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Correlates of low hemoglobin A1c in maintenance hemodialysis patients

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Abstract

Purpose—The optimal target for glycemic control has not been established for diabetic maintenance hemodialysis (MHD) patients.

Methods—A 6-year cohort (October 2001- December 2006) of 347 diabetic MHD patients with HbA1c data was examined for associations between HbA1c and mortality. Death hazard ratios (HR) were estimated using Cox regressions and cubic splines.

Results—In these 347 patients (age, 59 ± 11 years; 49 % women; 28 % African Americans; and 55 % Hispanics), each 0.5 % decline in HbA1c below 6 % was associated with a 4.7 times higher death risk (HR = 4.7; 95 % CI 1.7–12.7) in the fully adjusted model. Factors associated with lower HbA1c levels (<6 % compared to 6–7 %) were: Hispanic ethnicity (OR = 2.9; 95 % CI 1.1–7.9), higher mid-arm muscle circumstance (OR = 1.1; 95 % CI 1.0–1.3), higher total iron-binding capacity (OR = 1.03; 95 % CI 1.01–1.05), and higher iron saturation ratio (OR = 1.14; 95 % CI 1.03–1.26). HbA1c levels >7 % showed a consistent trend toward elevated mortality risk (HR = 1.18; 95 % CI 0.99–1.41) after multivariate adjustment.

Conclusions—In diabetic MHD patients with burnt-out diabetes, characterized by HbA1c <6 %, even lower HbA1c levels are associated with significantly higher death risk. Additional studies are needed to determine the optimal target for HbA1c levels in different subgroups of diabetic MHD patients.

Keywords

Diabetes mellitus; Burnt-out diabetes; Glucose; Hemoglobin A1c; Hemodialysis; Mortality; Malnutrition-inflammation complex syndrome

Introduction

Diabetes mellitus is a major global health threat and is currently the leading cause of end-stage renal disease (ESRD) in the United States and most developed countries [1]. According to the US renal data system, diabetes mellitus is now the cause of ESRD in almost 50 % of incident dialysis patients in the United States, which is 17.2 % higher than in 2000 [2]. Glycated hemoglobin (Hb), also known as HbA1c, is a marker of long-term glycemic control. Clinicians routinely change diabetic therapies based on HbA1c level according to national guidelines. A strong body of evidence supports intensive therapy to

keep HbA1c low in order to prevent microvascular complications in diabetics [3–5]. Intensive diabetes therapy also has long-term beneficial effects on the risk of cardiovascular diseases in type I diabetics [6]; however, the role of the intensive therapy and cardiovascular disease in type II diabetes is less well established. In addition, a recent meta-analysis of clinical trials examining the effects of intensive glucose control in type II diabetics did not reduce the risk for cardiovascular or all-cause mortality, but increased risk for severe hypoglycemia [7].

In diabetic hemodialysis patients, the importance of tight glycemic control may even be more controversial. Data from small observational studies mainly from Japan suggested that poor glycemic control reflected by high HbA1c levels predicted poorer outcomes [8–11]. No such relationship was found in a large cohort of US diabetic hemodialysis patients with 12 months of follow-up [12], although another study in a large US dialysis patients did show unfavorable outcomes with increasing HbA1c levels after adjustment for multiple confounding factors [13]. Nevertheless, for the past two decades, the main focus of glycemic control has been the lowering of HbA1c levels without much attention to detrimental effects of low HbA1c levels other than the increased risk of hypoglycemia. Recently, several clinical trials demonstrated that intensive treatment of blood glucose has no significant effect on cardiovascular disease outcomes and may even paradoxically increase cardiovascular and all-cause mortality in patients with either normal renal function or mild kidney disease, especially in older patients with long-standing type 2 diabetes and pre-existing cardiovascular disease [14, 15].

In ESRD, diabetes management research has focused on the relationship between poor glycemic control and clinical outcomes as well. Recent observational studies in large cohorts of dialysis patients indicate that 30–50 % of patients have an HbA1c level below the upper threshold of normal HbA1c [12, 13].

Indeed in up to one-third of diabetic dialysis patients with a presumptive diagnosis of diabetic nephropathy, glycemic control improves spontaneously with the progression of CKD, loss of residual renal function, and the initiation of dialysis therapy, leading to normal-to-low hemoglobin HbA1c (<6 %) and glucose levels, requiring cessation of insulin or other anti-diabetic medications [16]. Causes and consequences of this so-called burnt-out diabetes are not clearly included [16–18]. Potential contributors to burnt-out diabetes include a decline in renal gluco-neogenesis, decreased renal and hepatic insulin clearance, diminished food intake, deficient catecholamine release, protein-energy wasting, and the hypoglycemic effects of dialysis treatment. Although the concept of “burnt-out diabetes” appears in sharp contradistinction to the natural history of diabetes mellitus, studying this condition and its potential causes and consequences may lead to a better understanding of the pathophysiology of metabolic syndrome and diabetes mellitus in the CKD population and in many other individuals with chronic disease states associated with wasting syndrome that can confound the natural history of diabetes. We therefore sought to investigate and compare the likelihood of having either low or high HbA1c level and to examine the relationship between low (<6 %) HbA1c levels on mortality in diabetic MHD patients in a well-studied cohort of hemodialysis patients.

