter. OR usually ranged from to 1.5 do 4.0, and RR was close to 2.0.

The most important data on clinical utility of QUS in osteoporosis provide longitudinal studies. In some such studies the clinical utility of QUS was assessed [19-23], and calcaneal QUS measurements were able to predict future osteoporotic fracture.

The only one skeletal site besides calcaneus in fracture prediction were hand phalanges [24]. In some studies authors compared the value of DXA and QUS measurements and authors stated that fracture discrimination or prediction may be performed in a comparable manner using QUS and DXA [20,21,23,25]. Clinical utility of QUS was also evaluated using Receiving Operating Characteristic (ROC). ROC analysis allows to assess how the method may discriminate between subjects with and without fractures. ROC analysis plots a sensitivity versus specificity curve and summarizes the accuracy of used tool by estimating the area under the ROC curve (AUC). A perfect tool which correctly classifies individuals into a disease or no-disease state 100% of the time would have an AUC estimate of 1.0. AUC for QUS parameter ranged from 0.62 [23] to 0.96 [15]. An interesting algorithm how to use QUS in postmenopausal women was recently proposed by Gambacciani *et al.* [26] including several steps regarding current QUS results and clinical risk factors for osteoporotic fractures. According to this proposal it is possible to select only a part of population for further DXA measurements, thus reducing the costs and limiting the amount of patients exposed to ionizing radiation.

Concluding, QUS proved an utility in fracture risk assessment in osteoporotic populations, and may be easily recommended as a diagnostic tool at least in screening procedures.

STUDIES IN MALES

Many studies using QUS measurements were performed in female populations, and only some studies documented possibility of the method to detect also skeletal changes in males. Majority of them were conducted in normal, healthy males [27-32], and some studies were aimed to discriminate fractured from non-fractured males [33,34]. OR ranged from 1.05 to 3.4 [33,34]. Sensitivity and specificity of ultrasound measurements were also established and AUC were from 0.66 to 0.81 [33,34]. Prospective fracture studies are not available.

Generally, QUS parameters showed comparable trends in age-related changes as in female populations (in bone growth and bone involution) and were able to assess fracture discrimination. Ultrasound measurements at the calcaneus were able to discriminate between normal and osteoporotic male/female populations in a similar manner [35]. The most important weakness concerns the lack of prospective fracture studies confirming data from case-control studies, and further validation of QUS measurements in males are urgently needed.

THE EFFICACY OF PHARMACOLOGIC OSTEOPOROSIS MANAGEMENT

Currently, using available medications it is possible to treat osteoporosis and fracture risk is decreased. Several treatment options including bisphoshonates, PTH, estrogen receptor modulators, hormone replacement therapy (HRT), strontium ranelate or calcitonin proved their efficacy in fracture reduction in studies performed using rules of Evidence Based Medicine. It could be stated that these medications reduce new fracture occurrence by approximately 50%. Paralelly to fracture reduction, BMD increases only by some percents what emphasizes that not only bone quantity (=BMD), but also improvement in bone quality may contribute to fracture reduction. Bone quality is treated as an important factor influencing biomechanical competence of bone so QUS may play a significant role as a method assessing bone quality. QUS measurements proved ability to monitor therapeutic efficacy of alendronate [36] and HRT at the hand phalanges [14,37,38] and calcaneus [39]. One of the most important study was a prospective four-year observation of a group of 27 females [37]. In 56% of them, an increase was observed, and in majority of controls QUS parameters decreased. Other, important data were provided by Hadji *et al.* [39], who noted in 611 females on HRT constant increase in QUS values while in 1395 controls a decrease was observed.

Despite these promising results, relatively poor precision, especially expressed by SCV limits the possibility of longitudinal observation of bone changes and further use of a method on this area would be dependent on precision improvement.

SKELETAL GROWTH

Many years ago C. Dent stated that osteoporosis is a disease with roots in childhood and adolescence [40]. Therefore, studies of skeletal growth are an important part of

knowledge on human bone physiology and pathology. QUS seems to an excellent tool in assessment of skeletal status in young populations: it does not use ionizing radiation, duration of bone scans is short, and devices are portable. The knowledge on rate of skeletal growth, determination of age when this process is accelerated and age of peak bone mass achievement are essential factors in early prevention of osteoporosis. QUS measurements were performed mainly at the hand phalanges [32,41-44]. Especially important is a possibility to reveal a rapid bone changes in adolescents. This process accelerates at the age of 10-11 years in girls and two years later in boys, and phalangeal QUS measurements very well express these changes. It could be stated that generally QUS gives comparable view of bone growth processes as bone densitometry methods and may be easily used in children and adolescents.

