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Inverse correlation of free triiodothyronine with glycated albumin and the glycated albumin/glycated hemoglobin ratio in hemodialysis patients: a cross-sectional study

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Abstract

Background That the prevalence of low triiodothyronine (T3) syndrome is high among hemodialysis (HD) patients has been previously established. Herein, we examined the association of glycated albumin (GA) and the GA to glycated hemoglobin (HbA1c) ratio (GA/HbA1c) with free triiodothyronine (FT3) in HD patients.

Methods We conducted a cross-sectional study on 134 patients (68 patients with diabetes mellitus [DM group] and 66 patients without diabetes mellitus [non-DM group]) who received maintenance HD at our dialysis clinic between 2014 and 2018. Univariate linear regression analyses of GA, GA/HbA1c, or HbA1c with several clinical variables were primarily conducted. Multiple regression analyses with GA (or GA/HbA1c) as the objective variable were conducted with explanatory variable FT3 adjusted for age, sex, Hb, Alb, and average plasma glucose (Av-PG) (or HbA1c).

Results In the DM and non-DM groups, GA tended to be inversely correlated with FT3, although significantly so only in the non-DM group. GA/HbA1c also showed a strong significant inverse correlation with FT3 in the DM group and the non-DM group. FT3 and GA/HbA1c were also significantly correlated with the Geriatric Nutritional Risk Index in the DM group and non-DM group. In the multivariate analysis, which was adjusted for age, sex, Hb, Alb, and HbA1c, FT3 was a significant and independent factor associated with GA in the DM group ($\beta = -0.334$, $p < 0.001$) and in the non-DM group ($\beta = -0.412$, $p < 0.001$). The regression equations obtained by stepwise multiple regression analyses using all of these variables as independent variables were GA = 3.3HbA1c − 4.4FT3 + 1.9sex + 8.8 for the DM group and GA = − 2.4FT3 + 0.04Age − 0.5Hb + 25.2 for the non-DM group. These contribution rates (i.e., coefficient of determination) were $R^2 = 0.708$ in the DM group and $R^2 = 0.347$ in the non-DM group, In the DM group, the estimation formulas, based on the regression equation [GA (men) = 3.3HbA1c − 4.4FT3 + 10.7 and GA (women) = 3.3HbA1c − 4.4FT3 + 8.8], showed very high contribution rates (i.e., coefficient of determination $R^2 = 0.674$ for men and 0.761 for women) for the GA measured values.

Conclusions GA and GA/HbA1c have a close relationship with FT3 in HD patients. The estimation formulas of GA could be obtained. In particular, the estimation formulas in the DM group are believed to be useful in considering HbA1c and FT3 simultaneously when evaluating GA.

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Keywords Glycated albumin, Free triiodothyronine, Glycated albumin to glycated hemoglobin ratio, Hemodialysis patient, Geriatric Nutritional Risk Index

Background

Patients undergoing hemodialysis (HD) in Japan are typically the older population. Furthermore, sarcopenia and frailty associated with nutritional disorders, which may be caused by low energy and protein intake, are steadily gaining attention. These clinical statuses are similar to those in low triiodothyronine (T3) syndrome, a condition prevalent among HD patients [1–3]. This syndrome is associated with malnutrition and is an independent risk factor for cardiovascular events and mortality in HD patients [1, 2].

Moreover, for HD patients with diabetes, glycated albumin (GA) has been adopted as a better indicator of glycemic control than glycated hemoglobin (HbA1c) because the HbA1c level is lower than the blood glucose level [4, 5]. However, indicators of nutritional status such as body mass index (BMI) have been inversely correlated with GA [6–9] and with the GA to HbA1c ratio (GA/HbA1c) [10]. A relationship between GA levels, the risk of cardiovascular events, and the prognosis of HD patients have been reported [5, 11]. We, therefore, considered that GA and free triiodothyronine (FT3) levels are associated with nutritional status.

In untreated overt hypothyroidism [12], euthyroidism, and subclinical hypothyroidism [13], thyroid hormones have been associated with GA. We previously reported that GA showed a significant inverse correlation with FT3 in HD patients [14]. However, an annual statistical review at our clinic revealed that this correlation was often insignificant, especially in the diabetes mellitus (DM) group; thus, poor reproducibility is an issue. Therefore, in light of a previous report [10] demonstrating that GA/HbA1c is inversely correlated with the indices of nutritional status, we primarily conducted this study to clarify the relationships of GA and GA/HbA1c with FT3, HbA1c, average plasma glucose (Av-PG), and the Geriatric Nutritional Risk Index (GNRI) in the DM and non-DM groups.

Methods

Patients who received HD at our clinic for >2 years between 2014 and 2018 were included in our study. The exclusion criteria were as follows: (1) a history of blood transfusion within 1 year; (2) albumin (Alb) level below 3.0 mg/dL due to cirrhosis, cancer, or other comorbidities; (3) intake of steroids; (4) intake of thyroid medication; and (5) hypo- or hyperthyroidism, including latent thyroid function abnormalities. The classification was based on the following reference ranges: FT3, 2.3–4.3 pg/mL; free thyroxine (FT4), 0.9–1.7 ng/dL; and thyroid-stimulating hormone (TSH), 0.5–5.0 μIU/mL. Low T3 syndrome was defined as a serum FT3 level below the lower limit of the reference range (<2.3 pg/mL), with TSH levels within the normal range (0.5–5.0 μIU/mL) and normal or low FT4 levels (normal range: 0.9–1.7 ng/dL). DM was diagnosed at the start of HD or at the time of referral to our clinic. DM was diagnosed, based on the criteria of the Japan Diabetes Society (clinical data: blood glucose level of 200 mg/dL or higher, and HbA1c 6.5 or higher); if the diagnostic criteria of diabetes were insufficient, the presence of diabetic retinopathy and the treatment history of diabetes were used as references for a diagnosis [15]. In total, 134 HD patients (68 patients in the DM group and 66 patients in the non-DM group) were examined.

