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Association of glycated albumin, but not glycated hemoglobin, with calcaneus quantitative ultrasound in male hemodialysis patients with type 2 diabetes mellitus

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Abstract

Sustained high glucose impairs bone metabolism in patients with type 2 diabetes mellitus (T2DM). In this study, the relationship between glycemic control and bone metabolism was examined in male hemodialysis (HD) patients with T2DM. To avoid the effect of menstruation and the menstrual cycle, obesity, and glycosuria-induced hypercalciuria on bone metabolism, male anuric nonobese HD patients with T2DM (n = 42) were enrolled. Calcaneus stiffness index (SI) was determined using ultrasound after HD session. Casual plasma glucose (PG), glycated hemoglobin (HbA_{1c}), and glycated albumin (GA) were measured before the HD session. In simple regression analysis, log PG ($r = -0.333$, $P < .05$) and log GA ($r = -0.350$, $P < .05$), but not log HbA_{1c} ($r = -0.134$, $P = .3985$), exhibited significant and negative correlations with calcaneus SI. In multiple regression analysis including log BMI, log cCa × Pi product, and log PG, log PG was associated significantly in a negative manner with calcaneus SI, in addition to log cCa × Pi product. When log PG was replaced with log GA or log HbA_{1c}, log GA, but not log HbA_{1c}, emerged as a significant factor associated. The mechanism as to why HbA_{1c} failed to associate could be explained by its false reduction by erythropoietin injection. The present study supported the notion of GA as an appropriate indicator for glycemic control in HD patients with T2DM. Furthermore, it is suggested that poor glycemic control might be a significant factor toward decreasing calcaneus SI in T2DM HD patients.

1. Introduction

It was recently concluded that patients with type 2 diabetes mellitus (T2DM) [1], as well as type 1 diabetes mellitus, exhibited higher rate of bone fracture [2], indicating the presence of bone abnormality in those patients. Although many factors are postulated to be involved in the development of diabetic osteopenia, it is suggested that sustained high-glucose condition might play a major role in its development in T2DM because T2DM does not exhibit deficiencies of insulin, insulin-like growth factor–I deficiency, or other pancreatic polypeptide such as amylin that have direct effect on bone [3].

We and others have previously reported that high-glucose condition impaired osteoblast function to proliferate [4] and to respond to various hormones including parathyroid hormone (PTH) [5] and 1,25-dihydroxyvitamin D_3 (1,25 $[OH]_2D_3$) [6]. Furthermore, poor glycemic control induces osteoblast dysfunction in T2DM patients, as reflected by the attenuation of an incremental response of serum osteocalcin after oral administration of $1,25(OH)_2D_3$ [7]. On bone histomorphometric analysis, the reduction of osteoblast number is characteristic of T2DM patients [8]. However, poor glycemic control indirectly stimulates bone resorption by inducing secondary hyperparathyroidism through an increase of Ca loss into urine, which is associated with urinary glucose excretion [9]. Because hemodialysis (HD) patients do not excrete Ca into urine because of anuria, it might be possible to examine the direct effect of sustained high-glucose condition on bone formation by measuring

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bone mineral density in HD patients. Furthermore, although obesity, which is frequently observed in most of the patients with T2DM, acts protective against bone loss [2], HD patients with T2DM could escape the effect of obesity because of normal body mass index (BMI) [10].

We recently reported that the evaluation by glycated hemoglobin (HbA_{1c}) of glycemic control in erythropoietin (EPO)-treated HD patients with T2DM leads to underestimation due to an increased proportion of younger erythrocytes and that glycated albumin (GA) might provide a better marker than HbA_{1c} in those patients [11]. In fact, we found that GA, but not HbA_{1c}, is independently associated with diabetic complication, such as arterial stiffening [12] and peripheral vascular calcification in diabetic HD patients [13]. The present study was performed to establish the significance of glycemic control, assessed by GA, HbA_{1c}, and plasma glucose (PG), on bone in HD patients with T2DM.

