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Low serum butyrylcholinesterase is independently related to low fetuin-A in patients on hemodialysis: a cross-sectional study

Teppei Okamoto[1] · Chikako Tsutaya[2] · Shingo Hatakeyama[3] · Sakae Konishi[3] · Kazutaka Okita[3] · Yoshimi Tanaka[1,3] · Kengo Imanishi[1] · Tooru Takashima[1] · Fumitada Saitoh[1] · Tadashi Suzuki[2] · Chikara Ohyama[3]

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Abstract

Purpose Fetuin-A, which plays a protective role against the atherosclerosis and progression of vascular calcification, is decreased in patients on hemodialysis (HD). Fetuin-A and serum butyrylcholinesterase (BChE) levels decrease during malnutrition. We explored whether BChE was independently related to fetuin-A in patients on HD.

Methods Laboratory data including BChE and serum fetuin-A were acquired from 230 patients on HD between August 2017 and April 2018. Nutritional status was evaluated using the Geriatric Nutritional Risk Index (GNRI). Abdominal aortic calcification index (ACI) was measured using computed tomography. Patients were stratified into two groups: low fetuin-A (< lowest quartile) and non-low fetuin-A (≥ lowest quartile) groups. Patient background, medication, and laboratory data were compared. The receiver operating characteristic analysis was conducted to determine the optimal cutoff values of BChE and GNRI for lower fetuin-A level. Factors independently related with lower fetuin-A levels were determined using multivariate logistic regression analysis.

Results The lowest quartile value of fetuin-A and optimal cutoff values of BChE and GNRI were 0.213 g/L, 200 IU/L, and 92.6, respectively. The study included 57 and 173 patients in the low fetuin-A and non-low fetuin-A groups, respectively. Significant between-group differences were observed for age, C-reactive protein (CRP), history of cardiovascular disease, serum albumin, GNRI, and BChE. Multivariate analysis showed that BChE of < 200 IU/L [odds ratio (OR) 3.05], CRP (OR 2.49), and GNRI of < 92.6 (OR 2.34) were independent factors for lower fetuin-A level after adjusting for confounders.

Conclusions BChE was a significant independent marker for fetuin-A levels in patients on HD, in addition to GNRI.

Keywords Fetuin-A · Butyrylcholinesterase · Vascular calcification · Hemodialysis · Geriatric Nutritional Risk Index

Introduction

Fetuin-A, a circulating calcium-regulatory glycoprotein synthesized in the liver, has been reported to be associated with atherosclerosis and cardiovascular mortality [1, 2]. Fetuin-A is also known to play a protective role against the progression of vascular calcification and is decreased among dialyzed patients [1–3]. Vascular calcification is a complication that is typically associated with adverse clinical events in patients with end-stage renal disease (ESRD) and those on hemodialysis (HD) [4, 5]. Recently, there has been growing interest in the idea of malnutrition–inflammation–atherosclerosis (MIA) syndrome with regard to the progression of vascular calcification in patients on HD [6]. MIA syndrome is defined as the interaction between ESRD-related inflammation and atherosclerosis and malnutrition, which is deeply associated with poor clinical outcomes in dialyzed patients [7]. Fetuin-A has been focused as one of the key factors for MIA syndrome. Furthermore, the serum levels of fetuin-A are positively correlated with nutritional indicators, including serum albumin level, pre-albumin level, and Subjective Global Assessment [1, 8, 9]. However, the impact of butyrylcholinesterase (BChE) as a nutritional indicator in patients on HD has not been fully elucidated.

✉ Teppei Okamoto
tepperococcus@yahoo.co.jp

[1] Department of Urology, Oyokyo Kidney Research Institute Aomori Hospital, 101-1 Okabe, Ishie, Aomori 038-0003, Japan

[2] Oyokyo Kidney Research Institute, 90, Yamazaki, Ozawa, Hirosaki 036-8243, Japan

[3] Department of Urology, Hirosaki University Graduate School of Medicine, 5 Zaifu-chou, Hirosaki 036-8562, Japan

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BChE is one of the alpha-glycoproteins found in the nervous system and liver [10]. The serum levels of BChE decrease in many clinical settings, such as liver damage, inflammation, malnutrition, malignant disease, and cardiovascular disease (CVD) [10–15]. Serum BChE levels are also positively correlated with serum albumin, triglyceride, and total cholesterol levels [15]. BChE is an indicator for nutritional status [10, 16] and is a predictor for several clinical outcomes, such as malignancy [17] and CVD in the absence of inflammation [15]. Moreover, a previous study demonstrated that BChE levels in patients on HD were significantly lower than those in the healthy population [18]. However, the association between serum BChE and fetuin-A levels has not been clarified. Fetuin-A is not of clinical use despite its importance, because its measurement requires complicated and specialized laboratory techniques. To explore simple and useful marker of fetuin-A is important for clinical practice. We therefore aimed to explore the association between BChE and fetuin-A levels in patients on maintenance HD.

