Dielectric Characterization of Diseased Human Trabecular Bones at Microwave Frequency

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Abstract

The objective of this study is to determine whether *in vitro* dielectric properties of human trabecular bones, can distinguish between osteoporotic and osteoarthritis patients' bone samples. Specifically this study enlightens intra-patient variation of trabecular bone microarchitecture and dielectric properties, inter-disease comparison of bone dielectric properties, and finally establishes the correlation to traditional bone histomorphometry parameter (bone volume fraction) for diseased bone tissue. Bone cores were obtained from osteoporotic and osteoarthritis patients ($n = 12$). These were scanned using microCT to examine bone volume fraction. An open-ended coaxial probe measurement technique was employed to measure dielectric properties over the 0.5 – 8.5 GHz frequency range. The dielectric properties of osteoarthritis patients are significantly higher than osteoporotic patients; with an increase of 41% and 45% for relative permittivity and conductivity respectively. The dielectric properties within each patient vary significantly, variation in relative permittivity and conductivity was found to be greater than 25% and 1.4% respectively. A weak correlation ($r = 0.5$) is observed between relative permittivity and bone volume fraction. Osteoporotic and osteoarthritis bones can be differentiated based on difference of dielectric properties. Although these do not correlate strongly to bone volume fraction, it should be noted that bone volume fraction is a poor predictor of fracture risk. The dielectric properties of bones are found to be influenced by mineralization levels of bones. Therefore, dielectric properties of bones may have potential as a diagnostic measure of osteoporosis.

Keywords: Dielectric properties, Bone volume fraction, Osteoporosis, Osteoarthritis, Open-ended coaxial probe.

1. Introduction

The phenomena of electromagnetic (EM) wave reflection and propagation through biological tissues can be characterized by dielectric properties namely, the relative permittivity and conductivity [1]. Dielectric properties of biological tissues have formed the basis for the development of a number of EM diagnostic and therapeutic medical devices [2], [3]. Some applications of dielectric properties of biological tissues include microwave hyperthermia for breast cancer treatment [4], microwave imaging for breast health monitoring [5] and microwave ablation for treating liver, lung, kidney and adrenal tumours [6], [7]. Microwave imaging has been used to measure *in vivo* dielectric properties of the breast, and recently to measure the dielectric properties of calcaneus bone [5], [8]. It has been proposed that the dielectric properties of bones can be used to monitor osteoporosis [9], [10]. Bone dielectric properties are influenced by mineralization and it was proposed that a dielectric property based medical device could diagnose osteoporosis [8], albeit that this has never been established.

Osteoporosis is characterized by continuous progressive loss of bone density and systematic deterioration of trabecular bone microarchitecture, which leads to bone fragility and fracture [11]. Annually, osteoporosis results in 8.9 million fractures worldwide [12]. Almost 50% of women and 25% of men aged above 50 years in the US experience an osteoporotic fracture, and approximately 43.6 million suffer from osteopenia, a term used to describe low bone density [8], [13], [14]. In the EU a hip fracture is reported after every 30 seconds, and about 1700 fractures are reported per day [15]. Due to an aging population, these fractures are expected to double by 2050 and by 2025 the economic burden will be $25.3billion [16].

Dual-energy X-ray absorptiometry (DXA) is the standard modality for clinical diagnosis of osteoporosis [17], [18]. DXA calculates the bone mass from the Bone mineral density (BMD, g/cm^2) of central (hip, lumbar spine) and peripheral sites (heel, distal forearm) [18]. Bone volume fraction (BV/TV) encompasses changes in the trabecular bone volume [9], [10] and can also inform detection of osteoporosis [10]. DXA scan uses ionizing radiation, and therefore frequent DXA scans are associated with long term health risks [8]. Further, DXA systems are expensive and not portable. Therefore, a low cost, portable and non-ionizing diagnostic device is required for monitoring of osteoporosis [19]. Most importantly, BMD commonly fails to identify individuals that are likely to experience fracture [20], because it does not capture bone quality which is dictated by tissue microarchitecture, composition and the degree of microdamage, each of which contribute to different degrees to fracture risk. A microwave imaging device could potentially be used for diagnosis of osteoporosis to overcome the limitations of existing approaches [21]. However, the development of such a device requires detailed knowledge of the dielectric properties of diseased and normal human bones and quantification of their relationship to bone mineralization.

Experimental work has been performed over the last four decades to characterize bone dielectric properties [10]. Numerous studies were performed to measure dielectric properties of bone, both in the low frequency range [22–30,30,30–32] and in the microwave frequency range [8–10,19,33–36]. A comprehensive review on bone dielectric properties in microwave frequency range was reported by Amin *et al.* [15]. The authors reported that most studies measured dielectric properties of trabecular and cortical bone samples from porcine or bovine animals. Comparative analysis of these studies found significant differences between dielectric properties of trabecular and cortical animal bone samples. The differences in the dielectric properties were attributed to source of bone location which is associated with inherent variability in bone composition and microstructure, measurement techniques, and sample preparation. There were only two studies that measured dielectric properties of human bone samples. Meaney *et al.* [8] reported *in vivo* dielectric properties of human bone by using Microwave tomography imaging (MTI) for a frequency range of 900-1700 MHz. However, this study only considered two patients suffering from lower leg injury and

dielectric properties were reported at a single frequency of 1300 MHz. Therefore, due to limited sample size, no definite conclusion regarding dielectric properties of human bones can be drawn from these results. Irastorza *et al.* [10], measured *in vitro* dielectric properties of human trabecular bones using Open Ended Coaxial Line (OECL) probes in the frequency range of 100-1300 MHz. In this study, bulk dielectric properties of human trabecular bone samples were estimated from bone samples submerged in phosphate buffered saline (PBS). The patients were going through total hip replacement surgery. The dielectric properties of human trabecular bone were observed to be significantly high compared to dielectric properties of animal trabecular bone samples [15]. The fact that only two studies have been conducted on human bone with limited sample size ($n = 2, 6$) motivates further studies on characterization of human bone dielectric properties. Indeed, no study has ever measured diseased human bone samples, which is of paramount importance for development of EM-based diagnostic and therapeutic medical devices for bone diseases.