INVOLUTION OF SKELETON

Age is one of the most important risk factor for osteoporotic fracture [45] and understanding of nature of bone loss occurred due to ageing may improve patients' management. Majority of QUS studies was based on heel measurements [13,27,35,46] but also other skeletal sites were used [15,47,48]. One of the most important contribution is given by multicentral European study on QUS hand phalanges measurements [15]. In this study a total of 10,115 females aged up to 100 years were assessed and measured QUS parameter was able to express bone changes over a whole period of observation. Generally, trends of changes in QUS parameters were comparable irrespective of site of measurements. It ought to be taken into consideration that trends of changes in QUS variables do not differ significantly from changes observed for DXA measurements, and QUS may be successfully used to detect bone changes over a whole period of life.

OTHER AREAS OF THE USE OF QUS

- Pregnancy and Lactation

Pregnancy and lactation may affect bone status. Due to obvious ethic reasons during pregnancy any ionizing radiation cannot be accepted and QUS may be easily used. In several studies QUS measurements at calcaneus [49,51,52] and hand phalanges [50,53] showed decreases during pregnancy. Till now no studies on pregnancy-associated osteoporosis using QUS were published. Pregnancy-associated osteoporosis is probably diagnosed too rare, and QUS could be of special interest in pregnant females.

- Assessement of Bone Side Effects of Therapies

The most important treatment affecting bone status is glicocorticotherapy, and in several studies QUS measurements showed an utility of calcaneal [54-57] and phalangeal measurements [58]. QUS variables were decreased in a course of therapy. Calcaneus consisted of almost only active metabolically trabecular bone seems to be better site of measurements in patients receiving glicocorticoids but also hand phalanges showed an ability to follow bone changes [58]. Hand phalanges as a mainly cortical bone may be more prone to express bone changes due to secondary hyperparathyroidism commonly present under this therapy. Hand phalanges and calcaneus showed also an ability to detect bone side effects in epileptic patients on long-term anticonvulsant therapy [59]. No prospective studies on the use of QUS in patients on therapy affecting bone status were published so far.

It seems that QUS could be especially fitted in patients on glicocorticoids because additional to diminution in bone quantity deterioration of bone quality is present, and further studies ought to validate the role of QUS. Despite these limitations it seems that yet published data allow to propose QUS as a useful method expressing bone-side effects of some therapies.

- Renal Osteodystrophy

In a course of renal failure skeleton is commonly affected and bone disturbances are called renal osteodystrophy. In about 50% of patients with mild and moderate renal insufficiency, in bone tissue are shown histologic abnormalities [40]. Renal osteodystrophy covers several quantitative and qualitative disturbances of bone tissue, and QUS seems to be especially fitted to follow such changes. In several studies measurements of calcaneus [60-63], hand phalanges [61,64-69] and tibia [70], QUS measurements were diminished in comparison to controls and correlated with densitometric measurements. Some of yet published studies were performed in children and adolescents [60-62], and QUS due to the lack of ionizing is especially profitable in young subjects.

QUS could be especially useful in subjects with end-stage renal failure because deterioration of bone quality and quantity are commonly present in such population. Further studies ought to validate the role of QUS in patients with renal failure, but it seems that yet published data allow to propose the use of QUS especially in children and adolescents.

- Oncologic Diseases

Prevalence of oncologic diseases increases steadily, and improvement in patients management is associated with longer life duration. Among many possible side effects of therapeutic regimes also a skeleton may be affected and there is urgent necessity to introduce methods which are able to detect them.

QUS was used in order to detect and monitor skeletal changes during chemotherapy and radiotherapy in children and adolescents with acute lymphoblastic leucaemia or other types of childhood malignancy [71-73]. In a prospective study by Lequin *et al.* [72], in a group of 36 children measured over a period of 3 years the most pronounced decrease in tibial QUS parameter was observed in first 6 months of therapy. After therapy completion slow process of improvement was noted. The study proved a possibility to monitor skeletal changes using QUS measurements. In other longitudinal study hand measurements were performed in survivors of acute lymphoblastic leucaemia and 3 years after therapy completion skeletal status did not differ between patients and controls [73]. It ought to be emphasized that the lack of ionizing radiation is especially important in young individuals with oncologic diseases and QUS could be used wider on this area.