Methods

Study design

This was a single-center, cross-sectional observational study. It was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine (Authorization number: 2017-089). The trial is registered in the UMIN Clinical Trials Registry (UMIN000028064). All participants in this study provided written informed consent.

Patient selection and classification

In total, 275 patients received 3–4 h of HD on three occasions per week at the Oyokyo Kidney Research Institute at Aomori Hospital, Japan, from August 2017 to April 2018. Of these, 253 patients provided written informed consent to participate in our study. Because serum BChE levels are increased or decreased in case of fatty liver, active inflammation, hepatitis, and malignancy, we excluded 23 patients as follows: patients with active infection ($n=9$), liver cirrhosis and/or hepatitis ($n=5$), autoimmune diseases ($n=6$), and end-stage malignancy ($n=3$). Thus, 230 patients who met our specific inclusion criteria were included (Fig. 1).

Evaluation of outcome variables

Prior to HD, standard laboratory techniques (JCA-BM9130 BioMajesty™, JEOL, Tokyo, Japan) were used to acquire a range of biochemical laboratory data from each patient, including BChE, serum albumin, serum phosphate (P), serum creatinine, i-PTH, C-reactive protein (CRP), and lipid profile. Our reference range for serum BChE levels was 214–466 IU/L. The dialysis dose (Kt/V) was calculated using the following equation: $\mathrm{Kt/V} = -\mathrm{Ln}\,(C_t/C_0 - 0.008 \times t) + (4 - 3.5 \times C_t/C_0) \times \Delta\mathrm{BW/BW}$. In this equation, "$C_t$" represents post-dialysis serum nitrogen level, "C_0" represents pre-dialysis serum nitrogen level, "t" represents the time of dialysis, and "W" (kg) represents the patient's post-dialysis body weight. When the serum albumin levels were <4.0 g/dL, serum calcium levels were corrected using the following formula: corrected Ca = total Ca + 0.8 × (4 − serum albumin). Calcium phosphorus product was determined by multiplying the corrected calcium concentration with serum

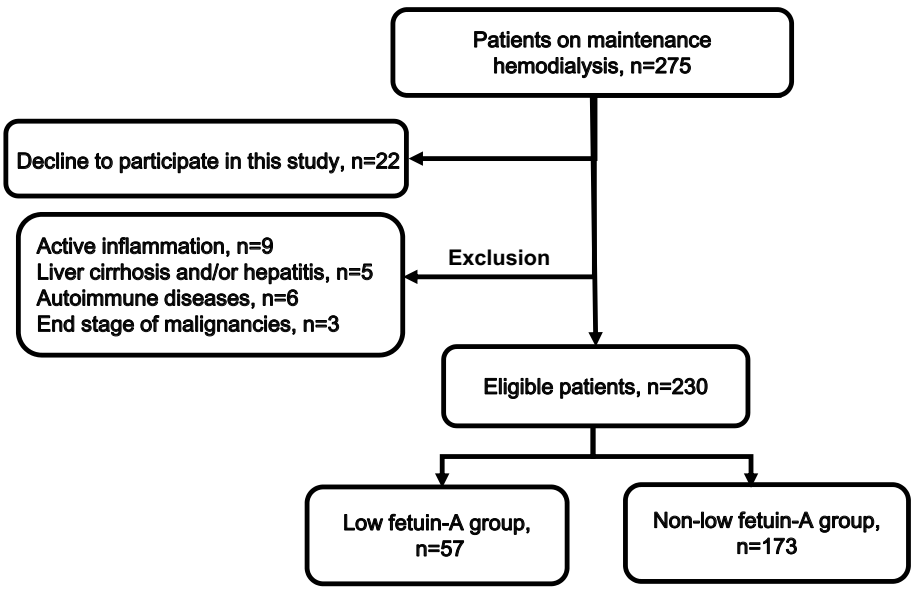

Fig. 1 Patient selection and classification. This study investigated 275 patients who received 3–4 h of hemodialysis (HD) sessions three times a week. Of these, 22 did not provide informed consent. Patients with active infection, liver cirrhosis, autoimmune diseases, and end-stage malignancies were excluded. Finally, 230 patients on HD were included and divided into two groups: low fetuin-A and non-low fetuin-A