Blood samples were collected on the first day of the weekly HD. The main general examinations in both groups and GA measurements in the DM group were performed monthly. HbA1c, FT3, FT4, and TSH levels in the DM and non-DM groups and GA levels in the non-DM group were analyzed twice annually. The Av-PG level represented the mean of the three pre-HD casual PG levels at the time of regular blood sampling over the previous 3 months.

Erythropoiesis-stimulating agents (ESAs) (i.e., darbepoetin alfa [DA] and epoetin beta [EPO]) were used in 91.9% of the cases (92.6% in the DM group and 91.0% in the non-DM group), and the ESA dosages were expressed as DA conversion (EPO:DA = 200:1).

GA was measured by using the enzymatic method; HbA1c (National Glycohemoglobin Standardization Program), by using the latex immune agglutination method; serum Alb, by using the bromocresol purple improvement method; C-reactive protein (CRP), by using the latex agglutination turbidimetric method; blood glucose, by using the HK-G6PDH method; and FT3, FT4, and TSH, by using electrochemiluminescence immunoassay. Furthermore, the GNRI was calculated [16].

Statistical analysis

Statistical analysis was conducted using Excel Statistics 2012 (Social Survey Research Information Co. Ltd., Tokyo, Japan). CRP (a continuous variable with a positively skewed distribution) was log-transformed ($\log_{10}$) before the correlation study. For univariate analysis, a

Table 1 Clinical characteristics of the hemodialysis patients

	DM ($n=68$)	non-DM ($n=66$)	*P*-value
Age (y)	68.7 ± 11.0	66.0 ± 12.8	0.422
Men/Women (n/n)	48/20	35/31	0.037
HD duration (mo.)	59.1 ± 45.5	111.6 ± 108.7	< 0.001
Body weight (kg)	59.0 ± 13.3	52.9 ± 11.1	0.005
BMI (kg/m^2)	22.8 ± 4.2	20.9 ± 3.8	0.007
Hb (g/dL)	10.5 ± 1.0	10.5 ± 0.9	0.998
Alb (g/dL)	3.6 ± 0.3	3.7 ± 0.3	0.245
Average PG (mg/dL)	146 ± 45	116 ± 21	< 0.001
GA (%)	22.1 ± 4.5	17.8 ± 2.4	< 0.001
HbA1c (%)	6.2 ± 1.2	5.2 ± 0.4	< 0.001
GA/HbA1c ratio	3.56 ± 0.48	3.42 ± 0.49	0.093
ESA dose (μg kg/w)	0.51 ± 0.40	0.54 ± 0.56	0.680
CRP (mg/dL)	0.44 ± 0.80	0.31 ± 0.53	0.277
GNRI	93.6 ± 7.0	92.8 ± 6.3	0.476
ChE (U/L)	199 ± 47	207 ± 49	0.309
T.Chol (mg/dL)	155 ± 38	157 ± 30	0.808
Cr (mg/dL)	9.8 ± 2.4	10.9 ± 2.2	0.009
P (mg/dL)	5.1 ± 1.2	5.4 ± 1.3	0.218
TSH (μIU/mL)	2.2 ± 0.9	2.4 ± 1.9	0.408
FT4 (ng/dL)	1.0 ± 0.2	1.2 ± 0.9	0.166
FT3 (pg/mL)	1.9 ± 0.3	2.0 ± 0.4	0.245

Values are expressed as the mean ± the standard deviation

DM, Diabetes mellitus; HD, hemodialysis; BMI, body mass index; Hb, hemoglobin; Alb, albumin; PG, plasma glucose; GA, glycated albumin; HbA1c, glycated hemoglobin; ESA, erythropoiesis-stimulating agent; CRP, C-reactive protein; GNRI, Geriatric Nutritional Risk Index; ChE, cholinesterase; T.Chol, total cholesterol; Cr, creatinine; P, phosphate; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine

single correlation analysis was conducted using the Pearson correlation coefficient. Multivariate analysis was conducted using multiple linear regression analysis with GA (or GA/HbA1c) as the objective variable, and with FT3 as the explanatory variable, which was adjusted for Av-PG (or HbA1c), age, sex, hemoglobin [Hb], and Alb as the explanatory variables. Statistical significance was set at $p<0.05$. Values are expressed as the mean ± the standard deviation.

Results

In total, 134 HD patients, including 68 patients in the DM group and 66 patients in the non-DM group, were examined. The clinical characteristics of the patients are summarized in Table 1. GA, HbA1c, Av-PG, body weight, and BMI were significantly higher in the DM group than in the non-DM group. Significantly more men were in the DM group than in the non-DM group. HD duration and Cr levels were lower in the DM group than in the non-DM group. In the DM group, all patients had type 2 diabetes with 28 patients, 26 patients, and 14 patients receiving insulin therapy, oral hypoglycemic agents, and diet therapy, respectively.

Univariate analysis of clinical parameters with GA, GA/HbA1c, and HbA1c in HD patients with and without DM

In the DM group, GA tended to be inversely correlated with FT3, and significantly positively correlated with Av-PG, HD duration, and T.Chol. GA/HbA1c was significantly inversely correlated with FT3, BMI, Cr, ChE, and GNRI, and significantly positively correlated with HD duration. HbA1c was significantly inversely correlated with sex, and significantly positively correlated with the Av-PG, BMI, Alb, T.Chol, ChE, and GNRI (Table 2).

In the non-DM group, GA was significantly inversely correlated with FT3, BMI, Hb, Alb, P, ChE, and GNRI, and significantly positively correlated with Av-PG, age, and ESA dose. GA/HbA1c was significantly inversely correlated with FT3, HbA1c, BMI, Hb, P, ChE, and GNRI, and significantly positively correlated with age and HD duration. HbA1c was significantly inversely correlated with HD duration and significantly positively correlated with Av-PG and BMI (Table 3).