- Rheumatology

In patients with rheumatoid arthritis (RA), a prevalence of hip and spine fractures is high [74]. Therefore, skeletal measurements in rheumatic patients may be important in order to assess fracture risk. Some studies have shown possibilities of QUS in evaluation of skeletal status in such subjects. Martin and al. [75] proved that calcaneal QUS measurements were significantly lower in patients with RA than in controls. Similar data were given by phalangeal measurements [76,77]. It seems that phalanges may be especially fitted in estimation of bone status because activity of a disease is high within hand. Low calcaneal QUS values were also shown in patients with lupus erythematosus [78].

- Immobilization

Long-term immobilization is one of well established risk factors of osteoporosis [79]. In stroke patients immobilization may lead to "hemiosteoporosis". In this group of patients are common hip fractures; 4-15% of total number of subjects with hip fractures occur in patients after stroke, and 79-100% of hip fractures were present within affected side [80,81]. Our yet unpublished data indicate that in patients being almost 3 years after a stroke, hand phalangeal measurements were significantly lower in affected side in comparison to opposite side. Haddaway *et al*. [82], in a group of 31 stroke patients being 1 month to 25 years (mean age is not given) did not observe differences between calcaneal QUS values in affected side versus results in opposite site. However, the authors observed a positive correlation of patients' mobility and QUS parameters.

In a prospective study by Warden *et al.* [83], a rapid rate of a decrease in calcaneal QUS measurements was observed in first two months following spine cord injury what proved an ability of method to monitor bone changes due to immobilization. Also in subjects after brain injury immobilized for long period calcaneal QUS values were diminished by 40% [84].

- Endocrinology

Disorders of endocrine system may significantly affect skeletal status. Among other methods also QUS was successfully used in order to assess bone side effects [85-89]. QUS values were decreased in patients with Cushing syndrome [85]. QUS was used to evaluate bone status in girls treated by growth hormone [89], and in women on long-term therapy using non-supressive doses of thyroid hormones QUS values at calcaneus were decreased in comparison to controls [88]. The latter observation seems of clinical importance because the number of females taking thyroid hormones is high and bone-side effects in this group of patients usually is not adequately estimated. An important endocrinological risk factor for osteoporosis is primary hyperparathyroidism, and in some studies calcaneal and phalangeal QUS was used to detect and monitor skeletal changes before and after surgery [85,87]. It was possible to detect baseline low values and to follow a process of recover after successful therapy.

- Other

QUS served also to follow bone status in other groups. In twins QUS proved an ability to assess an influence of genetic and environmental factors on bone status [90-92]. For example, phalangeal QUS measurements showed correlation within pairs of monozygotic twins as high as 0.96-0.98, and in dizygotic twins 0.92-0.93 [90]. Differences within pairs increased with age what demonstrates the ability of the method to follow changes due to environmental factors.

QUS measurements in mother and their daughters allowed to predict future QUS values in daughters [22]. In the study were evaluated 21 fractured mothers, their 21 daughters and 27 non-fractured mothers and their 27 daughters. As expected, mothers with past fractures had lower QUS values than other mothers, and the same view gave a comparison in daughters. Heritability of QUS values in daughters of mothers with fracture ranged from 52 to 76%, and only in their daughters future QUS values could be predicted as shown by stepwise, multiple regression analysis.

Recently, calcaneal QUS measurements showed an ability to detect an influence of cigarette smoking on current skeletal status what was not possible to obtain using DXA [93]. This study suggests that QUS was able to express some qualitative features of bone tissue what was not possible to obtain using routine densitometric measurements.

In some studies QUS was used as a method evaluating skeletal status in patients with genetic disorders and QUS values were lower both in calcaneus [94] and hand phalanges [95]. In 170 subjects with mental retardation QUS at the calcaneus showed low values in comparison to 108 healthy controls. Low phalangeal QUS results were noted in patients with Down syndrome, single-gene human defects and in other rare abberations but subjects with Marfan-Mass phenotype did not differ from controls [95].