P level (Ca × P). Mean blood pressure calculated over three consecutive pre-dialysis sessions was used as a representative blood pressure reading for the week in which blood samples were obtained. The following phosphate binders were used: lanthanum carbonate, calcium carbonate, polymeric phosphate binders (bixalomer or sevelamer), and iron-based phosphate binders (ferric citrate hydrate or sucroferric oxyhydroxide). The specific causes of ESRD were stratified between diabetic nephropathy (DMN) and non-DMN groups. Patients were defined as having a history of CVD if their medical records indicated that they had previously experienced ischemic heart disease, cerebrovascular disease, or peripheral arterial disease.

Abdominal aortic calcification index (ACI)

Almost all patients on HD in our hospital had undergone annual abdominal computed tomography (CT) scans to detect incidental renal tumor and other malignancies at least once a year. Abdominal aortic calcification was evaluated using computed tomography (CT; SOMATOM Perspective, Siemens Healthineers, Tokyo, Japan), and images were generated using 5-mm slice thickness. The data were semiquantitatively evaluated using CT images of the area above the common iliac artery bifurcation; this was performed by at 5-mm intervals [19]. ACI (%), which represents the proportion of calcification in 12 sectors, was calculated as follows: ACI (%) = (total calcification score on all slices)/12/10 × 100.

All procedures were performed by a single assessor who was unaware of the patients' clinical data or background. To investigate the variability of measurement, the same assessor re-examined 30 randomly selected CT images. The intraclass correlation coefficient for ACI was 0.920 [95% confidence interval (CI) 0.85–0.94].

Measurement of serum fetuin-A levels

Serum samples were stored at − 70 °C until analysis, and supernatants were diluted to a ratio of 1:10,000. Fetuin-A levels were measured in diluted serum solutions using human enzyme-linked immunosorbent assay (ELISA) kit (BioVendor, Brno Czech Republic). The assay applied the two-site "sandwich" technique with two selected polyclonal antibodies that combined different epitopes on fetuin-A. Patients were divided into two groups: low fetuin-A (< lowest quartile) and non-low fetuin-A (≥ lowest quartile) groups.

Geriatric Nutritional Risk Index (GNRI)

GNRI represents simplified NRI for elderly patients [20] and was calculated as follows: GNRI = 14.89 × serum albumin (g/dL) + 41.7 × (body weight/ideal body weight). Ideal body weight is determined using height and body mass index (BMI) of 22 kg/m^2. Body weight/ideal body weight is set at 1 when the patient's body weight exceeded the ideal body weight.

Optimal cutoff value of BChE for low fetuin-A levels

Lower serum albumin level, BChE level, and GNRI were defined on the basis of the area under curves (AUC) of the receiver operating characteristic (ROC) curves for a lower fetuin-A level. The optimal cutoff value for lower fetuin-A levels was defined as the maximum value for sensitivity + specificity − 1, based on the Youden index [21].

Comparison of clinical characteristics between the low fetuin-A and non-low fetuin-A groups

The low fetuin-A and non-low fetuin-A groups were compared with respect to age, gender, BMI, previous history of CVD, HD vintage, and serum data, including BChE levels. Multivariate logistic regression analysis was performed to identify the factors that were independently associated with low fetuin-A levels. Considering that GNRI is composed of serum albumin levels and BMI, we included these parameters in our regression models separately; thus, two types of regression analyses were performed.

