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ORIGINAL ARTICLE

Determinants of phase angle in Japanese patients with diabetes

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Abstract

Phase angle, obtained using bioelectrical impedance analysis, non-invasively reflects the whole-body cellular condition and nutritional status and may be helpful as a prognostic factor. Patients with diabetes had a smaller phase angle than healthy subjects. However, the clinical significance of phase angle has not yet been elucidated. Therefore, the purpose of this study was to clarify the relationship between phase angle and HbA1c in patients with diabetes and the clinical relevance of phase angle. A retrospective, multicenter, cross-sectional study was conducted with Japanese patients with diabetes. Body composition was determined with bioelectrical impedance analysis, and this was used to obtain phase angle. Phase angle was assessed in relation to clinical parameters, body composition parameters, and HbA1c levels. A total of 655 patients were enrolled (400 men and 255 women, aged 57.1 ± 14.8 years, body mass index 25.6 ± 5.2 kg/m^2, HbA1c 8.1 ± 1.9%). Even in patients with diabetes, the phase angle was higher in men than in women and did not differ between the types of diabetes. Multiple regression analysis, performed with phase angle as the objective variable, and age, sex, diabetes type, HbA1c, albumin level, and body mass index as explanatory variables, revealed that phase angle was negatively affected by HbA1c (B = − 0.043, 95% Confidence interval: − 0.07 to − 0.02, p < 0.001). HbA1c, age, sex, albumin level, and body mass index were independent determinants of phase angle in participants with diabetes.

Keywords Phase angle · Bioimpedance · Diabetes · HbA1c

Introduction

Bioimpedance analysis (BIA) estimates body components non-invasively by applying a weak alternating current to a living body and measuring its impedance. This analysis is used in various fields, including medicine, nutrition, and sports. Impedance, measured by the BIA method, is the collective term for the resistive component that opposes current. Impedance is divided into resistance (R), meaning resistance inside and outside the cell, such as lipid components; and reactance (Xc), meaning resistance specific to the cell membrane [1].

Phase angle (PhA) is calculated as the value of the arctangent of Xc divided by R (arctangent (Xc/R × 180/π)). The level of PhA is not affected by excess body fluid as well as height and weight. Rather, PhA could be an indicator of cellular health and function because it reflects cell membrane properties as well as intra- and extracellular water conditions [2–4]. Furthermore, PhA levels are positively correlated with nutritional indicators such as transthyretin [5]. Low PhA levels have been reported to be significantly related to malnutrition, length of hospital stay, and intensive care unit mortality [6, 7].

Several studies on PhA in patients with diabetes have been reported. PhA was lower in patients with diabetes than patients without diabetes, and this could be useful in diagnosing diabetes [8]. PhA levels in 32 newly diagnosed

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pediatric patients with type 1 diabetes mellitus (T1DM) were also reported to be lower than that of age- and body mass index (BMI)-matched controls [9]. Buscemi et al. [4] also reported significantly lower PhA levels in male T1DM patients than in control subjects, but no significant difference in females. In patients with type 2 diabetes, a positive relationship between PhA levels and disease duration has been reported, indicating the potential for PhA to be used as a marker to predict disease progression and the development of complications [10, 11]. Only one report has examined the independent association between PhA and HbA1c, with correction for background factors [12].

This study aimed to determine the clinical significance of PhA in patients with diabetes, especially the relationship between PhA and HbA1c, using the largest number of subjects to date.

Methods

Patients

A total of 655 diabetic outpatients who underwent body composition analysis with the BIA method at Kobe University Hospital and related facilities from April 2016 to 2020 were included in the study.

Study design and measurements

Body composition was analyzed using InBody® (InBody Japan Inc. Tokyo, Japan). Data on height, weight, BMI, and body composition parameters [body cell mass (BCM), body fat percentage (BFP), body fat mass (BFM), trunk fat mass (TFM), skeletal muscle index (SMI), skeletal muscle mass (SMM), trunk muscle mass (TMM), bone mineral content (BMC), intracellular water (ICW), extracellular water (ECW), extracellular water ratio (ECW/TBW), and basal metabolic rate (BEE)] were obtained. In addition, HbA1c, and serum albumin (Alb) levels were obtained on the same day that the body composition analysis was performed.

Statistical analysis

First, subjects were divided into groups by diabetes type (type 1 or type 2 diabetes) or gender to examine whether there were differences in the mean values of PhA by t-test. Next, the correlation between PhA and the parameters of age, BMI, HbA1c, Alb, and body composition was examined by Pearson correlation analysis. Finally, factors influencing PhA were analyzed by multiple regression analysis with PhA as the objective variable and patient attributes (age, gender, diabetes type), HbA1c, Alb, and BMI as explanatory variables. As explanatory variables, in addition to the items found to be relevant in previous studies in Korea [12], we included albumin, considering that PhA is associated with nutritional status [13]. As this study had a mix of type 1 and type 2 diabetes, the type of diabetes was also included in the model as a confounding factor. Statistical analysis was performed using IBM SPSS version 26.0 (SPSS, Chicago, IL, USA). Data were expressed as mean ± SD, with $p < 0.05$ as the significance level.

