BRIEF COMMUNICATION

Artificial Kidney / Dialysis

Influence of albumin leakage on glycated albumin in patients with type 2 diabetes undergoing hemodialysis

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Abstract

Glycated albumin (GA) is recommended as a better glycemic indicator than HbA1c in patients undergoing hemodialysis, because the red blood cell lifespan is generally faster than that in normal subjects. However, GA can be also affected by protein loss in urine and hemodialysis fluid. Therefore, in this study, we investigated the effect of albumin leakage induced by hemodialysis on GA. Nine patients undergoing hemodialysis with a large or small amount of albumin leakage were observed for 9 months in a crossover manner. As a result, it was shown that albumin leakage could affect GA, but the effect was practically small considering the prescription of diabetic drugs. The correlations between HbA1c and blood glucose levels and between GA and blood glucose levels were similar in our study. In conclusion, GA was a reliable indicator, even with the change of hemodialysis modality. The influence of albumin leakage induced by hemodialysis on GA was negligible practically. We should recognize that the preferable glycemic indicator in patients undergoing hemodialysis depends on the hemoglobin and albumin metabolism of each patient.

Keywords Albumin · Hemodialysis · Glycated albumin · HbA1c

Introduction

Glycated albumin (GA) is believed to be a more reliable marker for glycemic control in patients with end stage kidney disease than HbA1c. In addition to blood glucose levels, HbA1c is influenced by other factors including the lifespan of red blood cells [1]. However, GA can also be affected by several conditions that influence albumin metabolism [2]. For instance, in patients undergoing peritoneal dialysis (PD), there is a large amount of protein loss in dialysis fluid. Watanabe et al. showed that HbA1c was a preferable marker in patients undergoing PD [3].

Recently, hemodialysis (HD) using high flux dialyzers and online hemodiafiltration (HDF) have become familiar. However, albumin leakage caused by these modalities is larger than that caused by conventional HD [4, 5]. No one has estimated the effect of albumin leakage on GA.

Therefore, in this study, we investigated the effect of albumin leakage on GA in patients with type 2 diabetes undergoing HD or online HDF in a crossover manner. We also wanted to clarify how much difference of GA there was according to the amount of albumin leakage.

Materials and methods

Ethics statement

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. All subjects enrolled in this research have given their written informed consent which has been approved by the Research Ethics Committee of Kawashima Hospital. This protocol has

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been found acceptable by them. The registration number by the committee was 0291.

Design and subjects

This study included 16 patients undergoing HD or online HDF at Kawashima Hospital. Inclusion criteria were patients: (1) with type 2 diabetes; (2) without hospitalization; (3) without the change of diabetic medication or dialysis modality for the previous six months; (4) without obvious liver dysfunction, significant infection or malignancy. During the following nine months observation period, seven patients were excluded from this study due to diabetic medication changes ($n = 2$), and hospitalization ($n = 5$). Finally, nine patients were analyzed. They were aged 50–74 years (mean $\pm$ SD 64.7 ± 8.3 years). All of them were men. The dialysis duration ranged from 0.6 to 11.1 years (7.0 ± 3.2 years). In the original setting, five underwent online HDF and four underwent HD. Every patient received 4-h dialysis started at the same time, 3 times/week.

As shown in Fig. 1a, patients were treated in the original dialysis settings for 3 months (pre-treatment with large albumin leakage: pre-large period). Albumin leakage was determined by collecting the whole dialysis waste liquid in the first dialysis session of the week. Albumin leakage ranged from 2.8 to 5.9 g/session (4.1 ± 1.2 g/session). Next, HD using a dialyzer of FB-210UPeco (Nipro, Osaka, Japan) was performed for 3 months (treatment with small albumin leakage: Small period). Albumin leakage was small, ranging from 0.06 to 0.24 g/session (0.13 ± 0.06 g/session). Finally, the dialysis setting was returned to the original one for 3 months (post-treatment with large albumin leakage: post-large period). The dose of erythropoiesis-stimulating agent (ESA) in every patient was not changed through the observation period [none ($n = 5$), epoetin kappa 750 IU/session ($n = 2$), darbepoetin alfa 30 μg/week ($n = 1$)] except one patient [darbepoetin alfa 520 in pre-large period → 340 in small period → 155 μg/3 months in post-large period].

Demographic characteristics were collected at enrollment. Blood samples were obtained from arteriovenous shunt just before starting the first dialysis session of the first week of each month. Normalized protein catabolic rate (n-PCR) and creatinine generation rate (CGR) were calculated using the method of Shinzato [6, 7]. The biochemical data for individuals were mean values of the results from 3 months in each period.