Statistical analysis

All statistical analyses were carried out using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables (e.g., gender) were expressed as percentages, normally distributed continuous variables as means [with standard deviations (SDs)], and non-normally distributed variables as medians [interquartile ranges (IQRs)]. Correlation analyses between fetuin-A levels and serum albumin levels, GNRI, and BChE levels were performed. In addition, correlation analysis between BChE levels and GNRI was also performed. Because fetuin-A, BChE, serum albumin, and GNRI were not normally distributed variables in this study, we conducted the Spearman's correlation coefficient. The low and non-low fetuin-A groups were compared using the Chi-square test, Student's *t* test (when data were normally distributed), or Mann–Whitney *U* test (when data were not normally distributed). The model included the following variables: gender (0, female; 1, male), DMN (0, other; 1, presence), CVD history (0, without, 1, with), lower GNRI (0, absence; 1, presence), and lower BChE level (0, absence; 1, presence). Previously identified factors related to fetuin-A levels, including nutritional status (GNRI) and CRP levels, were included in our multivariate models in addition to age, gender, cause of ESRD, and HD vintage. We calculated the odds ratio (OR) with 95% confidence intervals (CIs) for each

factor after adjustment for potential confounders. P values of <0.05 were considered to be statistically significant.

Results

Patient background

This cross-sectional study included 230 patients on HD (152 males and 78 females), with a median age of 68 years (IQR 59–75). The median values of fetuin-A levels, serum albumin levels, GNRI, BChE levels, and ACI were 0.243 g/L (0.213–0.274), 3.5 g/dL (3.3–3.7), 92.3 (88.7–96.8), 211 IU/L (175–249), and 50.8% (25.0–77.8), respectively. The low fetuin-A (fetuin-A <0.213 g/L) and non-low fetuin-A (fetuin-A ≥ 0.213 g/L) groups consisted of 57 (25%) and 173 patients (75%), respectively (Fig. 1).

Spearman's correlation coefficient between fetuin-A levels and serum albumin levels, GNRI, and BChE levels, between BChE levels and GNRI

Figure 2 shows scatter plot graphs between fetuin-A levels and serum albumin levels, GNRI, and BChE levels. Spearman's correlation analysis revealed that there were significant positive correlations between fetuin-A and serum albumin levels ($r=0.432$, $P<0.001$), fetuin-A and GNRI ($r=0.408$, $P<0.001$), and fetuin-A and BChE levels ($r=0.412$, $P<0.001$). There was a significant positive correlation between BChE levels and GNRI ($r=0.454$, $P<0.001$).

ROC curves for low fetuin-A levels

Figure 3 shows ROC curves for lower fetuin-A levels. The AUC values associated with these ROC curves were 0.718 ($P<0.001$; 95% CI 0.640–0.797), 0.716 ($P<0.001$; 95% CI 0.637–0.794), and 0.702 ($P<0.001$; 95% CI 0.625–0.780) for BChE levels, serum albumin levels, and GNRI, respectively. We determined that the optimal cutoff values of BChE levels, serum albumin levels, and GNRI for lower fetuin-A levels were 200 IU/L (sensitivity; 68.4%, specificity; 67.1%), 3.5 g/dL (sensitivity; 66.7%, specificity; 68.8%), and 92.6 (sensitivity; 78.9%, specificity; 54.9%), respectively.

Comparison of clinical characteristics between the low fetuin-A and non-low fetuin-A groups

Table 1 shows the clinical characteristics, medications, and laboratory data of patients in the low and non-low fetuin-A groups. The numbers of patients with history of CVD ($P=0.035$), those with serum albumin levels <3.5 g/dL ($P<0.001$), those with GNRI <92.6 ($P<0.001$), and those with BChE levels <200 IU/L ($P<0.001$) in the low fetuin-A group were significantly higher than those in the non-low fetuin-A group. Moreover, serum albumin levels ($P<0.001$), GNRI ($P<0.001$), BChE levels ($P<0.001$), and serum