The variation in bone dielectric properties with respect to bone mass parameters (BMD and BV/TV) has been reported in previous work by Meaney *et al*. [9] and Irastorza *et al.* [10]. Those studies found a negative relationship between BV/TV and dielectric properties. Three studies have reported variation of dielectric properties of bone with respect to bone mineralization levels [9], [8], [35]. Peyman *et al*. [35] found a positive correlation between bone mineralization levels and dielectric properties of porcine cortical bone. In contrast, Meaney *et al*. [9] reported a negative correlation between mineralization and dielectric properties of porcine trabecular bone from the femur. Similarly, Meaney *et al.* [8] found a negative correlation between BMD and dielectric properties for two patients. Based on these contradictory results, further investigation is required to study relationship between bone mineralization and bone dielectric properties over a wide frequency range and on larger sample size. This relationship is of paramount importance for characterizing bone dielectric properties in osteoporosis.

This study focuses on measurement of diseased human bone samples. A total of forty-five trabecular bone samples were acquired from osteoporotic and osteoarthritis patient populations. Osteoarthritis patients have compact and dense trabecular bone microarchitecture compared to osteoporotic patients [37]. These two populations provide bone samples to allow us to establish the variation in bone dielectric properties due to disease states.

Microarchitecture of these bone samples was obtained from microCT scans and then dielectric properties were measured *in vitro* using an open-ended coaxial probe across the microwave frequency range of 0.5-8.5 GHz. Microwave imaging is a modality of choice for imaging heterogeneous organs such as human breast due to better imaging resolution that can be achieved at microwave frequencies [38]. Bone itself has a heterogeneous structure and distribution of bone mineralization is not uniform [39]. Therefore, imaging

resolution of any future bone imaging modality would be an important consideration. This study chose microwave frequency range of 0.5 – 8.5 GHz, which is similar to frequency range used in preclinical breast imaging systems [40]. This frequency range could provide a good compromise between penetration depth and imaging resolution [41].

Since bone is a heterogenous structure and in human anatomy many layers proceeds before the bone Both microarchitectural parameters and dielectric properties were compared between osteoarthritis and osteoporotic patient populations. Finally, the relationship between dielectric properties and bone quality in terms of BV/TV was investigated.

2. Methodology

A. Experimental Design

Twelve patients were considered (osteoporotic $n = 7$ patients, osteoarthritis $n = 5$ patients) in this study, which were obtained from a separate study examining bone composition of human osteoarthritis and osteoporosis patients [42]. For that study, human femoral heads were obtained from patients that were undergoing total hip replacement surgeries under ethical approval and informed written patient consent. The ethical approval was granted by the Clinical Research Ethics Committee, Galway University Hospitals, Galway, Ireland. The mean age of osteoporotic patients was 70.5 ± 8 years and the mean age of osteoarthritis patients was 73.4 ± 1 years. During surgery, upon removal from the patient, femoral heads were wrapped in PBS soaked gauze and stored in a sterile container prior to freezing at -20^{o} C. After thawing, cores of approximately 13mm × 5mm × 5mm were sectioned from the femoral head using a Buehler Isomet Low Speed Saw fitted with a 5 inch diamond watering blade at speeds of approximately 40rpm.

For this study, we investigated multiple trabecular bone samples (12.7 ± 1.4 mm × 5 ± 0.5 mm × 5 ± 1 mm) from each patient resulting in samples sizes for osteoporotic ($n = 23$) and osteoarthritis ($n = 22$). The temperature of bone samples was recorded before each sample was measured (21 ± 0.1°C).

B. CT Scanning

Immediately after cutting, each core was scanned by microCT at 17.2 μm voxel size (Scanco μCT100, Energy Intensity: 70kVp, 114 μA, 8 W, using 0.1mm aluminium filter to minimize beam hardening, integration time: 500msec) while submerged in PBS to keep samples hydrated. For trabecular microarchitecture analysis, volumes of interest (VOIs) were contoured manually from each bone core and thresholded (using a single global threshold of 355 mgHA/cm^3 for all cores). The contoured images were segmented to create a binary image, isolating bone tissue. Weekly calibration of the microCT machine using hydroxyapatite phantoms ensured consistency between scans. Manufacturer supplied evaluation scripts were run on segmented VOIs to quantify BV/TV.

C. Dielectric Measurements

The open-ended coaxial probe (OECL) technique was employed to measure bone dielectric properties. The measurements were recorded in the frequency range of 0.5-8.5 GHz over 101 linearly spaced frequency points. In order to avoid uncertainty in measurements due to probe movement and repositioning, the Keysight slim form probe 85070E was connected directly to the Keysight E5063A vector network analyser (VNA) [1]. In order to avoid movement of sample, the bone sample was placed on a lifting stand for solid contact with the probe. The temperature of each bone sample was measured by using digital infrared thermometer with dual-laser targeting (N85FR). The temperature of liquids for calibration and validation was measured using a digital thermometer (HI98509). The VNA was used to measure reflection coefficient (S_{11}) at 101 linearly spaced frequency points, and a commercially available software suite (Keysight N1500A) was used to convert the S_{11} parameters to real (ε') and imaginary (ε'') parts of complex permittivity [2]. The complex permittivity is defined as:

$$\varepsilon(\omega) = \varepsilon'(\omega) - j\varepsilon''(\omega)$$

where $\varepsilon'(\omega)$ is the relative permittivity also termed as dielectric constant, $\varepsilon''(\omega)$ is the dielectric loss, and ω represents frequency in radians. The relative permittivity represents the ability of a material to store energy and the dielectric loss represents the energy dissipated in the material. The imaginary part of the complex permittivity also termed as dielectric loss is used to compute electrical conductivity as follows:

$$\sigma(\omega) = \omega\varepsilon_0\varepsilon''(\omega)$$

where ε_0 is the permittivity of free space.