Methods

Patient population

We studied MHD patients who were participating in the *Nutritional and Inflammatory Evaluation in Dialysis* (NIED) Study [19]. The original patient cohort was derived from a pool of over 3,000 MHD outpatients over 5 years in eight DaVita chronic dialysis facilities in the South Bay Los Angeles area [see NIED Study website at www.NIEDStudy.org for more details]. Inclusion criteria were outpatients who had been undergoing MHD for at least 8 weeks, were 18 years or older, and who signed the institutional review board approved consent form. October 1, 2001, through December 31, 2006, 892 MHD patients from eight DaVita dialysis facilities in the Los Angeles South Bay area signed the informed consent form and underwent the periodic evaluations of the NIED Study. For this study, data including baseline HbA1c levels were available in 347 MHD patients. The definition of diabetic patients in this study is the ones who developed kidney failure and required dialysis based on documented diagnosis of "diabetic nephropathy." A modified version of the Charlson comorbidity index, that is, without the age and kidney disease components, was used to assess the severity of comorbidities [20].

Anthropometric measures

Body weight assessment and anthropometric measurements were performed while patients were undergoing a hemodialysis treatment or within 5–20 min after termination of the treatment. Biceps skinfold (BSF) and triceps skinfold (TSF) thicknesses were measured with a conventional skinfold calliper using standard techniques as previously described [21]. To estimate the percentage of body fat and fat-free body mass, near infra-red (NIR) interactance was measured at the same time as the anthropometric measurements [22].

Laboratory tests

Pre-dialysis blood samples and post-dialysis serum urea nitrogen were obtained on a mid-week day, which coincided chronologically with the drawing of quarterly blood tests in the DaVita facilities. The single pool Kt/V was used to represent the weekly dialysis dose. All routine laboratory measurements were taken by DaVita® Laboratories (Deland, FL, USA) using automated methods. All laboratory values, including HbA1c and serum glucose, were measured by automated and standardized methods.

Serum high sensitivity C-reactive protein (CRP) was measured by a turbidometric immunoassay in which a serum sample is mixed with latex beads coated with anti-human CRP antibodies forming an insoluble aggregate (manufacturer, WPCI, Osaka, Japan; unit, mg/L; normal range, <3.0 mg/1). Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) were measured with immunoassay kits based on a solid-phase sandwich ELISA using recombinant human IL-6 and TNF-α (manufacturer, R&D Systems, Minneapolis, MN; units, pg/ml; normal range, IL-6: <9.9 pg/ml, TNF-α: <4.7 pg/ml) [23]. CRP and the cytokines were measured in the General Clinical Research Centre Laboratories of Harbor-UCLA Medical Centre. Serum transthyretin (prealbumin) was measured using immunoprecipitin analysis [24]. Plasma total homocysteine concentrations were determined

by high-performance liquid chromatography in the Harbor-UCLA Clinical Laboratories [25].

Statistical methods

Case-mix and comorbidity covariates include age, gender, race/ethnicity (Hispanics, Blacks, Asians and others), dialysis vintage (number of months on MHD treatment), insurance (medicare), marital status, modified Charlson comorbidity index, dialysis dose (Kt/ V), and kidney residual urine. The malnutrition-inflammation complex syndrome (MICS) variables include triglyceride, albumin, prealbumin, creatinine, ferritin, TIBC, iron saturation ratio, iron, calcium, phosphorus, bicarbonate, total homocysteine, CRP, IL-6, TNF-α, hemoglobin, white blood cell count, lymphocyte percentage, malnutrition-inflammation score, BMI, triceps and biceps skin fold, mid-arm muscle circumference, near infrared measured body fat, nPCR, erythropoietin dose, and vitamin D dose. Fiducial limits are given as mean ± SD (standard deviation) or median and inter-quartile range; odds ratios include 95 % confidence interval (CI) levels. A p value <0.05 or a 95 % CI that did not span 1.0 was considered to be statistically significant. Descriptive and multivariate statistics were carried out with the statistical software “Stata version 9.0” (Stata Corporation, College Station, Texas).

ANOVA was employed to examine the differences between the three groups of patients with HbA1c <6 %, ≥6-<7 %, and ≥7 %. Unadjusted and multivariate-adjusted correlation coefficients of HbA1c were explored to examine the crude and adjusted linear correlations between HbA1c and relevant variable. CRP, IL-6, and TNF-α were log-transformed because of their severe skewness. Multivariate logistic regression analyses were utilized to examine the strength of association between different HbA1c levels (i.e., “low (6 %) vs. target (6-<7 %)” or “high (≥7 %) vs. target (6-<7 %)”) and case-mix and other variables of nutrition and inflammation. Multivariable-adjusted log hazards ratios (95 % confidence intervals) of all-cause mortality associated with three different ranges of HbA1c.

Results

Out of 892 MHD patients of the NIED Study cohort, 475 non-diabetic and 385 diabetic MHD patients were identified, whereas in 22 patients, the diabetic status was not clear. Diabetic and non-diabetic patients had similar demographics (see Table S-1 in the on-line Appendix). Among 385 diabetic MHD patients, a total of 347 diabetic MHD patients had HbA1c data, who were included for analyses in this study. The average (mean ± SD) baseline HbA1c and glucose in the diabetic patients were 6.8 ± 1.5 % and 172 ± 65 mg/ dl, respectively. The distribution of HbA1c was normal as it shown in Fig. 1. Almost one-third of patients had HbA1c <6 %.

Table 1 shows demographic, clinical, and laboratory values according to the 3 classified groups of HbA1c, <6 % (n =111), ≥6 and <7 (n = 93), or ≥7% (n = 143), in 347 diabetic MHD patients with HbA1c data. The group with HbA1c ≥6 and <7 had a higher proportion of older patients and higher WBC counts. Body mass index and mid-arm muscle circumference were higher in the group with the highest HbA1c (≥7 %).