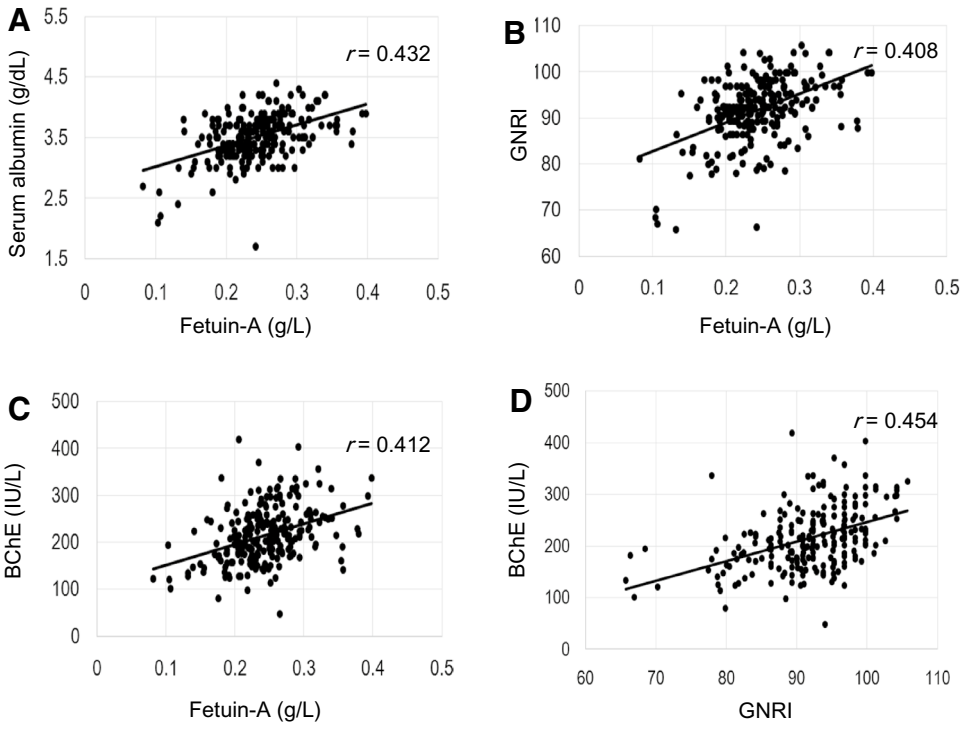

Fig. 2 Spearman's correlation analysis between fetuin-A levels and serum albumin levels, Geriatric Nutritional Risk Index (GNRI), and butyrylcholinesterase (BChE) levels. Spearman's correlation analysis revealed that there were significant positive correlations between fetuin-A levels and **a** serum albumin levels ($r=0.432$ $P<0.001$), **b** GNRI ($r=0.408$, $P<0.001$), and **c** BChE levels ($r=0.412$, $P<0.001$). A significant positive correlation was also observed between BChE levels and GNRI ($r=0.454$, $P<0.001$) (**d**)

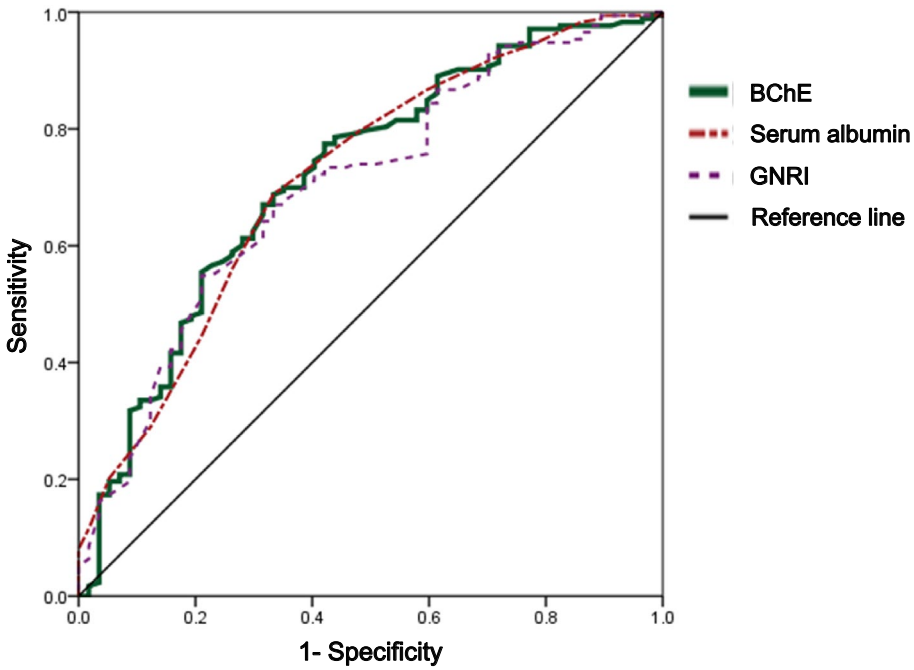

Fig. 3 Receiver operating characteristic (ROC) curve for low fetuin-A levels. Receiver operating characteristic (ROC) curve analysis showed that the area under curve (AUC) values were 0.718, 0.716, and 0.702 for serum butyrylcholinesterase (BChE) level serum albumin level, and Geriatric Nutritional Risk Index (GNRI), respectively. *AUC* area under curve, *CI* confidence interval

creatinine levels in the low fetuin-A group were significantly lower than those in the non-low fetuin-A group. On the other hand, age ($P = 0.001$) and CRP level ($P < 0.001$) in the low fetuin-A group were significantly higher than those in the non-low fetuin-A group.

