タイトル	Change of plasma ketone bodies and skin gas acetone in hemodialysis patients
別タイトル	透析患者における血漿ケトンと皮膚ガスアセトンの変化
作成者（著者）	鈴木, 健志
公開者	東邦大学
発行日	2021.03.17
掲載情報	東邦大学大学院医学研究科 博士論文.
資料種別	学位論文
内容記述	主査 : 酒井謙 / タイトル : Change of plasma ketone bodies and skin gas acetone in hemodialysis patients /著者 : Takeshi Suzuki, Yosuke Sasaki, Fumiya Komatsu, Tadashi Maeda, Kensuke Suzuki, Yoshihisa Urita /掲載誌 : Toho Journal of Medicine /巻号・発行年等 : 7(1): 57-65, 2021 /本文ファイル: 出版社版
著者版フラグ	ETD
報告番号	32661甲第1002号
学位記番号	甲第690号
学位授与年月日	2021.03.17
学位授与機関	東邦大学
DOI	info:doi/10.14994/tohojmed.2020-010
その他資源識別子	https://mylibrary.toho-u.ac.jp/webopac/TD46919605
メタデータのＵＲＬ	https://mylibrary.toho-u.ac.jp/webopac/TD48838469

Original Article

Change of Plasma Ketone Bodies and Skin Gas Acetone in Hemodialysis Patients

Takeshi Suzuki[1, 3] Yosuke Sasaki[2] * Fumiya Komatsu[2]
Tadashi Maeda[2] Kensuke Suzuki[3] and Yoshihisa Urita[2]

[1]Department of General Medicine and Emergency Care, Toho University Graduate School of Medicine, Tokyo, Japan
[2]Department of General Medicine and Emergency Care, Toho University Omori Medical Center, Tokyo, Japan
[3]Kitamachi Clinic, Niigata, Japan

ABSTRACT

Introduction: Ketone body metabolism increases under various pathological conditions, including insulin resistance, inflammation, and heart failure, which are common in hemodialysis patients. This study investigated whether plasma ketone bodies and skin-gas acetone are useful biomarkers of metabolic conditions during hemodialysis.

Methods: Twenty patients with end-stage renal disease undergoing maintenance dialysis for at least 9 months were enrolled. To measure plasma ketone body concentrations before and immediately after hemodialysis, blood samples were collected from the shunt vessel. Also, we measured acetone concentration in the vapors emanating from the skin.

Results: Plasma ketone body concentrations increased 6-fold after hemodialysis, with a remarkable increase of β-hydroxybutyrate (BOHB) and plasma BOHB/acetoacetate ratio. Conversely, no significant change of skin-gas acetone concentration was observed. Therefore, no association was found between the concentration of plasma ketone bodies and skin-gas acetone. Increased ratio of glucose level and ketone bodies exhibited a positive correlation; however, other laboratory data did not. Increased ratio of plasma BOHB significantly correlated with water removal ratio.

Conclusions: We found a significant increase in BOHB-dominant plasma ketone bodies, which significantly correlated with the water removal ratio, and dissociation between the changes in skin-gas acetone and plasma ketone body concentrations after hemodialysis. These results suggest an association between two independently reported cardiovascular risk factors, plasma BOHB concentration and fluid removal amount in hemodialysis patients. Although no association between skin-gas acetone and plasma ketone bodies was observed, the dissociation suggests an increase in ketone body synthesis during hemodialysis.

Toho J Med 7 (1): 57–65, 2021

KEYWORDS: acetone, plasma ketone body concentration, hemodialysis, end-stage renal disease, skin gas

*Corresponding Author: Yosuke Sasaki, 6-11-1, Omorinishi, Ota-ku, Tokyo 143-8541, Japan, tel: +81–3–3762–4151
e-mail: yousuke.sasaki@med.toho-u.ac.jp
DOI: 10.14994/tohojmed.2020-010

Received June 5, 2020: Accepted Dec. 2, 2020
Toho Journal of Medicine 7 (1), Mar. 1, 2021.
ISSN 2189–1990, CODEN: TJMOA2

Introduction

Acetone is a component of ketone bodies resulting from the metabolism of fatty acids when the plasma glucose level is low. As a part of ketone body metabolism, production of acetone is known to increase in the fasting state[1] during exercise[2] and during a myriad of pathological conditions, including insulin resistance, diabetic ketoacidosis, inflammation, and heart failure.[3] Because these conditions are common in patients receiving regular hemodialysis, increased ketone body levels may be frequently observed in these patients. However, data on the relationship between acetone production and ketogenesis in dialysis patients are limited because acetone is a small molecular volatile substance, which is immediately eliminated during hemodialysis.