Figure 2a–f illustrates the associations between HbA1c and triceps skinfold thickness, erythropoietin dose, glucose, triglyceride, albumin, and WBC count. Table 2 shows the correlation coefficients of relevant clinical, nutritional, and inflammatory measures with serum HbA1c levels in 347 diabetic MHD patients. HbA1c showed a weak positive correlation with triceps skinfold thickness, triglyceride level, ferritin, and WBC and moderate correlations with glucose ($r = 0.48$) after controlling for case-mix and MICS variables. However, HbA1c was negatively correlated with age, erythropoietin dose, and serum albumin level.

Table 3 demonstrates the unadjusted and multivariate-adjusted odds ratios (OR) of having low HbA1c levels (<6 %) among the study population. On multiple logistic regression analyses, Hispanic (OR = 2.87; 95 % CI 1.05–7.85, $p < 0.05$), each centimeter higher mid-arm muscle circumference (OR = 1.14; 95 % CI 1.01–1.29, $p < 0.05$), each 10 mg/dl higher TIBC level (OR =1.03; 95 % CI 1.01–1.05, $p<0.01$), and each 10% higher iron saturation ratio (OR = 1.14; 95 % CI 1.03–1.26, $p < 0.05$) were more likely associated with patients with low HbA1c level (<6 %) compared to those with target HbA1c level (6-<7 %) even after adjustment for case-mix and MICS. Table 3 also shows that HD vintage shorter than 6 months (OR = 0.25; 95 % CI 0.07–0.87, $p < 0.01$), HD vintage between 2 and 5 years (OR = 0.23; 95 % CI 0.07–0.81, $p < 0.01$), each millimetre higher biceps skinfold thickness (OR = 0.91; 95 % CI 0.83–0.99, $p < 0.01$), higher levels of serum iron (OR = 0.94; 95 % CI 0.90–0.99, $p < 0.01$), and higher WBC count (OR = 0.71; 95 % CI 0.57–0.89, $p < 0.01$) were less likely associated with patients having low HbA1c level compared to those having target HbA1c level even after adjustment for case-mix and MICS.

We also examined the correlates of high HbA1c level (≥7 %) among the study population (see Table S2. in the Appendix). Table 4 shows that patients with HbA1c <6 % had a 4.7 times higher death risk (HR = 4.67; CI 1.68–12.69; $p = 0.003$) with each 0.5 % lower HbA1c level. In addition, we found similar trends in patients with HbA1c <6 % and treated with insulin or oral anti-diabetic agents (Table 5). Table 4 also demonstrates that patients with HbA1c ≥7 % had a 13 % mortality increase (HR = 1.13; CI 1.01–1.26; $p = 0.028$) with each 0.5 % increase in HbA1c after case-mix adjustment. However, the findings were attenuated after controlling for both case-mix and MICS variables (HR = 1.18; CI 0.99–1.41; $p = 0.068$). Cubic spline graphs verified these associations (data not shown).

Discussion

We found that among 347 diabetic MHD patients, whose ESRD etiology was diabetic nephropathy, 32 % had HbA1c <6 %. Among these patients with so-called burnt-out diabetes, a strong association between lower HbA1c and higher risk of mortality was observed, in that each 0.5 % decrease in HbA1c level below 6 % was associated with 4.7 times higher death risk after multivariate adjustments.

Many individuals with diabetic nephropathy, the leading cause of CKD in the United States, progress to ESRD and undergo maintenance dialysis treatment [16–18]. As in our current study, recent data indicate that in up to one-third of diabetic dialysis patients with a presumptive diagnosis of diabetic nephropathy, glycemic control improves spontaneously

with the progression of CKD, loss of residual renal function, and the initiation of dialysis therapy, leading to seeming normal-to-low HbA1c (<6 %), requiring cessation of insulin or other anti-diabetic medications [16].

The most notable finding in our study is that patients with HbA1c <6 % were associated with higher death risk. In our study, 32 % of diabetic MHD patients had HbA1c levels <6 % comparable to two previous studies on large national dialysis organizations database [12, 13]. In Japan, Hayashino et al. [10] reported that almost 60 % of patients had HbA1c values <6.1 % and no correlation between mortality and a low HbA1c level of less than 7.2 % was found. William et al. [12] reported that about 40 % of all study patients had an HbA1c level <6 %, and 37 % of these patients were on neither insulin nor oral hypoglycemic agents. In our recent study in patients on maintenance peritoneal and hemodialysis dialysis, we found similar results in that very high and low HbA1c levels were associated with increased mortality [26, 27]. In William study, no significant correlation between HbA1c and survival at 12 month was found even in groups with HbA1c level <6 % [12]. In contrast, another similar study showed a trend toward higher cardiovascular and all-cause mortality in 23,618 US MHD diabetic patients when HbA1c level was less than 6 % [13]. It is not clear why there is increased mortality in the low HbA1c group. In patients with normal to mild kidney disease with diabetes, the “Action to Control Cardiovascular Risk in Diabetes (ACCORD)” trial showed the increase in the rate of death from any cause in the intensive therapy group targeting HbA1c level below 6 % [14]. Hence, overzealous glycemic control in diabetic MHD patients should be avoided.

There is at least one explanation of the association between low HbA1c level and higher risk of death. Hypoglycemia may be playing a role in our findings. Patients with HbA1c <6 % had almost 5 times higher death risk with each 0.5 % lower HbA1c level. In Table 5, we showed similar trends in patients with HbA1c <6 % and treated with insulin or oral antidiabetic agents. This result supported the hypothesis that hypoglycemic events could contribute the elevated mortality risk in these patients.

Hispanic race, higher mid-arm muscle circumstance, high TIBC level, and high iron saturation ratio were associated with higher likelihood of low HbA1c level (< 6 %) compared to those with target HbA1c (6-<7 %). Compared to normal and high HbA1c groups, no significant difference in demographics, nutritional status, body composition, or biochemical measurements was noted in patients with HbA1c <6 % except lower glucose, triglyceride level, and WBC count. Plasma triglyceride level has been used as a surrogate marker for the degree of insulin resistance, and more insulin resistant an individual, the higher the plasma triglyceride concentration. In this group, plasma triglyceride level was significantly lower than two groups; thus, the degree of insulin resistance may not explain the difference seen in overall glycemic control.