An interesting data on strategy how to use QUS measurements in identification of women at high risk for hip fracture were shown by EPIDOS prospective study [96]. The study population consisted of 5910 women and four strategies to identify elderly women with risk for hip fracture greater than 20 per 100 woman-year were evaluated alone, QUS followed by densitometric measurement or densitometric measurement followed by clinical evaluation. The authors considered that a strategy including QUS followed by densitometric measurements allows to improve identification of women at high risk.

In several studies QUS parameters were correlated with DXA parameters and usually correlations between them were weak to moderate [1,2]. The lack of strong relationships is obvious because QUS and DXA express, at least partly, different features of bone tissue. Therefore, QUS and DXA ought to be treated rather as complementary than competitive methods.

CONCLUSIONS

Results of the studies described in the current paper indicate that a potential of QUS is really great. Despite worldwide use of QUS, this method is not commonly recommended in a clinical practice for bone metabolic diseases. What ought to be improved before acceptance of the value of QUS:

- firstly, basic studies ought to provide an exact information which bone features are measured by QUS (SOS or BUA only express some bone features),

- secondly, hip and spine could be measurable by QUS,

- thirdly, relatively poor precision needs corrections,

If these conditions would be fulfilled, the nature of QUS measurements will be better understood and allowed for wider clinical applications.

REFERENCES

[1] Njeh CF, Boivin CM, Langton CM. The role of ultrasound in the assessment of osteoporosis: a review. Osteoporos Int 1997; 7: 7-22.

[2] Gregg EW, Kriska AM, Salamone LM, *et al.* The epidemiology of quantitative ultrasound: a review of the relationships with mass, osteoporosis and fracture risk. Osteoporos Int 1997; 7: 89-99.

[3] Rice JC, Cowin SC, Bowmann JA. On the dependence of the elasticity and strength of cancellous bone apparent density. J Biomech 1999; 27: 1159-1168.

[4] Gluer C, Wu CY, Genant HK. Broadband attenuation signals depend on trabecular orientation: an *in vitro* study. Osteoporos Int 1993; 3: 185-191.

[5] Abendschein WF, Hyatt GW. Ultrasonics and physical properties of healing bone. J Trauma 1972; 12: 297-301.

[6] Han S, Medige J, Ziv I. Combined models of ultrasound velocity and attenuation for predicting trabecular bone strength and mineral density. Clin Biomech 1996; 11: 348-353.

[7] Njeh CF, Fuerst T, Diessel E, Genant HK. Is quantitative ultrasound dependent on bone structure? A reflection. Osteoporos Int 2001; 12: 1-15.

[8] Bouxsein ML, Coan BS, Lee SC. Prediction of the strength of the elderly proximal femur by bone mineral density and quantitative ultrasound measurements of the heel and tibia. Bone 1999; 25: 49-54.

[9] Lochmuller EM, Eckstein F, Zeller JB, *et al.* Comparison of quantitative ultrasound in the human calcaneus with mechanical failure loads of the hip and spine. Ultrasound Obstet Gynecol 1999; 14: 125-133.

[10] Cavani F, Fini M., de Terlizzi F, *et al.* Effect of trabecular orientation on mechanical resistance and ultrasound propagation in specimens of equine vertebrae. Ultrasound in Med. and Biol 2003; 29; 1777-1785.

[11] Bauer DC, Glüer CC, Genant HK, *et al.* Quantitative ultrasound and vertebral fracture in postmenopausal women. J Bone Miner Res 1995; 10: 353-358.

[12] Schott AM, Weill-Engerer S, Hans D, *et al.* Ultrasound discriminates patients with hip fracture equally well as dual energy X-ray densitometry and independently of bone mineral density. J Bone Miner Res 1995; 10: 243-249.

[13] Pluskiewicz W, Drozdzowska B. Ultrasonic measurement of the calcaneus in Polish normal and osteoporotic women and men. Bone 1999; 24: 611-617.

[14] Benitez CL, Schneider DL, Barrett-Connor E, *et al.* 2000 Hand ultrasound for osteoporosis screening in postmenopausal women. Osteoporos Int 11: 203-210.

[15] Wuster Ch, Albanese C, de Aloysio D, *et al.* Phalangeal osteosonogrammetry study: age-related changes, diagnostic sensitivity, and discrimination power. J Bone Miner Res 2000; 15: 1603-1614.

[16] Drozdzowska B, Pluskiewicz W. Quantitative ultrasound at the calcaneus in premenopausal women and their postmenopausal mothers. Bone 2001; 29 (1): 79-83.