Statistical analysis

All values are expressed as mean $\pm$ SD. Statistical analysis was performed using SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA). The serological changes were analyzed using paired t test. F-test was used for comparing the factors of the total deviation. Correlation was analyzed by Spearman's
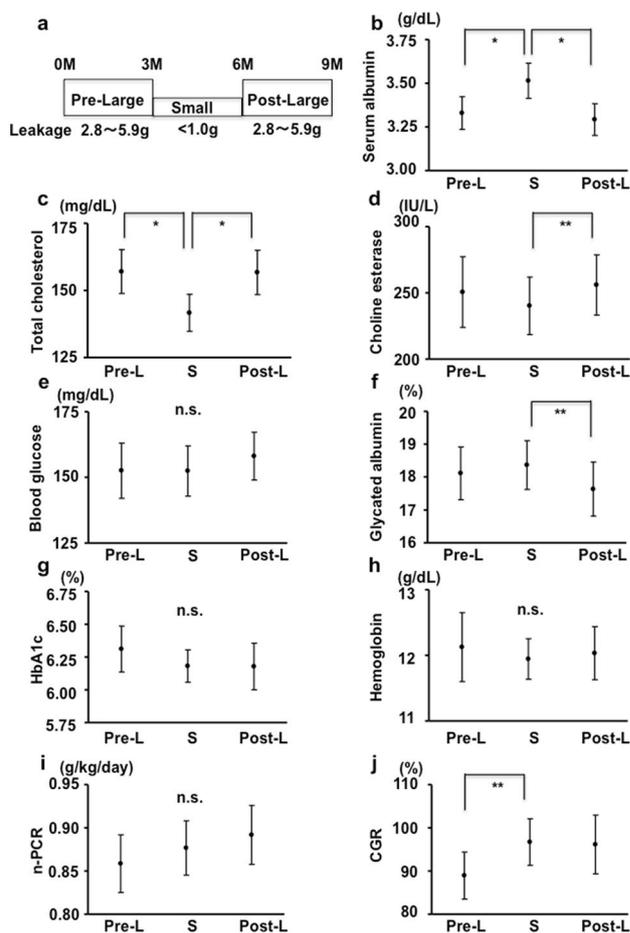

Fig. 1 Effects of albumin leakage on glycated albumin and other valuables. **a** The scheme of experiments. Nine patients were treated in the original dialysis settings that caused 2.8–5.9 g albumin leakage/session for 3 months (pre-large period). Then, hemodialysis with < 1.0 g albumin leakage was applied for 3 months (small period). Upon conclusion of small period, the modality was changed to the original setting for 3 months (post-large period). **b** Serum albumin levels increased significantly in small period. **c, d** Total cholesterol (**c**) and cholinesterase (**d**) decreased in small period. **e** Casual blood glucose levels did not change significantly. **f** Glycated albumin increased in small period. **g, h** HbA1c and hemoglobin were not different. **i, j** Normalized protein catabolic rate (n-PCR) and creatinine generation rate (CGR) were not different except CGR between pre-large and small period. All values are expressed as mean $\pm$ SD ($n = 9$). *$p < 0.01$. **$p < 0.05$. *n.s.* not significant. *M* month. *Pre-L* pre-large period. *S* small period. *Post-L* post-large period

rank correlation. Spearman's coefficients were denoted by r_s. Significance was defined by P less than 0.05.

Results

Enrolled patients were observed for 9 months (Fig. 1a). In small period, serum albumin levels became significantly higher accompanied with the lower levels of total

cholesterol and choline esterase than those in pre-large and post-large periods, suggesting effective suppression of albumin leakage, followed by the modulation of lipid metabolism and liver function, as well as the condition in patients with nephrotic syndrome (Fig. 1b–d) [8].

Compared with pre-large and small period, casual blood glucose levels were not different. GA did not increase significantly, even though serum albumin levels became significantly higher. HbA1c and hemoglobin were not different. Regarding nutritional markers, CGR increased significantly in small period.

Compared with small and post-large period, casual blood glucose levels were not different. GA and serum albumin levels became significantly lower. However, the difference of mean GA was only 0.8%. HbA1c and hemoglobin were not different. Neither n-PCR nor CGR changed, indicating nutritional status was not different (Fig. 1b, e–j).