D. Measurement Protocol & System Uncertainty Analysis

Before measuring the dielectric properties of bone samples, the measurement equipment was calibrated. The equipment was calibrated by using Air/Short/Deionized water calibration procedure. Deionized water was used as standard load material during calibration procedure. A validation measurement was carried by verifying the dielectric properties of 0.1 M NaCl (saline) at 22 ^{o}C [4]. A total of 9 validation measurements were performed. The uncertainty of the equipment's accuracy is reported in Table I. The uncertainty in accuracy in terms of percentage is defined as:

$$UC_{ACC}(f) = \left(\frac{x_{meas}(f) - x_{ref}(f)}{x_{ref}(f)}\right) \times 100 \quad (3)$$

where x_{meas} represents measured dielectric properties of 0.1 M NaCl and x_{ref} represents standard dielectric properties of 0.1 M NaCl [43] at the measured temperature. The uncertainty in repeatability of

measurements is also reported in Table I. The uncertainty in repeatability of measurements in terms of percentage is defined as:

$$UC_{REP}(f) = \left(\frac{x_{meas}(f) - x_{mean}(f)}{x_{mean}(f)}\right) \times 100 \quad (4)$$

where x_{mean} represents the mean of the measured dielectric properties. The total combined uncertainty is reported in Table 1.

Table 1. Percent uncertainty in accuracy and repeatability of measurements.

Parameter	$\boldsymbol{\varepsilon_r}$ (%)	**σ (%)**
$\boldsymbol{UC_{ACC}}$	0.41	2.5
$\boldsymbol{UC_{REP}}$	0.2	0.04
Combined	0.61	2.54

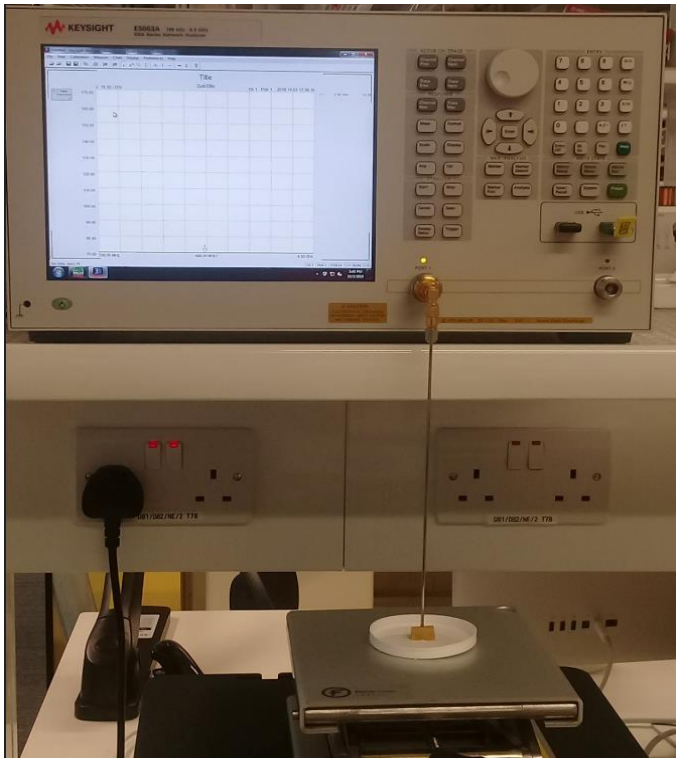


Fig. 1. Photograph of experimental setup.

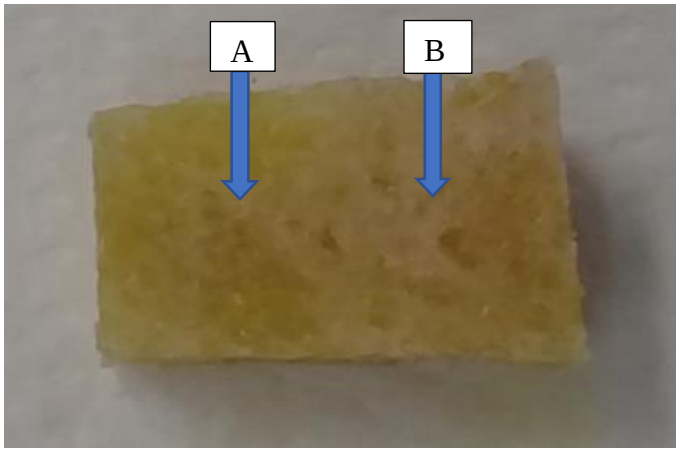


Fig. 2. Photograph of bone sample. The arrows show the measurement points. Approximately similar locations were selected as measurement points on the other side of sample.

