J. Pure Appl. Ultrason. **27** (2005) pp. 55-60

Quantitative ultrasound technique for the assessment of osteoporosis and prediction of fracture risk

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Osteoporosis in men and women is increasingly recognised as an important health issue. Bone mineral density (BMD) and bone strength appears to be major determinants of osteoporotic fracture. Measurement of bone strength by ultrasound is found to be a competitive means of measuring osteoporotic fracture risk and provide additional information about bone's structure and composition. In the present work quantitative ultrasound assessment of osteoporosis is carried out in Indian men and women by measuring broadband ultrasound attenuation (BUA) and speed of sound (SOS) through calcaneum bone to provide a clinical measure called the stiffness index (SI). The SI is the sum of the scaled and normalised BUA and SOS values, which is a measure of bone strength and is sensitive to bone structure used to predict the risk of bone fracture due to osteoporosis. Measurement of SI is carried out in 283 men, 108 premenopausal and 85 postmenopausal women. SI results expressed as T-score and Z-score are used to assist the physicians in the diagnosis of osteoporosis. The presence of osteoporosis is defined as T-score lower than -2.5. Observation shows that osteoporosis is predominant in postmenopausal women population who are at greater risk of fracture compared to premenopausal women and men. The effect of age, weight, height and body mass index (BMI) on SI in men and women is analyzed. The SI has negative correlation with age and is found to be a significant factor in both men and women with a high percentage of bone mineral loss in early menopausal women. In univariate analysis body weight and BMI have moderate positive correlation with SI in men and women. Height seems to have no significant effect on SI. There is a rapid loss of bone mineral content leading sudden decrease in SI during the first five years after menopause and it continues to decrease at a lesser rate with increasing age.

INTRODUCTION

Osteoporosis is defined as a systematic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture [1-2]. The osteoporosis population is ever increasing and studies in both advanced and developing nations indicate high prevalence of osteoporosis. Osteoporosis affects an estimated 75 million people in Europe and United States, of which about 75% are women [3]. Estimated number of hip fractures worldwide due to osteoporosis is expected to rise three-fold by the middle of the century [4]. In India, accurate data is not available at present, but osteoporosis is found to be epidemic due to increasing population of elderly men and women, and an unprecedented increase in patients suffering from fractures, thereby implying an urgent need for early detection, diagnosis and preventive strategies.

The diagnosis and clinical management of osteoporosis relies mainly on the measurement of bone density, because low bone density is associated with future risk of atraumatic and fragility fractures. During the last three decades several techniques have been developed for the measurement of bone density which are safe, precise, and accurate. Most of these techniques used some form of ionizing radiation (x-rays), and the measurement obtained is based on the attenuation of a beam of energy as it passes through bone and soft tissues. Although bone density shows a high correlation with bone strength, as much as 25-30% of the observed variation in bone strength may be due to the cumulative and synergistic effects of other factors, such as bone microstructure, architecture, and state of remodelling [5-6]. Bone density measurements are incapable of measuring directly the effects of any of these factors on bone. In particular a measure of the biomechanical competence of the skeleton cannot be obtained using bone densitometer technique [7].

The use of acoustic energy in the form of ultrasound wave has been suggested as possible choice for the assessment of bone integrity and to determine bone's response to mechanical loads to predict the risk of fracture [8]. As a mechanical wave ultrasound may have the ability to provide information on several properties of bone since it interacts with bone in a fundamentally different way compared with ionizing electromagnetic radiation. This, combined with the fact that ultrasound involves no radiation and is relatively simple to implement and process, accounts for the widespread interest it has received recently. Ionizing radiation attenuates at the atomic level whereas ultrasound attenuates at the macroscopic structural level. However, what distinguishes ultrasound from bone densitometry is the potential for sound to be modified by bone's structure, composition, and mass in such a way as to provide additional information about the tissue which can be related to the mechanical competence of the skeletal condition. Moreover, quantitative ultrasound does not measure the density or content of bone mineral directly, it has frequently been described as a measure of bone quality [9]. There is a need to understand the relationship between the biomechanical properties of bone and the probability of a fracture risk using ultrasound.

There are two basic approaches for ultrasonic interrogation of materials exist. The first uses a single transducer that acts as both transmitter and receiver. This is known as the 'reflection mode' and it is the method used to produce medical ultrasound images. In this mode, a portion of the ultrasound signal is reflected back to the transducer whenever a change in the acoustic properties of the media occurs. The reflection mode is simple to implement, as it requires only a single transducer. The alternative approach for tissue analysis uses two transducers, one acting as transmitter and the other as a receiver of the ultrasound wave. This method is known as the 'transmission mode'. In this approach, the acoustic properties of the tissue can be obtained by comparing the received signal with a standard or reference waveform. The transmission mode requires two transducers, as well as access to both sides of the interrogated tissue. Transmission mode ultrasound has been used in assessment of bone strength and quality. The ability of an ultrasound wave to provide information about the medium or tissue through which it is being propagated depends on the way by which the wave is altered by the medium. Two principal types of alteration can occur: (i) the medium can alter the velocity of the wave, and (ii) the medium can reduce the amount of energy transmitted and thereby attenuate the wave.