Correlations of GA and HbA1c with Av-PG, GA with HbA1c, and Av-PG with FT3, GNRI, and GA/HbA1c in HD patients with and without DM

GA and HbA1c showed significant positive correlations with Av-PG in the DM group ($r=0.292$, $p=0$ 0.016 and $r=0.297$, $p=0.014$, respectively) and in the non-DM group ($r=0.380$, $p=0.002$ and $r=0.354$, $p=0.004$, respectively). GA showed a significant positive correlation with HbA1c in the DM group ($r=0.772$, $p<0.001$) but not in the non-DM group ($r=0.146$, $p=0.241$) (Fig. 1a–c).

In the DM group, no relationship existed between FT3, GNRI, or GA/HbA1c with the Av-PG ($r=-0.006$, $p=0.963$; $r=-0.042$, $p=0.732$; and $r=0.014$, $p=0.909$, respectively). Moreover, in the non-DM group, the AV-PG tended to be inversely correlated with FT3 ($r=-0.233$, $p=0.060$) and GNRI ($r=-0.240$, $p=0.052$), and positively correlated with GA/HbA1c ($r=0.203$, $p=0.103$) but without statistical significance (Fig. 1d–f).

Correlations of GA, HbA1c, and GA/HbA1c with FT3 in HD patients with and without DM

GA was inversely correlated with FT3 without statistical significance ($r=-0.228$, $p=0.062$) and GA/HbA1c was inversely correlated with FT3 with statistical significance ($r=-0.477$, $p<0.001$). However, HbA1c was not correlated with FT3 in the DM group ($r=0.065$, $p=0.598$). Furthermore, GA was significantly inversely correlated with FT3 ($r=-0.511$, $p<0.001$), as was GA/

Table 2 Univariate analysis of clinical parameters with GA, GA/HbA1c, and HbA1c in HD patients with DM

DM	GA		GA/HbA1c		HbA1c	
	r	*P*	*r*	*P*	*r*	*P*
Av-PG	0.292	0.016	0.014	0.909	0.297	0.014
HbA1c	0.772	< 0.001	− 0.188	0.124		
GA/HbA1c	0.468	< 0.001			− 0.188	0.124
FT3	− 0.228	0.062	− 0.477	< 0.001	0.065	0.598
Age	− 0.082	0.505	0.154	0.210	− 0.221	0.071
Men (= 1)/Women (= 0)	− 0.105	0.393	0.177	0.148	− 0.258	0.034
Hb	− 0.033	0.788	− 0.059	0.634	0.010	0.938
Alb	0.237	0.051	− 0.158	0.200	0.342	0.004
BMI	0.034	0.780	− 0.339	0.005	0.277	0.022
GNRI	0.115	0.351	− 0.309	0.010	0.315	0.007
ChE	0.094	0.447	− 0.453	< 0.001	0.404	0.001
Cr	− 0.095	0.441	− 0.250	0.040	0.064	0.607
P	− 0.024	0.849	− 0.170	0.165	0.101	0.413
T.Chol	0.249	0.040	− 0.137	0.266	0.374	0.002
Log CRP	− 0.096	0.434	− 0.093	0.449	− 0.023	0.850
HD duration	0.263	0.030	0.287	0.018	0.068	0.583
ESA dose	− 0.006	0.959	0.200	0.102	− 0.125	0.311

GA, Glycated albumin; HbA1c, glycated hemoglobin; HD, hemodialysis; DM, diabetes mellitus; r, correlation coefficient; Av-PG, average plasma glucose; FT3, free triiodothyronine; Hb, hemoglobin; Alb, albumin; BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; ChE, cholinesterase; Cr, creatinine; P, phosphate; T.Chol, total cholesterol; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent

Table 3 Univariate analysis of clinical parameters with GA, GA/HbA1c, and HbA1c in HD patients without DM

non-DM	GA		GA/HbA1c		HbA1c	
	r	*P*	*r*	*P*	*r*	*P*
Av-PG	0.380	0.002	0.203	0.103	0.354	0.004
HbA1c	0.146	0.241	− 0.329	0.007		
GA/HbA1c	0.884	< 0.001			− 0.329	0.007
FT3	− 0.511	< 0.001	− 0.514	< 0.001	0.053	0.673
Age	0.355	0.003	0.254	0.040	0.189	0.129
Men(= 1)/Women(= 0)	− 0.017	0.894	− 0.085	0.498	0.139	0.268
Hb	− 0.285	0.021	− 0.254	0.040	− 0.006	0.963
Alb	− 0.271	0.028	− 0.184	0.138	− 0.197	0.114
BMI	− 0.423	< 0.001	− 0.582	< 0.001	0.399	< 0.001
GNRI	− 0.405	< 0.001	− 0.446	< 0.001	0.091	0.469
ChE	− 0.393	0.001	− 0.351	0.004	− 0.036	0.777
Cr	− 0.228	0.065	− 0.191	0.125	− 0.095	0.449
P	− 0.362	0.003	− 0.361	0.003	0.027	0.831
T.Chol	− 0.191	0.125	− 0.099	0.427	− 0.181	0.146
Log CRP	− 0.029	0.815	− 0.111	0.374	0.206	0.097
HD duration	0.201	0.106	0.310	0.012	− 0.247	0.045
ESA dose	0.277	0.024	0.219	0.078	0.082	0.512

GA, Glycated albumin; HbA1c, glycated hemoglobin; HD, hemodialysis; DM, diabetes mellitus; r, correlation coefficient; Av-PG, average plasma glucose; FT3, free triiodothyronine; Hb, hemoglobin; Alb, albumin; BMI, body mass index; GNRI, Geriatric Nutritional Risk Index; ChE, cholinesterase; Cr, creatinine; P, phosphate; T.Chol, total cholesterol; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent

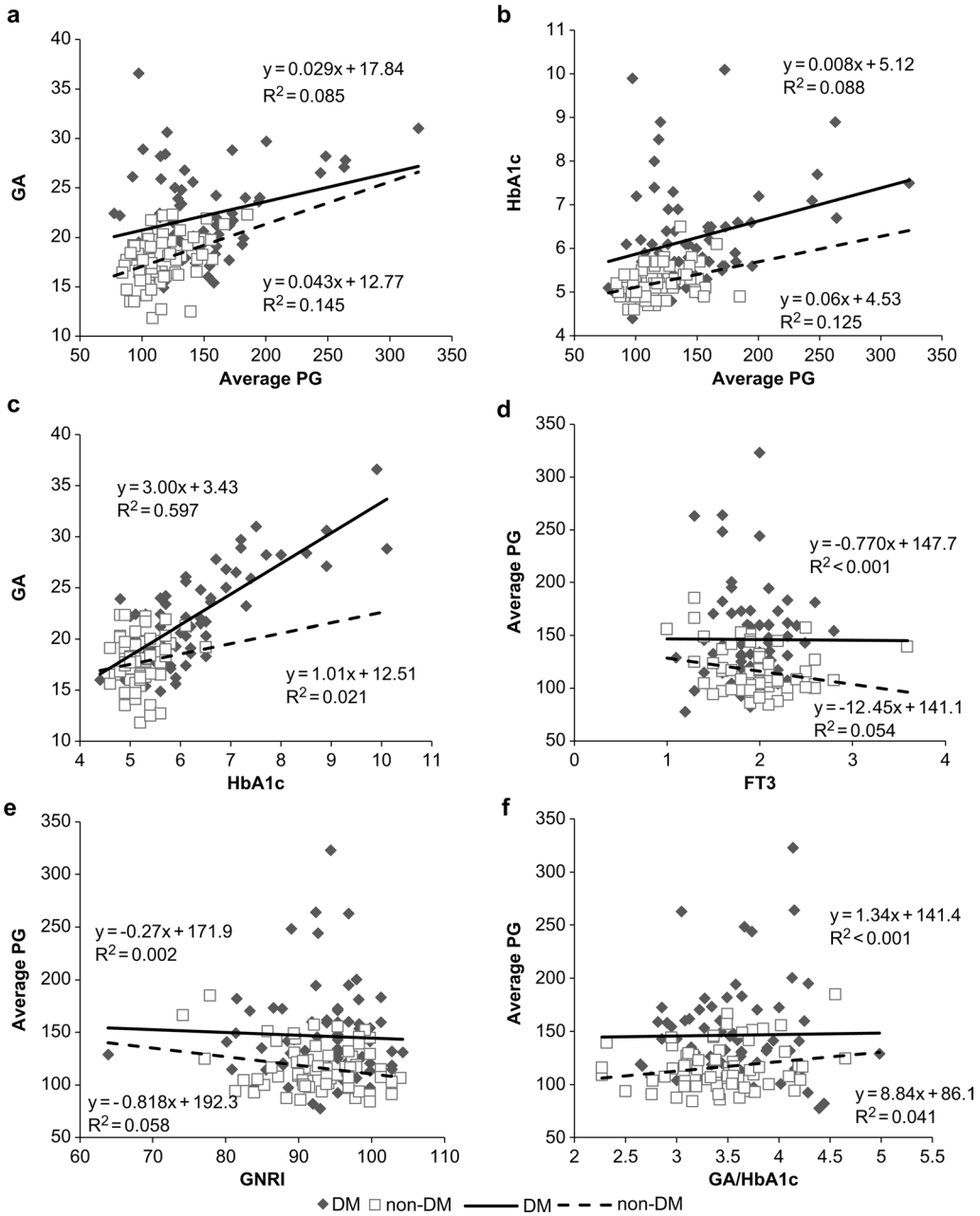

Fig. 1 Correlations between GA, HbA1c, and average PG. The figure illustrates the correlations of GA and HbA1c with average PG, GA with HbA1c, and average PG with FT3, GNRI, and GA/HbA1c among hemodialysis patients with and without DM. **a** Correlation between GA and average PG. **b** Correlation between HbA1c and average PG. **c** Correlation between GA and HbA1c. **d** Correlation between average PG and FT3. **e** Correlation between average PG and GNRI. **f** Correlation between average PG and GA/HbA1c. GA, glycated albumin; HbA1c, glycated hemoglobin; PG, plasma glucose; FT3, free triiodothyronine; GNRI, Geriatric Nutritional Risk Index; DM, diabetes mellitus

HbA1c ($r = -0.514$, $p < 0.001$). However, HbA1c was not correlated with FT3 in the non-DM group ($r = 0.053$, $p = 0.673$) (Fig. 2).

