

Original Article



Independent Association of Phase Angle with Fasting Blood Glucose and Hemoglobin A1c in Korean Type 2 Diabetes Patients

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ABSTRACT

The relationship between phase angle (PhA) of bioelectrical impedance analysis (BIA) and glycemic parameters in diabetes mellitus (DM) patients has not been well studied. To evaluate the prognostic value of the PhA from BIA as a glycemic marker, we investigated the relationship of PhA with various variables such as age, body mass index (BMI), and glycemic parameters in Korean patients with type 2 DM (T2DM). We evaluated the anthropometric data, body composition, glycemic parameters, and PhA of 321 T2DM patients aged 30–83 years. The patients were classified by sex into men (n = 133) and women (n = 188). General linear models identified the independent effects of PhA after covarying for age, sex and BMI. The PhA, body cell mass (BCM), extracellular mass (ECM), lean body mass, intracellular water (ICW), extracellular water (ECW), total body water (TBW), fasting blood glucose, and hemoglobin A1c (HbA1c) of T2DM Korean patients were significantly higher in men than in women. However, fat mass, ECM/BCM, ECW/ICW, ECW/TBW, and serum insulin were significantly higher in women than in men. Statistically significant independent associations were observed between PhA and age, BCM, ECM, ECM/BCM, ICW, ECW, ECW/ICW, and ECW/TBW for both sexes. There was no significant association between PhA and BMI the patients. Glycemic parameters, such as HbA1c and fasting blood glucose were independently associated with PhA. These results suggest that PhA could be an indicator for assessing ability to control fasting blood glucose in T2DM patients in Korea.

Keywords: Bioelectrical impedance; Phase angle; Blood glucose; HbA1c

INTRODUCTION

Bioelectrical impedance analysis (BIA) is a simple, reliable, non-expensive, reproducible, and non-invasive method for assessing body composition and nutritional status in the clinical situation [1]. Thus, BIA is a method commonly used for estimating clinical conditions, as well as body fat and muscle mass in patients [2]. BIA determines the electric impedance of an electric current passing through the body [3]. The electrical impedance consists of resistance and reactance [3]. Low resistance is correlated to lean body mass (LBM), and high resistance

Conflict of Interest

The authors declare that they have no competing interests.

is correlated to a reduced LBM. Resistance is the opposition of a conductor to the alternating electrical current, and it is the same in non-biological systems. Reactance is generated by the additional opposition to the current from the storage effects of tissue interfaces and cell membranes [4].

Phase angle (PhA) is an established bioelectrical impedance parameter for the monitoring of malnutrition and diagnosis of clinical prognosis, both associated with changes in cellular integrity and alterations in fluid balance [5,6]. PhA expresses both changes in the amount as well as the quality of soft tissue mass (i.e., cell membrane permeability and soft tissue hydration). PhA can be affected by changes in the amount and quality of the soft tissues, in cell size and mass, in cell membrane permeability, or intracellular composition [7]. PhA can be directly calculated as resistance and reactance as arc-tangent (reactance/resistance) $\times 180^\circ/\pi$. Therefore, the PhA is dependent on the cell size, cellularity, integrity of the cell membrane, and the hydration of the tissue [8].

The PhA values change depending on age, sex, body mass index (BMI), ethnic group, body shape, and clinical conditions of the patient [9-11]. Máttar has reported that in most people, PhA is represented between 3–15° [11]. PhA levels in Asians are generally lower compared to other ethnic groups [9-11]. The mean PhA of men and women were $6.5 \pm 0.5^\circ$ and $5.3 \pm 0.5^\circ$, respectively, with a significant difference ($p < 0.001$) to healthy Korean [12]. PhA has been known as a prognostic factor for assessing cell health, however, its biological indications remain to be elucidated. It was reported that PhA was positively correlated with cell health, membrane integrity, and function of cells [13,14].