[17] Drozdzowska B, Pluskiewicz W. The ability of quantitative ultrasound at the calcaneus to identify postmenopausal women with different types of non-traumatic fractures. Ultrasound Med Biol 2002; 28: 1491-1497.

[18] Drozdzowska B, Pluskiewicz W. The usefulness of quantitative ultrasound at the hand phalanges in the detection of different types of non-traumatic fractures. Ultrasound Med Biol 2003; 29: 1545-1550.

[19] Porter RW, Miller CG, Grainger D, Palmer SB. Prediction of hip fracture in elderly women: a prospective study. BMJ 1990; 29: 638-641.

[20] Hans D, Dargent-Molina P, Schott AM, *et al.* Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. Lancet 1996; 348: 511-514.

[21] Bauer DC, Gluer CC, Cauley JA, *et al.* Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women: A prospective study. Study of Osteoporotic Fractures Research Group. Arch Int Med 1997; 157: 629-634.

[22] Pluijm SMF, Graafmans WC, Bouter LM, *et al.* Ultrasound measurements for the prediction of osteoporotic fractures in elderly people. Osteoporos Int 1999; 9: 550-556.

[23] Huopio J, Kroger H, Honkanen R, Jurvelin J, Saarikoski S, Alhava E. Calcaneal ultrasound predicts early postmenopausal fractures as well as axial BMD. A prospective study of 422 women. Osteoopros Int 2004; 15: 190-195.

[24] Mele R, Masci G, Ventura V, *et al.* Three-year longitudinal study with quantitative ultrasound at the hand phalanx in a female population. Osteoporos Int 1997; 7: 550-557.

[25] Langton CM, Langton DK. Comparison of bone mineral density and quantitative ultrasound of the calcaneus: site-matched correlation and discrimination of axial BMD status. Br J Radiol 2000; 73: 31-35.

[26] Gambacciani M, de Aloysio D, Elia D, van der Mooren MJ, Hadji P, Wuster Ch. Quantitative ultrasound (QUS) of bone in the management of postmenopausal women. Maturitas 2004; 47: 139-149.

[27] Cepollaro C, Agnusdei D, Gonnelli S, *et al.* Ultrasonographic assessment of bone in normal Italian males and females. Br J Radiol 1995; 68: 910-914.

[28] Moris M, Peretz A, Tjeka R, *et al.* Quantitative ultrasound bone measurements: normal values and comparison with bone mineral density by dual X-ray absorptiometry. Calcif Tissue Int 1995; 57: 6-10.

[29] Langton CM, Langton DK. Male and female normative data for ultrasound measurement of the os calcaneus within the UK adult population. Br J Radiol 1997; 70: 580-585.

[30] Montagnani A, Gonelli S, Cepollaro C, *et al.* Quantitative ultrasound at the phalanges in healthy Italian men. Osteoporos Int 2000; 11: 499-504.

[31] Drozdzowska B, Pluskiewicz W. Skeletal status in males aged 7-80 years assessed by quantitative ultrasound at the hand phalanges. Osteoporos Int 2003; 14: 295-300.

[32] Halaba Z, Pluskiewicz W. Quantitative ultrasound in the assessment of skeletal status in children and adolescents. Ultrasound in Med & Biol 2004; 30: 239-243.

[33] Pluskiewicz W, Drozdzowska B. Ultrasound measurements at the calcaneus in men: differences between healthy and fractured persons and the influence of age and antropometric features on ultrasound parameters Osteoporos Int 1999; 10: 47-51.

[34] Mullemann D, Legroux-Gerot I, Duquesnoy B, *et al.* Quantitative ultrasound of bone in male osteoporosis. Osteoporos Int 2002; 13: 388-393.

[35] Pluskiewicz W, Drozdzowska B. Ultrasonic measurement of the calcaneus in Polish normal and osteoporotic women and men. Bone 1999; 24: 611-617.

[36] Gonelli S, Cepollaro C, Montagnani A, *et al.* Heel ultrasonography in monitoring alendronate therapy: a four-year longitudinal study. Osteoporos Int 2002; 13: 415-421.

[37] Mauloni M, Rovatti LC, Cadossi R, *et al.* Monitoring bone effect of transdermal hormone replacement therapy by ultrasound investigation at the phalanx: a four-year follow-up study. Menopause 2000; 7: 402-412.