Ketone bodies are composed of acetone, beta-hydroxybutyrate (BOHB), and acetoacetate (AA), which are mostly produced in the liver.[4] Two molecules of acetyl-CoA combine to form acetoacetyl-CoA, which undergoes enzymatic conversion to yield AA. Because AA is either reduced to BOHB mediated by BOHB dehydrogenase or spontaneously converts to acetone, the production of BOHB may be inversely associated with that of acetone. The direction of the interconversion of BOHB and AA depends on the mitochondrial redox state,[5, 6] which is the intramitochondrial ratio of oxidized flavoprotein to reduced pyridine nucleotide and is closely correlated with the arterial ketone body ratio (AKBR), i.e., the ratio of AA to BOHB in arterial blood.[6, 7] Although no previous validation study exists on the direct comparison of plasma ketone bodies from the shunt vessels and those from the arteries, we believe that we can infer the change in the mitochondrial redox state during hemodialysis by evaluating the plasma ratio of BOHB to AA from shunt vessel samples as a surrogate of AKBR without arterial blood sampling because the blood samples from the shunt vessels are similar to arterial blood.

Because recent studies elucidated that gases emanated from the skin reflect internal metabolism or bacterial fermentation that occurs on the skin surface,[8, 9] gases emanating from the skin have been recently evaluated as noninvasive biomarkers. Skin-gas acetone concentration has been reportedly correlated with plasma ketone bodies.[10, 11] Skin-gas sampling is noninvasive and easier to collect compared to blood sampling. Therefore, this study was designed to investigate whether plasma ketone bodies and skin-gas acetone are useful biomarkers of metabolic conditions during hemodialysis.

Methods

Patients

We enrolled 20 hemodialysis patients who consented to the prospective study and were on maintenance dialysis at Kitamachi Clinic, Nagaoka, Japan for at least 9 months. Patient characteristics and laboratory findings are shown in Table 1. Of the 20 patients, 14 (70%) were men, and the mean patient age was 65.6 (range: 39-87) years. The patients underwent hemodialysis three times a week (range: 3-5 h/day). The mean duration for which the patients underwent dialysis was 6.56 years (range: 9 months to 24.4 years). The main causes of renal insufficiency were diabetes (n = 12; 60%) and non-diabetic (n = 8; 40%). Patients with an active malignancy at enrollment and appetite loss for $>$ 2 days before enrollment were excluded. The study was approved by the Ethical Committee of Toho University Omori Medical Center (No. M16204, M18087), and the patients provided written informed consent.

Skin-gas sampling and measurement of acetone concentration

Skin-gas was sampled 1 h before and after a dialysis session using the passive flux sampler method.[12] The sampler, which was purchased from AIREX Inc, Kanagawa, Japan, exhibited a 1-cm diameter and comprised of a sampler body, a trapping filter, and stoppers. We collected gas sample (trapped through the filter) by attaching the sampler on the radial aspect of the forearm without an arteriovenous shunt. It takes approximately 1-hour to collect an adequate amount of skin-gas. The acetone concentration in the trapped gas sample was extracted with carbon disulfide and determined by Gas Chromatography Mass Spectrometry (Fig. 1). The measurement was performed by AIREX Inc. as a contract service.

Plasma sampling and measurement of plasma ketone body concentration and oxygen saturation

Blood was collected from the shunt vessel to measure plasma ketone bodies before and immediately after the dialysis session. The blood was centrifuged and stored at -80℃ until the assay was performed. We analyzed the BOHB and AA of the stored plasma using an enzymatic assay (SANWA KAGAKU KENKYUSHO CO., LTD, Nagoya, Japan), which is a modification of the method described by Williams et al..[13] We calculated the plasma BOHB/AA ratio because we could not evaluate AKBR for

Table 1 Patient characteristics and laboratory findings (n = 20)

	mean or number	SD or percentage	Range
Male *	14	70%	N/A
Diabetes mellitus *	12	60%	N/A
Age (years)	65.6	15.2	39–87
Height (cm)	160.8	11.2	141.7–182.8
Dry weight (kg)	59.1	16	34.1–98.6
BMI	22.7	4.8	16.6–36.0
WBC count (/mm^3)	5973	1737	3300–9600
Hemoglobin level (g/dL)	10.6	1.0	9.1–13.0
Hematocrit level (%)	33.0	3.5	28.4–41.7
Platelet count (10^3/mm^3)	18.1	6.1	6.2–29.2
Sodium level (mEq/L)	138.9	2.9	134–144
Potassium level (mEq/L)	4.9	0.6	3.9–6.0
Chloride level (mEq/L)	102.9	3.6	97–109
BUN level (mg/dL)	58.4	14.1	28.4–79.6
Creatinine level (mg/dL)	10.02	2.50	6.18–14.45
AST level (IU/L)	12.6	4.6	6–22
ALT level (IU/L)	8.4	2.6	5–14
LDH level (IU/L)	190	52	137–352
Γ-GTP (IU/L)	20.1	13	9–57
CK level (U/L)	100.9	130	13–614
Albumin level (g/dL)	3.6	0.3	3.0–3.9
Total protein level (g/dL)	6.5	0.4	5.7–7.3
Total cholesterol (mg/dL)	159.3	28	121–206
LDL cholesterol (mg/dL)	88.5	19	57–129
HDL cholesterol (mg/dL)	42.1	17	20–83
Triglyceride (mg/dL)	144.1	79	35–305
Glycoalbumin (%)	18.9	5.4	12.5–31.7