Results

The total number of participants was 655 (400 men and 255 women). The subjects' characteristics and body composition parameters are shown in Table 1.

Parameters were compared between groups divided by type of diabetes. There was no significant difference in PhA between T1DM and T2DM (T1DM: 5.3 ± 0.9, T2DM: 5.3 ± 0.8, $p = 0.90$). However, Age, BMI, BCM, BFP, BFM, TFM, SMI, SMM, TMM, BMC, ICW, ECW, and BEE were significantly higher in T2DM than in T1DM. On the other hand, ECW/ TBW, HbA1c, and Alb levels did not differ between diabetes types.

Next, we compared various parameters between genders. PhA was significantly higher in men than in women (Men: 5.5 ± 0.8, Women: 4.9 ± 0.8, $p < 0.01$). Alb, BCM, SMI, SMM, TMM, BMC, ICW, ECW, ECW/TBW, and BEE were significantly higher in men than women. Contrary to this, BFP and BFM were higher in women than men.

We performed a single correlation analysis between age, HbA1c, Alb, BMI, and body composition parameters in relation to PhA (Table 2). PhA was positively correlated with Alb ($r = 0.44$), BCM ($r = 0.62$), SMI ($r = 0.62$), TMM ($r = 0.61$), ICW ($r = 0.62$), ECW ($r = 0.51$), BMC ($r = 0.53$), and BEE ($r = 0.59$). PhA also showed a negative correlation with age ($r = -0.56$) and a strongest negative correlation with ECW/TBW ($r = -0.86$) (Fig. 1).

Finally, multiple regression analysis was performed, where PhA was the objective variable, and patient attributes (age, gender, disease type), HbA1c, Alb, and BMI were explanatory variables. The overall regression was statistically significant ($R^2 = 0.53$, $F(6, 647) = 119.6$, $p < 0.001$) as Table 3 shows. HbA1c was revealed to be an independent determinate of PhA ($R^2 = 0.53$, standardized $\beta = -0.043$, 95% CI -0.07 to -0.02, $p < 0.001$).

Discussion

We investigated the relationship between PhA and demographics, anthropometrics, and clinical parameters in 655 Japanese patients with diabetes; the largest number that has ever been reported for this type of study. PhA values were

Table 1 Basal characteristics and bioimpedance analysis of participants

Attributes and laboratory data	Data
Men (n)/Women (n)	400/255
T1DM (n)/T2DM (n)	74/581
Age (yr)	57.1 ± 14.8
HbA1c (%)	8.1 ± 1.9
Alb (g/dL)	4.2 ± 0.3
BMI (kg/m^2)	25.6 ± 5.2
Parameters of bioimpedance analysis	**Data**
PhA	5.3 ± 0.8
BCM (kg)	31.1 ± 6.7
BFP (%)	29.6 ± 9.3
BFM (kg)	21.1 ± 10.4
TFM (kg)	10.5 ± 5.0
SMI (kg/m^2)	7.4 ± 1.2
SMM (kg)	40.1 ± 12.8
TMM (kg)	21.4 ± 4.7
BMC (kg)	2.7 ± 0.5
ICW (L)	21.7 ± 4.7
ECW (L)	13.7 ± 2.7
ECW/TBW	0.39 ± 0.01
BEE (kcal)	1408 ± 218

Data are means ± standard deviation

T1DM Type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *HbA1c* glycohemoglobin, *Alb* albumin, *BMI* body mass index, *PhA* phase angle, *BCM* body cell mass, *BFP* body fat percentage, *BFM* body fat mass, *TFM* trunk fat mass, *SMI* skeletal muscle index, *SMM* skeletal muscle mass, *TMM* trunk muscle mass, *BMC* bone mineral content, *ICW* intracellular water, *ECW* extracellular water, *TBW* total body water, *BEE* basal energy expenditure

higher in men than in women, decreased with age, and were positively correlated with parameters related to body protein levels; PhA was strongly negatively correlated with ECW/TBW. In addition, multiple regression analysis revealed that HbA1c was independently associated with PhA.

The gender differences in PhA were consistent with previous reports in healthy subjects [13] and patients with diabetes [12]. BCM, composed of body protein and ICW has been reported to be responsible for higher PhA in men [14, 15]. The indices reflecting body protein (Alb, SMI, SMM, TMM) and ICW were all higher in men, indicating that this contributed to the high PhA in this study.

A relationship between age and PhA in healthy subjects has been reported, with gradually increasing levels during adolescence and stabilization in adulthood, and decreased levels in the elderly [16]. Since most of the participants in this study were middle-aged or older, it was observed that there seemed to be a negative association between PhA levels and age, as has been noted in previous studies.

