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Association of glycated albumin, but not glycated hemoglobin, with peripheral vascular calcification in hemodialysis patients with type 2 diabetes

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ABSTRACT

Aims: Elevated HbA_{1C} is a predictor of mortality as well as peripheral vascular calcification in hemodialysis (HD) patients with diabetes. However, improved glycemic control as reflected by reduction in HbA_{1C} may dismiss the relationship between HbA_{1C} and mortality in those patients, due possibly to the underestimation of HbA_{1C} by erythropoietin use. This study was to establish the significance of glycated albumin (GA) as a useful marker of peripheral vascular calcification in diabetic HD patients, in comparison with HbA_{1C}.
Main methods: We examined 49 HD patients with type 2 diabetes (37 men and 12 women). Peripheral vascular calcification at hand arteries was checked on a simple X-ray photograph. GA and HbA_{1C} were determined just before HD session.
Key findings: The prevalence of peripheral vascular calcification was significantly higher in diabetic patients (65.3%) than in non-diabetic patients (27.0%). Multiple regression analyses in diabetic patients showed that both HD duration and GA were significantly associated with the presence of peripheral vascular calcification. When GA was replaced by HbA_{1C} in the same model, HbA_{1C} failed to show a significant association. However, when a weekly dose of erythropoietin was simultaneously included in addition to HD duration and HbA_{1C}, both HbA_{1C} as well as HD duration emerged as a significant factor associated with the presence of peripheral vascular calcification.
Significance: The present study suggested that GA might be a better indicator of glycemic control, and raise the possibility that improvement of glycemic control might prevent against the development of peripheral vascular calcification in diabetic HD patients.

Introduction

Vascular calcification increases cardiovascular and other causes of mortality (Lehto et al., 1996; Davies and Hruska, 2001), and is highly prevalent in dialysis patients. Factors affecting vascular calcification in dialysis patients include advanced age, derangement of calcium-phosphate metabolism (Davies and Hruska, 2001; Cozzolino et al., 2001; Goodman and Salusky, 2001), and diabetes (O'Hare et al., 2002; Raggi et al., 2002; Cheung et al., 2000). We have reported that the factors affecting peripheral vascular calcification differ between hemodialysis (HD) patients with and without diabetes, and that poor glycemic control, as reflected by increased HbA_{1C}, is the strongest predictor of vascular calcification in diabetic HD patients (Ishimura et al., 2002). HbA_{1C} is also a good predictor for mortality in diabetic HD patients with high HbA_{1C} (Wu et al., 1997; Morioka et al., 2001), although improved glycemic control dismiss the significance of HbA_{1C} as a significant predictor in those patients having lower values of HbA_{1C} (Williams et al., 2006).

We recently showed that glycemic control assessed by HbA_{1C} in these patients may be underestimated due to an increased proportion of younger erythrocytes produced by erythropoietin use (Inaba et al., 2007). Particularly in those with lower HbA_{1C} values, the influence of erythropoietin to induce false-reduction of HbA_{1C} might be augmented. We found that glycated albumin (GA), which is independent of erythropoietin use, gives a significantly better estimate of glycemic control in diabetic HD patients (Inaba et al., 2007; Kumeda et al., in press).

The present study was performed to establish the significance of GA, in comparison with HbA_{1C}, as a useful marker of peripheral vascular calcification in diabetic HD patients having better glycemic control.

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Subjects and methods

Subjects

One hundred twenty three HD patients, including 49 with type 2 diabetes and 74 without, were enrolled in the study from April to June in 2007 in Okada Clinic, Osaka, Japan. All patients provided written informed consent before participation in this study, which was approved by institutional ethics committees (Osaka City University Graduate School of Medicine) and was conducted in accordance with the principles of the Declaration of Helsinki. Diabetic patients included 37 men and 12 women, and their ages ranged from 33 to 80 years old (62.3±10.3; mean±SD). Of the 49 diabetic patients, 20 were treated with insulin, 4 with oral anti-diabetic drugs, and 25 with diet only. The non-diabetic patients included 45 men and 29 women, and their ages ranged from 23 to 84 years old (55.5±14.7).

Sample collection

From April to June in 2007, hand roentgenography was carried out in each patient at a voltage of 50 kV (100 mA, 0.03 s). Vascular calcification of the hand arteries distal to the wrist joints was evaluated by one of the authors (S.Y.) who was blinded to other patient data. Blood was taken just before the HD session under non-fasting conditions to measure casual plasma glucose (PG), GA, HbA_{1C} and other serum parameters.