Notes: *Number of patients and percentage were listed for dichotomous variables.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CK, creatinine kinase; GTP, Glutamyl Trans Peptidase; HDL, High density lipoprotein; LDH, lactate dehydrogenase; LDL, low density lipoprotein; N/A, not applicable; SD, standard deviation; WBC, white blood cell.

the sample from the shunt vessels; a lack of data exist on direct comparison of plasma ketone bodies in the blood samples from the shunt vessels and those from the arteries. Although AKBR is a ratio of AA to BOHB,[6] we used the plasma BOHB/AA ratio instead of the plasma AA/BOHB ratio because it is easier to demonstrate a BOHB-dominant increase in plasma ketone bodies with the plasma BOHB/AA ratio compared to the AA/BOHB ratio. To evaluate whether the specimen was similar to arterial blood, we also evaluated oxygen saturation of the blood specimen collected from the shunt vessel.

Hemodialysis procedure

All patients underwent hemodialysis thrice a week for at least 4 h/week. The rate of dialysate delivery was set at 500 mL/min, and the composition of the dialysis fluid used was as follows: Na^+, 140 mEq/L; K^+, 2.0 mEq/L; Ca^{2+}, 2.75 mEq/L; Mg^+, 1.0 mEq/L; Cl^-, 112.25 mEq/L; CH_3COOH^-, 8 mEq/L; HCO_3^-, 27.5 mEq/L; and $C_6H_{12}O_6$, 125 mg/dL (Kindaly 4E, Fuso Pharmaceutical Industries, Ltd., Osaka, Japan). A unidirectional blood flow rate of 300 mL/min was observed in all patients except one (250 mL/min).

Statistical analysis

The results of the analysis of continuous variables are expressed as means, standard deviations, and minimum and maximum values. For the paired group comparison, we used the paired t-test and Wilcoxon signed-rank test for normally and non-normally distributed variables, respectively. We calculated "increase ratios" of ketone body

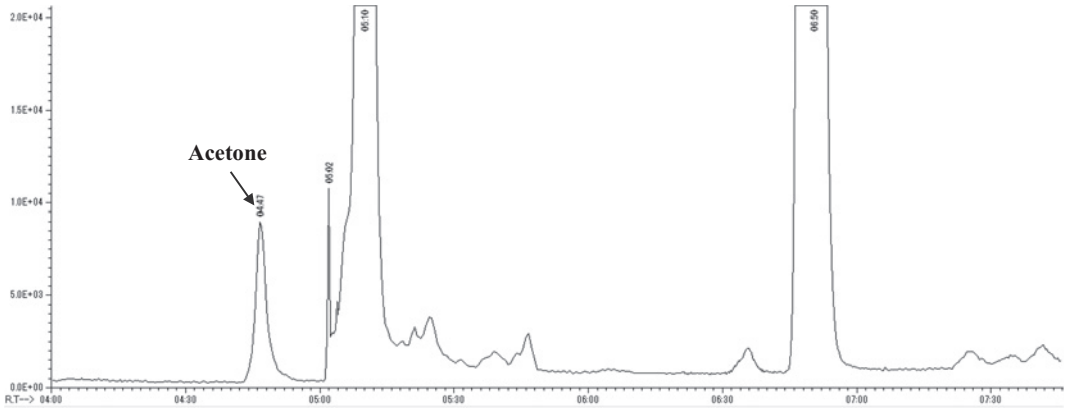

Fig. 1 Standard chromatogram of acetone.
Notes: Acetone is detected as the first peak.

concentration and other laboratory data using the following formula: (post-dialysis value - pre-dialysis value)/pre-dialysis value. Also, we calculated "water removal ratio" using (pre-dialysis body weight - post-dialysis body weight)/ pre-dialysis body weight. We subsequently evaluated the correlations between the increased ratios of plasma ketone bodies and other parameters (increased ratios of laboratory data and water removal ratio) using the Pearson product-moment correlation coefficient and the Spearman rank correlation coefficient for normally and non-normally distributed variables, respectively. Data were analyzed using R software version 3.3.1. A p-value of less than 0.05 was considered statistically significant.