Our study also showed that in patients with HbA1c ≥7 %, there was a 13 % mortality increase (HR = 1.13, $p = 0.028$) for each 0.5 % increase in HbA1c level after case-mix adjustment, even though this association was somewhat attenuated after controlling for both case-mix and MICS variables. William et al. [12] found no relationship between HbA1c

level and survival at 12 months in 24, 875 diabetic MHD patients, but in our recent study we found similar results examining more than 50,000 MHD patients [27].

A potential limitation of our study is a selection bias during enrollment. However, since the mortality in the original NIED Study cohort was less than the base population [19], it might be argued that a selection bias with such a direction would lead to a bias toward the null hypothesis, so that without this bias, our positive results might have been even stronger. A potential limitation of our study is that HbA1c is not a good reflection of blood glucose levels in individuals with advanced chronic kidney disease. It may be difficult to accurately assess glycemic control in this population due to changes in red blood cell survival in renal failure and the effects of erythropoiesis-stimulating agents (ESA) on A1c levels [28]. We were not able to be taken into account the difference between a low HbA1c due to good diabetic control in a patient who is eating well and one due to lowering of serum glucose to the point where insulin and oral glucose-lowering medications. Another potential limitation is the possibility that our statistical analyses could have been overadjusted by introducing and controlling for too many confounders, given the relative small size of the patient cohort. However, rigorous adjustment was necessary to address the effect of HbA1c on mortality without significant influence of confounders. In addition, we did not include the information about treatment for diabetes and related medications. Moreover, some of our analysis did not reach the level of statistical significance, because of lack of statistical power due to small cohort. However, these results can be used to plan other confirmatory studies. Increased mortality in patients with HbA1c <6 % might be related to treatment intensity [29].

The strengths of our study include the well-characterized cohort, the comprehensive clinical and laboratory evaluations including body composition measures, detailed evaluation of comorbid states by study physicians at baseline, and the measurements of pro-inflammatory cytokines and markers. In addition, the subjects were selected without having any prior knowledge of their inflammatory status.

In summary, we found that in diabetic MHD patients with HbA1c <6 %, comprising almost one-third of all diabetic MHD patients, lower HbA1c levels were associated with significantly higher death risk. Clinical trials are needed to better define the target HbA1c levels in different subgroups of diabetic MHD patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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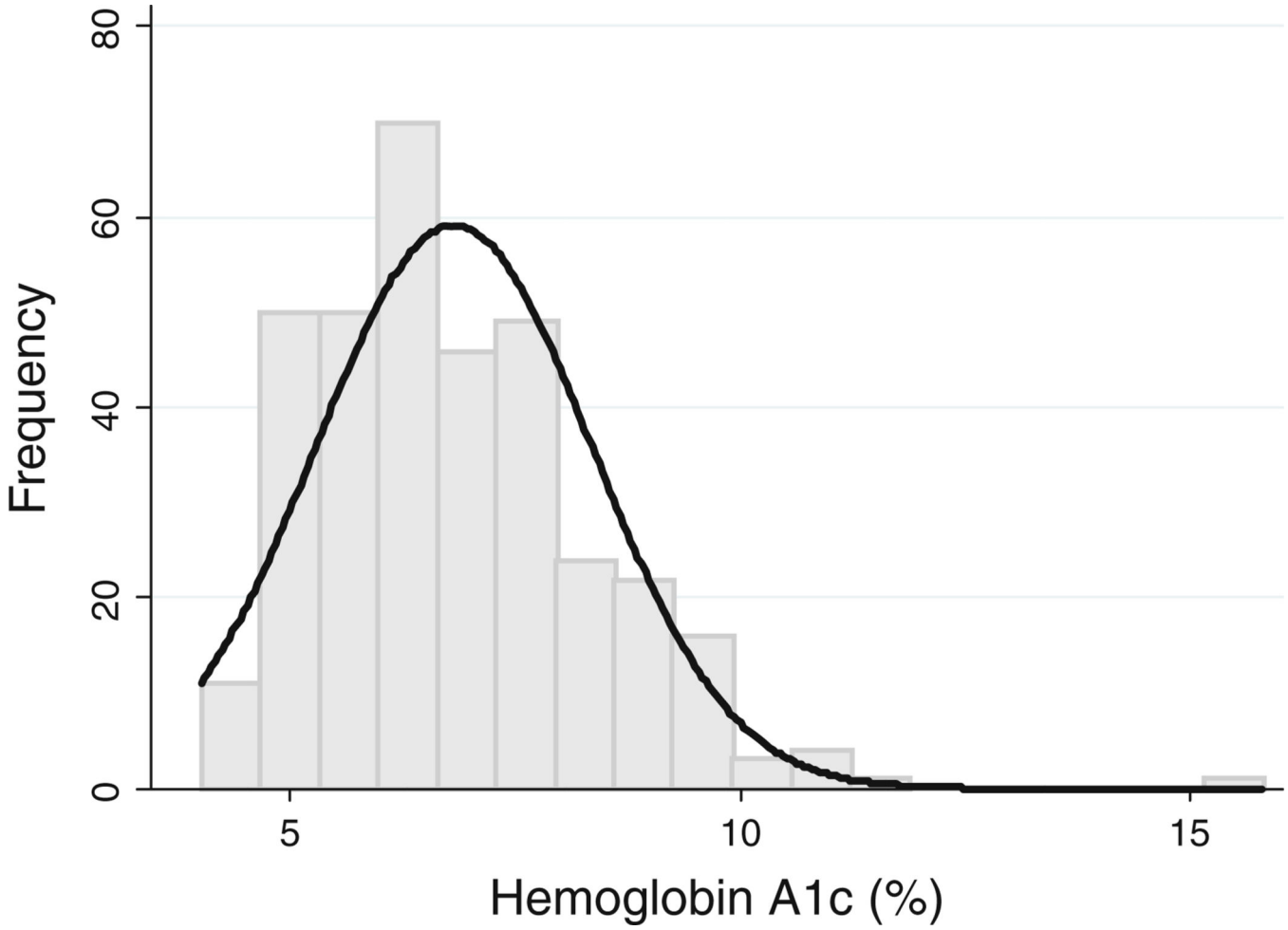