MATERIALS AND METHODS

In the present work, Achilles Express bone ultrasonometer is used to evaluate bone status by measuring stiffness index in the heel (calcaneus bone) for the diagnosis and assessment of osteoporosis as shown in Figure 1. A typical ultrasonometer consist of high frequency ultrasound transmitter (Tx) and receiver (Rx), liquid crystal display (LCD), foot positioner, water filled membranes, calf support, strap and a toe peg. Measurements are performed with patient seated, with left foot placed on the foot positioner. The LCD consists of a menu for the measurement of patient data and display of results. Foot positioner keeps the patient's foot stationary during the measurement. The membranes are filled with water to provide coupling of the ultrasound signal from the transducer to the heel. Calf support aligns the heel with the transducer and the strap holds the leg and calf in the proper position. Toe peg helps the patient to keep the foot stationary and keep the heel aligned with transducers during measurement.

The choice of the calcaneus as a measurement site is validated by the fact that it contains 75 - 90% cancellous bone by volume 10-11. Cancellous bone is eight times more metabolically active than cortical bone and age and disease related bone loss are more readily apparent at sites where there is a high percentage of cancellous bone. Moreover, calcaneus is highly stressed and weight-bearing bone and very active in remodeling process that shows changes within bone tissue earlier than compact bone. There is little soft tissue surrounding the calcaneus bone making it an excellent site for measurement and hence determination of a patients risk of fracture.

The heel is surrounded by warm water encapsulated in inflated membranes, because water is the optimum medium for the transmission of ultrasound. A transducer on one side of the heel (Tx) converts an electrical signal into sound wave, which passes through water membranes and the patient's heel. A transducer at a fixed distance on the opposite side of the heel (Rx) receives the sound wave and converts it to an electrical signal that is analyzed by the Achilles Express program. The instrument measures the speed of sound (SOS) and the frequency dependent broadband ultrasound attenuation (BUA), and combines them to form a clinical measure called stiffness index (SI).

Speed of Sound (SOS)

Measurement of SOS in the heel involves accurate determination of the transit time (time of flight) of a sound wave as it passes through the heel. Transit time (Δt) is the elapsed time between the beginning of the transmitted wave pulse on one side of the heel and the beginning of the received wave pulse on the other side of the heel. The time is measured using high frequency, crystal controlled clock. SOS value is directly proportional to the bone mineral density.

Broadband Ultrasound Attenuation (BUA)

Measurement of BUA involves sending a broadband ultrasound pulse through the bone and measuring the reduction in intensity at different frequencies. Sending a voltage spike into the transducer generates a sound wave with a wide frequency spectrum ranging from 200-1000 kHz (a broadband pulse) with the strongest power signals centered at 500 kHz. This broadband frequency spectrum allows measurement of attenuation to occur over a range of frequencies. The bone acts as a low-pass filter allowing lower frequency sound to pass through with relatively little loss while transmission of higher frequencies is substantially impaired, or attenuated. Subtracting the values in this spectrum from a spectrum obtained by transmitting a sound wave through a weakly attenuating reference medium, such as water, provides the net attenuation at each frequency. A regression line is then drawn through the points on

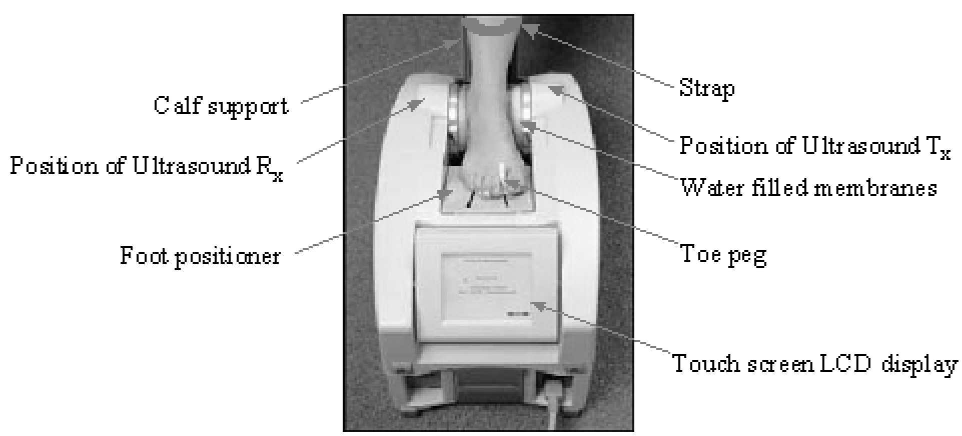

Fig. 1. Schematic of Achilles Express bone ultrasonometer

the net attenuation curve to obtain the attenuation slope (dB/MHz). Langton et al (1990) found that the preferential attenuation of the higher frequencies was greater in strong bone than it was in weak bone.