Results

Plasma ketone bodies

Changes in plasma concentrations of ketone bodies, AA, and BOHB before and after hemodialysis are listed in Fig. 2 and Table 2. Before hemodialysis, the concentrations were 97.7 ± 144.4, 31.3 ± 24.5, and 66.3 ± 120.9 μmol/L, respectively. Plasma ketone body concentrations increased 6-fold (608.5 ± 397.6 μmol/L) after hemodialysis (Fig. 2a). The largest change was observed for plasma BOHB (i.e., from 66.3 ± 120.9 to 488.4 ± 334.0 μmol/L; Fig. 2b). The plasma AA concentration increased to 120.2 ± 69.0 μmol/L after hemodialysis; this increase was smaller compared to that of plasma BOHB (Fig. 2c). No change was found in arterial blood gas analysis, whereas plasma glucose and potassium significantly decreased after hemodialysis (Table 2).

The plasma BOHB/AA ratio significantly increased from 1.65 ± 1.03 to 3.91 ± 1.62 after hemodialysis (Fig. 2d). Oxygen saturation of the blood samples was examined before measuring the plasma ketone bodies, and the mean value was 97.3% (standard deviation, 1.2), suggesting that the shunt vessel blood samples were similar to arterial blood.

Skin-gas acetone concentration and association between plasma ketone bodies

The skin-gas acetone concentration was 23.5 ± 19.9 ng/cm^2/h and 21.4 ± 16.1 ng/cm^2/h before and after hemodialysis, respectively (Fig. 2e). No significant increase was found in acetone production after hemodialysis, unlike plasma ketone bodies. In both before and after hemodialysis, no significant correlation between skin-gas acetone and plasma BOHB or plasma AA was observed (Table 3).

Associations between plasma ketone body concentrations and other variables

The correlation between the increased ratio of plasma ketone bodies and laboratory data is shown in Table 4 and Fig. 3. The increase in the ratios of plasma ketone bodies, acetone, and BOHB was positively correlated with increased plasma glucose levels. The increased ratio of plasma BOHB was significantly correlated with water removal ratio. No correlation was observed between the increased ratio of plasma ketone bodies and that of the plasma pH, bicarbonate, or potassium levels.

Discussion

In the current study, we found a significant increase in BOHB-dominant plasma ketone bodies, which significantly correlated with the water removal ratio, and dissociation between the changes in skin-gas acetone and plasma ketone body concentrations after hemodialysis.

Next, the increase in plasma ketone bodies after hemodialysis in our study is compatible with that reported in