Independent risk factors for low fetuin-A levels

Independent risk factors for low fetuin-A levels were evaluated using multivariate logistic regression analyses (Table 2). Model 1 showed that BChE level of < 200 IU/L (OR 3.15) and CRP level (OR 2.37) were independent factors. Model 2 showed that BChE levels of < 200 IU/L (OR 3.05), CRP levels (OR 2.49), and GNRI of < 92.6 (OR 2.34) were independent factors for low fetuin-A levels.

Discussion

In the current study, we revealed that serum BChE and fetuin-A had a positive correlation ($r = 0.412$), and ROC curves for low fetuin-A levels of BChE had the widest AUC (AUC = 0.718) among other factors related to nutritional status. Moreover, our present results also suggested that patients on HD with BChE levels < 200 IU/L had an approximately threefold higher risk of having lower fetuin-A levels than those with BChE levels ≥ 200 IU/L; this association showed a higher OR compared with GNRI (< 92.6).

Acetylcholine and other choline esters are hydrolyzed by two types of cholinesterases, namely acetylcholinesterase and BChE, which have distinct biochemical attributes [22]. Acetylcholinesterase and BChE have been detected in almost all types of biological tissues, including the central and peripheral nerve systems, skeletal muscles, and erythrocytes. Serum BChE levels are known to decrease in patients with liver diseases owing to its synthesis in the liver [11]. Serum BChE levels are greatly influenced by inflammation [13]. Fetuin-A is also known as a negative acute phase reactant; its levels are reduced in case of inflammation and are negatively correlated with CRP and high-sensitivity CRP levels [2, 8]. Our results showed that CRP level was one of the independent factors associated with lower fetuin-A level. In addition, several studies have shown that BChE has a significant inverse association with serum interleukin-6 levels, which are also correlated with fetuin-A levels in patients on HD [23, 24]. Serum levels of BChE show the positive correlation with serum albumin and are decreased in patients with protein–energy malnutrition, probably due to insufficient availability of substrates for its synthesis rather than due to liver dysfunction [10]. The half-life of BChE is approximately 12 days, which is shorter than that of serum albumin [25]. Some researchers therefore hypothesized that serum BChE is a useful nutritional marker in rapidly changing general conditions [10]. BChE is speculated to be more appropriate for repeated evaluation rather than for a single measurement of the nutritional status due to its wide reference range [22]. Similar to BChE, fetuin-A levels also have a positive correlation with serum albumin and are decreased in case of malnutrition [1]. A range of factors, including anorexia, protein–energy wasting, and metabolic disorders, can affect the nutritional and metabolic status of patients on HD. Previous studies have shown that additional protein