2. Patients and methods

2.1. Subjects

The subjects were restricted to male patients to avoid the sex difference of bone metabolism between male and female patients and the effect of menopause in female patients [14]. Eighty-three male HD patients, including 42 with T2DM and 41 without, were enrolled in the study from November 2006 to March 2007 in Okada Clinic, Osaka, Japan. All patients provided written informed consent before participation, and the study was approved by the Institutional Ethics Committees and conducted in accordance with the principles of the Declaration of Helsinki. Diagnosis of T2DM was based on a history of diabetes or on the criteria in the "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus" [15]. The DM patients were restricted to those whose treatment of DM had not been altered during the preceding 6 months before determination of GA and HbA_{1c}. Of 42 DM patients, 18 were treated with insulin, 4 with oral sulfonylurea, and 20 with diet only. The mean values of HbA_{1c} in 20 DM patients treated with diet only, 18 with insulin, and 4 with oral sulfonylurea were 5.4% ± 1.0%, 6.5% ± 1.6%, and 5.5% ± 0.6%, respectively.

2.2. Biochemical measurements

To measure serum parameters in HD patients, blood was drawn immediately before the morning Monday/Tuesday session of HD without an overnight fast, as described previously [16]. The mean values of 3 casual monthly measurements of PG obtained during the 2 months before determination of serum GA and HbA_{1c} were used in the analysis. Serum GA and HbA_{1c} were measured once, as also described previously [11].

2.3. 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, Tokyo, Japan) [17]. 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 GA relative to total albumin, which was measured in the same serum sample using a new bromocresol purple method [17]. The GA assay is not influenced by the physiologic concentrations of ascorbic acid, bilirubin, or glucose up to 1000 mg/dL. HbA_{1c} was measured by routine high-performance liquid chromatography, which was standardized according to the Japan Diabetes Society [18].

2.4. Quantitative ultrasound assessment of calcaneus

Quantitative ultrasound assessment of calcaneus was performed using an ultrasound system (Lunar Achilles system; Lunar, Madison, WI), as previously described [19-21]. Briefly, it measures both speed of sound (SOS) and broadband ultrasound attenuation (BUA). The "stiffness" index (SI) is a combination of normalized BUA and SOS as follows: stiffness = 1/2 (nBUA + nSOS), with nBUA = (BUA − 50)/75 * 100 and nSOS = (SOS − 1380)/180 * 100 [22]. The

Table 1
Clinical characteristics of 83 male HD patients in this study

	DM HD patients	Non-DM HD patients	*P*
n	42	41	–
Age (y)	62.7 ± 10.2	56.3 ± 14.7	.0318‡
HD duration (mo)	55.5 ± 36.6	95.6 ± 69.5	.0065†
Dry weight (kg)	62.8 ± 10.1	60.6 ± 9.1	.3075
BMI (kg/m^2)	22.6 ± 2.9	21.7 ± 2.5	.1160
Systolic BP (mm Hg)	168.8 ± 18.0	161.6 ± 20.1	.1430
Diastolic BP (mm Hg)	80.1 ± 11.3	83.6 ± 14.7	.1699
Smokers/nonsmokers	9/33	10/31	.7496
Albumin (g/dL)	3.9 ± 0.3	3.9 ± 0.3	.2936
Creatinine (mg/dL)	10.2 ± 2.7	12.2 ± 2.6	.0001†
Hemoglobin (g/dL)	10.5 ± 1.1	10.8 ± 1.0	.2819
EPO user/nonuser	38/4	36/5	.6973
EPO dose (U/wk)	4696.4 ± 2782.0	4335.4 ± 3873.2	.5029
Casual PG (mg/dL)	190.8 ± 76.4	104.4 ± 17.5	<.0001*
GA (%)	23.5 ± 6.4	14.9 ± 1.5	<.0001*
HbA_{1c} (%)	5.8 ± 1.1	4.5 ± 0.2	<.0001*
Corrected Ca (mg/dL)	9.2 ± 0.7	9.6 ± 1.0	.0561
Phosphate (mg/dL)	5.2 ± 1.3	5.5 ± 1.4	.3942
cCa × P product	48.3 ± 13.4	52.3 ± 14.3	.2665
Intact PTH (pg/mL)	191.1 ± 111.8	268.5 ± 174.5	.0491‡
Calcaneus SI (*z* score)	-0.26 ± 1.58	-1.06 ± 0.68	.0194‡
Vitamin D user/nonuser	33/9	39/2	.0271‡
Ca-binding P inhibitor user/nonuser	28/14	31/10	.3781