Clinical studies have reported that BIA and PhA might serve as a prognostic indicator for the nutritional assessment of liver cirrhosis, several types of cancer, sepsis, diabetes mellitus (DM) and renal diseases [15-20]. Low levels of PhA are related to the inability to store energy and selective penetrability of cell tissue. High levels of PhA mean high reactance and low resistance, which coincide with high amount of intact cell mass, suggesting healthy status [14]. The metabolic changes, including cell membranes, are first affected by malnutrition. Thus, PhA reflects the quantity of fat and muscle mass as well as hydration status and may be able to reflect malnutrition at an early stage and might be useful in assessing the effectiveness of nutrition intervention [21]. PhA is measured by secondary analysis of BIA without using anthropometric data. Therefore, it can be used as a useful parameter for patients with difficult anthropometry [5]. A decreased PhA was associated with an increased mortality rate in a variety of diseases [22]. PhA values are also used as a predicting marker to monitor DM complications, the progression and duration of DM [23].

The relationship between PhA of BIA and glycemic parameters in type 1 and type 2 DM (T2DM) patients has also been investigated. However, their application in DM may be limited in Korea. Therefore, this study was conducted to establish sex-, age-, and BMI-specific reference values for PhA in Korean diabetes patients.

MATERIALS AND METHODS

Subject

We recruited 321 T2DM subjects (aged 30–83 years and BMI 24.9 ± 3.1 kg/m²) from the Korean National Diabetes Program study. All subjects were divided into 2 groups by sex. Consent

included, informing the subjects of their rights, and the objective and method of this study. Informed consent was obtained from all participants. The Institutional Review Board of Kyung Hee Medical Center approved this study (IRB No. KMC IRB 1428-02).

Study procedures and PhA measurement

Participants were assessed 8 hours of restricting food and fluid intakes. Body weight and height were measured using a weight and height scale. BMI was calculated by dividing subject's weight (kg) by subject's height squared (m^2). BIA was performed with the use of a BIA 450 instrument (Biodynamics Co., Seattle, WA, USA). PhA was estimated as follows: $PhA = (\text{reactance/resistance}) \times (180/\pi)$.

Biochemical analysis

Subjects had fasted overnight and blood samples were collected for biochemical analysis. The collected blood was centrifuged at $1,500 \times g$ for 15 minutes to separate the serum and erythrocyte, which were stored at $-80^\circ C$ for analysis. Fasting blood glucose levels (Asan Pharmaceutical corporation, Seoul, Korea) and hemoglobin A1c (HbA1c; Crystal Chem, Downers Grove, IL, USA) were measured by enzymatic methods using commercial kits, respectively. Serum insulin was determined by enzyme-linked immunosorbent assay kit (ALPCO Diagnostics, Windham, NH, USA).

Statistical analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The correlations between PhA and the other variables were estimated. The crude effect of sex, age, and BMI on PhA was assessed by comparing the means with t-test and the correlation between the PhA and body composition was analyzed using Pearson correlation. The independent effects of PhA after covarying for age, sex and BMI were compared using general linear models. All data are represented as mean \pm standard deviation and the statistical significance was set at $p < 0.05$.

RESULTS

Baseline and biochemical characteristics

The age, weight, height, and BMI of the 321 study participants are presented in **Table 1**. The subjects were further classified into women ($n = 188$) and men ($n = 133$). The women (58%) in this study were significantly older than the men, but no significant difference of BMI was observed between the 2 groups.

The BCM, ECM, LBM, intracellular water (ICW), extracellular water (ECW), and total body water (TBW) were significantly higher in men than in women. The body cell mass (BCM), extracellular mass (ECM), LBM, ICW, ECW, TBW of T2DM Korean subjects were significantly higher in men than in women. Additionally, PhA of T2DM Korean subjects was significantly larger in the men ($n = 133$, $6.84 \pm 0.99^\circ$) than in the women ($n = 188$, $6.02 \pm 1.09^\circ$; $p < 0.05$). However, fat mass (FM), ECM/BCM, ECW/ICW, and ECW/TBW were significantly higher in women than in men.

As shown in **Table 2**, the levels of fasting blood glucose and HbA1c of T2DM Korean subjects were significantly higher in men than in women, while the serum insulin level was significantly higher in women than in men.