Stiffness Index (SI)

Stiffness Index which represents bone mineral density, combines BUA and SOS into a single clinical measure that has a lower precision error than either variable alone. This index is formulated by normalizing BUA and SOS through subtracting the lowest observable values (50 dB/MHz and 1380 m/sec) from each and then scaling the resultant values. The stiffness index is the sum of the scaled and normalised BUA and SOS values. The resultant formula is empirically derived such that the index has 50% contribution due to SOS and 50% contribution from BUA.

$$SI = [(0.67 * BUA) + (0.28 * SOS)] - 420$$

The SI is scaled in such a way to make the young adult value equal to 100. The normalised and scaled BUA and SOS values contribute about equally to the resulting stiffness index over the adult age range. Stiffness index results expressed as T-score and Z-score are used to assist physicians in the diagnosis of osteoporosis.

T-score and Z-score

The T-score is the most significant parameter for the assessment of osteoporosis, which compares BMD of the subject with average BMD of young normal population. T-score above -1 is normal, between -1 to -2.5 is osteopenic (early stage of osteoporosis), and T-score lower than -2.5 is osteoporotic which is an indication of risk of fracture. Z-score compares BMD of the subject with average BMD of a population of the same age. This comparison determines whether the subject deviates from the normal pattern for his/her age and sex.

Data Collection

The study was conducted at Institute Hospital, IIT-Madras. Study includes 108 premenopausal women between 24 and 50 years of age, 85 postmenopausal women between 45 and 78 years, and 283 men between 30 and 68 years of age. Informed consent was obtained from all the subjects and the study was approved by the local ethics committee. Postmenopausal women had natural menopause. Table 1 presents the baseline characteristics of three groups: men, premenopausal and postmenopausal women.

RESULTS AND DISCUSSION

Assessment of osteoporosis based on T-score was carried out and the results are presented in Table 2. Results show that the percentage of osteoporosis cases are more in postmenopausal women (~ 45%) compared premenopausal women (~ 4%) and men (~ 9%). Because of higher age

Table 1. Baseline characteristics

Characteristics	Premenopausal women	Postmenopausal women	Men
Number of subjects	108	85	283
Age (years)	43.3 (4.9)	53.1 (6.0)	50.3 (8.2)
Height (cm)	154.8 (5.6)	155.0 (6.0)	165.9 (6.9)
Weight (kg)	59.4 (7.8)	57.4 (8.3)	65.14 (9.35)
BMI (kg/m^2)	23.9 (3.4)	23.8 (3.67)	23.7 (3.4)
Age at menopause	-	48.8 (2.8)	-
Years since menopause	-	10.7 (7.8)	-

Data presented as Mean (SD)

Table 2. Assessment of osteoporosis based on T-score

Group	N	Normal	Osteopenia	Osteoporosis
Premenopausal women	108	65	39	04
Postmenopausal women	85	22	25	38
Men	283	151	106	26

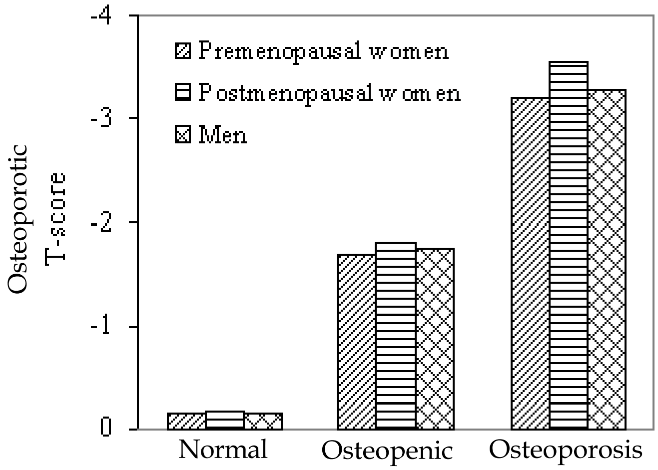

Fig. 2. Average T-score in pre and postmenopausal women and in men

group, the percentage of osteoporosis cases are higher in men compared to premenopausal women.

Figure 2 shows the average T-score value for pre and postmenopausal women and men in normal, osteopenic and osteoporotic condition. The average T-score is found to be very low in osteoporotic postmenopausal women compared to premenopausal women and men and they are at a greater risk of encountering osteoporotic fractures.

