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Screening Post-Menopausal Women for Osteoporosis by Complex Impedance Measurements of the Dominant Arm

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***Abstract*—**Cole-Cole parameters of 40 post-menopausal women are compared with their DEXA bone mineral density measurements. Impedance characteristics of four extremities are compared; left and right extremities are statistically same, but lower extremities are statistically different than upper ones due to their different fat content. The correlation of Cole-Cole impedance parameters to bone mineral density (BMD) is observed to be higher for dominant arm. With the post-menopausal population, ANOVA tests of the dominant arm characteristic frequency, as a predictor for DEXA classified osteopenic and osteoporic population around lumbar spine, is statistically very significant. When used for total lumbar spine osteoporosis diagnosis, the area under the Receiver Operating Curve of the characteristic frequency is 0.830, suggesting that the Cole-Cole plot characteristic frequency could be a useful diagnostic parameter when integrated into standard screening methods for osteoporosis. Moreover, the characteristic frequency can be directly measured by monitoring frequency driven angular behavior of the dominant arm without performing any complex calculation.

***Keywords*—**Bio-impedance spectroscopy, bone mineral density, characteristic frequency, osteoporosis, receiver operating curve.

I. Introduction

SUBJECTS are women age 40 and above, with no hip or arm fracture history, no metabolic bone diseases. Women with no menstruation for at least 12 months are classified as postmenopausal [1]. The experiments are conducted with 40 menopausal women, according to Declaration of Helsinki and all subjects have signed an informed consent form prior to participating in this study. To minimize overnight fasting effects on BI measurements trunk measurements are ignored; the dominant body segment for impedance measurement is right arm, for right handed subjects.

Following their body impedance measurements in sitting position, subjects are scanned in the bone densitometer to obtain reference BMD and T scores from L1-L4 lumbar spine and from hip. T score is the standard deviation departure from BMD mean of the young normal population and based on World Health Organization (WHO) Study Group classifications. T scores are verified by a radiologist. The Dual-energy X-ray Absorptiometry (DEXA) machine measurement precision is 1.14% or better. For T ≥ -1 the subject is classified as "Normal"; for -2.5 < T < -1 "Osteopenic", and for T ≤ -2.5 as "Osteoporic".

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II. Methodology

Body Impedance measurements are performed by using the HP4284A Precision LCR Meter, at 20 different frequencies between 10 kHz to 800 kHz; with frequencies evenly distributed over the logarithmic scale [2]. Based on EN60601 electrical safety standard, the maximum current that is allowed to pass through a patient is limited to 100μA at 1 kHz [3]. Tetra-polar measurement model is used to eliminate the electrode-skin impedances [4], [5]. To ensure measurement stability of HP4284A during measurements, internal A/D integration level set is set to medium to allow 180 ms time window. Four consecutive measurements are averaged to obtain the final reading [6]. In impedance measurements, standard Ag/AgCl Arbo Kendall electrodes (48 x 34 mm) are used and no additional lubricant is applied to electrode contact points. Electrodes are placed at the outer side of the hands along the 3rd metacarpal bones, and over the feet, along the feet 3rd metacarpal bones. Current is applied to anterior electrodes while voltages are measured from the posterior ones. By using 4 electrodes and interchanging electrode positions, it is possible to measure arm, leg or trunk impedances separately [7]. To reduce effect of overnight fasting on BI measurements, trunk impedance measurements are ignored. Although, different tissues will contribute to measured impedance proportionally to their volume share, the body segment can be modeled as a R_e resistance in parallel to a R_i serial to a Z_{CPA}. The impedance is calculated as in (1), where R_i is intracellular fluid resistance, R_e is the extracellular fluid resistance, R_0 and R_∞ are extrapolated resistance values obtained from Cole-Cole plot where plot crosses real axis, α is the depression angle constant and K is a constant with dimension of (ohm.sec-α), ω is the angular frequency [8], [9]. The frequency at which imaginary part of impedance model is minimized, is the Cole-Cole characteristic frequency f_c.

$$Z^* = R_\infty + \frac{R_0 - R_\infty}{1 + \frac{R_i + R_e}{K}(j\omega)^\alpha} \quad (1)$$

Capacitive effects of cell membranes are usually lumped in constant phase angle impedance Z_{CPA} as defined in

$$Z_{CPA} = K(j\omega)^{-\alpha} \quad (2)$$

TABLE I
ANOVA STUDENT-NEWMAN-KEULS TEST RESULTS OF COLE-COLE MODEL CHARACTERISTIC FREQUENCY FOR ALL PAIRWISE COMPARISONS OF DEXA SCORES

	Total Lumbar SPINE		Total HIP	
	p	Different from [a]	*p*	Different from [a]
Characteristic frequency				
Dominant Arm	0.001 [b]	(1-2)(1-3)(2-3)	0.569	N/A
Inferior Arm	0.099 [c]	(1-2)(1-3)(2-3)	0.553	N/A
Right Leg	0.368		0.701	N/A
Left Leg	0.462		0.516	N/A
Anthropometric parameters				N/A
Age	0.763		0.651	N/A
Weight	0.717		0.163	N/A
BMI	0.413		0.353	N/A