Mann-Whitney *U* test. Data are expressed as mean ± SD. BP indicates blood pressure; Ca, calcium; P, phosphate.

* $P < .0001$.

† $P < .01$.

‡ $P < .05$.

Table 2
Correlation of the calcaneus SI *z* score with clinical variables including glycemic control in HD patients with T2DM

	Calcaneus SI (*z* score)	
	R	*P*
Log BMI	0.193	.2271
Log HD duration	0207	.1893
Log casual PG	−0.333	.0311†
Log GA	−0.350	.0232†
Log HbA_{1c}	−0.134	.3985
Log corrected Ca	0.169	.2860
Log phosphate	0.381	.0129†
Log cCa × P product	0.394	.0099*
Log intact PTH	−0.041	.7985

* $P < .01$.
† $P < .05$.

mean coefficient of variation (standard deviation [SD]/mean), without repositioning, calculated by measuring each of the 17 samples twice was 0.76% (±0.61%) for BUA, 0.18% (±0.11%) for SOS, and 1.27% (±1.12%) for SI [23]. Calcaneus SI was expressed in *z* score, which indicates how many SDs an observation differs from the mean of a sex- and age-matched reference population.

2.5. Statistical analysis

Data are expressed as means ± SD. Correlation coefficients were calculated by simple regression analysis, and differences in means between the 2 groups were analyzed by Mann-Whitney *U* test. Multivariate regression analyses were performed to explore the association of PG, GA, and HbA_{1c} with calcaneus SI *z* score. All analyses were performed using Stat View 5 statistical software for Windows (SAS Institute, Cary, NC).

3. Results

3.1. Clinical characteristics of 42 T2DM and 41 non-DM HD patients

The clinical characteristics of HD patients enrolled in the present study are shown in Table 1. Three different glycemic parameters, casual PG, GA, and HbA_{1c}, were significantly higher in the DM HD patients than in the non-DM counterparts. The T2DM patients exhibited significantly older age, longer HD duration, lower serum creatinine, and intact PTH. As a result of significantly lower serum PTH, calcaneus SI was significantly higher in T2DM patients than in their non-DM counterparts, although significantly lower proportion of T2DM patients had taken vitamin D and they were significantly older.

3.2. Correlation of the calcaneus SI z score with clinical variables including glycemic control in HD patients with T2DM

Clinical variables, which exhibited nonnormal distribution, were analyzed after logarithmic transformation to examine their correlation by simple regression analysis. Table 2 shows the summary of correlations of various clinical variables including markers for glycemic control with the calcaneus SI. Among the clinical variables examined, log BMI and log HD duration did not correlate with the calcaneus SI *z* score. Log casual PG and log GA significantly correlated in a negative manner with the calcaneus SI *z* score, although log HbA_{1c} failed (Fig. 1). Although log serum Pi and log cCa × Pi product correlated in a positive manner with calcaneus SI *z* score, log cCa and log intact PTH failed to correlate.