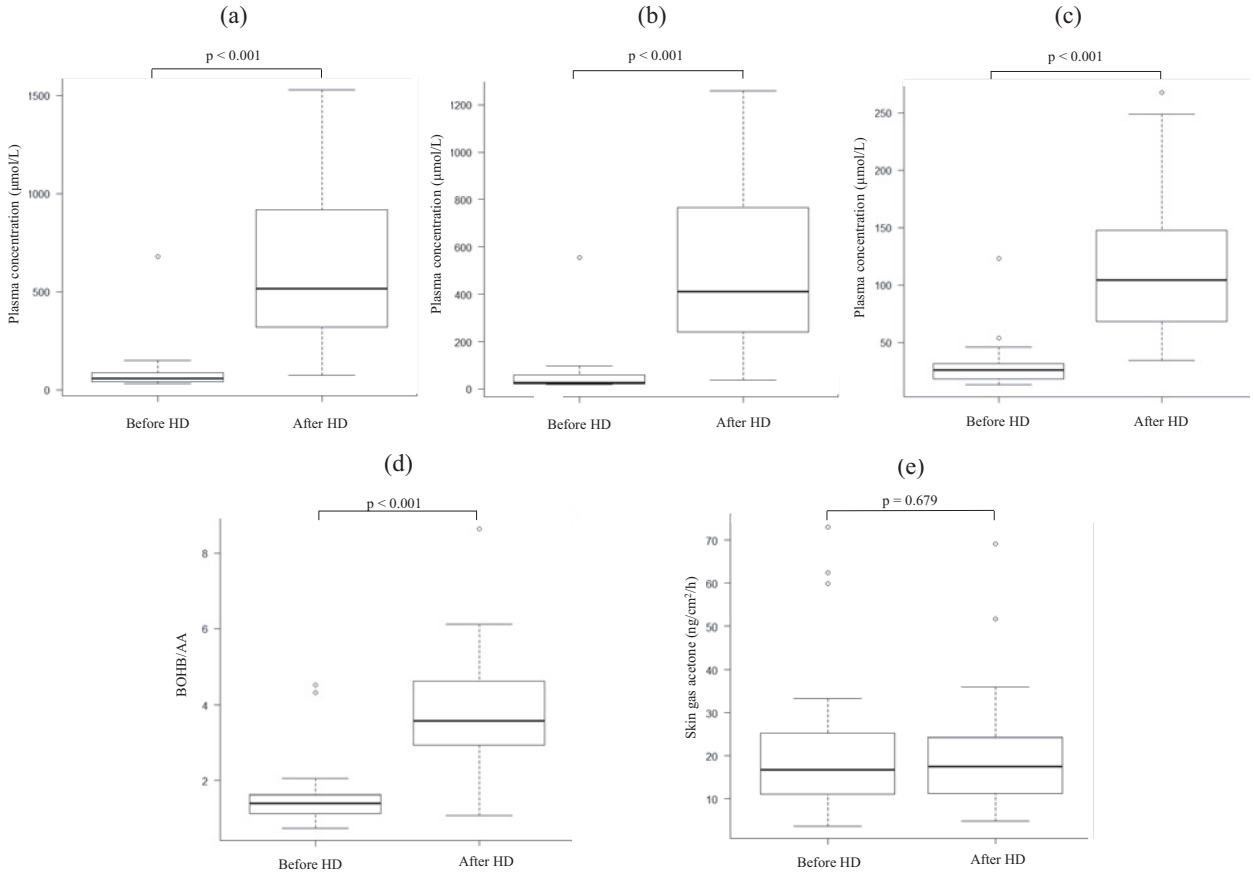

Fig. 2 Changes in plasma and skin-gas ketone bodies after hemodialysis.

Notes: (a) plasma ketone bodies, (b) beta-hydroxybutyrate (BOHB), (c) plasma acetoacetate (AA), (d) plasma BOHB/AA ratio, and (e) skin-gas acetone.

A significant increase in plasma ketone bodies and the plasma BOHB/AA ratio after hemodialysis was found. Conversely, skin-gas acetone concentration did not change significantly before and after hemodialysis.

Abbreviations: AA, acetoacetate; BOHB, β-hydroxybutyrate; HD, hemodialysis.

Table 2 Changes in plasma ketone bodies, skin gas acetone, and other parameters before and after hemodialysis

	Before HD	After HD	p value
pH	7.374 (7.303–7.455)	7.444 (7.385–7.501)	<0.001
pCO_2 (mm Hg)	36.7 (28.2–43.3)	37.8 (28.8–47.4)	0.534
pO_2 (mm Hg)	100.4 (79.7–133.0)	103.6 (83.9–122.2)	0.489
Bicarbonate (mmol/L)	21.4 (16.7–24.8)	25.7 (22.5–29.8)	<0.001
Oxygen saturation (%)	97.3 (94.7–99.2)	98.1 (97.0–99.0)	0.008
Potassium (mmol/L)	4.1 (3.0–4.9)	3.0 (2.5–3.4)	<0.001
Plasma glucose (mg/dL)	154 (76–265)	104 (54–155)	0.002
Weight (kg)	63.9 (41.7–104.1)	61.0 (40.3–99.8)	<0.001
Plasma ketone bodies (μmol/L)	97.7 (31.0–679)	608.5 (74.1–1530)	<0.001
Plasma acetoacetate (μmol/L)	31.3 (12.9–123)	120.2 (34–268)	<0.001
Plasma BOHB (μmol/L)	66.3 (18.1–556)	488.4 (38.2–1260)	<0.001
Skin gas acetone ($ng \cdot cm^{-2} \cdot h^{-1}$)	23.5 (3.7–73.1)	21.4 (4.9–69.2)	0.679

Abbreviations: BOHB, β-hydroxybutyrate; HD, hemodialysis.

Table 3 Correlation between skin gas acetone and plasma ketone bodies

	Plasma ketone bodies	Plasma acetoacetate	Plasma BOHB
Skin gas acetone before HD	− 0.044 (p = 0.860)	− 0.074 (p = 0.765)	− 0.097 (p = 0.694)
Skin gas acetone after HD	− 0.168 (p = 0.489)	− 0.135 (p = 0.580)	− 0.133 (p = 0.585)

Abbreviations: BOHB, β-hydroxybutyrate; HD, hemodialysis.

Table 4 Correlation between increase ratios of plasma ketone bodies and other variables

	Plasma ketone bodies	Plasma acetoacetate	Plasma BOHB
pH[a]	0.098 (p = 0.687)	0.223 (p = 0.358)	0.0158 (p = 0.951)
Bicarbonate[a]	− 0.029 (p = 0.905)	− 0.173 (p = 0.480)	− 0.0193 (p = 0.940)
Potassium[a]	− 0.310 (p = 0.197)	− 0.297 (p = 0.216)	− 0.196 (p = 0.418)
Plasma glucose[a]	0.518 (p = 0.023) *	0.519 (p = 0.022) *	0.481 (p = 0.039) *
Water removal[b]	0.400 (p = 0.090)	0.267 (p = 0.269)	0.470 (p = 0.044) *

Notes: *p < 0.05

[a]increase ratios were calculated by (post-dialysis value–pre-dialysis value) /pre-dialysis value.

[b]water removal ratio was calculated as (pre-dialysis weight–post-dialysis weight) /pre-dialysis weight.

Abbreviation: BOHB, β-hydroxybutyrate.

the previous studies.[14–16] Earlier reports showed that plasma BOHB and AA levels after dialysis were higher than before dialysis, regardless of any dialysate.