3. Results and Discussion

A. Trabecular Microarchitecture of Bone Samples

In order to analyse the microarchitecture of bone samples, BV/TV was measured using microCT. Firstly, intra-patient variation of BV/TV was analysed for four osteoporotic patients. Four samples were obtained from patient 1 and 2, while, six samples were obtained from patient 3 and 4. From the microCT scan data, it was confirmed that BV/TV varies within each patient's femoral head as shown in Fig. 3. Fig. 3 represents mean and standard deviation of BV/TV for four osteoporotic patients. These intra-patient variations confirmed that the bone has a heterogenous structure and its microarchitecture varies within each human's femoral head.

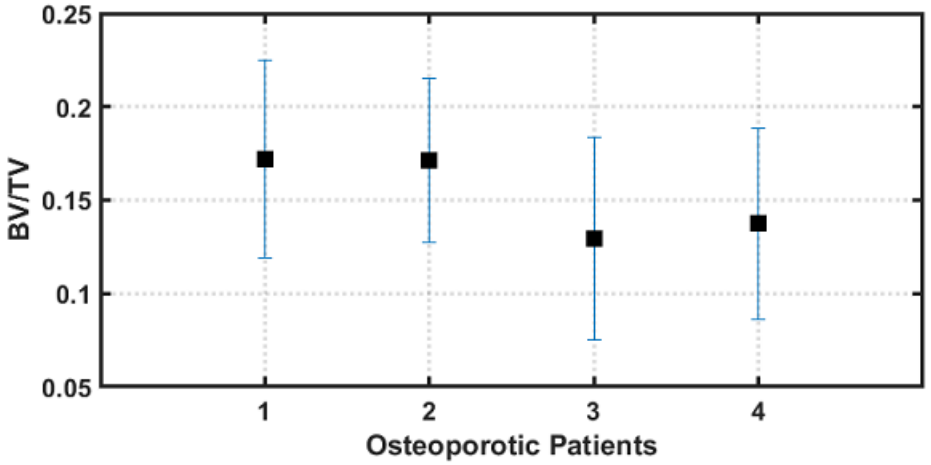


Fig. 3. Intra-patient variation of BV/TV for Osteoporotic Patients.

To examine the inter-disease variation between osteoporotic and osteoarthritis patients in terms of BV/TV, BV/TV of bone samples obtained from both set of patients is shown in Fig. 4. The mean BV/TV of

osteoarthritis patients is 69% higher than osteoporotic patients. The mean ± SD of BV/TV of osteoporotic patients is found to be 0.1451 ± 0.0538 and for osteoarthritis patients is 0.2979 ± 0.0910. The difference in means of BV/TV confirm that osteoarthritis patients have compact and dense trabecular microarchitecture as compared to osteoporotic patients. The osteoporotic patients have more porous trabecular bone microarchitecture.

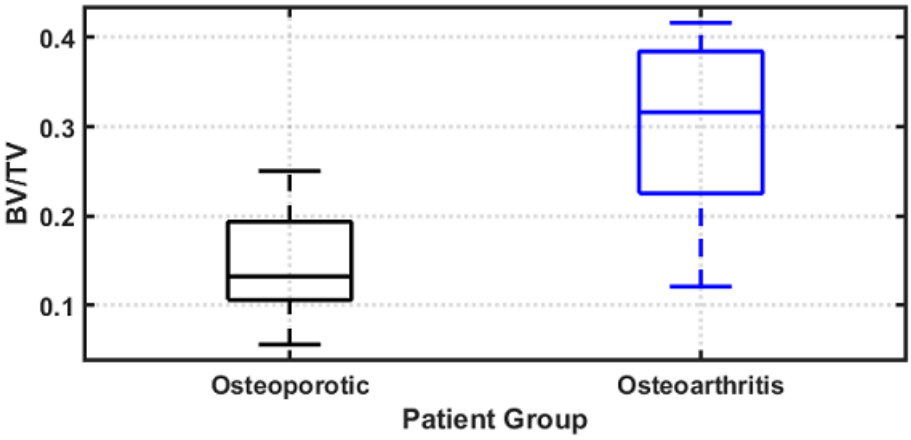
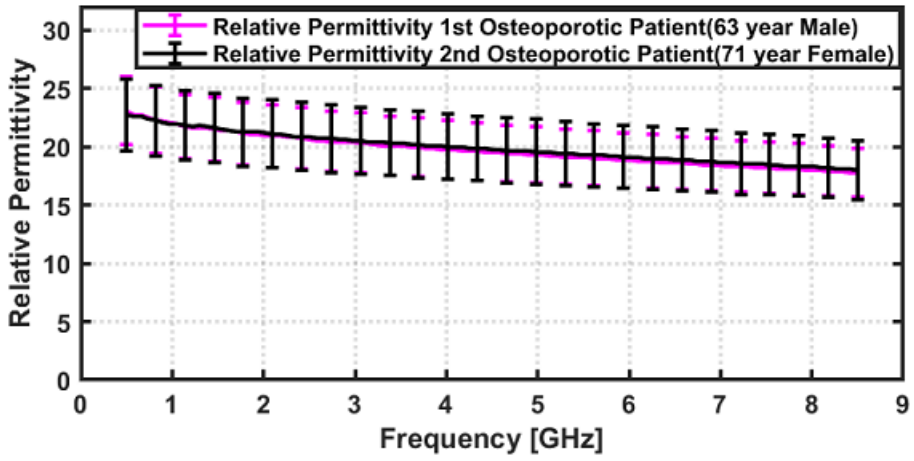


Fig. 4. Comparison of BV/TV between Osteoporotic and Osteoarthritis bone samples.