3.3. Multiple regression analysis of factors independently associated with the calcaneus SI z score in HD patients with T2DM

The results of multiple regression analyses to explore the association of log casual PG, log GA, log HbA_{1c}, and other factors with the calcaneus SI *z* score in DM HD patients are shown in Table 3. In model 1, which included log BMI, log cCa × Pi product, and log casual PG, log casual PG, in addition to log cCa × Pi product, was significantly and independent associated with the calcaneus SI *z* score. In model 2, which included log GA in place of log casual PG, log GA emerged as a factor significantly associated with calcaneus SI *z* score. In contrast, in model 3, in which log

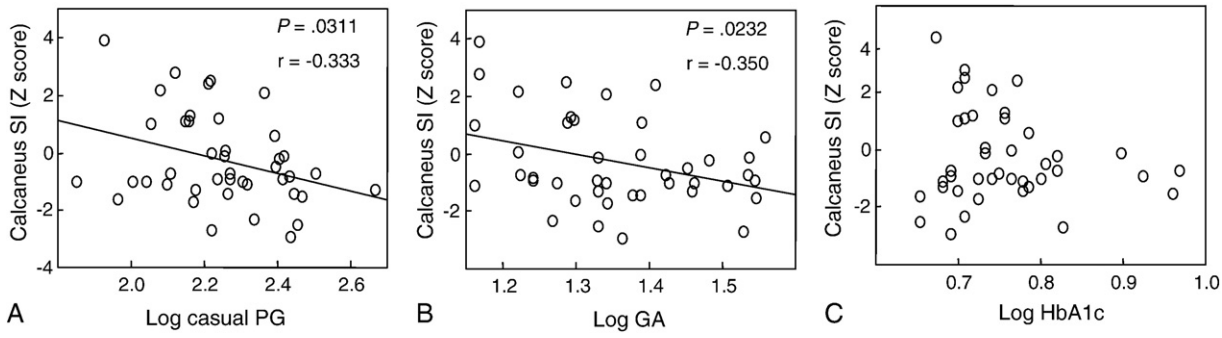

Fig. 1. Correlation of the calcaneus SI (*z* score) with log casual PG, log GA and log HbA_{1c} in male HD patients with T2DM (n = 42). A significant negative correlation was found between log calcaneus SI (*z* score) and log casual PG ($r = -0.333$, $P = .0311$) or log GA ($r = -0.350$, $P = .0232$), but not log HbA_{1c}, by single regression analysis.

Table 3
Multiple regression analysis of factors independently associated with the calcaneus SI z score in HD patients with T2DM

	Calcaneus SI (z score)					
	Model 1		Model 2		Model 3	
	β	P	β	P	β	P
Log BMI	0.235	.1037	0.176	.2162	0.221	.1466
Log cCa × P product	0.295	.0457†	0.353	.0159†	0.358	.0206†
Log casual PG	−0.340	.0228†				
Log GA			−0.339	.0204†		
Log HbA_{1c}					−0.160	.2892
R^2	0.275*		.279*		0.189†	

Values are standard regression coefficients (β). R^2 = multiple coefficient of determination.
* $P < .01$.
† $P < .05$.

casual PG was replaced with log HbA_{1c}, log HbA_{1c} failed to associate. In all models, log cCa × Pi product remained a significant factor independently and positively associated with calcaneus SI z score.

4. Discussion

In the present study, we confirmed our previous findings [11] that HbA_{1c} might not provide a clinically relevant assay to estimate glycemic control in HD patients with T2DM in terms of the effect of poor glycemic control on bone metabolism and demonstrated that improved glycemic control might protect against the hyperglycemia-induced bone loss in those patients, as evidenced by the significant and negative association of PG and GA, but not HbA_{1c}, with calcaneus SI (z score). Because bone mass is expressed in z score, it escapes the influence of sex and age on bone mass. Because serum PTH level was significantly lower in T2DM HD patients than in non-DM counterparts, calcaneus SI might become higher in the former group of patients because of attenuated PTH effect on bone to stimulate bone resorption. However, sustained hyperglycemia is reported to affect directly bone metabolism to impair bone formation and stimulate bone resorption. In fact, the distribution of calcaneus SI z score relative to serum PTH level seems to vary widely in T2DM HD patients in comparison with non-DM patients (data not shown), which might be explained by the additional influence of glycemic control on bone metabolism in T2DM HD patients. We have previously reported that high glucose might induce osteoblast dysfunction because high-glucose condition impairs osteoblast-like MG-63 cell proliferation [4] and its responsiveness to PTH [5] and $1,25(OH)_2D_3$ [6]. Furthermore, the suppressive effect of high glucose on osteoblast is in part responsible for the intracellular accumulation of sorbitol [24]. In T2DM patients without renal dysfunction, as glycemic control became poorer, osteoblast function might be weaker on the basis of the magnitude of incremental response of serum osteocalcin after oral administration of $1,25(OH)_2D_3$ [6]. These data supported that poor glycemic control might reduce bone mass by impairing bone formation in HD patients with T2DM. In those with normal renal function, because sustained high-glucose condition induces glycosuria, it might decrease bone mass by inducing secondary hyperparathyroidism due to increased Ca loss into urine [9]. However, because no such mechanism should occur in the patients enrolled in the present study because of anuria, the direct effect of sustained hyperglycemia on bone could be precisely evaluated. Furthermore, as shown by BMI of 22.0 in the patients enrolled in the present study, the effect of obesity, often observed in T2DM patients with normal renal function, to protect bone mass [25] could be neglected. These reasons have made us precisely evaluate the direct effect of sustained high-glucose condition on bone mass in man by examining nonobese anuric HD patients.