Although the previous studies also reported a BOHB-dominant increase in plasma ketone bodies, the authors did not focus on evaluating the ratio of ketone bodies.[14–16] In the present study, we evaluated the plasma BOHB/AA ratio and revealed that the plasma BOHB/AA ratio increased after hemodialysis. Starvation during hemodialysis and sympathetic nervous system activation may explain this increase. As 20%-30% of patients experience a drop in systolic blood pressure by 20 mmHg during hemodialysis,[17] acute hemodynamic instability during hemodialysis is common. Acute hemodynamic changes during hemodialysis may cause an increase in plasma ketone body levels via sympathetic nervous system activation.[18] Given that the decrease in AKBR reportedly reflects changes in the mitochondrial redox state due to hemodynamic changes in hemodynamically unstable patients,[7] the increase in plasma BOHB/AA ratio after hemodialysis in the present study may also reflect the alterations in the mitochondrial redox state during hemodialysis. (As mentioned above, we considered the plasma BOHB/AA ratio as a reciprocal value of AKBR.)

Furthermore, our study also revealed that an increase in the ratio of plasma BOHB was correlated with the water removal ratio. This association may support the "sympathetic nervous activation due to acute hemodynamic change" hypothesis. We believe this association is important because both a large amount of fluid removal and higher plasma BOHB levels have been independently reported as risk factors of cardiovascular events in hemodialysis patients. For example, Obokata et al. demonstrated a significant and independent association between plasma BOHB concentrations and adverse cardiovascular events in hemodialysis patients.[19] A large amount of fluid removal is a well-known risk factor for cardiac sudden death.[20] Unlike the long-standing elevation of plasma BOHB concentration reported in a previous study by Obokata et al.,[19] the present study revealed only transient elevation of plasma BOHB concentration during hemodialysis. However, we believe that this study indicates a possible association between BOHB increase and the amount of fluid removal during hemodialysis. Next, acute hemodynamic changes associated with fluid removal during hemodialysis possibly caused an increase in plasma BOHB level as a metabolic change due to sympathetic nervous system activation. Therefore, transient, and possibly even persistent, elevation of the plasma BOHB level may reflect sympathetic nervous activation because of hemodynamic changes and subsequent risk of cardiovascular events in patients undergoing hemodialysis.

As an alternate mechanism, ketone body synthesis secondary to gluconeogenesis to maintain the plasma glucose