ECW/TBW, which showed the strongest negative correlation with PhA in this study, has been reported to reflect water balance [17]. Furthermore, multiple regression analysis

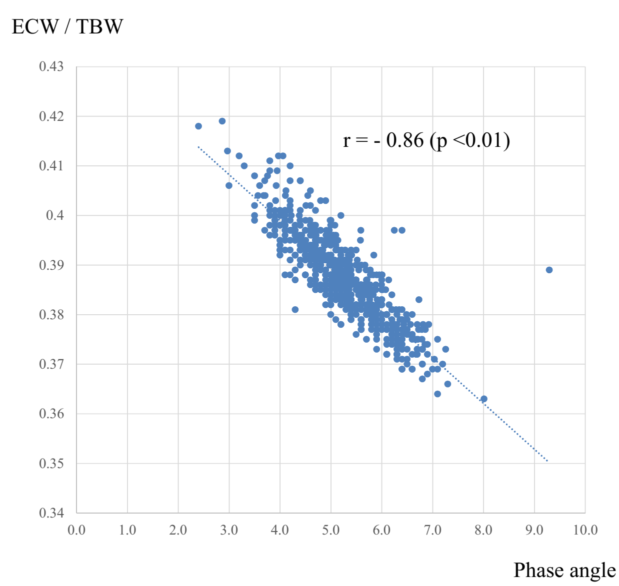

Fig. 1 Significant negative correlation between Phase Angle and ECW/TBW. *ECW* extracellular water, *TBW* total body water

excluding body composition parameters also showed that

Table 2 Spearman's rank correlation coefficient between phase angle and each parameters

Characteristics	Correlation coefficient
Age (yr)	− 0.56*
HbA1c (%)	− 0.02
Alb (g/dL)	0.44*
BMI (kg/m^2)	0.31*
BCM (kg)	0.62*
BFP (%)	− 0.11*
BFM (kg)	0.15*
TFM (kg)	0.19*
SMI (kg/m^2)	0.62*
SMM (kg)	0.36*
TMM (kg)	0.61*
BMC (kg)	0.53*
ICW (L)	0.62*
ECW (L)	0.51*
ECW/TBW	− 0.86*
BEE (kcal)	0.59*

HbA1c Glycohemoglobin, *Alb* albumin, *BMI* body mass index, *PhA* phase angle, *BCM* body cell mass, *BFP* body fat percentage, *BFM* body fat mass, *TFM* trunk fat mass, *SMI* skeletal muscle index, *SMM* skeletal muscle mass, *TMM* trunk muscle mass, *BMC* bone mineral content, *ICW* intracellular water, *ECW* extracellular water, *TBW* total body water, *BEE* basal energy expenditure

*p value is statistically significant (<0.05)

HbA1c levels negatively influenced PhA. Hyperglycemia is thought to induce extracellular osmotic pressure, causing water movement from the intracellular space to the extracellular space [18]. Thus, hyperglycemia-induced changes in plasma osmolality and reduction in active cell mass [19] might be related to the decrease in PhA. Advanced glycated endproducts might affect PhA because PhA has been reported to decrease with a longer duration of diabetes [11]. Further basic research is awaited. Although the mechanisms by which chronic hyperglycemia affects PhA are not fully understood, the fact that PhA is decreased in patients with diabetes suggests that long-term exposure to hyperglycemia affects cellular health and nutritional status. Based on this, PhA may be a prognostic indicator in patients with diabetes.

This study was the largest ever to examine the determinants of PhA using multiple regression analysis in patients with diabetes. However, its limitation was that it did not examine the effect of disease treatment or diabetes duration, as well as comorbidities and complications on PhA. Therefore, a further longitudinal study of PhA and disease prognosis and complications is also warranted.

In conclusion, PhA was higher in men than in women, decreased with age, and was positively correlated with BCM and muscle mass and negatively correlated with ECW/TBW, even in patients with diabetes. Multiple regression analysis also revealed that HbA1c had a negative effect on PhA.

Table 3 Multiple regression analysis for phase angle

Variables	Unstandardized beta	SE	Standardized beta	Sig.	95% CI
Constant	3.71	0.42		<0.01	2.89 to 4.53
Age	− 0.02	0.00	− 0.415	<0.01	− 0.03 to 0.02
Sex[a]	− 0.56	0.05	− 0.324	<0.01	− 0.66 to − 0.47
Diabetes type[b]	0.02	0.08	0.006	0.842	− 0.15 to 0.18
HbA1c	− 0.04	0.01	− 0.095	<0.01	− 0.07 to − 0.02
Alb	0.62	0.07	0.249	<0.01	0.48 to 0.77
BMI	0.03	0.00	0.189	<0.01	0.02 to 0.04

HbA1c Glycohemoglobin, *BMI* body mass index, *SE* standard error, *Sig* significance

[a]Sex is dummy variable (Men = 0, Women = 1)

[b]Diabetes type is dummy variable (T1DM = 1, T2DM = 2)

Declarations

Conflict of interest TM have received lecture fees from Eli Lilly Japan.

Human rights statement This retrospective observational cross-sectional study was approved by the Institutional Review Board of Kobe University Hospital (date of approval: Aug 13, 2020, approval number: B200154) and complied with the provisions of the Declaration of Helsinki (revised 2013). Informed consent was obtained in the form of an opt-out on the website.

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