Table 1 Clinical characteristics of the low and non-low fetuin-A groups

	Low fetuin-A (< 0.213 g/L)	Non-low fetuin-A (≥ 0.213 g/L)	*P* value
Number	57 (25%)	173 (75%)	–
Age[a] (year)	73 (65–79)	66 (58–73)	0.001
Sex[b] (male), *n* (%)	35 (61%)	117 (68%)	0.400
Fetuin-A[a] (g/L)	0.189 (0.172–0.204)	0.258 (0.234–0.284)	< 0.001
Cause of ESRD[b]			0.150
DMN (presence), *n* (%)	35 (61%)	87 (50%)	–
Non-DMN (presence), *n* (%)	22 (39%)	86 (50%)	–
Modality of HD[b]			0.840
HD, *n* (%)	16 (28%)	51 (29%)	–
Hemodiafiltration, *n* (%)	41 (72%)	122 (71%)	–
Systolic blood pressure[c] (mmHg)	149 (22)	151 (21)	0.580
Diastolic blood pressure[c] (mmHg)	74 (15)	79 (12)	0.016
History of CVD (presence)[b], *n* (%)	28 (49%)	58 (34%)	0.035
HD vintage[a] (months)	57 (17–100)	49 (21–103)	0.510
Kt/V[c]	1.41 (0.24)	1.42 (0.31)	0.810
Serum creatinine[c] (mg/dL)	8.8 (2.8)	10.3 (2.9)	0.001
Calcium carbonate[b] (presence), *n* (%)	13 (23%)	57 (33%)	0.150
Lanthanum carbonate[b] (presence), *n* (%)	19 (33%)	82 (47%)	0.063
Polymeric phosphate binders[b] (presence), *n* (%)	11 (19%)	49 (28%)	0.180
Iron-containing phosphate binders[b] (presence), *n* (%)	16 (28%)	53 (31%)	0.710
Cinacalcet[b] (presence), *n* (%)	11 (19%)	48 (28%)	0.210
Warfarin[b] (presence), *n* (%)	4 (7.0%)	10 (5.0%)	0.740
BMI[a]	21.6 (19.7–23.8)	22.3 (19.9–25.1)	0.070
Serum albumin[a] (g/dL)	3.3 (3.1–3.6)	3.6 (3.4–3.8)	< 0.001
Serum albumin < 3.5 g/dL[b] (presence), *n* (%)	38 (67%)	54 (31%)	< 0.001
GNRI[a]	89.3 (82.3–92.3)	93.8 (89.3–96.8)	< 0.001
GNRI < 92.6[b] (presence), *n* (%)	45 (79%)	78 (45%)	< 0.001
BChE[a] (IU/L)	177 (146–212)	219 (187–258)	< 0.001
BChE < 200 IU/L[b] (presence), *n* (%)	39 (68%)	57 (33%)	< 0.001
CRP[a] (mg/dL)	0.41 (0.12–1.11)	0.10 (0.04–0.31)	< 0.001
Triglyceride[a] (mg/dL)	87 (73–121)	102 (72–147)	0.100
Total cholesterol[a] (mg/dL)	147 (128–170)	155 (134–178)	0.250
High-density lipoprotein cholesterol[a] (mg/dL)	49 (40–58)	48 (39–61)	0.600
Low-density lipoprotein cholesterol[a] (mg/dL)	82 (64–100)	81 (67–98)	0.980
Serum phosphate[a] (mg/dL)	5.1 (4.3–6.3)	5.3 (4.6–6.5)	0.630
Corrected calcium[a] (mg/dL)	9.4 (9.0–9.7)	9.3 (8.9–9.7)	0.570
Ca × P[a]	48 (40–59)	50 (41–59)	0.690
ACI[a] (%)	59.2 (37.7–81.5)	50.0 (23.3–75.8)	0.060
i-PTH[a] (pg/mL)	141 (102–243)	141 (96–220)	0.640

ESRD end-stage renal disease, *DMN* diabetic nephropathy, *HD* hemodialysis, *CVD* cardiovascular disease, *BMI* body mass index, *GNRI* Geriatric Nutritional Risk Index, *BChE* butyrylcholinesterase, *CRP* C-reactive protein, *Ca × P* calcium phosphorus product, *ACI* abdominal aortic calcification index, *i-PTH* intact parathyroid hormone

[a]Mann–Whitney *U* test

[b]Chi-square test

[c]Student *t* test

catabolic processes, such as the inevitable loss of amino acids (10–12 g per HD session) [26], and inflammatory stimuli are associated with dialysis [27]. It is very likely that the synthesis of glycoprotein is impeded if there is an inadequate supply of amino acids during the dialysis-induced catabolic state in patients on HD. In sum, these findings may support

Table 2 Independent risk factors for low fetuin-A level as predicted by multivariate logistic regression analysis