Measurements of GA and HBA_{1C}

GA and HbA_{1C} were measured as described previously. Briefly, GA was measured by an enzymatic method using the Lucica® GA-L kit (Asahi Kasei Pharma Corp., Tokyo, Japan) (Kouzuma et al., 2004). GA was hydrolyzed to amino acids by an albumin-specific proteinase and then oxidized by ketoamine oxidase to produce hydrogen peroxide, which was measured quantitatively. The GA value was calculated as the percentage of glycated albumin relative to total albumin, which was measured in the same serum sample using a new bromocresol purple method (Kouzuma et al., 2004). The GA assay is not influenced by the physiological concentrations of ascorbic acid, bilirubin, or glucose up to 1000 mg/dl. HbA_{1C} was measured by routine HPLC, which was standardized according to the Japan Diabetes Society (Tominaga et al., 2005).

Table 1
Clinical characteristics of 49 diabetic HD patients

Number	49
Age (years)	62.3±10.3
Gender (male/female)	37/12
BMI (kg/m^2)	22.5±3.3
Systolic blood pressure (mm Hg)	169.2±17.7
Smoker/non-smoker	18/31
HD duration (months)	59.8±39.5
CTR (%)	49.2±4.6
Erythropoietin use/non-use	43/6
Dose of erythropoietin (U/week)	4668.4±3020.5
Creatinine (mg/dl)	10.2±2.6
Hemoglobin (mg/dl)	10.6±1.0
Total cholesterol (mg/dl)	162.8±31.4
Albumin (g/dl)	3.9±0.3
Corrected calcium (mg/dl)	9.2±0.7
Phosphate (mg/dl)	5.1±1.2
Calcium-phosphorus product	46.6±12.3
Intact PTH (ng/l)	205.9±100.8
Casual plasma glucose (mg/dl)	178.9±77.0
Glycated albumin (%)	24.5±8.4
HbA_{1C} (%)	5.9±1.3

Data are expressed as means±SD.

Table 2
Multiple regression analysis of factors independently associated with the presence of vascular calcification in 123 HD patients

	Presence of vascular calcification	
	ß	p
Presence of diabetes	0.553	<0.0001‡
Age	0.026	0.7652
Gender	−0.178	0.0345§
BMI	−0.118	0.1508
Systolic blood pressure	−0.121	0.1382
HD duration	0.316	0.0004†
Corrected calcium	0.031	0.7070
Creatinine	0.192	0.0369§
R^2	0.336‡	

Values are standard regression coefficients (ß). R^2=multiple coefficient of determination.
‡$p<0.0001$, †$p<0.001$, §$p<0.05$.
Presence of vascular calcification: (−)=0, (+)=1. Presence of diabetes: no diabetes=1, diabetes=2. Gender: male=1, female=2.

Biochemical measurements

To measure serum parameters in HD patients, blood was drawn immediately before the morning Monday/Tuesday session of HD without overnight fasting, as described previously (Inaba et al., 2002). The mean values of three casual monthly measurements of PG obtained during the 2 months prior to determination of serum GA and HbA_{1C} were used in the analysis. Serum GA and HbA_{1C} were measured once, as also described previously (Inaba et al., 2007).

Statistical analysis

Data are expressed as means±SD. Correlation coefficients were calculated by simple regression analysis, and differences in means between the two groups were analyzed by Student *t* test. Multivariate regression analyses were performed to explore the association of plasma glucose, GA, and HbA_{1C} with peripheral vascular calcification. All analyses were performed using StatView 5 statistical software for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Clinical characteristics of subjects

The clinical characteristics of diabetic HD patients are shown in Table 1. As parameters for assessment of glycemic control, casual PG, GA, and HbA_{1C} in DM patients were 178.9±77.0 mg/dl, 24.5±8.4%, and 5.9±1.3%, respectively, suggesting that glycemic control of diabetic HD patients were rather good.

Calcification in the hand artery

Thirty two out of the 49 (65.3%) diabetic HD patients had vascular calcification in the hand artery, which was significantly higher than the 27.4% in non-diabetic HD patients, as we previously reported (Ishimura et al., 2002). Multivariate logistic regression analyses to explore factors affecting vascular calcification clearly showed that the presence of diabetes is positively associated with the occurrence of vascular calcification (Table 2).

Diabetic HD patients with and without vascular calcification

Among various parameters, HD duration was significantly longer in diabetic HD patients with hand-artery calcification than those without. In terms of 3 markers for glycemic control, GA was significantly higher in the former than in the latter group of patients. In contrast,