Table 1. Anthropometric and body composition characteristics of subjects

Characteristics	Men (n = 133)	Women (n = 188)
Age (yr)	58.29 ± 10.16	61.53 ± 9.84*
Weight (kg)	69.31 ± 9.41	59.54 ± 8.03*
Height (cm)	167.63 ± 5.38	154.23 ± 5.47*
BMI (kg/m ²)	24.63 ± 2.80	25.04 ± 3.21
Phase angle (°)	6.84 ± 0.99	5.99 ± 1.01*
BCM (kg)	26.57 ± 4.15	18.28 ± 2.76*
ECM (kg)	28.56 ± 3.68	22.59 ± 2.73*
LBM (kg)	55.13 ± 7.13	40.87 ± 4.86*
FM (kg)	14.23 ± 4.66	18.67 ± 4.71*
ECM/BCM	1.09 ± 0.13	1.25 ± 0.15*
ICW (L)	22.99 ± 3.40	15.30 ± 1.91*
ECW (L)	16.96 ± 2.80	14.88 ± 1.88*
ECW/ICW	0.74 ± 0.11	0.98 ± 0.13*
TBW (L)	39.95 ± 5.51	30.18 ± 3.12*
ECW/TBW	0.42 ± 0.04	0.49 ± 0.04*

All values are means ± standard deviation.

BMI, body mass index; BCM, body cell mass; ECM, extracellular mass; LBM, lean body mass; FM, fat mass; ICW, intracellular water; ECW, extracellular water; TBW, total body water.

*p < 0.05.

Table 2. Biochemical characteristics of subjects

Characteristics	Men (n = 133)	Women (n = 188)
Glucose (mg/dL)	153.49 ± 55.20	135.72 ± 48.61*
HbA1c (%)	7.35 ± 1.68	6.95 ± 1.24*
Insulin (μIU/mL)	8.38 ± 9.98	14.47 ± 20.14*

All values are means ± standard deviation.

HbA1c, hemoglobin A1c.

*p < 0.05.

Correlation of PhA with anthropometric characteristics and diabetic indicators

PhA was negatively correlated with age, ECM, ECM/BCM, ECW, ECW/ICW and ECW/TBW in T2DM Korean subjects (**Table 3**). Furthermore, PhA was positively correlated with BCM and ICW. However, there was no significant association of PhA with BMI, LBM, FM, and TBW. Statistically significant independent associations were observed between PhA with fasting blood glucose and HbA1c in T2DM Korean patients (**Table 4**). Thus, PhA was independent association with fasting blood glucose and HbA1c.

Table 3. Correlation of phase angle with anthropometric characteristics

Characteristics	Men (n = 133)	Women (n = 188)
Age (yr)	-0.26*	-0.39*
Weight (kg)	0.07	0.09
Height (cm)	-0.12	0.16*
BMI (kg/m ²)	0.16	0.01
BCM (kg)	0.47*	0.60*
ECM (kg)	-0.31*	-0.36*
LBM (kg)	0.11	0.12
FM (kg)	-0.02	0.01
ECM/BCM	-0.95*	-0.95*
ICW (L)	0.49*	0.68*
ECW (L)	-0.38*	-0.47*
ECW/ICW	-0.95*	-0.93*
TBW (L)	0.10	0.14
ECW/TBW	-0.96*	-0.96*

BMI, body mass index; BCM, body cell mass; ECM, extracellular mass; LBM, lean body mass; FM, fat mass; ICW, intracellular water; ECW, extracellular water; TBW, total body water.

*p < 0.05.

Table 4. Independent association of phase angle with glucose and HbA1c

Variables	Glucose	HbA1c
Phase angle	-12.47 ± 3.13 [†]	-0.44 ± 0.10 [†]
Age	-1.04 ± 0.31 [*]	-0.04 ± 0.01
Weight	0.47 ± 0.36	0.01 ± 0.01
Sex [‡]	-19.09 ± 7.34 [*]	-0.56 ± 0.21
Intercept	266.85 ± 42.68 [†]	12.23 ± 1.26 [†]
R ²	0.09	0.10
SEE	52.47	1.44

Values are regression coefficients ± SEE. Phase angle was adjusted for age, weight, and sex.

SEE, standard error of the estimate; HbA1c, hemoglobin A1c.

Significantly different from zero at: ^{*}p < 0.01; [†]p < 0.001; [‡]A dummy codes are 0 = men, 1 = women.