B. Dielectric Properties of Trabecular Bone Samples

1) Intra-patient Variation of Dielectric Properties

In order to examine intra-patient variation in terms of bone dielectric properties two osteoporotic patients were considered. Four bone samples were obtained from both patient's femoral head and their dielectric properties were examined. The mean and standard deviation of dielectric properties are shown in Fig. 5. The solid curve in Fig. 5 represents mean dielectric properties from one patient's femoral head and the error bars on each curve indicate the variation of dielectric properties from each patient's femoral head. The intra-patient variation of bone dielectric properties in terms of mean percentage difference of relative permittivity and conductivity values for 63 year male are 25% and 1.4% respectively. Similarly, the intra-patient variation in terms of mean percentage difference of relative permittivity and conductivity values of 71 year female are 28% and 1.6% respectively. The intra-patient variation in dielectric properties is mainly due to heterogeneous trabecular microarchitecture of femoral head, which varies within each patient as can be seen in Fig. 3.



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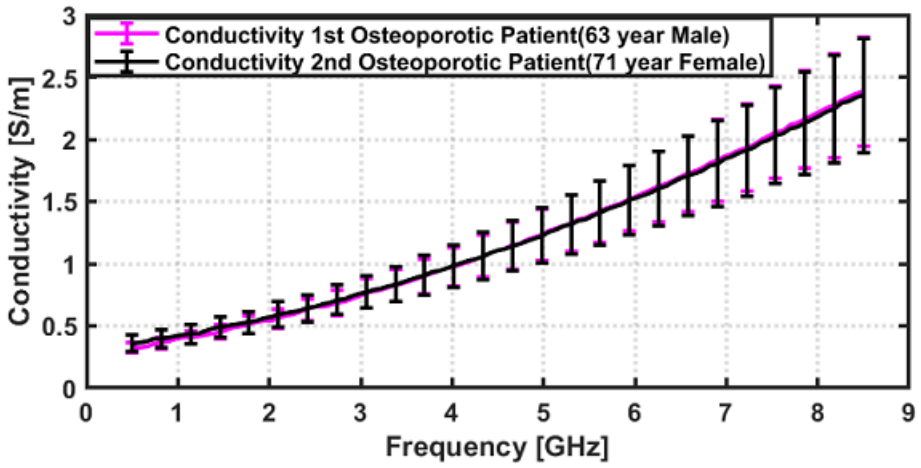


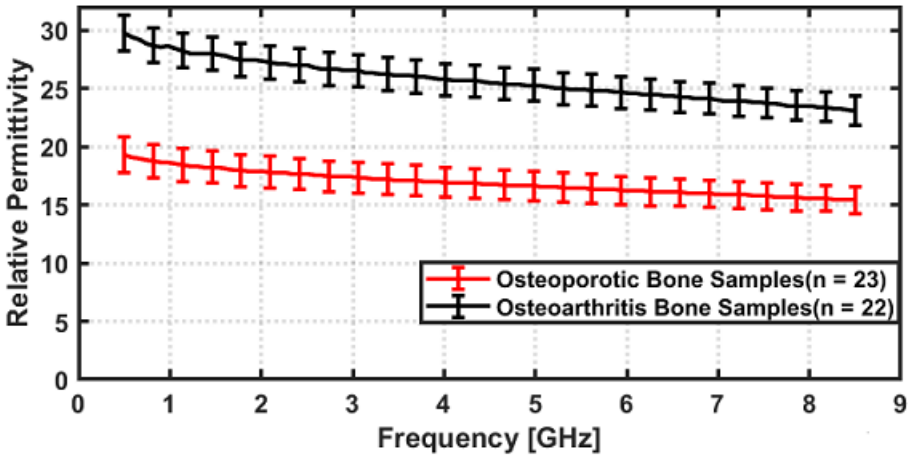
(b)

Fig. 5. Intra-patient variation of (a) Relative Permittivity (b) Conductivity in 2 Osteoporotic Patients outliers in data.

2) Dielectric properties of Osteoporotic and Osteoarthritis Patient's Bones

The dielectric properties of osteoporotic and osteoarthritis patients' bone samples are shown in Fig. 6. The solid curve represents mean dielectric properties from each patients' population and error bars on each curve indicate standard error of dielectric properties. The mean dielectric properties of osteoarthritis patients' bone samples are higher in magnitude than osteoporotic patients' bone samples with overall mean percentage difference of 41% and 45% for relative permittivity and conductivity values respectively. The difference of dielectric properties between two sets of patients' bone samples can be due to the fact that the microarchitecture of trabecular bone pattern of osteoarthritis patients is much more compact and dense compared to osteoporotic patients. Clinically, it is examined that the porous regions of osteoporotic bones have more fat than normal bones, these porous regions are occupied with yellow marrow during aging process [44],[45]. Since, the dielectric properties of fats are lower than the dielectric properties of bones, it would be

expected that this contributes to the lower dielectric properties of osteoporotic bone compared to those of osteoarthritis samples [45],[46].