[a] (X-Y): X is statistically different from Y, where 1: Normal, 2: Osteopenic, 3: Osteoporic groups, [b] Confidence interval is 95%, [c] Confidence interval is 90%

With foot to foot bio-impedance measurements, Heidi H. Y. Ngai et al. have shown that bio-impedance is correlated to BMD, with a higher correlation in men [1]. In his study, the difference in gender is explained by the fact that women have less lean muscle mass and lower electrolyte content, making women potentially more susceptible to the factors that can induce errors in BI measurements [1], [10]. In (3)-(7), s refers to segment, V volume, FFB fat free body, w water, m soft tissue, f fat and b bone. To incorporate the effect of bone mass in the measurements, bio-impedance measurements are taken from all extremities of subjects. Dominant arm is the right arm for a right handed person. Correlation between dominant arm Cole-Cole parameters and DEXA reference results is expected be higher compared to other extremities [11]-[13].

$$V_S = V_f + V_{FFB} \tag{3}$$

$$V_{FFB} = (d_s - d_f)/(d_{FFB} - d_f) \tag{4}$$

$$V_{FFB} = V_m + V_b + V_w \tag{5}$$

$$d_{FFB} = (d_m.V_m + d_b V_b + 1 + V_W)/V_{FFB} \tag{6}$$

$$V_b\big|_{V_m=V_w} = \frac{2d_s - d_m - d_w + V_{FFB}(d_m + d_w - 2d_f)}{2d_b - d_m - d_f} \tag{7}$$

Cole-Cole parameters R_0 and R_∞ of four extremities are normalized with respect to their anthropometric shapes, i.e. conical shapes, of the segments [3]. Conical impedance circumference parameters for arms are measured around loose biceps and wrists, while L is the stretched arm length from shoulder tip. For legs however, the upper and lower circumference parameters are measured from thigh and ankle and the length is measured between femur head and ankle. With C_b and C_w as circumferences around biceps and wrist, and L as the stretched arm length from shoulder tip, conically normalized arm specific impedance can be estimated from (8) [14]. Right extremity anthropometric data are also used for left extremities, assuming perfect body symmetry around vertical axis.

All measurements are performed as magnitude-phase pair and normalized with load dependent gain and phase shift characteristics of the measurement system, by 2-D interpolation [15]. Statistical analysis is performed by using Stata SE/12.0 and by MedCalc v12.7.3 [16], [17]. The statistical F test is performed to analyze the BI measured Cole-Cole parameters symmetricity around upper versus lower and left versus right extremities. One way ANOVA test is applied to measure the statistical meaning of Cole-Cole parameters over DEXA T classifications of total lumbar spine BMD and total hip BMD. Diagnostic capability of the anthropometrically normalized impedance values are also identified by area under curve AUC and Youden index J using Receiver Operating Curve (ROC) analysis [18], [19]. The Youden Index is the summary measure of the ROC (Receiver Operating Characteristic), and measures the effectiveness of a diagnostic marker and enables the selection of an optimal threshold value (cutoff point) for the marker. Youden index is the maximum difference between sensitivity, the probability of correctly classifying diseased individuals, and 1-specificity, the probability of incorrectly classifying health individuals. In all statistical analysis, all parameters are assumed to have normal distribution and 95% confidence interval is used unless it is explicitly specified.

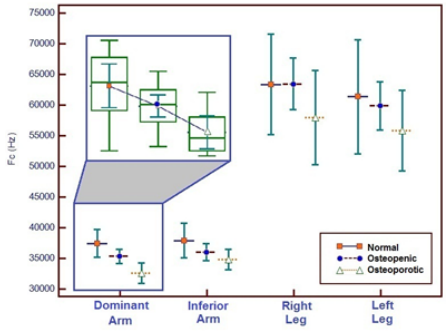

Fig. 1 Characteristic frequency of extremities against DEXA lumbar spine T scores

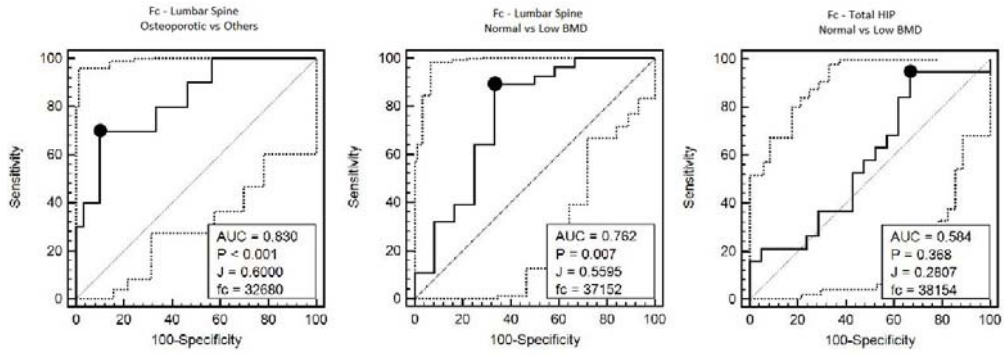

Fig. 2 For total lumbar spine, AUC of dominant arm characteristic frequency for predicting osteoporic population is 0.830 with optimal cutoff frequency of 32680 Hz; for lowered BMD, AUC is 0.762. For total hip, AUC is 0.584 for predicting lowered BMD