The ratio of GA to HbA1c was higher in small period, but not significantly different between pre-large and small periods (Fig. 2a). HbA1c was correlated with GA (Fig. 2b). The correlations between casual blood glucose levels and HbA1c and between casual blood glucose levels and GA in all periods were similar (Fig. 2c, d). The correlations between casual blood glucose levels and HbA1c or GA in each period were not significant (data not shown).

Discussion

In this study, we demonstrated that GA can be affected by dialysis-induced albumin leakage, but the effect of albumin leakage on GA was not practically important in controlling diabetic medication.

HD with high-flux dialyzers and online HDF are now the major prescriptions for patients undergoing dialysis, even though albumin leakage is inevitable. In this study, the mean value of albumin leakage was 4.1 g/session, which was equivalent to 1.8 g/day. Therefore, albumin leakage in this study was similar with the leakage in patients with nephrotic syndrome (protein loss $\geq$ 3.5 g/day). Okada et al. concluded that nephrotic-range proteinuria decreased GA independent of glycemic status, while non-nephrotic range proteinuria did not influence GA [2]. Our study results were consistent with this previous report. A significant difference of serum albumin levels and GA between small and post-large period was observed, whereas we could not find a difference of GA between pre-large and small period, even with a significant increase of serum albumin levels, probably due to minor condition changes suggested by the significant difference of CGR. In addition, the GA change induced by albumin leakage was practically negligible considering a guide for diabetic treatment in patients undergoing HD (Fig. 1) [9].

Fig. 2 Relationship among HbA1c, glycated albumin and casual blood glucose levels. **a** The ratio of glycated albumin to HbA1c was high in small period. **b** Relationship between HbA1c and glycated albumin. **c, d** Relationship of HbA1c or glycated albumin with casual blood glucose levels. The values shown with black circles were ones in small periods. HbA1c was correlated with glycated albumin. The correlations between HbA1c or glycated albumin and blood glucose levels were similar. **$p < 0.05$. *Pre-L* pre-large period. *S* small period. *Post-L* post-large period
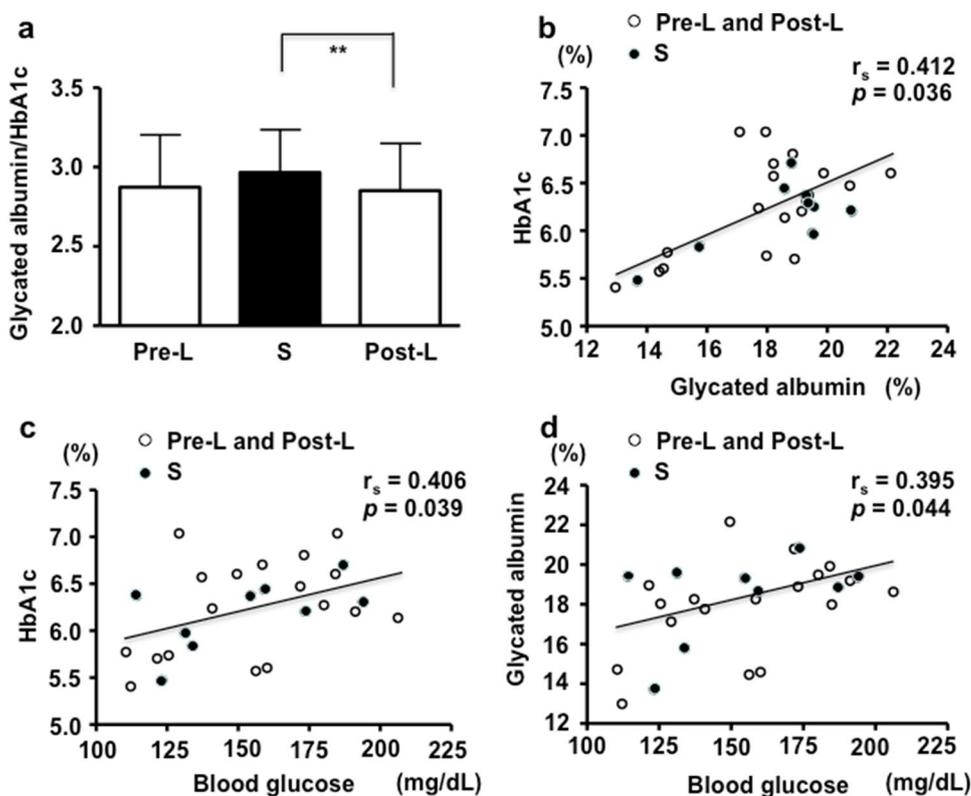
In patients undergoing PD, mean protein loss of 6–7.8 g/day can be more than that in patients with nephrotic syndrome [3, 10]. Watanabe et al. investigated 71 patients undergoing PD and suggested HbA1c was correlated more closely to blood glucose levels than GA in their group [3]. On the other hand, Kobayashi et al. investigated 20 patients undergoing PD and demonstrated that GA was associated with blood glucose levels better than HbA1c [10]. We believe that the difference between the above two studies will be the diversity of red blood cell lifespan and albumin loss in the participants analyzed. In our study, the ratio of GA to HbA1c was slightly low in the period with large albumin leakage compared to that in small period, suggesting GA could underestimate glycemic status in the period with large albumin leakage (Fig. 2a). However, the correlations between blood glucose levels and HbA1c and between blood glucose levels and GA in all periods were similar, maybe because ESA doses were relatively low and almost the same without apparent hemorrhage, and the effect of albumin leakage change on GA was small during the observation period (Fig. 2c, d). Therefore, even in patients undergoing HD or online HDF, if albumin leakage is clinically acceptable and red blood cell lifespan is stable with a relatively low amount of ESA use, both GA and HbA1c can be glycemic indicators, whereas both can underestimate glycemic status.