[38] Pluskiewicz W, Drozdzowska B. Ultrasound measurements of proximal phalanges in Polish early postmenopausal women. Osteoporos Int 1998; 8: 578-583.

[39] Hadji P, Hars O, Schuler M, *et al.* Asssesment by quantitative ultrasonometry of the effects of hormone replacement therapy on bone mass. 2000 Am J Obstet Gynecol 182(3): 529-534.

[40] Dent CE. Keynote adress: problems in metabolic bone disease. W: Frame B, Duncan H. (ed.) Clinical aspects of metabolic bone disease. Amsterdam; Exerpta Medica 1973; 1-7.

[41] Baroncelli GI, Federico G, Bertelloni S, *et al.* G. Bone quality assessment by quantitative ultrasound of proximal phalanxes of the hand in healthy subjects aged 3-21 years. Pediatric Research 2001; 49: 713-718.

[42] Barkmann R, Rohrschneider W, Vierling M, *et al.* German pediatric reference data for quantitative transverse transmission ultrasound of finger phalanges. Osteoporos Int 2002; 13: 55-61.

[43] Halaba Z, Pluskiewicz W. The assessment of development of bone mass in children by quantitative ultrasound through the proximal phalanxes of the hand. Ultrasound Med Biol 1997; 23: 1331-1335.
[44] Zadik Z, Price D, Diamond G. Pediatric reference curves for multi-site quantitative ultrasound and its modulators. Osteoporos Int 2003; 14: 857-862.
[45] Espallargues M, Sampietro-Colom L, Estrada MD, Sola M, del Rio L, Setoain J. Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: a systemic review of the literature. Osteoporos Int 2001; 12: 811-822.
[46] Baran DT, Kelly AM, Karellas A, *et al.* Ultrasound attenuation of the os calcis in women with osteoporosis and hip fractures. Calcify Tissue Int 1988; 43: 138-142.
[47] Ventura V, Mauloni M, Mura M, *et al.* Ultrasound velocity changes at the proximal phalanges of the hand in pre-, peri- and postmenopausal women. Osteoporos Int 1996; 6: 368-375.
[48] Pluskiewicz W, Drozdzowska B. Ultrasound measurement of proximal phalanges in a normal Polish female population. Osteoporos Int 1998; 8: 349-354.
[49] Sowers M, Jannausch M, Scholl T, *et al.* The reproducibility of ultrasound bone measures in a triethnic population of pregnant adolescents and adult women. J Bone Miner Res 1998; 13: 1768-74.
[50] Aguado F, Revilla M, Hernandez ER, *et al.* Ultrasonographic bone velocity in pregnancy: a longitudinal study. Am J Obstet Gynecol 1998; 178 (5): 1016-1021.
[51] Fiore CE, Pennisi P, DiStefano A, *et al.* Pregnancy-associated changes in bone density and bone turnover in the physiological state: prospective data on sixteen women. Horm Metab Res 2003; 35: 313-318.
[52] To WWK, Wong MWN, Leung TW. Relationship between bone mineral density changes in pregnancy and maternal and pregnancy characteristics: a longitudinal study. Acta Obstet Gynecol Scand 2003; 82: 820-827.
[53] Pluskiewicz W, Drozdzowka B, Stolecki M. Quantitative ultrasound at the hand phalanges in pregnancy: a longitudinal study. Ultrasound in Med. and Biol 2004 (in press)
[54] Daens S, Peretz A, de Maerteler V. Efficiency of quantitative ultrasound measurements compared with dual-energy X-ray absorptiometry in the assessment of corticosteroid-induced bone impairment. Osteoporos Int 1999; 10: 278-283.
[55] Sambrook P, Raj A, Hunter D, *et al.* Osteoporosis with low dose corticosteroids: contribution of underlyeing disease effects and discriminatory ability of ultrasound versus bone densitometry. J Rheumatol 2001; 28: 1063-1067.
[56] Drozdzowska B. Skeletal Status Asssessed by Quantitative Ultrasound at the Calcaneus in Females with Bronchial Asthma on Prolonged Corticosteroid Therapy Ultrasound in Med. and Biol 2004; 30: 1057-1061.
[57] Drozdzowska B**.** Quantitative Ultrasound at the Calcaneus in Corticosteroid-treated Male Patients with Bronchial Asthma Maturitas 2004 (in press).
[58] Olivieri B, Di Gregorio S, Parisi MS, *et al.* Is ultrasound of bone relevant for corticosteroid-treated patients? A comparative study with bone densitometry measured by DEXA. Joint Bone Spine 2002; 70: 46-51.
[59] Pluskiewicz W, Nowakowska J. Bone status after long-term anticonvulsant therapy in epileptic patients: evaluation using quantitative ultrasound of calcaneus and phalanges. Ultrasound Med and Biol 1997; 23(4): 553-558.
[60] Malluche HH, Ritz E, Lange HP, *et al.* Bone histology in incipient and advanced renal failure. Kidney Int. 1976; 9: 355-362.
[61] Arici M, Erturk H, Altun B. Bone mineral density in haemodialysis patients: a comparative study of dual-energy X-ray absorptiometry and quantitative ultrasound. Nephrol Dial Transplant 2000; 15: 1847-1851.
[62] Peretz A, Penaloza A, Mesquita M, *et al.* Quantitative ultrasound and dual X-ray absorptiometry measurements of the calcaneus in patients on maintenance hemodialysis. Bone 2000; 27: 287-292.