Fig. 1.

Histogram of hemoglobin A1c (hemoglobin A1c *N* = 347; hemoglobin A1c mean ± SD = 6.81 ± 1.53)

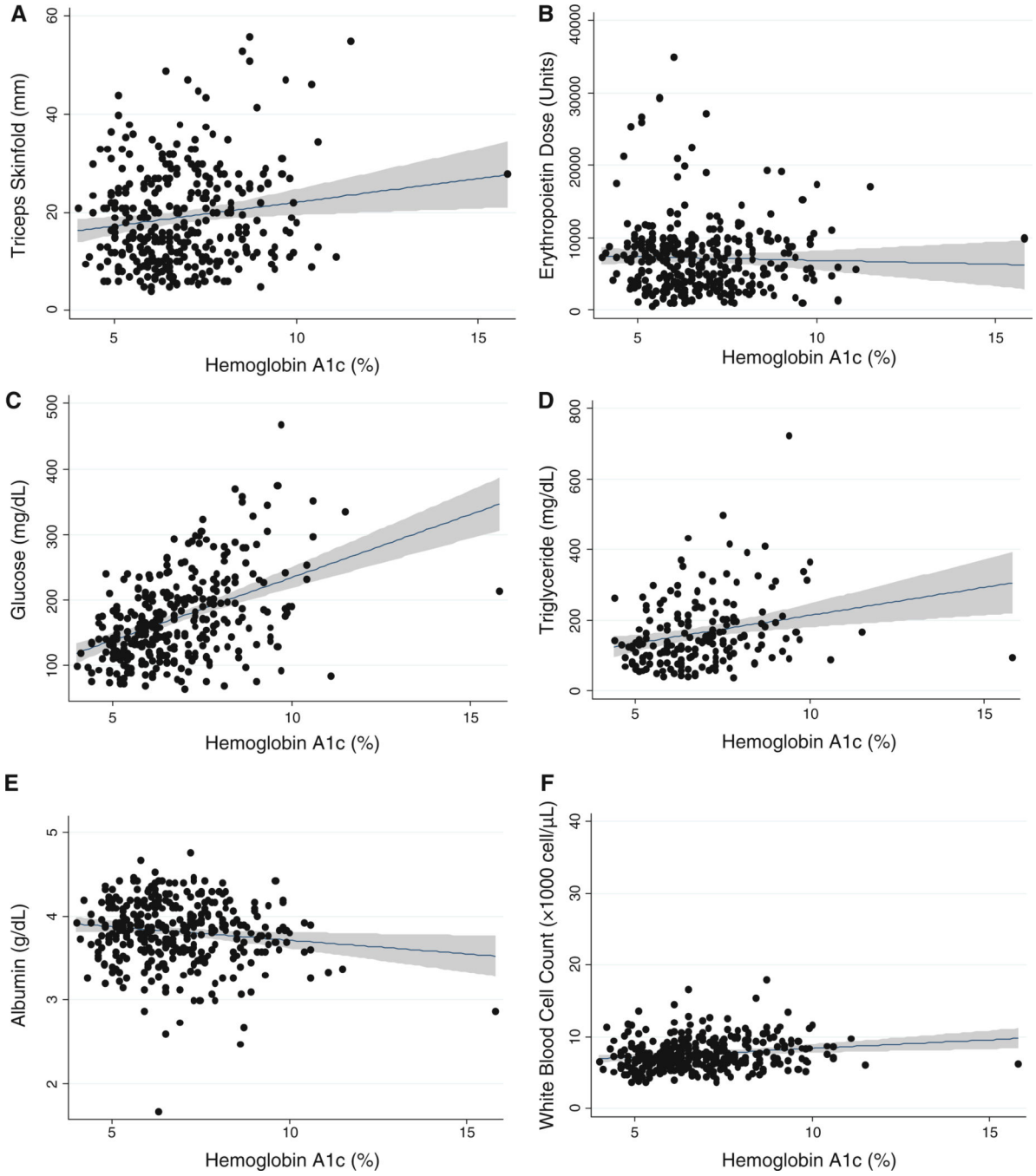

Fig. 2.