In the present study, we used mean value of casual PG, GA, and HbA_{1c} as marker for glycemic control in HD patients with T2DM. We [11] and others [26] reported recently that the measurement of GA is a more relevant method than HbA_{1c} in assessing glycemic control in those patients and that EPO use, which is used for renal anemia in around 90% of HD patients, suppresses HbA_{1c} values by 33% on average independent of glycemic control [11]. Glycated hemoglobin is the product of the chemical condensation of hemoglobin and glucose, and the glycated rate of de novo young erythrocytes induced by EPO is reported to be lower than that of old cells [27]. Therefore, it would appear that the decrease of HbA_{1c} levels relative to PG or GA in DM HD patients treated with EPO might be due to the increasing proportion of young vs old erythrocytes in peripheral blood of these patients [28]. The lack of a significant correlation between HbA_{1c} values and survival rate at 12 months after HbA_{1c} measurement was recently clearly demonstrated in a large-scale study of 76,178 HD patients drawn from the United States end-stage renal disease database [29]. Therefore, the lack of significant association of HbA_{1c} value with calcaneus SI z score, in contrast with the significant and negative association of PG and GA, could be explained by the false reduction of HbA_{1c} by EPO. Resultantly, these data might support the notion that HbA_{1c} might not provide a clinically relevant assay for glycemic control in HD patients with T2DM.

Taken collectively, the present study suggested that poorer glycemic control might reduce bone mass at calcaneus in HD patients with T2DM and that the improvement of glycemic control, as reflected by lower PG and GA, might be capable of protecting against bone loss at calcaneus in those patients. This notion is in good agreement with the previous report that poorer glycemic control significantly impaired osteoblast function both in vivo [4] and in vitro [24].

Because the mean values of monthly determined PG were essentially the same throughout the study period, it was suggested that glycemic control had been stable during the

preceding 2 months before the determination of GA and HbA_{1c} and that a single determination just before the Monday/Tuesday HD session might be representative of glycemic control in DM HD patients. Although HbA_{1c} and GA reflected glycemic control over the preceding 4 to 6 weeks and 1 to 2 weeks [28], respectively, stable glycemic control during the preceding 2 months could negate the impact of acute changes of glycemic control between HbA_{1c} and GA in the present study, as previously described [11].

A limitation of the GA assay also exists. Albumin turnover should change in patients who are maintained on peritoneal dialysis and in patients with chronic renal failure having massive proteinuria, in whom GA values would theoretically be reduced because of shorter exposure to plasma albumin.

In summary, it was demonstrated that improvement of glycemic control is capable of protecting bone loss at calcaneus in HD patients with T2DM and suggested that mean PG and GA provides a significantly better measure to reflect bone loss at calcaneus more precisely than HbA_{1c}. The lack of a significant relation of HbA_{1c} with bone mass in those patients might result in part from the apparent reduction of HbA_{1c} by EPO.

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