[63] Taal MW, Cassidy MJD, Pearson D, *et al.* Usefulness of quantitative heel ultrasound compared with dual-energy X-ray absorptiometry in determining bone mineral of skeletal status in uremic patients. J Clin Densitom 1999; 2: 389-395.
[64] Montagnani A, Gonelli S, Cepollaro Ch, *et al.* Quantitative ultrasound in the assessment of skeletal status in uremic patients. J Clin Densitom 1999; 2: 389-395.
[65] Pluskiewicz W, Adamczyk P, Drozdzowska B, *et al.* Skeletal status in children, adolescents and young adults with end-stage renal failure treated with hemo- or peritoneal dialysis. Osteoporos Int 2002; 13: 353-357.
[66] Pluskiewicz W, Adamczyk P, Drozdzowska B, *et al.* Skeletal status in children and adolescents with chronic renal failure before onset dialysis of dialysis or on dialysis. Osteoporos Int 2003; 14: 283-288.
[67] Pluskiewicz W, Adamczyk P, Drozdzowska B, *et al.* Skeletal status in adolescents with end-stage renal failure: a longitudinal study. Osteoporos Int; 2004; 5 (in press).
[68] Przedlacki J, Pluskiewicz W, Wieliczko M, *et al.* Quantitative ultrasound of phalanges and dual-energy X-ray absorptiometry of forearm and hand in patients with end-stage renal failure treated with dialysis. Osteoporos Int. 1999; 10: 1-6.
[69] Rico H, Aguado F, Revilla M, *et al.* Ultrasound bone velocity and metacarpal radiogrammetry in hemodialysed patients. Miner Electrolyte Metab 1994; 20: 103-106.
[70] Foldes AJ, Arnon E, Popovtzer. Reduced speed of sound in tibial bone of haemodialysed patients: association with serum PTH level. Nephrol Dial Transplant 1996; 11: 1318-1321.
[71] Azcona C, Burghard E, Ruza E. Reduced bone mineralization in adolescent survivors of malignant bone tumors: comparison of quantitative ultrasound and dual-energy X-ray absorptiometry. J Pediatr Hematol Onc 2003; 25: 297-302.
[72] Lequin MH, Sluis IM, van den Heuvel-Eibrink MM, *et al.* A longitudinal study using tibial ultrasonometry as a bone assessment technique in children with acute lymphoblastic leukaemia. Pediatr Radiol 2003; 33: 162-167.
[73] Pluskiewicz W, Luszczynska A, Halaba Z, *et al.* Skeletal status in survivors of acute lymphoblastic leukemia assessed by quantitative ultrasound at the hand phalanges: a longitudinal study. Ultrasound in Med & Biol 2004; 30: 893-898.
[74] Gough AK, Lilley J, Eyre S, *et al.* Generalised bone loss in patients with early rheumatoid arthritis. Lancet 1994; 344: 23-27.
[75] Martin JC, Munro R, Campbell MK, *et al.* Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. Br J Rheumatol 1997; 36: 43-49.
[76] Diessel E, Alenfeld FE, Braun J, *et al.* Ultrasound measurements of structural in phalanges of patients with rheumatoid arthritis. J Bone Miner Res 1997; 12: S388.
[77] Njeh CF, Boivin CM, Gough A, *et al.* Evaluation of finger ultrasound in the assessment of bone status with application of rheumatoid arthritis. Osteoporos Int 1999; 9: 82-90.
[78] Lernbass I, Wutzl A, Grisar J, *et al.* Quantitative ultrasound in the assessment of bone status of patients suffering from rheumatoid diseases. Skeletal Radiol 2002; 31: 270-276.
[79] Donaldson ChL, Hulley SB, Vogel JM, *et al.* Effects of prolonged bed rest on bone mineral. Metabolism 1970; 19(12): 1071-1084.
[80] Mulley G, Espley AJ. Hip fracture after hemiplegia. Postgrad Med J 1979; 55: 264-265.
[81] Poplingher AR, Pillar T. Hip fracture in stroke patients. Acta Orthop Scand 1985; 56: 226-227.
[82] Haddaway M, Davie MWJ, Steele R. Ultrasound densitometry of the os calcis in patients with hemiparesis following a cerebrovascular accident. Calcif Tissue Int 1999; 65: 436-441.
[83] Warden SJ, Bennell KL, Matthews B, *et al.* Quantitative ultrasound assessment of acute bone loss following spinal cord injury: a longitudinal pilot study. Osteoporos Int 2002; 13: 586-592.
[84] Meys E, Sutter B. Bone loss after traumatic brain injury: cross – sectional study using Quantitative Ultrasound of the calcaneus. Osteoporos Int 1999: 8: 523 (abstract 106).
[85] Bolanowski M, Pluskiewicz W. Quantitative ultrasound of the hand phalanges and calcaneus revealed skeletal abnormalities due to primary hyperparathyroidism: a case report. Ultrasound Med Biol 2002; 28: 265-269.
[86] Cortet B, Cortet C, Blanckaert F, *et al.* Quantitative ultrasound of bone and markers of bone turnover in Cushing's syndrome. Osteoporos Int 2001; 12: 117-123.
[87] Gonelli S, Montagnani A, Cepollaro C, *et al.* Quantitative ultrasound and bone mineral in patients with primary hyperparathyroidism before and after surgical treatment. Osteoporos Int 2000; 11: 255-260.