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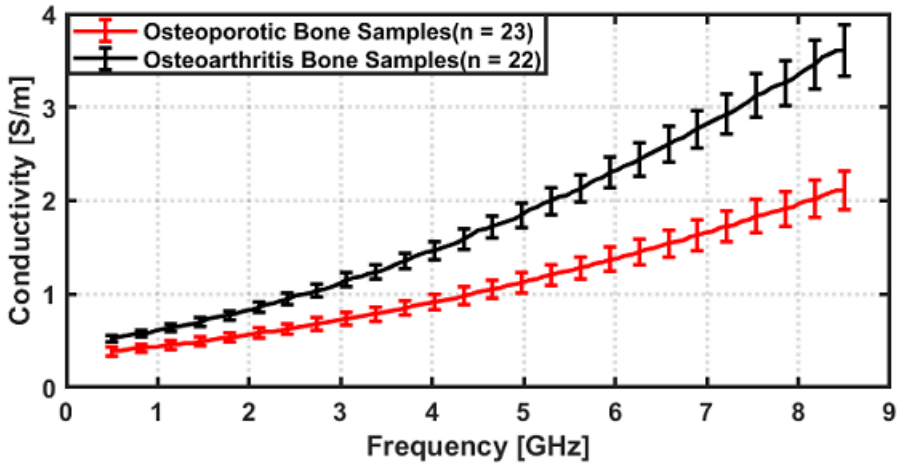
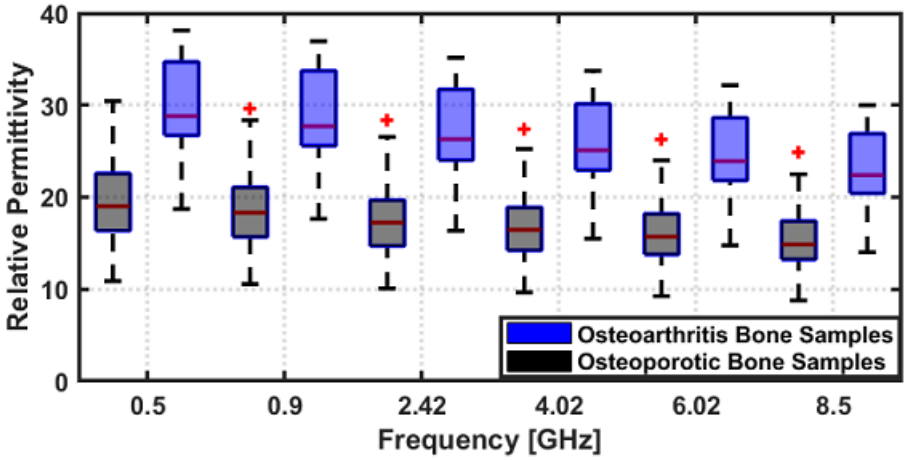


(b)

Fig. 6. Comparison of Osteoporotic and Osteoarthritis bone samples in terms of (a) Relative Permittivity (b) Conductivity.

A comparison between osteoporotic and osteoarthritis patients in terms of relative permittivity and conductivity at discrete frequency points is presented in Fig. 7. The boxes represent the corresponding dielectric properties of each patient population. It is evident from Fig. 7 that the difference between dielectric properties of osteoporotic and osteoarthritis patients is significant over the observed frequency points. A maximum percentage difference of 42.5% is found at 500 MHz in relative permittivity and 52.3% at 8.5 GHz in conductivity.



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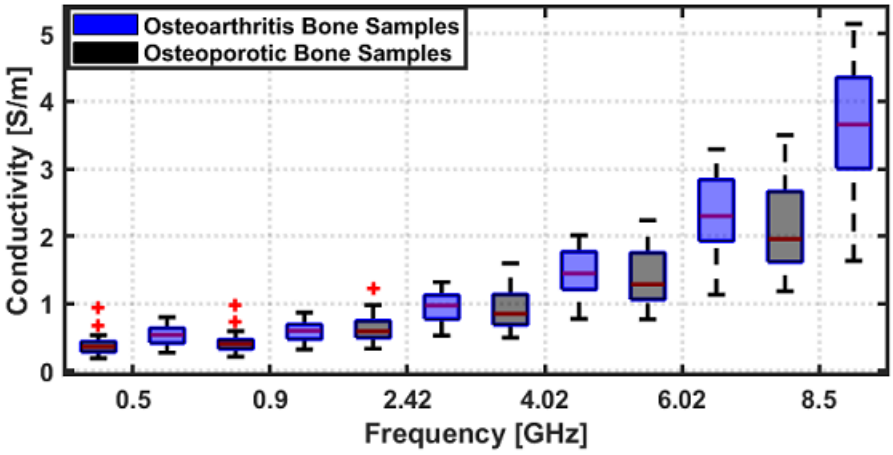


(b)

Fig. 7. Comparison of Osteoporotic and Osteoarthritis bone samples in terms of (a) Relative Permittivity (b) Conductivity at 0.5 GHz, 0.9 GHz, 2.42 GHz, 4.02 GHz, 6.02 GHz and 8.5 GHz. The red markers in plots represents the outliers in data.

The mean percentage difference between osteoporotic and osteoarthritis patients in terms of relative permittivity and conductivity is tabulated in Table 2.

Table 2. Mean percentage difference between osteoporotic and osteoarthritis bone samples.

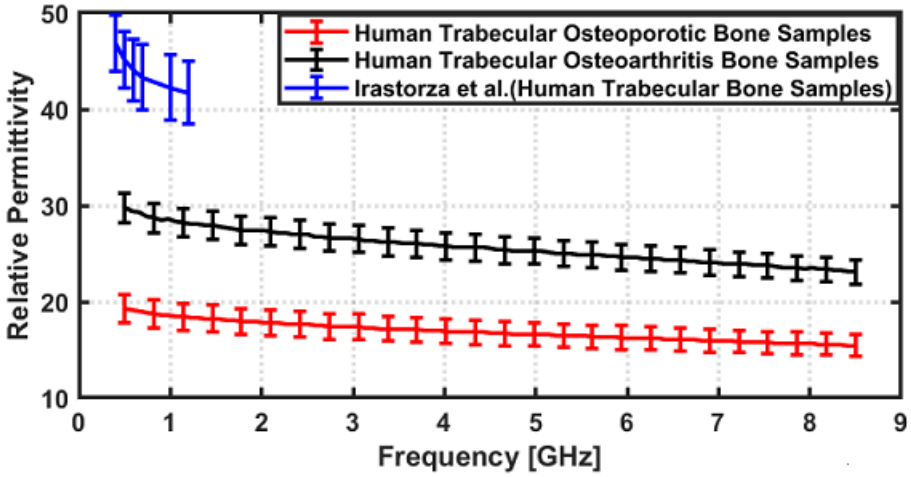
Frequency	**0.5 GHz**	**0.9 GHz**	**2.42 GHz**	**4.02 GHz**	**6.02 GHz**	**8.5 GHz**
$\boldsymbol{\varepsilon_r}$ (% **diff**)	42.5*	42.1*	41.8*	41.3*	40.9*	39.8*
$\boldsymbol{\sigma}$ (% **diff**)	30.1**	31.5**	40.7*	46.4*	50.8*	52.3*