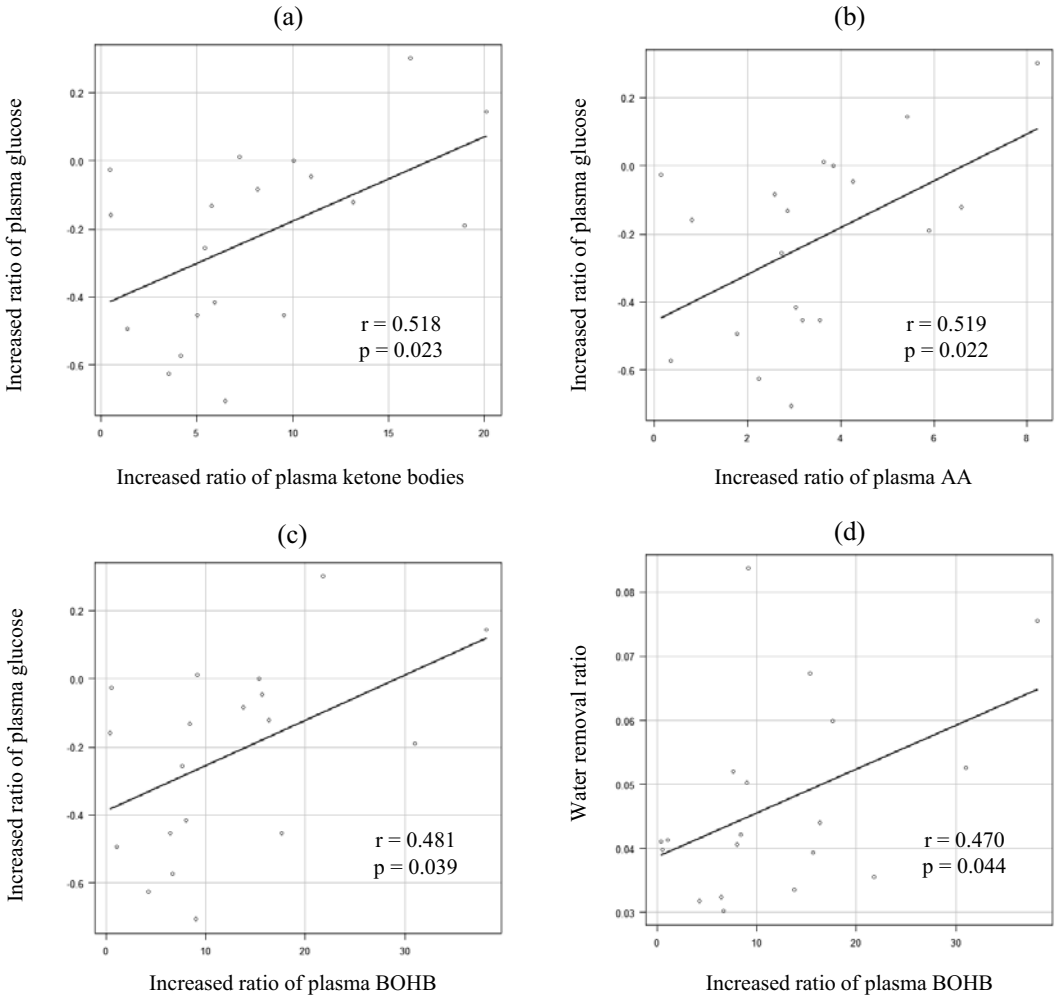

Fig. 3 Scatter plots of plasma glucose, ketone bodies, and water removal ratio

Notes: (a) Plasma glucose level vs. plasma ketone body level, (b) plasma glucose level vs. plasma acetoacetate (AA) level, (c) plasma glucose level vs. plasma β-hydroxybutyrate (BOHB) level, (d) plasma BOHB level vs. water removal ratio.

Significant correlations were observed.

Increase ratios were calculated by using the following formula: (post-dialysis value - pre-dialysis value) / pre-dialysis value. The water removal ratio was calculated as (pre-dialysis weight - post-dialysis weight) /pre-dialysis weight.

Abbreviations: AA, acetoacetate; BOHB, β-hydroxybutyrate.

level during hemodialysis may explain the increased plasma ketone body levels during hemodialysis. Previous studies that used dialysates containing no or small amounts of glucose reported significant increases in AA and BOHB. The authors hypothesized that the increase in ketone bodies is caused by ketone body synthesis secondary to the oxidation of fatty acids to provide energy for gluconeogenesis.[14, 21, 22] Although we used glucose-containing dialysate in the present study, the correlation between the increased ratios of plasma glucose level and plasma ketone bodies after hemodialysis may support this hypothesis (Table 4, Fig. 3). Post-hemodialysis plasma glucose levels may have been elevated owing to accelerated ketone body synthesis for providing energy for gluconeogenesis during hemodialysis.

Although a previous study demonstrated the correlation between plasma ketone bodies and skin-gas acetone,[10, 11] we could not find any association between them in the present study. We could not establish the usefulness of skin-gas acetone as a surrogate marker of changes in plasma ketone bodies associated with hemodialysis. However, under the assumption that the skin-gas acetone con-

centration reflects acetone production in the body, the dissociation between the changes in skin-gas acetone and plasma BOHB may imply that the direction of conversion of AA to other ketone bodies tends to exhibit an enzyme-dependent reduction to BOHB instead of spontaneous decarboxylation to acetone during hemodialysis. This may be because the production of BOHB can be inversely associated with that of acetone (AA is either reduced to BOHB or converted to acetone). We believe our findings in the present study will contribute to the understanding of ketone body metabolism during hemodialysis.

Our study exhibits several limitations. First, we could not evaluate the confounding factors due to dialysate and diet because we did not compare different types of dialysates or restrict food intake during hemodialysis. The dialysate used in this study included acetate, which may be metabolized to ketone bodies. Also, food intake affects the outcome because glucose administration promptly suppresses ketogenesis. Further studies using other dialysates and oral intake restriction are needed to determine the influence of these factors. Because 10%-20% of ketone bodies may be lost in the urine during ketosis,[4] measurement of urinary ketone body concentrations is also warranted. Second, the time-consuming methods of sampling and measuring of skin-gas might result in the discrepancy between skin-gas acetone levels and plasma ketone bodies that were collected and measured in a short time. Finally, the lack of direct measurement of plasma acetone is the largest limitation of our study. We could not measure it because of the difficulties in detecting volatile substances quantitatively in human plasma. Although we evaluated the skin-gas acetone concentration as a surrogate marker of ketone body metabolism, under the assumption that skin-gas acetone reflects internal ketone body metabolism, we could not exclude the influence of sweat and skin moisture on the skin-gas acetone concentration. Considering that patients usually exhibit more moisture on the skin before hemodialysis than after hemodialysis, these factors might confound the skin-gas acetone concentration.

In summary, we found a significant increase in plasma ketone bodies with an elevated plasma BOHB/AA ratio after hemodialysis, a significant correlation between the increased ratio of plasma BOHB and the water removal ratio, and dissociation between the changes in skin-gas acetone and plasma ketone body concentrations during hemodialysis. Also, we found the possibility of evaluating the mitochondrial redox state by measuring the plasma BOHB/AA ratio as a surrogate of AKBR without arterial blood sampling. Although we could not find an association between skin-gas acetone and plasma ketone bodies, the dissociation may suggest an increase in ketone body synthesis during hemodialysis. Lastly, we believe that our study contributes to the understanding of metabolic changes during hemodialysis.