Correlation between HbA1c and triceps skinfold (**a**), erythropoietin dose (**b**), serum glucose (**c**), trygliceride (**d**), albumin (**e**), and white blood cell count (**f**)

Table 1

Baseline demographic, clinical, and laboratory variables in patients with different hemoglobin Ale levels in 347 diabetic MHD patients with A1C data

Mean ± SD	**<6 (*n* = 111)**	**≥6–<7 (*n* = 93)**	**≥7 (*n* = 143)**	***p* value**
Demographics				
Age (years)	59 ± 12	61 ± 10	57 ± 11	**0.01**
Women (%)	50	45	51	0.65
Race: % African American	33	25	24	0.23
Ethnicity: % Hispanic	55	51	58	0.53
Marital status: % married	38	51	53	0.07
Primary insurance: % medicare	51	57	52	0.74
Charlson comorbidity score	2.7 ± 1.5	2.8 ± 1.4	2.9 ± 1.3	0.58
Nutritional status and body composition				
Malnutrition-inflammation score	5.5 ± 3.6	5.7 ± 4.3	5.4 ± 3.9	0.90
Body mass index (kg/m^2)	26.7 ± 5.5	26.5 ± 5.2	28.3 ± 7.0	0.07
Triceps skinfold (mm)	18.2 ± 8.9	17.2 ± 9.2	20.8 ± 11.3	**0.03**
Biceps skinfold (mm)	9.5 ± 7.7	10.8 ± 9.3	12.1 ± 9.1	0.08
Mid-arm muscle circumference (cm)	31.6 ± 6.2	30.9 ± 6.1	32.8 ± 6.7	**0.05**
Near infrared measured body fat (%)	28.1 ± 10.3	28.5 ± 9.7	30.5 ± 10.3	0.13
nPNA or nPCR (g kg^{-1} day^{-1})	1.06 ± 0.26	1.08 ± 0.24	1.08 ± 0.25	0.82
Hemodialysis treatment measures				
Dialysis vintage <6 months (%)	22	32	27	0.25
Dialysis vintage (months)	27 ±29	24 ±25	22 ±20	0.19
Dialysis dose (Kt/V single pool)	1.57 ± 0.31	1.61 ± 0.30	1.60 ± 0.33	0.51
Erythropoietin dose (average units/week)	7829 ± 5427	6995 ± 5818	6824 ± 4007	0.26
Treatment for diabetes mellitus				
Insulin (%)	33	52	69	<0.001
Oral anti-diabetic medications (%)	22	24	17	0.48
Biochemical measurements				
Glucose (mg/dl)	139 ±41	162 ± 51	203 ± 74	**<0.001**
Triglyceride(mg/dl)	135 ± 64	159 ± 97	188 ± 113	**0.008**
Albumin (g/dl)	3.8 ± 0.4	3.8 ± 0.4	3.8 ± 0.4	0.59
Transthyretin (prealbumin) (mg/dl)	25.6 ± 9.1	27.7 ± 9.1	25.5 ± 8.4	0.14
Creatinine (mg/dl)	9.3 ± 2.9	8.8 ± 2.8	8.8 ± 2.8	0.24
Ferritin (ng/ml)	572 ± 522	597 ± 446	606 ± 425	0.83
TIBC (mg/dl)	209 ± 43	206 ± 40	209 ± 37	0.78
Iron saturation ratio (%)	32 ± 10	31 ±9	31 ± 10	0.68
Iron (mg/dl)	66 ±23	66 ±24	64 ±22	0.72
Calcium (mg/dl)	9.3 ± 0.6	9.3 ± 0.6	9.2 ± 0.7	0.38
Phosphorus (mg/dl)	5.6 ± 1.3	5.5 ± 1.5	5.7 ± 1.4	0.64
Bicarbonate (mg/dl)	22.4 ± 2.9	22.2 ± 2.8	22.5 ± 2.8	0.62

Mean ± SD	**<6 (*n* = 111)**	**≥6–<7 (*n* = 93)**	**≥7 (*n* = 143)**	***p* value**
Intact PTH (pg/ml)	256 ± 268	250 ± 245	230 ± 163	0.64
Total homocysteine (umol/1)	23.4 ± 11.9	23.8 ± 8.6	22.2 ± 10.6	0.47
C-reactive protein (mg/1)	5.9 ± 5.9	5.5 ± 4.8	6.9 ± 7.4	0.22
IL-6 (pg/ml)	15.4 ± 16.3	18.5 ± 48.0	21.0 ± 51.6	0.59
TNF-α (pg/ml)	8.7 ± 8.5	8.9 ± 10.7	7.9 ± 8.4	0.70
Hemoglobin (g/dl)	12.1 ± 1.0	12.2 ± 1.0	12.0 ± 0.9	0.21
WBC (×1,000 cell/μl)	7.0 ± 1.8	8.0 ± 2.2	7.9 ± 2.2	<0.001
Lymphocyte (% of total WBC)	21.3 ±7.3	20.5 ± 6.8	21.8 ± 8.1	0.42
Death counts (total: 119/347)	34 (31 %)	39 (41 %)	46 (32 %)	0.21

All values are presented as Mean ± SD or percentages

Bold values are statistically significant ($p < 0.05$)

Kt/V dialysis dose, *TIBC* total iron binding capacity, *nPCR* normalized protein catabolic rate, *IL-6* Interleukin 6, *TNF-α* tumor necrosis factor-α

p values are based on *ANOVA* or χ^2 test where indicated

Table 2

Unadjusted and multivariate-adjusted correlation coefficients of HbA1c and selected variables in 347 diabetic MHD hemodialysis patients