In summary, GA in patients undergoing HD or online HDF was practically reliable even if dialysis modality was changed. The preferable marker of glycemic status depends on the albumin and hemoglobin metabolism in each patient undergoing dialysis.

The strong point of this study is that patients were analyzed in a crossover manner so that we could neglect the effect of protein loss in urine. The limitation is that a small number of patients were evaluated without continuous blood glucose monitoring. In addition, we hypothesized that the condition of each patient including food intake and exercise habits was not different during the observation period. To confirm the hypothesis, we monitored nutritional markers such as n-PCR and CGR in this study.

Conclusion

Albumin leakage in HD or online HDF fluid could affect GA, but was not practically important in controlling diabetic medication. If albumin leakage is clinically acceptable and red blood cell lifespan is stable, both GA and HbA1c will be correlated with glycemic status. We need to figure out which or what combination is the best among HbA1c, GA, and blood glucose levels to prescribe diabetic medication to each patient.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Vos FE, Schollum JB, Walker RJ. Glycated albumin is the preferred marker for assessing glycaemic control in advanced chronic kidney disease. NDT Plus. 2011;4:368–75.
2. Okada T, Nakao T, Matsumoto H, Nagaoka Y, Tomaru R, Iwasawa H, Wada T. Influence of proteinuria on glycated albumin values in diabetic patients with chronic kidney disease. Intern Med. 2011;50:23–9.
3. Watanabe Y, Ohno Y, Inoue T, Takane H, Okada H, Suzuki H. Blood glucose levels in peritoneal dialysis are better reflected by HbA1c than by glycated albumin. Adv Perit Dial. 2014;30:75–82.
4. Locatelli F, Manzoni C, Del Vecchio L, Cavalli A, Pontoriero G. Recent trials on hemodiafiltration. Contrib Nephrol. 2011;171:92–100.
5. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.
6. Shinzato T, Nakai S, Fujita Y, et al. Determination of Kt/V and protein catabolic rate using pre- and postdialysis blood urea nitrogen concentrations. Nephron. 1994;67:280–90.
7. Shinzato T, Nakai S, Miwa M, Iwayama N, Takai I, Matsumoto Y, Morita H, Maeda K. New method to calculate creatinine generation rate using pre- and postdialysis creatinine concentrations. Artif Organs. 1997;21:864–72.
8. Nagai K, Tsuchida K, Hirose D, Michiwaki H, Hann M, Kanayama HO, Doi T, Minakuchi J. The effect of albumin leakage in hemodialysis patients on redox status of serum albumin. J Artif Organs. 2016;19:310–4.
9. Nakao T, Inaba M, Abe M, Kaizu K, Shima K, Babazono T, Tomo T, Hirakata H, Akizawa T, Japanese Society for Dialysis Therapy. Best practice for diabetic patients on hemodialysis 2012. Ther Apher Dial. 2015;19:40–66.
10. Kobayashi H, Abe M, Yoshida Y, Suzuki H, Maruyama N, Okada K. Glycated albumin versus glycated hemoglobin as a glycemic indicator in diabetic patients on peritoneal dialysis. Int J Mol Sci. 2016;17:E619.