Correlations of FT3 and GA/HbA1c with GNRI in HD patients with and without DM

In the DM and non-DM groups, FT3 showed a significant positive correlation with the GNRI (DM: $r = 0.392$, $p < 0.001$; non-DM: $r = 0.358$, $p = 0.003$), while GA/HbA1c showed a significant inverse correlation with the

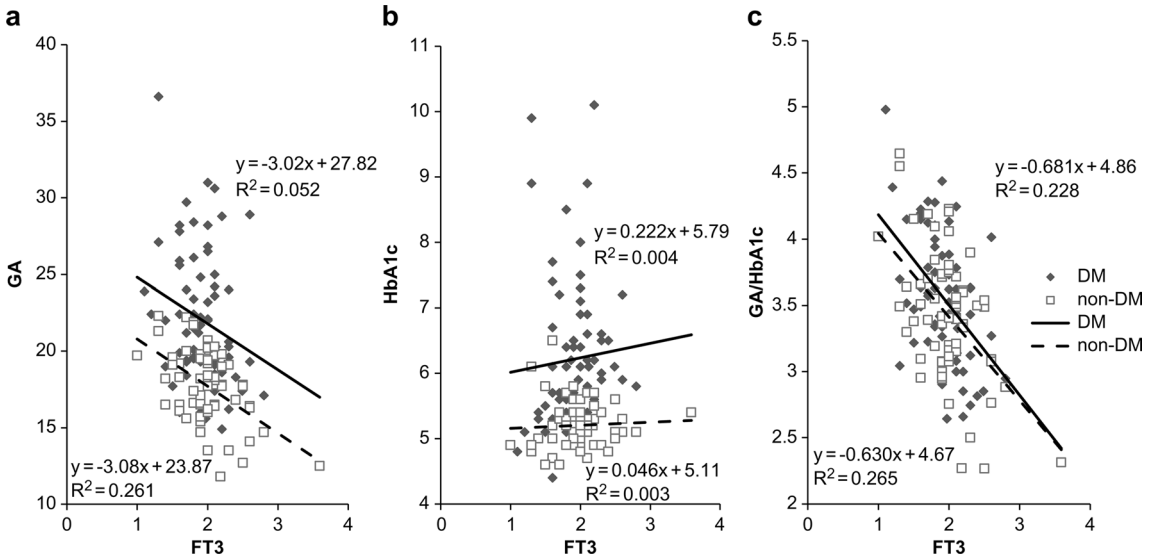

Fig. 2 The correlation of GA, HbA1c, and GA/HbA1c with FT3. The figure illustrates the correlations of GA, HbA1c, and GA/HbA1c with FT3 in hemodialysis patients with and without DM. **a** Correlation between GA and FT3. **b** Correlation between HbA1c and FT3. **c** Correlation between GA/HbA1c and FT3. GA, glycated albumin; HbA1c, glycated hemoglobin; FT3, free triiodothyronine; DM, diabetes mellitus

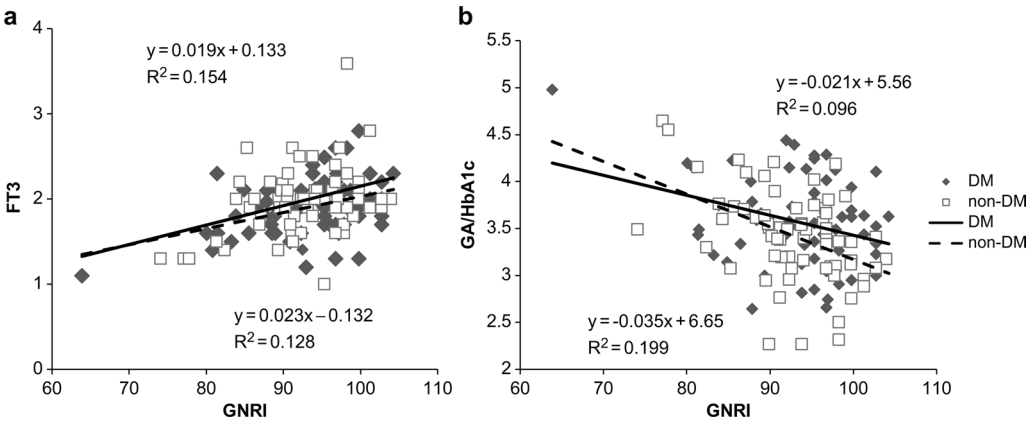

Fig. 3 The correlation of FT3 and GA/HbA1c with GNRI. The figure illustrates the correlations of FT3 and GA/HbA1c with GNRI in hemodialysis patients with and without DM. **a** Correlation between FT3 and GNRI. **b** Correlation between GA/HbA1c and GNRI. FT3, free triiodothyronine; GA, glycated albumin; HbA1c, glycated hemoglobin. GNRI, Geriatric Nutritional Risk Index; DM, diabetes mellitus

GNRI (DM: $r = -0.309$, $p = 0.010$; non-DM: $r = -0.446$, $p < 0.001$) (Fig. 3).

Multiple linear regression analysis of GA and GA/HbA1c with FT3 in HD patients with and without DM

In the multivariate analysis of GA or GA/HbA1c adjusted for age, sex, Hb, Alb, and Av-PG, FT3 was a significant and independent factor associated with GA ($\beta = -0.334$, $p = 0.008$) and GA/HbA1c ($\beta = -0.550$, $p < 0.001$) in the DM group. It was also a significant and independent factor associated with GA ($\beta = -0.387$, $p = 0.001$) and GA/HbA1c ($\beta = -0.438$, $p < 0.001$) in the non-DM group. In GA, these contribution rates (i.e., coefficient of determination) were $R^2 = 0.244$ in the DM group and $R^2 = 0.390$ in the non-DM group. In GA/HbA1c, these contribution rates (i.e., coefficient of determination) were $R^2 = 0.326$ in the DM group and $R^2 = 0.304$ in the non-DM group. The regression equations, obtained with stepwise multiple regression analysis using all of these variables as independent variables, were GA/HbA1c = −0.80FT3 + 0.33sex + 4.85 in the DM group and GA/HbA1c = −0.59FT3 − 0.084Hb + 5.48 in the non-DM group, with contribution rates (i.e., coefficient of determination) of $R^2 = 0.323$ in the DM group and ($R^2 = 0.289$) in the non-DM group.