Variables	Unadjusted	Case-mix[a] adjusted	Case-mix + MICS (full model)[b] adjusted
Demographics			
Age	−0.11*	−0.15Δ	−0.11Δ
Charlson comorbidity score	0.06	0.09	0.03
Dialysis vintage	−0.09	−0.10	−0.12
Nutritional status and body composition			
Malnutrition-inflammation score	0.01	0.02	−0.03
Body mass index	0.11Δ	0.09	−0.08
Triceps skinfold	0.15**	0.18**	0.15*
Biceps skinfold	0.09Δ	0.12*	−0.01
Mid-arm muscle circumference	0.07	0.08	−0.07
Near infrared measured body fat	0.07	0.11Δ	0.12
Hemodialysis treatment measures			
Dialysis dose	0.00	−0.02	0.00
nPCR	0.01	−0.03	0.03
Erythropoietin dose	−0.03	−0.05	−0.10Δ
Vitamin D dose	−0.04	−0.02	−0.01
Biochemical measurements			
Glucose	0.45**	0.46***	0.48***
Triglyceride	0.24**	0.21**	0.18*
Albumin	−0.13*	−0.12Δ	−0.12*
Transthyretin (prealbumin)	−0.04	−0.03	0.02
Creatinine	−0.10Δ	−0.06	−0.02
Ferritin	0.05	0.07	0.10Δ
TIBC	0.02	−0.03	0.04
Iron saturation ratio	−0.05	−0.05	0.03
Iron	−0.05	−0.07	−0.05
Calcium	−0.10Δ	−0.06	−0.02
Phosphorus	0.02	0.01	0.00
Bicarbonate	0.03	0.06	0.03
Total homocysteine	−0.09	−0.06	−0.04
C-reactive protein	0.10Δ	0.09	0.04
Log C-reactive protein	0.07	0.06	0.00
IL-6	0.04	0.02	−0.01
Log IL-6	−0.03	−0.02	−0.01
TNF-α	−0.06	−0.09	−0.06

Variables	Unadjusted	Case-mix[a] adjusted	Case-mix + MICS (full model)[b] adjusted
Log TNF-α	−0.04	−0.07	−0.06
Hemoglobin (g/dl)	−0.03	−0.05	−0.01
White blood cell count (x 1,000 cell/μl)	0.17**	0.15**	0.12*
Lymphocyte (% of total WBC)	0.04	0.04	0.07

nPCR normalized protein catabolic rate, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor-α

[a] Case-mix variables include age, gender, race/ethnicity, diabetes, dialysis vintage, primary insurance (medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V single pool), and kidney residual urine (KRU)

[b] Full model consists of case-mix variables and MICS

Δ $0.05 \le p < 0.20$;

* $0.01 \le p < 0.05$;

** $0.001 \le p < 0.01$;

*** $p < 0.001$

Table 3

Odds ratios (95 % CIs) of having a low (<6 %) versus target (6-<7 %) hemoglobin A1c (as reference) level in 204 diabetic MHD patients

Variables	Unadjusted	Case-mix[a] adjusted	Case-mix + MICS[b] adjusted
Demographics			
Age (each 10 year increase)	0.98 (0.95–1.00)	1.00 (0.95–1.04)	0.97 (0.94–1.01)
Women (vs. men)	1.24 (0.71–2.18)	1.65 (0.60–4.53)	3.69 (0.92–12.30)
Race/ethnicity			
African American versus others	1.52 (0.82–2.81)	3.88 (0.86–17.5)	2.17 (0.66–7.10)
Hispanic versus others	1.19 (0.69–2.01)	4.08 (1.04–16.04)*	2.87 (1.05–7.85)*
Primary insurance			
Medicare versus others	0.78 (0.40–1.54)	1.46 (0.58–3.68)	0.89 (0.35–2.25)
Charlson comorbidity score (each 1 unit ↑)	0.98 (0.81–1.19)	0.91 (0.65–1.26)	0.81 (0.62–1.07)
Dialysis vintage (vs. 6 ≤ vintage < 12 months)			
Vintage < 6 months	0.39 (0.16–0.99)*	0.43 (0.06–2.83)	0.25 (0.07–0.87)*
12 months ≤ vintage < 2 years	0.86 (0.33–2.22)	0.86 (0.17–1.40)	0.90 (0.26–3.09)
2 years ≤ vintage < 5 years	0.48 (0.18–1.23)	0.29 (0.06–1.36)	0.23 (0.07–0.81)*
5 years ≤ vintage	0.85 (0.27–2.67)	0.22 (0.04–1.30)	0.55 (0.12–2.54)
Nutritional status and body composition			
Malnutrition-inflammation score (each 5 ↑)	0.99 (0.92–1.07)	1.01 (0.93–1.09)	1.09 (0.95–1.24)
Body mass index (each 1 kg/m^2 increase)	1.01 (0.95–1.06)	1.01 (0.95–1.08)	1.04 (0.89–1.21)
Triceps skinfold (each 1 mm ↑)	1.01 (0.98–1.05)	1.01 (0.97–1.05)	1.03 (0.96–1.11)
Biceps skinfold (each 1 mm ↑)	0.98 (0.95–1.02)	0.97 (0.93–1.00)	0.91 (0.83–0.99)**
Mid-arm muscle circumference (each 1 cm ↑)	1.02 (0.98–1.07)	1.02 (0.97–1.08)	1.14 (1.01–1.29)*
Near infrared measured body fat (each 1% ↑)	1.00 (0.97–1.03)	0.99 (0.95–1.04)	0.92 (0.84–1.01)
Hemodialysis treatment measures			
Dialysis dose (each 1 unit Kt/V sp increase)	0.77 (0.31–1.89)	0.61 (0.21–1.83)	1.07 (0.23–5.06)
nPNA or nPCR (each 0.1 g kg^{-1} day^{-1} incr.)	0.73 (0.23–2.30)	0.79 (0.23–2.77)	1.43 (0.21–9.55)
Erythropoietin dose (each 1,000 μ/wk up)	1.02 (0.97–1.08)	1.02 (0.96–1.08)	1.00 (0.99–1.00)
Vitamin D dose (each 10 unit increase)	1.01 (1.00–1.02)	1.01 (1.00–1.02)	1.01 (0.99–1.01)
Biochemical measurements			
Glucose	0.99 (0.98–0.10)**	0.99 (0.98–1.00)*	See note[c]
Triglyceride (each 10 mg/dl)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	0.99 (0.99–1.00)
Albumin (each 1 g/dl)	1.29 (0.62–2.67)	1.29 (0.55–3.03)	1.64 (0.42–6.37)
Transthyretin (prealbumin) (each 10 mg/dl)	0.98 (0.95–1.01)	0.98 (0.95–1.02)	0.98 (0.93–1.03)
Creatinine (each 1 mg/dl)	1.06 (0.96–1.17)	1.07 (0.95–1.21)	1.07 (0.90–1.27)
Ferritin (each 100 ng/ml)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)
TIBC (each 10 mg/dl)	1.00 (0.99–1.00)	1.00 (1.00–1.01)	1.03 (1.01–1.05)**
Iron saturation ratio (each 10 %)	1.01 (0.98–1.04)	1.00 (0.97–1.03)	1.14 (1.03–1.26)*
Iron (each 10 mg/dl)	1.00 (0.99–1.01)	1.00 (0.98–1.01)	0.94 (0.90–0.99)*

