Associations of Serum Insulin-Like Growth Factor 1 with New Cardiovascular Events and Subsequent Death in Hemodialysis Patients: The DREAM Cohort

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Aim: Patients with chronic kidney disease (CKD) have elevated risk of death from cardiovascular disease (CVD). A low serum insulin-like growth factor 1 (IGF-1) level is known to predict higher risk for all-cause mortality in incident dialysis patients, although it is unknown whether IGF-1 predicts cardiovascular outcomes.

Methods: This was a prospective cohort study of maintenance hemodialysis patients followed up for 5 years. Serum IGF-1 levels were measured at baseline, and patients were divided into IGF-1 tertiles. The key outcomes were all-cause mortality, a composite of new CVD, and death after new CVD events. Additional outcomes were hospitalization for infection and subsequent death. Association was analyzed using Cox proportional hazards models.

Results: In the 516 patients that were analyzed, we identified 106 all-cause deaths, 190 new CVD events, and 61 subsequent deaths. In addition, there were 169 hospitalizations for infection and 47 subsequent deaths. The risk of all-cause death was the highest in the lowest IGF-1 tertile, and this association remained significant in multivariable-adjusted models. Regarding CVD outcomes, IGF-1 was not associated with new CVD events but significantly associated with subsequent death in adjusted models. Similarly, IGF-1 was not an independent predictor of hospitalization for infection, but it predicted subsequent death.

Conclusions: A low IGF-1 level was not a significant predictor of new CVD events but an independent predictor of subsequent death in hemodialysis patients. Since similar associations with infection outcomes were observed, IGF-1 may be a biomarker of fragility or frailty in this population.

Introduction

The risk of cardiovascular death is 10–30 times higher in patients with kidney failure undergoing hemodialysis as compared with the general population1). Hemodialysis patients have a higher risk not only for the incidence of cardiovascular disease (CVD) but also for death after CVD events2). These two factors synergistically increase the risk of cardiovascular death3).

The elevated risk of CVD death in patients with chronic kidney disease (CKD), including those on hemodialysis, has been explained by the traditional and nontraditional risk factors4). Obesity is one of the

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Key words: Chronic kidney disease, Insulin-like growth factor 1, Dialysis, Cardiovascular disease, Frailty
Identifying the factors associated with post-event mortality risk would enhance our understanding of the mechanism for the extremely high mortality rate in this population.

**Aim**

This study was started to examine the associations between serum IGF-1 concentration and the two CVD outcomes in a cohort of hemodialysis patients.

**Methods**

**Study Design**

This is a single-center prospective cohort study of patients on maintenance hemodialysis. In this analysis, the key exposure was IGF-1 serum levels. The key outcomes were all-cause mortality, new CVD events, and death after new CVD events. In additional analyses, we examined the associations of serum IGF-1 with hospitalization for infection and death after hospitalization for infection.

**Study Participants**

The participants of this analysis were prevalent hemodialysis patients with serum IGF-1 measurement at baseline who were selected from the 518 total participants of the DREAM cohort, which was followed up from the end of 2004 to the end of 2009. The DREAM cohort study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies by the Ministry of Health, Labor and Welfare of Japan (the original 2003 version, which was modified in 2004 and 2006). The protocol was approved by the ethics committee of Inoue Hospital (approval no. 121). All participants gave written informed consent prior to enrollment. The DREAM cohort study was registered in the University hospital Medical Information Network Clinical Trial Registry (UMIN-CTR; ID, UMIN000006168).

**Serum IGF-1 Assay**

Blood was taken from blood access before the start of dialysis at the beginning of the week, and serum was separated and kept frozen at −80°C. IGF-1 was measured later using fresh frozen samples with an immunoradiometric assay at Special Reference Laboratory (Tokyo, Japan). The intra- and inter-assay coefficients of variation were <2.4% and <2.6%, respectively.
Outcomes

The preplanned key outcomes of this study were all-cause mortality, new CVD events, and death after CVD events. In this cohort, CVD events were defined as a composite of ischemic heart disease, stroke, peripheral arterial disease (PAD), congestive heart failure (CHF), valvular disease, and sudden death during the observation period. Death after a CVD event was defined as all-cause death after the new CVD event. The detailed definitions of CVD events were previously described\(^{10}\) and available in Supplemental Table 1.