III. Results

The age, weight and height of post-menopausal women are 60.2±8.4 year's 74.9±12.4 kg and 152.4±6.6 cm respectively. Number of post-menopausal subjects classified as normal, osteopenic and osteoporic from total lumbar spine DEXA measurements are 12, 18 and 10 respectively; whereas among postmenopausal subjects, 21 of them are classified normal, 18 of them osteopenic and one of them osteoporic, from total hip DEXA measurements. The dominant arm Cole-Cole plot characteristic frequency of menopaused women is 35279±3246 Hz. R_0 and R_∞ parameters are 341.7±43.8 and 279.8±37.4 Ω.cm. When variances of similar Cole-Cole parameters of left and right extremities are compared with F test, parameters of upper extremities had minimum p value of 0.533 for depression angle and a maximum value of 0.969 for R_0. When the same test is performed for lower extremities, the maximum p value of 0.990 is observed for depression angle where minimum p value is 0.761 for R_∞. These p values are suggesting that Cole-Cole parameters of upper and lower extremities are statistically indifferent. Similarly, when F test is repeated to check variances of lower versus upper extremities including cross symmetries, for all Cole-Cole parameters excluding depression angle, p values are 0.001, which is suggesting that upper and lower extremities have statistically very different Cole-Cole parameters (Tab. I). When individual Cole-Cole parameters are tested with one way ANOVA, only dominant arm Cole-Cole characteristic frequency has scored statistically important p value of 0.001 at 95% confidence interval for T scores over total lumbar spine. Characteristic frequency of inferior hand however, which previous F tests is suggesting that it has similar parameters as the dominant arm, could score only a p value of 0.099 which is showing statistically a low meaning. For any other extremity, all other BI parameters have failed to show a statistical meaningfulness to DEXA T score classifications. When DEXA classifications of total hip are of concern, none of the BI or anthropometric parameters has shown a statistically meaningful correlation. Although, box-and-whisker plots of Cole-Cole characteristic frequency at all extremities are visually showing some degree of correlation to DEXA T scores, the maximum correlation between BMD is measured between dominant hand characteristic frequency and total lumbar spine BMD score and it is 0.570 (0.314 to 0.749, p<0.001). For the inferior hand, this correlation factor is 0.445 (0.155 to 0.664, p=0.004). The only Cole-Cole characteristic parameter that is statistically meaningful for both of upper extremities is the characteristic frequency (Fig. 1).

The ability of dominant arm characteristic frequency to identify osteoporosis as a single predictor is inspected with Receiver Operating Curve analysis [18], [19]. The area under ROC curve representing the diagnostic performance of dominant arm characteristic frequency against lumbar spine DEXA measurements is 0.830 with Youden index J value of 0.600 and 36762 Hz (p<0.001) associated cutoff criteria. And when the area of concern is total hip, the AUC is 0.584 with Youden index J value of 0.281 and 38154 Hz (p=0.368) associated cutoff criteria. However, note that there is only one subject classified as osteoporic at total hip.

TABLE II
Correlation of Limb Characteristic Frequency with DEXA BMD Scores

Limb	Total Lumbar Spine r [a]	HIP r [a]
Dominant arm	0.5700 [b]	0.1083
Inferior arm	0.4450 [c]	0.1411
Right leg	-0.0028	-0.2179
Left leg	-0.0578	-0.2119

[a] Confidence interval is 95%, [b] p = 0.001, [c] p = 0.004

IV. Discussion

For menopausal women, it is found that, with the value of 0.570 (p=0.001) the dominant arm characteristic frequency has the strongest correlation to total lumbar spine BMD, than any of other anthropometric or BI parameters; furthermore, the partial correlations of all bio-impedance parameters of dominant arm have higher correlation factors then weight and age. Reduced correlation at other extremities is due to body shape and fat mass, which is a function of weight also has relatively high correlation with total hip BMD [10]. For hip BMD the BI parameters are not giving any statistically meaningful information. Age and weight have higher relations to total hip BMD although dominant arm extrapolated extracellular fluid impedance also shows some correlations [11]. Based on ROC analysis AUC of 0.830, the dominant arm

BI characteristic frequency can be considered as a complementary osteoporosis screening method for lumbar spine alone. For the measured population, the optimal frequency is found as 32680 Hz (p=0.001), but the experiments should be repeated with larger population to form a normative standard value.

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