Table 4 Multiple linear regression analysis of GA and GA/HbA1c with FT3 in HD patients with DM

Ob.va	GA	GA	GA	GA	GA/HbA1c	GA/HbA1c
Ex.va	Av-PG	Av-PG	HbA1c	HbA1c	Av-PG	Av-PG
Method	All β	Stepwise β	All β	Stepwise β	All β	Stepwise β
Av-PG	0.311 (0.009)	0.290 (0.011)			0.029 (0.795)	○
HbA1c			0.836 (< 0.001)	0.845 (< 0.001)		
FT3	− 0.334 (0.008)	− 0.307 (0.009)	− 0.334 (< 0.001)	− 0.333 (< 0.001)	− 0.550 (< 0.001)	− 0.558 (< 0.001)
Age	− 0.130 (0.279)	○	0.042 (0.573)	○	0.029 (0.799)	○
Men/Women	0.006 (0.961)	○	0.204 (0.008)	0.197 (0.009)	0.324 (0.005)	0.319 (0.004)
Hb	0.013 (0.914)	○	− 0.035 (0.620)	○	− 0.028 (0.805)	○
Alb	0.285 (0.021)	0.315 (0.007)	0.060 (0.438)	○	0.004 (0.970)	○
R^2	0.244	0.229	0.712	0.708	0.326	0.323
R^{*2}	0.170 (0.007)	0.193 (< 0.001)	0.684 (< 0.001)	0.694 (< 0.001)	0.259 (< 0.001)	0.302 (< 0.001)

The values: β are presented as the standard regression coefficient (p-value). Age, sex, hemoglobin, albumin, and average plasma glucose (or HbA1c) were adjusted for in the analysis. The symbol ○ indicates that the stepwise multiple regression analysis was conducted by using all variables listed in this table

GA, Glycated albumin; HbA1c, glycated hemoglobin; FT3, free triiodothyronine; HD, hemodialysis; DM, diabetes mellitus; Ob.va, objective variable; Ex.va, explanatory variable; Av-PG, average plasma glucose; Hb, hemoglobin; Alb, albumin; R^2, multiple coefficient of determination; R^{*2}, adjusted multiple coefficient of determination

In the multivariate analysis of GA, FT3 was used as the explanatory variable and was adjusted for age, sex, Hb, Alb, and HbA1c. The regression equations, obtained with stepwise multiple regression analysis using all of these variables as independent variables were GA = 3.3HbA1c − 4.4FT3 + 1.9sex + 8.8 for the DM group and GA = − 2 .4FT3 + 0.04age − 0.5Hb + 25.2 for the non-DM group, with contribution rates (i.e., coefficient of determination) of $R^2 = 0.708$ in the DM group and $R^2 = 0.347$ in the non-DM group. The contribution rates (i.e., adjusted coefficient of determination) were $R^{*2} = 0.694$ in the DM group and $R^{*2} = 0.315$ in the non-DM group (Tables 4 and 5).

Correlations of GA and GA/HbA1c with estimated GA and GA/HbA1c in HD patients with DM

In the DM group, the estimated GA of men was represented by GA = 3.3HbA1c − 4.4FT3 + 10.7, and the estimated GA of women by GA = 3.3HbA1c − 4.4FT3 + 8.8, based on the regression equations. The estimation formulas showed very high contribution rates (i.e., coefficient of determination) and were $R^2 = 0.674$ for men and 0.761 for women, for the GA measured values. The estimated GA/HbA1c of men was represented by GA/HbA1c = − 0.8FT3 + 5.2 and GA/HbA1c of women by GA/HbA1c = − 0.8FT3 + 4.9, based on the regression equations. The estimation formulas showed high

Table 5 Multiple linear regression analysis of GA and GA/HbA1c with FT3 in HD patients without DM

Ob.va	GA	GA	GA	GA	GA/HbA1c	GA/HbA1c
Ex.va	Av-PG	Av-PG	HbA1c	HbA1c	Av-PG	Av-PG
Method	All β	Stepwise β	All β	Stepwise β	All β	Stepwise β
Av-PG	0.189 (0104)	0.197 (0.084)			0.022 (0.855)	○
HbA1c			0.107 (0.325)	○		
FT3	− 0.387 (0.001)	− 0.380 (0.001)	− 0.412 (< 0.001)	− 0.398 (< 0.001)	− 0.438 (< 0.001)	− 0.483 (< 0.001)
Age	0.149 (0.206)	0.165 (0.151)	0.190 (0.101)	0.236 (0.033)	0.102 (0.414)	○
Men/Women	0.073 (0.491)	○	0.050 (0.645)	○	0.003 (0.981)	○
Hb	− 0.168 (0.118)	− 0.177 (0.096)	− 0.197 (0.068)	− 0.209 (0.050)	− 0.163 (0.156)	− 0.161 (0.143)
Alb	− 0.077 (0.483)	○	− 0.087 (0.438)	○	− 0.040 (0.730)	○
R^2	0.390	0.378	0.372	0.347	0.304	0.289
R^{*2}	0.328 (< 0.001)	0.337 (< 0.001)	0.308 (< 0.001)	0.315 (< 0.001)	0.234 (< 0.001)	0.267 (< 0.001)

The values: β are presented as the standard regression coefficient (p-value). Age, sex, hemoglobin, albumin, and average plasma glucose (or HbA1c) were adjusted for in the analysis. The symbol ○ indicates that the stepwise multiple regression analysis was conducted by using all variables listed in this table

GA, Glycated albumin; HbA1c, glycated hemoglobin; FT3, free triiodothyronine; HD, hemodialysis; DM, diabetes mellitus; Ob.va, objective variable; Ex.va, explanatory variable; Av-PG, average plasma glucose; Hb, hemoglobin; Alb, albumin; R^2, multiple coefficient of determination; R^{*2}, adjusted multiple coefficient of determination