Variables	Unadjusted	Case-mix[a] adjusted	Case-mix + MICS[b] adjusted
Calcium (each 1 mg/dl)	0.88 (0.56–1.38)	0.83 (0.49–1.40)	0.53 (0.25–1.09)
Phosphorus (each 1 mg/dl)	1.06 (0.87–1.30)	1.05 (0.84–1.31)	1.15 (0.86–1.54)
Bicarbonate (each 1 mg/dl)	1.07 (0.96–1.18)	1.05 (0.93–1.17)	1.11 (0.94–1.30)
Total homocysteine (each 1 μmol/1)	1.01 (0.98–1.03)	1.00 (0.97–1.03)	1.00 (0.96–1.04)
C-reactive protein (each 1 mg/1)	1.01 (0.96–1.07)	1.01 (0.95–1.07)	1.02 (0.95–1.10)
Log C-reactive protein (each 1 unit)	1.04 (0.79–1.36)	1.00 (0.74–1.34)	1.12 (0.75–1.67)
IL-6 (each 10 pg/ml)	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Log IL-6 (each 1 unit)	1.07 (0.77–1.49)	1.08 (0.76–1.55)	1.26 (0.76–2.09)
TNF-α (each 10 pg/ml)	1.00 (0.97–1.03)	1.00 (0.97–1.04)	1.00 (0.96–1.05)
Log TNF-α (each 1 unit)	1.13 (0.80–1.61)	1.18 (0.81–1.72)	1.12 (0.70–1.78)
Hemoglobin (g/dl)	0.87 (0.65–1.16)	0.87 (0.63–1.19)	0.71 (0.46–1.10)
WBC (xl,000cell/μl)	0.78 (0.67–0.97)**	0.76 (0.65–0.89)**	0.71 (0.57–0.89)**
Lymphocyte (% of total WBC)	1.02 (0.98–1.06)	1.01 (0.96–1.05)	0.99 (0.93–1.05)

[a]Variables include age, gender, race/ethnicity, dialysis vintage, insurance (medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V), and kidney residual urine (KRU)

[b]Variables include triglyceride, albumin, prealbumin, creatinine, ferritin, TIBC, iron saturation ration, iron, calcium, phosphorus, bicarbonate, total homocysteine, CRP, IL-6, TNF-α, hemoglobin, white blood cell count, lymphocyte percentage, malnutrition-inflammation score, BMI, triceps and biceps skin fold, mid-arm muscle circumference, near infrared measured body fat, nPCR, erythropoietin dose, and vitamin D dose

[c]Glucose was dropped from covariates due to collinearity

*$0.01 \leq p < 0.05$;

**$0.001 \leq p < 0.01$;

***$p < 0.001$

Table 4

Death hazard ratios for the three different ranges of hemoglobin A1c in 347 diabetic MHD patients

	Unadjusted		Case-mix[a] adjusted		Case-mix + MICS[b] adjusted	
	HR (95 % CI)	***P***	**HR (95 % CI)**	***p***	**HR (95 % CI)**	***p***
When Hb A1c <6 %, each 0.5 *decrease* in Hb A1c	1.21 (0.86–1.69)	0.281	1.41 (0.96–2.08)	0.079	**4.67 (1.68–12.96)**	**0.003**
When HbAl between 6 and 7 %, each 0.5 *increase* in Hb A1c	0.80 (0.44–1.46)	0.470	0.75 (0.38–1.49)	0.410	0.78 (0.27–2.32)	0.662
When Hb A1c ≥7 %, each 0.5 *increase* in Hb A1c	1.10 (0.99–1.23)	0.087	**1.13 (1.01–1.26)**	**0.028**	1.18 (0.99–1.41)	0.068

Bold values are statistically significant ($p < 0.05$)

[a]Case-mix variables include age, gender, race/ethnicity, dialysis vintage, primary insurance (medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V single pool), and kidney residual urine (KRU)

[b]Full model consists of case-mix variables and MICS

Table 5

Death hazard ratios for the three different subgroups of 111 diabetic MHD patients with Hb A1c <6 %

Each 0.5 *decrease* in Hb A1c	**Unadjusted**		**Case-mix[a] adjusted**	
	HR (95 % CI)	***P***	**HR (95 % CI)**	***P***
Patients on insulin	1.09 (0.65–.82)	0.75	2.06 (0.96–1.41)	0.06
Patients on oral anti-diabetic agent	2.13 (0.94–4.82)	0.07	N/A[b]	N/A[b]
No treatment	1.05 (0.56–1.96)	0.87	1.55 (0.73–3.29)	0.26

[a] Case-mix variables include age, gender, race/ethnicity, dialysis vintage, primary insurance (medicare), marital status, modified Charlson comorbidity score, dialysis dose (Kt/V single pool), and kidney residual urine (KRU)

[b] There is no enough event to perform the analysis