The values of ε_r and σ marked * have *p*-value < 0.00001and the values marked ** have *p*-value < 0.01.

In order to investigate the significance of the difference of dielectric properties of osteoportic and osteoarthritis patient's bone samples, a statistical two-tail *t-test* was perfomed on dielectric properties of both set of patients. A *p-value* < 0.01 was obtained at frequencies 500 MHz, 900 MHz, 2.42 GHz, 4.02 GHz, 6.02 GHz and 8.5 GHz. The two-tail *t-test* at all above mentioned frequencies showed there exists a statistical difference between dielectric properties of osteoporotic and osteoarthritis bone samples. This significant difference between two populations for both relative permittivity and conductivity suggests that a single frequency microwave imaging device can be used to classify osteoporotic and osteoarthritis patients bone samples.

3) Comparison of Dielectric Properties with Literature

A comparative analysis of the dielectric properties of human trabecular bone samples from the literature is presented in Fig. 8. Since, the dielectric properties are highly species dependent [15], the results are compared only with measurements of Irastorza *et al.* [10] who reported *in vitro* dielectric properties of human trabecular bones ($n = 6$) in frequency range of 100-1300 MHz by employing OECL probes on bone samples submerged in PBS solution. Since, PBS has high dielectric properties as compared to bone [47], thus the dielectric properties of bone samples would be impacted. In this study, we have measured the dielectric properties of bones without immersing the bone samples in PBS during measurement. We found that dielectic properties of osteoarthritis bone samples are higher in magnitude in comparison to dielectic properties of trabecular human bone samples reported by Irastorza *et al.* [10].



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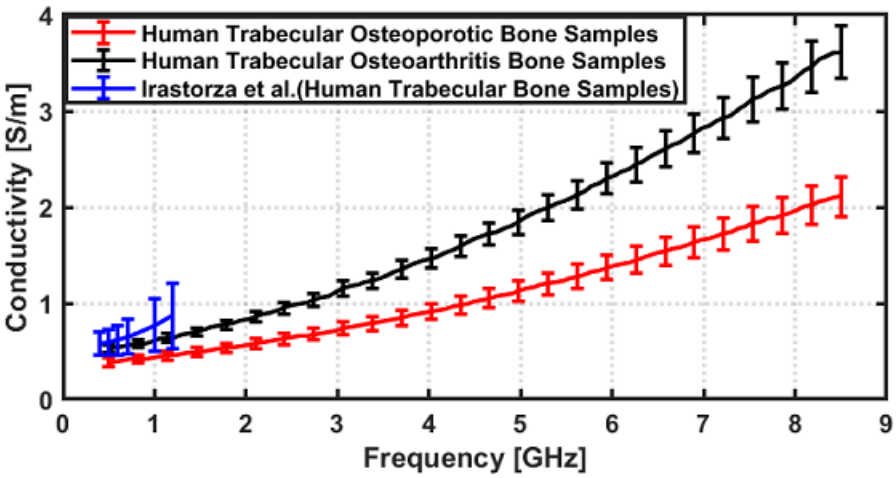


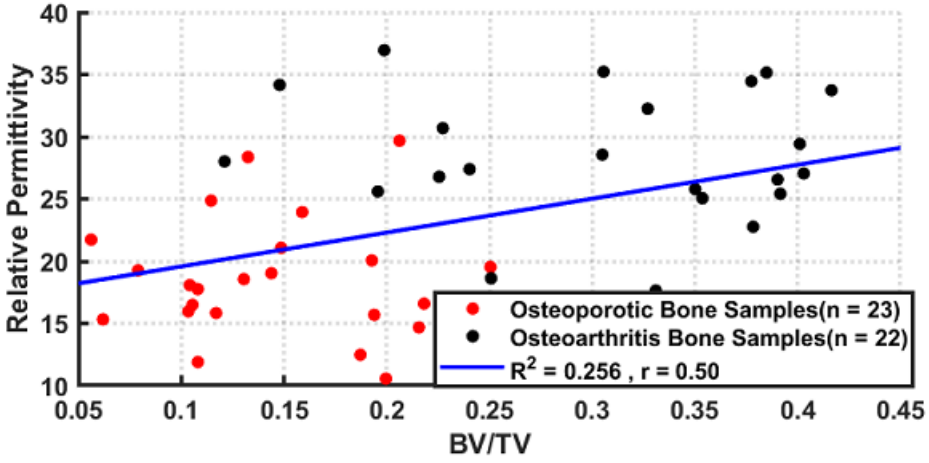
(b)

Fig. 8. Comparative analysis of trabecular bone dielectric properties with current study and literature (a) Relative Permittivity (b) Conductivity.