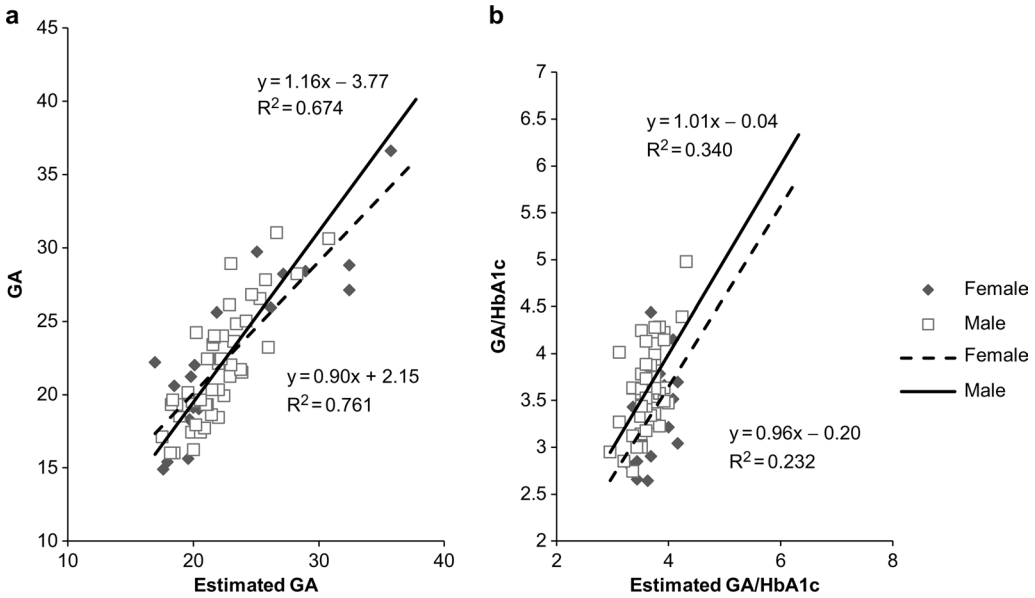

Fig. 4 The correlation of GA and GA/HbA1c with estimated GA and GA/HbA1c. The figure illustrates the correlations of GA and GA/HbA1c with the estimated GA and GA/HbA1c in hemodialysis patients with DM. **a** Correlation between GA and estimated GA. **b** Correlation between GA/HbA1c and estimated GA/HbA1c. GA, glycated albumin; HbA1c, glycated hemoglobin; DM, diabetes mellitus

contribution rates (i.e., coefficient of determination) and were $R^2 = 0.340$ for men and $R^2 = 0.232$ for women, for the GA/HbA1c measured values (Fig. 4).

Discussion

GA and GA/HbA1c were originally thought to represent blood glucose levels, particularly blood glucose fluctuation [11, 17]. However, other than the increase in GA caused by blood sugar, additional mechanisms are believed to depend on the result of the low turnover of serum Alb such as in hypothyroidism and liver cirrhosis [5, 12, 18]. Serum Alb levels have been reported to be significantly inversely correlated with GA levels [4, 6]. In previous reports on GA, age (positive correlation) [8, 9], BMI (inverse correlation) [6–9], and ChE (inverse correlation) [8] were significantly correlated with GA levels. Furthermore, GA levels in patients with low T3 syndrome may be influenced by the low turnover of serum Alb due to malnutrition.

Low T3 syndrome in end-stage renal disease [1] and among HD patients has been reported [2, 3]. Low FT3 includes primary and central hypothyroidism, but these conditions were excluded from this study. Most cases of low FT3 in our study were considered to have low T3 syndrome, which is seen in debilitating diseases, DM, and renal failure. Low T3 syndrome is triggered by poor nutrition or lack of calorie intake, which reduces the conversion of T4 to T3, decreases FT3 with high physiological activity, and slows the basal metabolic rate with fewer calories to conserve energy and protein, thereby delaying the turnover of serum Alb, which increases GA. Therefore, in the results of this study, we characterized the DM and non-DM groups separately.

In the non-DM group, GA had a significant inverse correlation with FT3, while Av-PG had a trend of inverse correlation with FT3. Therefore, when FT3 decreases, Av-PG presumedly increases because of glucose intolerance. However, the degree of increase in GA is presumed to be more significant than the degree of increase in the Av-PG.

In the DM group, the GA values tended to be inversely correlated with the FT3 values, and the Av-PG values were not affected by the FT3 values. Therefore, the GA values presumedly increase to some extent when the FT3 value decreases, regardless of the Av-PG values. In both groups, the GA values showed a higher increase relative to the Av-PG values when FT3 decreased.

GA/HbA1c showed a significant correlation with FT3 in both groups. GA/HbA1c values are presumed to show a significant increase independent of Av-PG values when the FT3 value decreases. The reason for this finding is as follows. First, the numerator and denominator contain factors associated with the blood sugar levels. Second, in the DM group, the denominator HbA1c had a significantly positive correlation with GNRI. FT3 did not show a positive correlation with HbA1c, but the GNRI showed a significant positive correlation with FT3. The FT3 and GA/HbA1c values showed a significant correlation with

GNRI in both groups. These correlations between GA/HbA1c, GNRI, and FT3 may be associated with other factors such as the erythrocyte lifespan. A significant inverse association between the ESA resistance index and GNRI of HD patients has been previously reported [19].

We investigated the role of FT3 in GA and GA/HbA1c, while taking into consideration factors associated with GA and HbA1c. In the multiple regression analysis, FT3 was a particularly significant explanatory variable for the objective variables GA (or GA/HbA1c). When GA in the DM group was the objective variable adjusted for age, sex, Hb, Alb, and HbA1c, the coefficient of determination for multiple regression analysis using the stepwise method ($R^2 = 0.708$) was not significantly different from the coefficient of determination for multiple regression analysis using all explanatory variables ($R^2 = 0.712$). In addition, the adjusted coefficients of determination ($R^{*2} = 0.694$) were higher than the adjusted coefficients of determination for multiple regression analysis using all explanatory variables ($R^{*2} = 0.684$), As mentioned above, the contribution rate was very high. The regression equation GA $= 3.3\text{HbA1c} - 4.4\text{FT3} + 1.9\text{sex} + 8.8$ is considered meaningful. From this regression equation, the following estimation formulas were adopted for each gender. The GA of men was $\text{GA} = 3.3\text{HbA1c} - 4.4\text{FT3} + 10.7$ and the GA of women was $\text{GA} = 3.3\text{HbA1c} - 4.4\text{FT3} + 8.8$. The estimation formulas showed very high contribution rates (i.e., coefficient of determination $R^2 = 0.674$ for men and 0.761 for women) for the GA measured values.