To interpret the results regarding the two CVD outcomes, we performed additional analyses of the associations of IGF-1 with infection outcomes. As additional outcomes, we identified hospitalization for infection and subsequent death. We defined hospitalization for infection as hospitalization for which the main reason was infectious disease observed during the study period. Death after infection was defined as all-cause death after the hospitalization for infection.

We also recorded, if any, transition from hemodialysis to peritoneal dialysis or kidney transplantation and transfer to other institutions during the 5-year observation period.

Other Variables

We collected data on major demographic factors (age, sex, diabetic kidney disease or not, duration of hemodialysis treatment, and prior CVD), traditional risk factors (current smoking, hypertension, and dyslipidemia), nontraditional risk factors related to PEW and inflammation (body mass index [BMI], serum albumin, and C-reactive protein [CRP]), mineral bone disorder (MBD) of CKD (serum calcium, phosphate, intact parathyroid hormone [PTH], and use of vitamin D receptor activator [VDRA]), and renal anemia (hematocrit, dose of erythropoiesis-stimulating agent [ESA], and use of intravenous iron). These data were obtained from medical records. Free T4 and thyroid-stimulating hormone (TSH) were also measured because hypothyroidism is known to lower serum IGF-1 levels. Hypertension was defined as 140/90 mmHg or higher and/or antihypertensive medication use. Dyslipidemia was defined as non-high-density lipoprotein cholesterol (Non-HDL-C) ≥ 150 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) ≤ 40 mg/dL and/or statin use. These lipid levels were derived from the target levels for patients with CKD recommended by the clinical practice guideline of the Japanese Society of Atherosclerosis. Hypothyroidism was defined by 1) being treated with levothyroxine replacement (treated hypothyroidism) or 2) low free T4 (<0.8 ng/dL) with high TSH (>4.0 IU/L).\(^{25}\) No patients had central hypothyroidism (low free T4 with low TSH).

Statistical Methods

The patients of this analysis were divided into IGF-1 tertiles, and the baseline characteristics were compared across IGF-1 tertiles. Categorical variables were summarized as numbers (percentages) and compared using \(\chi^2\) test. Continuous variables were summarized as medians (interquartile ranges) and compared using the Kruskal–Wallis test. Factors associated with IGF-1 were evaluated using multivariable-adjusted linear regression analysis in which serum IGF-1 level was logarithmically transformed to fit the model.

We first examined the unadjusted association of IGF-1 tertile with all-cause mortality using the Kaplan–Meier analysis with log-rank test. Then, the association was evaluated using multivariable-adjusted Cox proportional hazards models. First, the hazard ratio was calculated using an unadjusted Cox model (model 1). Then, adjustment was done for the major demographic factors (model 2). In addition to the major demographic factors, further adjustment was done for the traditional risk factors (model 3), the variables related to PEW and inflammation (model 4), the parameters of CKD-MBD (model 5), those related with renal anemia (model 6), or the presence of hypothyroidism (model 7).

To explore the association between IGF-1 and cause-specific death, all-cause mortality was divided into cardiovascular death, non-cardiovascular death, and death from unknown cause depending on the record of the direct causes of death. Non-cardiovascular causes were further divided into infection and other than infection. Because of the small numbers of these divided outcomes, IGF-1 was handled as a continuous variable, hazard ratio was expressed per 1-SD higher IGF-1, and adjustment was done only for age and sex.

The association between IGF-1 and new CVD events was analyzed similarly to the analysis of all-cause mortality using the same statistical models for adjustment.

The association between IGF-1 and death after a new CVD event was analyzed using the Kaplan–Meier method and a multivariate-adjusted Cox proportional hazards model. For this purpose, time from the first new CVD event to all-cause death was analyzed in patients who had new CVD events. Because of the limited number of deaths after CVD events, IGF-1
was handled as a continuous variable, hazard ratio was expressed per 1-SD higher IGF-1, and adjustment was done for the five major demographic factors.