The variation of SI with age in pre and postmenopausal women and in men is statistically analysed by linear regression analysis. Relationship between SI and age is established using Pearson's coefficient of correlation (r). The intergroup comparisons were made by Student's t-test in order to find significance of the mean SI values. All statistical analysis are carried out at 95% confidence level. Mean values of SI and results of regression analysis are presented in Table 3. Mean SI in postmenopausal women is low and significantly differs ($P<0.0005$) from that of premenopausal women and men. There is no significant difference in the mean value of SI between men and premenopausal women ($P>0.05$).

Correlation analysis showed significant relationship between age and SI. Strongest negative coefficient correlation was noted in postmenopausal women ($r = -0.60$, $P<0.0001$). Moderately negative correlation was noted in premenopausal women ($r = -0.40$, $P<0.0001$) and in men ($r = -0.41$, $P<0.0001$). Linear regression equations are used to plot the variation in SI in men and women with age as shown in Figure 3.

From regression equation it is found that bone stiffness decreases at a normal rate of 7-8% per decade in premenopausal women. After menopause due to estrogen deficiency bone mineral loss increases drastically, due to which bone stiffness decreases at a faster rate of 10-11% per decade in postmenopausal women. The increased rate of bone mineral loss impairs bone quality and strength leading to osteoporosis and increased risk of fracture. The variation of SI with age in men is found to be low with bone stiffness decreasing at a rate of 7-8% per decade. Since peak bone mass is found to be high in men, they are at a lesser risk of encountering osteoporotic fracture compared to women. There is a rapid loss of bone

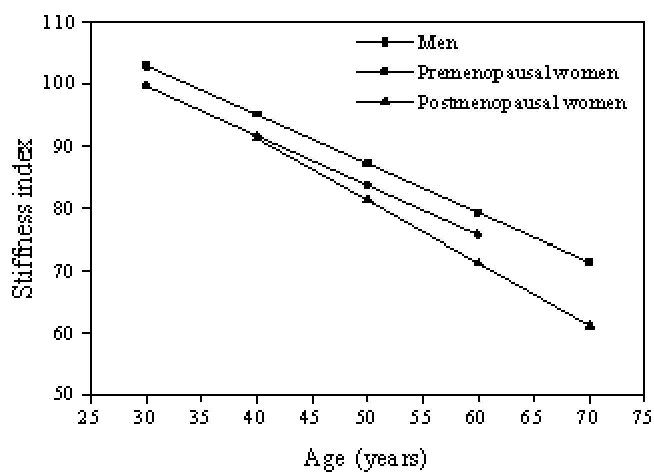

Fig. 3. Change in stiffness index with age in pre and postmenopausal women and in men.

Table 3. Correlation and regression analysis of ultrasound SI with age in men and women

	Group	Stiffness Index mean (SD)	Correlation coefficient (r)	Linear regression equation
1	Premenopausal women	86.53 (11.15)	- 0.40	(-0.80 * Age) + 123.6
2	Postmenopausal women	77.46 (10.78)	- 0.60	(-1.001 * Age) + 131.2
3	Men	86.89 (15.84)	- 0.41	(-0.79 * Age) + 126.6

Between 1 and 2, P<0.0005. Between 2 and 3 P<0.0005. Between 1 and 3, P>0.05

Table 4. Correlation of weight, height and BMI with SI

Factor	Correlation coefficient (r)	P	Regression equation (Stiffness index)
Weight	0.40	< 0.0001	(0.587 * Weight) + 0.848
Height	0.02	> 0.1000	(0.02 * Height) + 78.82
BMI	0.41	< 0.0001	(1.29 * BMI) + 51.39

mineral content leading sudden decrease in SI (11-12%) during the first five years after menopause and later it continues to decrease at a lesser rate with increasing age.

To study the effect of few other factors such as weight, height and BMI on bone stiffness, the data is statistically analyzed by liner regression and their relation with SI is established by Pearson's coefficient of correlation (r). The results are as shown in Table 4.

The body weight has moderately significant positive relationship with SI ($r = 0.4$, $P<0.0001$). Body height does not show any significant relationship with SI ($r = 0.02$, $P>0.1$). A moderately significant positive correlation is found between BMI and SI ($r = 0.41$, $P<0,0001$), indicating increase in SI with increase in BMI. Regression equations are used to find the change in SI with weight and BMI. SI increases at a rate of 1-1.2% per kg/m2 increase in BMI which is found to be two fold high compared to rate of increase in SI with weight which is found to be 0.5-0.6% per kg. It is concluded that women with higher BMI and body weight are associated with higher SI, indicating a greater bone mass and strength, which will be protective against osteoporotic fractures.

CONCLUSION

It is concluded that QUS can be effectively used to study the bone mineral loss and QUS clearly distinguishes between normal and osteoporotic subjects and can be a useful index in clinical management of osteoporosis. Risk factors help in the better assessment of bone mineral loss and osteoporosis.

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