Similarly, in the non-DM group, the estimated GA was obtained with $\text{GA} = -2.4\text{FT3} - 0.5\ \text{Hb} + 25.2$.

In particular, a 1 pg/mL decrease in FT3 in the DM and non-DM groups would increase the GA by 4.4% and 2.4%, respectively. We examined whether the GNRI, which is closely correlated with the FT3 value, can replace FT3 by using multiple regression analysis. However, the GNRI did not have a simple regression equation as did FT3, and the contribution rate was not very high.

High GA and low FT3 levels are independent risk factors for cardiovascular events and mortality in HD patients [1, 2, 5, 11]. Glycation or GA, a pathogenic protein that is a precursor of advanced glycation end products (AGEs), is one cause of aging and lifestyle-related diseases. Moreover, it exacerbates vascular complications [11]. However, a low FT3 level delays Alb catabolism due to malnutrition. This factor may increase the GA level, which may further increase AGEs and promote vascular complications. Another possibility is that a low FT3 level causes impaired glucose tolerance [20], thereby leading to increased blood glucose, which may further increase GA and AGEs and promote vascular complications, especially in patients without diabetes. The regression equations in this study are thought to represent these pathologies.

An interesting finding is that the GA/HbA1c has been significantly associated with the risk of Alzheimer`s disease in patients with and without glucose intolerance [21]. Higher serum GA levels are significantly associated with the development of cardiovascular disease, even after adjusting for the presence of DM [22]. These reports suggest that a mechanism, other than blood glucose levels, exists in the increase of GA in these diseases.

The present study has some limitations that should be acknowledged. First, the cases of this study are limited to a small geographic area and the study was conducted in one clinic. Second, we examined GA, HbA1c, GA/HbA1c, FT3, and GNRI, while focusing on the Av-PG. To determine the degree of dissociation between GA and blood glucose levels, observing the fluctuation in blood glucose levels is necessary. However, blood glucose fluctuation and blood glucose profile were not examined in this study. Third, the tendency of insulin therapy and sulfonylureas to increase blood glucose variability has been reported; the GA level in patients treated with these agents indeed appears to be higher than the HbA1c level [23]. However, the effects of insulin and sulfonylureas on blood glucose and GA have not yet been investigated. Fourth, the FT3 level had no significant correlation with the CRP level. The relationship between FT3 and CRP levels has been studied previously [2, 3]; therefore, the involvement of inflammation in a high-sensitivity CRP assay may need to be investigated. Fifth, thyroid autoantibodies were not measured. The profiles with low T3 with and without positive thyroid autoantibodies may have different clinical implications. This difference should be explored in future studies. Sixth, other variables may affect FT3. Therefore, the adjustments in the multivariable analysis may have been insufficient.

Conclusions

GA and GA/HbA1c have a close relationship with FT3 in HD patients. Moreover, FT3 and GA/HbA1c showed significant correlations with the GNRI. When evaluating GA and GA/HbA1c in HD patients, paying attention to FT3 may be necessary because of its correlation with GNRI. By using HbA1c instead of Av-PG for statistical processing, clinically useful estimation formulas were obtained from the regression equations. In particular, the estimation formulas of GA in the DM group were GA (men) $= 3.3\text{HbA1c-4.4FT3} + 10.7$ and GA (women) $= 3.3\text{HbA1c} - 4.4\text{FT3} + 8.8$. For the non-DM group, the estimation formula of GA was $\text{GA} = -2.4\text{FT3} + 0.04\text{Age} - 0.5\text{Hb} + 25.2$. A 1 pg/mL decrease in FT3 in the DM and non-DM groups would increase the GA by 4.4% and 2.4%, respectively.

In particular, the estimation formulas in the DM group are believed to be useful in considering HbA1c and FT3 simultaneously when evaluating GA.

Abbreviations

AGE	Advanced glycation end product
Alb	Albumin
Av-PG	Average plasma glucose
BMI	Body mass index
ChE	Cholinesterase
Cr	Creatinine
CRP	C-reactive protein
DA	Darbepoetin alfa
DM	Diabetes mellitus
EPO	Epoetin beta
ESAs	Erythropoiesis-stimulating agents
FT3	Free triiodothyronine
FT4	Free thyroxine
GA	Glycated albumin
GNRI	Geriatric Nutritional Risk Index
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HD	Hemodialysis
P	Phosphate
T.Chol	Total cholesterol
T3	Triiodothyronine
TSH	Thyroid-stimulating hormone

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Author contributions
KM carried out the investigation, methodology, formal analysis, and writing (original draft, review, and editing). TaN was responsible for the investigation and funding acquisition. ToN was responsible for the methodology, conceptualization, and writing (review and editing). YK was responsible for the software and data curation. SI was responsible for the investigation and validation. KN, NH, and YY were responsible for the investigation. RM was responsible for the investigation and writing (review and editing). ON was responsible for the investigation and supervision. SY was responsible for the project administration. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The purpose of this study was presented on the website of Kaizuka Nishide Clinic. Comprehensive informed consent was obtained from all participants, and the study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Shosei-kai Kaizuka Nishide Clinic Medical Corporation (approval number 2001).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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