Conflicts of interest: None declared.

References

1) Reichard GA Jr, Haff AC, Skutches CL, Paul P, Holroyde CP, Owen OE. Plasma acetone metabolism in the fasting human. J Clin Invest. 1979; 63: 619-26.
2) Mori K, Funada T, Kikuchi M, Ohkuwa T, Itoh H, et al. Influence of dynamic hand-grip exercise on acetone in gas emanating from human skin. Redox Rep. 2008; 13: 139-42.
3) Aubert G, Martin OJ, Horton JL, Lai L, Vega RB, Leone TC, et al. The failing heart relies on ketone bodies as a fuel. Circulation. 2016; 133: 698-705.
4) Carmant L. Assessing ketosis: Approaches and pitfalls. Epilepsia. 2008; 49: 20-2.
5) Williamson DH, Lund P, Krebs HA. The redox state of free nicotinamide-adenine dinucleotide in the cytoplasm and mitochondria of rat liver. Biochem J. 1967; 103: 514-27.
6) Tanaka A, Yamaoka Y. Assessment of hepatic function by blood ketone body ratio. J Hep Bil Pancr Surg. 1997; 4: 241-8.
7) Yamamoto M, Tanaka J, Ozawa K, Tobe T. Significance of acetoacetate/β-hydroxybutyrate ratio in arterial blood as an indicator of the severity of hemorrhagic shock. J Surg Res. 1980; 28: 124-31.
8) Turner C, Parekh B, Walton C, Spanel P, Smith D, Evans M. An exploratory comparative study of volatile compounds in exhaled breath and emitted by skin using selected ion flow tube mass spectrometry. Rapid Commun Mass Spectrom. 2008; 22: 526-32.
9) Yamai K, Ohkuwa T, Itoh H, Yamazaki Y, Tsuda T. Influence of cycle exercise on acetone in expired air and skin gas. Redox Report. 2013; 14: 285-9.
10) Yamane N, Tsuda T, Nose K, Yamamoto A, Ishiguro H, Kondo T. Relationship between skin acetone and blood β-hydroxybutyrate concentration in diabetes. Clin Chim Acta. 2006; 365: 325-9.
11) Yokokawa T, Sato T, Suzuki S, Oikawa M, Yoshihisa A, Kobayashi A, et al. Feasibility of skin acetone analysis in patients with cardiovascular diseases. Fukushima J Med Sci. 2018; 64: 60-3.
12) Kimura K, Sekine Y, Furukawa S, Takahashi M, Oikawa D. Measurement of 2-nonenal and diacetyl emanating from human skin surface employing passive flux sampler-GCMS system. J Chromatogr B. 2016; 1028: 181-5.
13) Williams DH, Mellanby J, Krebs HA. Enzymic determination of D(−) - β-hydroxybutyric acid and acetoacetic acid in blood. Biochem J. 1962; 82: 90-6.
14) Ward RA, Wathen RL, Williams TE, Harding GB. Hemodialysate composition and intradialytic metabolic, acid-base and potassium changes. Kidney Int. 1987; 32: 129-35.

15) Ward RA, Wathen RL. Utilization of bicarbonate for base repletion in hemodialysis. Artif Organs. 1982; 6: 396-405.
16) Wathen R, Keshaviah P, Hommeyer P, Cadwell K, Comty C. Role of dialysate glucose in preventing gluconeogenesis during hemodialysis. Trans Am Soc Artif Intern Organs. 1977; 23: 393-8.
17) Odudu A, McIntyre CW. An update on intradialytic cardiac dysfunction. Semin Dial. 2016; 29: 435-41.
18) Schlaich MP, Socratous F, Hennebry S, Eikelis N, Lambert EA, Straznicky N, et al. Sympathetic activation in chronic renal failure. J Am Soc Nephrol. 2009; 20: 933-9.
19) Obokata M, Negishi K, Sunaga H, Ishida H, Ito K, Ogawa T, et al. Association between circulating ketone bodies and worse outcomes in hemodialysis patients. J Am Heart Assoc. 2017; 6: e 006885.
20) Rhee CM, Chou JA, Kalantar-Zadeh K. Dialysis prescription and sudden death. Semin Nephrol. 2018; 38: 570-81.
21) Sharma R, Rosner MH. Glucose in the dialysate: historical perspective and possible implications? Hemodial Int. 2008; 12: 221-6.
22) Park S, Paredes W, Custodio M, Goel N, Sapkota D, Bandla A, et al. Intradialytic acid-base changes and organic anion production during high versus low bicarbonate hemodialysis. Am J Physiol Renal Physiol. 2020; 318: F1418-29.