[88] Hadji P, Hars O, Sturm G, *et al.* The effect of long-term, non-suppresive levothyroxine treatment on quantitative ultrasonometry of bone in women. Eur J of Endocrinol 2000; 142: 445-450.

[89] Kapteijns-van Kordelaar S, Noordam K, *et al.* Quantitative calcaneal ultrasound parameters and bone mineral density at final height treated with depot gonadotrophin-releasing hormone agonist for central precocious puberty or idiopathic short stature. Eur J Pediatr 2003; 162: 776-780.

[90] Drozdzowska B, Pluskiewicz W, de Terlizzi T. Quantitative ultrasound at the hand phalanges in monozygotic twins: a preliminary report. Ultrasound Med Biol 2002; 28: 1153-1156.

[91] Howard GM, Nguyen TV, Harris M, Kelly P, Eisman JA. Genetic and environmental contributions to the association between quantitative ultrasound and bone mineral density measurements study: a twin study. J Bone Miner Res 1998; 13: 1318-1327.

[92] Knapp KM, Andrew T, MacGregor AJ, Blake GM, Fogelman I, Spector TD. In investigation of unique and shared gene effects on speed of sound and bone density using axial transmission quantitative ultrasound and DXA in twins. J Bone Miner Res 2003; 18: 1525-1530.

[93] Bernaards CM, Twisk JWR, Snel J, van Mechelen W, Lips P, Kemper HCG. Smoking and quantitative ultrasound parameters in the calcaneus in 36-yesr-old men and women. Osteoporos Int 2004; 15; 735-741.

[94] Aspray TJ, Francis RM, Thompson A, Quilliam SJ, Rawlings DJ, Tyrer SP. Comparison of ultrasound measurements at the heel between adults with mental retardation and control subjects. Bone 1998; 22: 665-668.

[95] Pluskiewicz W, Pyrkosz A, Drozdzowska B, Halaba Z. Quantitative ultrasound of the hand phalanges in patients with genetic disorders: a pilot case-control study. Osteoporos Int 2003; 14: 787-792.

[96] Dargent-Molina P, Piault S, Breart G. A comparison of different screening strategies to identify elderly women at high risk of hip fracture: results from the EPIDOS prospective study. Osteoporos Int 2003; 14: 969-977.

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