Variable	Risk factor	*P* value	OR	95% CI
Model 1 (Including serum albumin levels < 3.5 mg/dL)				
BChE < 200 IU/L	Positive	0.003	3.15	1.46–6.77
Serum albumin < 3.5 g/dL	Positive	0.057	2.05	0.98–4.32
CRP (mg/dL)	Continuous	0.003	2.37	1.33–4.21
DMN	Positive	0.310	1.48	0.70–3.12
History of CVD	Positive	0.440	1.35	0.63–2.87
Age (years)	Continuous	0.079	1.03	0.98–1.06
HD vintage (months)	Continuous	0.940	1.00	1.00–1.01
Male sex	Positive	0.056	0.48	0.22–1.02
Model 2 (including GNRI < 92.6)				
BChE < 200 IU/L	Positive	0.005	3.05	1.41–6.57
CRP (mg/dL)	Continuous	0.002	2.49	1.40–4.44
GNRI < 92.6	Positive	0.033	2.34	1.07–5.14
DMN	Positive	0.300	1.48	0.70–3.12
History of CVD	Positive	0.410	1.37	0.65–2.93
Age (year)	Continuous	0.081	1.03	1.00–1.04
HD vintage (months)	Continuous	0.730	1.00	0.99–1.00
Male sex	Positive	0.060	0.48	0.23–1.03

BChE butyrylcholinesterase, *CRP* C-reactive protein, *DMN* diabetic nephropathy, *CVD* cardiovascular disease, *HD* hemodialysis, *OR* odds ratio, *CI* confidence interval, *GNRI* Geriatric Nutritional Risk Index

the conclusion that serum BChE is one of the important markers associated with fetuin-A in patients on HD.

Fetuin-A can inhibit the progression of vascular calcification in patients with ESRD by preventing Ca P crystal growth through forming calciprotein particles (calcium phosphate-containing nanoaggregates) [28]. Although not significant, patients with lower fetuin-A levels tended to have a higher ACI than those with non-lower fetuin-A levels in this study (59.2% vs 50.0%, $P = 0.06$). Our results were generally consistent with the findings that lower fetuin-A levels have also been associated with the severity of vascular calcification and the presence of history of CVD in patients on dialysis [2]. GNRI, which is a validated nutritional indicator and predictor for all-cause mortality in patients on HD [29, 30], was also a significant marker of fetuin-A. Moreover, our previous study demonstrated that patients on HD with lower GNRI had a significant risk of progression of abdominal aortic calcification for 1 year [19]. These findings implied that patients with lower GNRI may tend to experience rapid vascular calcification progression through lower fetuin-A. Our additional analysis showed that there was a significant positive correlation between GNRI and BChE ($r = 0.454$, Fig. 2d). Although we could not stress the degree of vascular calcification progression due to the nature of cross-sectional study, it is speculated that BChE may be one of potential indicators associated with vascular calcification progression in patients on HD. Hence, further investigation should be needed to clarify whether BChE can be an independent indicator of vascular calcification progression.

The optimal cutoff value of BChE levels for malnutrition in patients on HD should be debated. Our previous study showed that patients on HD with BChE levels of < 200 IU/L had significantly lower responsiveness to erythropoiesis-stimulating agents prescribed for the treatment of renal anemia [31]. Because lower fetuin-A levels and hypo-responsiveness to erythropoiesis-stimulating agents are both significantly associated with malnutrition and all-cause mortality in patients on HD [1, 23, 31–33], we speculated that BChE level may represent a strong indicator for poor clinical outcomes and malnutrition in patients on HD. The clinical implication and optimal cutoff value of BChE for malnutrition in patients on HD have not been fully elucidated. Our future study should therefore focus on BChE as a potential prognostic factor in comparison with other significant prognostic factors, including fetuin-A and GNRI.

Our present study had several limitations. First, this was a cross-sectional study with a small sample size which was performed at a single center. These factors prevented us from ascribing cause and effect. Second, serum BChE levels do not necessarily reflect nutritional status because of low specificity. Third, we were unable to acquire information related to dietary habits or normalized protein catabolic rates, which would have provided information regarding the patients' protein intake. Another limitation was that the median fetuin-A level in our patients was noticeably lower than that given in other studies involving non-Asian patients, which prevented the generalization of our results to non-Asian populations [1, 2, 8, 9, 23]. Finally, we were unable to determine the serum levels of other substrates that were associated with fetuin-A, such as interleukin-6, homocysteine, asymmetric dimethyl arginine, and malondialdehyde. Despite these limitations, we demonstrated an independent association between BChE and fetuin-A levels in patients on maintenance HD, even after the adjustment for serum albumin levels, GNRI, and CRP levels. Our findings may encourage clinicians to be more attentive to BChE levels as an important, simple, and useful marker for fetuin-A. In addition, our study helps clarify the relationship between BChE and fetuin-A. Further studies are needed to appreciate the clinical utility of our findings.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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