C. Relationship between dielectric properties and BV/TV of trabecular bone samples

Based on results reported by Irastorza *et al.* [10] for relationship between BV/TV and bone dielectric properties, we have performed a linear regression analysis to analyse the relationship between BV/TV and diseased bone dielectric properties. The analysis was performed at 500 MHz, 900 MHz, 2.42 GHz, 4.02 GHz and 6.02 GHz, shown in Fig. 9. Among selected frequencies, a relatively strong relationship was observed at 900 MHz. The linear regression analysis showed a weak positive relationship between BV/TV and relative permittivity with a R^2 value of 0.256 and a correlation coefficient r of 0.50 at 900 MHz. The R^2 value of 0.045 and a correlation coefficient r of 0.22 was found between BV/TV and conductivity of bone samples at 900 MHz. Irastorza *et al.* [10] reported a negative correlation between BV/TV and dielectric properties, with a maximum R^2 value of 0.77 and 0.60 for relative permittivity and conductivity respectively at 700 MHz.

Bone is a mineralized matrix composed of hydroxyapatite crystals ($[Ca_{10}\ (PO_4)_6\ (OH)_2]$) (50 – 70%), organic matrix (20 – 40%), water (5 – 10%) and lipids (<3%) [48]. The weak linear regression model suggests that BV/TV alone cannot predict the dielectric properties, since it only quantifies the bone volume in the overall sample volume. Since a major part of the bone constitutes the mineral matrix, BMD would play a significant role in characterizing bone dielectric properties. Thus, BMD along with BV/TV may be more suitable to correlate to the dielectric profiles in osteoporotic and osteoarthritis bone.



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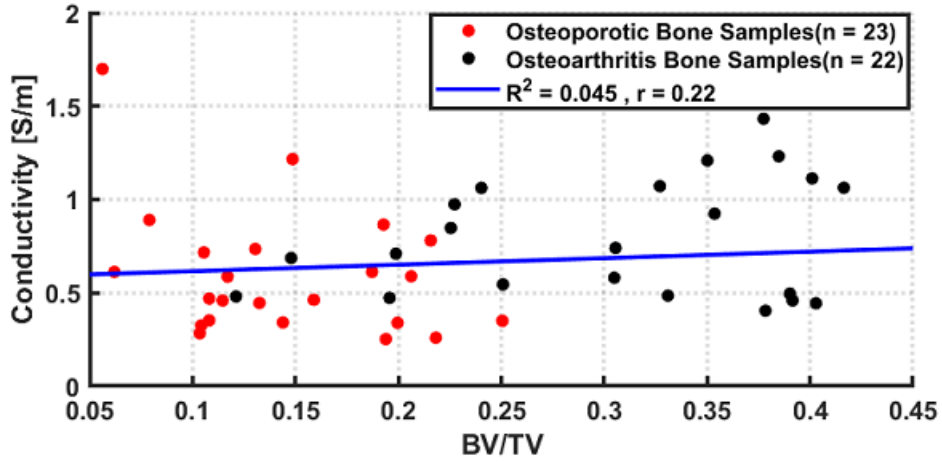

(b)

Fig. 9. Scatter plot between BV/TV and (a) Relative Permittivity (b) Conductivity at 900 MHz.

D. Effect of PBS on Bone Samples

Since the bone samples were preserved in PBS after surgical extraction, the impact of PBS on dielectric properties of bone samples was examined. To examine this effect, one bone sample was separately measured over time. The sample was taken out of the PBS and kept in open air for a period of 5 hours, so that the PBS evaporates thoroughly. During the drying process, dielectric measurements were recorded after every hour. A total of four measurements were recorded on the bone sample at each time instant. The overall mean percentage standard deviation of multiple measurements over time was found to be 0.6% and 0.03% for relative permittivity and conductivity values, respectively. These measurements indicate that PBS did not impact the bone dielectric properties.

4. Conclusion

In this study, the dielectric properties of diseased human trabecular bone samples were measured. The bone sample size was forty-five from twelve patients. Twenty-three bone samples were obtained from

osteoporotic patients and twenty-two bone samples were obtained from osteoarthritis patients. In this paper, we have presented the analysis on: BV/TV of osteoporotic and osteoarthritis bone samples, an analysis on intra-patient variation of bone dielectric properties, dielectric properties of osteoporotic and osteoarthritis bone samples, relationship between dielectric properties and BV/TV, and a comparison of the current study's findings with the literature.

The study showed an overall mean percentage difference of 41% and 45% for relative permittivity and conductivity values respectively between osteoarthritis and osteoporotic patients bone samples. The variation within femoral head for both observed osteoporotic patients in terms of relative permittivity and conductivity was found to be greater than 25% and 1.4% respectively. The analysis on microarchitecture parameters of bone suggests a significant difference between BV/TV of osteoarthritis and osteoporotic patients. The percentage difference between mean BV/TV of osteoarthritis and osteoporotic patients is 69%. Finally, the regression analysis suggests a weak positive relationship between BV/TV and relative permittivity (r = 0.50) and conductivity (r = 0.22) at 900 MHz. However, these preliminary findings have shown that there is statistically significant difference between dielectric properties of osteoporotic and osteoarthritis bone samples. These findings provide a foundation for the development of microwave-frequency based bone imaging device to diagnose and monitor osteoporosis.

It should be noted that this study only investigated the correlation between dielectric properties and BV/TV. The results show that the BV/TV, which quantifies trabecular bone microarchitecture does not solely account for dielectric properties. Dielectric properties are known to be influenced by mineralization and are also expected to be influenced by other bone constituents, including organic matrix, water, and lipids. Therefore, considering other major constituents of bone particularly bone mineralization (BMD) along with the BV/TV will allow for the development of a more realistic model that can predict bone quality based on dielectric properties.

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