DISCUSSION

The PhA calculation derives from resistance and reactance. Resistance is related to tissue hydration, whereas reactance is generating by the cell membrane capacitance in human body [24]. Recently, PhA has been used as a prognostic parameter for evaluating clinical outcomes and nutritional status in patients with different diseases [22,25]. PhA plays a key role for monitoring and screening disease progress in patients undergoing DM, hemodialysis, liver cirrhosis, several cancer and mortality of diseases [16-20]. The 50 KHz are most commonly used in humans to measure both maximum electric resistance and reactance. Thus, as most previous studies have referred to PhA values obtained at 50 kHz [5], we measured the PhA at 50 kHz.

We investigated the association with PhA, body composition, and glycemic indicators of 321 T2DM Korean patients. The PhA, BCM, ECM, LBM, ICW, ECW, TBW as well as fasting blood glucose and HbA1c of T2DM Korean subjects were significantly higher in men than in women. Statistically significant correlations were observed between PhA and age, BCM, ECM, ECM/BCM, ICW, ECW, ECW/ICW, and ECW/TBW for both sexes. Especially, HbA1c and fasting blood glucose levels were independently associated with PhA.

Mattiello et al. [14] reported that PhA gradually increases throughout puberty, stabilizes in the adult ages, and then decreases continuously in older patients. In this study, the PhA and BCM were significantly higher in men than in women. These results might be explained due to the higher amount of BCM in men compared to women [8,26]. Thus, our results are in line with those of previous studies.

Data regarding PhA in the DM patients are not fully understood. Buscemi et al. [27] reported that PhA values significantly lowered in young adult T1DM men subjects compared to control subjects, whereas this difference was insignificant in women. Dittmar et al. [23] showed that the lower PhA was found with T2DM subjects compared to a control group. They also found negative correlations between the PhA and HbA1c and suggested that lower PhA might indicate catabolism and long duration of the disease in T2DM patients. Di Mauro et al. [28] reported that DM patients have a reduced ECW and exchangeable potassium due to an alteration of the osmolarity in plasma and a decreased active cell mass. These results suggest that decreased PhA in DM patients indicates cell death or a decrease in cell mass. Hyperglycemia induced the osmolarity of the extracellular compartment, which causes water movement from the intracellular into the extracellular compartment, may cause advanced renal failure complications [29,30]. Changes in increased ECW have been found in T2DM subjects [31]. These results provide evidence that the PhA could be used as independent prognostic markers in T2DM patients, especially in those with uncontrolled fasting blood glucose.

The PhA values are influenced by age, sex, BMI, ethnic group, and clinical conditions [9-11]. A few studies are represented that the diets can affect the PhA [32,33]. Higher dietary quality decreased the odds of low PhA in health adults [32]. Barrea et al. [33] also reported that the mediterranean diet was associated to larger PhA independent of sex, age and BMI., as expression of cell membrane integrity [33]. Therefore, PhA evaluation could be a useful screening tool to assess the nutrition status as well as health condition.

This study had some limitations. We did not investigate a control group. Thus, there was a lack of consideration of the difference in PhA between the normal control group and the DM group. Additionally, we did not investigate correlation between PhA and disease duration in subjects. Thus, it is considered that a comparative study of PhA by disease duration is necessary for future studies. Another limitation is related to not analyzing the consumption of diet. Further studies are need to confirm the mechanism of dietary intake and PhA.

In conclusion, PhA reflected the cell function and BCM in T2DM subjects. We also found the independently association among the fasting blood glucose, HbA1c, and PhA. These findings of the present study indicate that PhA may be useful in assessment of clinical outcomes and severity of the T2DM patients. However, in order for PhA to be used as a prognostic indicator for diabetic patients, further studies are needed to evaluate the relationship with other parameters, such as inflammatory cytokine and antioxidant status, and the disease duration.

CONCLUSION

The PhA has been known as an indicator of cell health and function of cells. However, its key role of DM patients remains unclear. This study classified of the according to sex and examined the association of PhA with fasting blood glucose and HbA1c in Korean T2DM patients. The present data showed that the PhA were significant associations with age, BCM, ECM, ECM/BCM, ICW, ECW, ECW/ICW, and ECW/TBW of all subjects. HbA1c and fasting blood glucose were also independently negatively associated with the PhA of all subjects. Thus, the PhA could be a biomarker for assessing general health and regulation of fasting blood glucose in T2DM patients in Korea.

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