As additional analysis, we also investigated the associations of IGF-1 with hospitalization for infection and death after infection. Multivariable-adjusted Cox analysis was conducted using the same approach as described for the analysis of death after a new CVD event.

A two-sided $P$ value $< 0.05$ was considered statistically significant. All these analyses were performed using JMP version 14.2 (SAS Institute Japan Ltd., Tokyo, Japan).

**Results**

**Study Participants**

The patients for this analysis were selected from 518 total participants of the DREAM cohort. Because two participants were excluded because of missing data of IGF-1, the remaining 516 patients were analyzed (Fig. 1). Table 1 presents patient characteristics at baseline according to IGF-1 tertile. The patients with lower IGF-1 levels had higher age, lower BMI, lower albumin, lower phosphate levels, and higher prevalence of hypothyroidism, whereas there was no significant difference in CRP among the IGF-1 tertiles. Multivariable-adjusted linear regression analysis revealed that age, sex, the duration of dialysis, BMI, serum albumin, and the presence of hypothyroidism were independently associated with serum IGF-1 level (Supplemental Table 2).

**IGF-1 and All-Cause Mortality**

During the 5-year observation period, 106 (21%) participants died. Based on the direct cause of death, 38 patients died from cardiovascular causes (sudden death, N=14; heart failure, N=13; stroke, N=5; ischemic heart disease, N=3; arrhythmia, N=2; and ischemic colitis, N=1) and 48 patients died from non-cardiovascular causes (infection, N=24; malignancy, N=8; respiratory failure, N=3; hepatic cirrhosis, N=2; uremia, N=2; and others, N=9), whereas the direct cause of death was unknown for 20 patients. The Kaplan–Meier analysis showed that the risk of all-cause mortality was different among the IGF-1 tertiles (Fig. 2A). The association between IGF-1 and all-cause mortality was further analyzed using Cox proportional hazards models (Table 2). IGF-1 was found to be associated with all-cause mortality in various models adjusted for the major demographic factors and the factors related with PEW and inflammation, parameters of CKD-MBD, variables of renal anemia, or presence of hypothyroidism. Also, adjustment for the traditional risk factors (model 3) gave a marginally significant result.

**IGF-1 and Cause-Specific Death**

The Kaplan–Meier curves were significantly different by tertile of IGF-1 regarding cardiovascular and non-cardiovascular death, but not for death from unknown cause (Fig. 2B). The inverse associations of IGF-1 and cardiovascular and non-cardiovascular death remained significant in Cox models, in which IGF-1 was entered as a continuous variable and adjusted for age and sex. When non-cardiovascular causes were further divided into infection and other than infection, these outcomes were inversely associated with IGF-1 (Supplemental Table 3).

**IGF-1 and CVD Outcomes**

New CVD events were recorded in 190 patients (37%). The Kaplan–Meier analysis showed that IGF-1 tertile was significantly associated with new CVD events (Fig. 3A). However, this association was no longer significant when analyzed using Cox models adjusted for the major demographic factors (Table 3).

Of the 190 patients who experienced new CVD events, 61 patients died after such event. Based on the direct cause of death, 38 patients died from cardiovascular causes (sudden death, N=14; heart failure, N=13; stroke, N=5; ischemic heart disease, N=3; arrhythmia, N=2; and ischemic colitis, N=1) and 14 patients died from non-cardiovascular causes (infection, N=9; respiratory failure, N=2; and others, N=3), whereas the direct cause was unknown for the remaining 9 patients. The Kaplan–Meier analysis showed that a lower IGF-1 level was significantly associated with a higher risk of death after new CVD event (Fig. 4A). This association remained significant when analyzed using a Cox model adjusted for the possible confounders (Table 4).

**IGF-1 and Infection Outcomes**

We identified 169 patients (33%) who experienced hospitalization for infection. The Kaplan–Meier analysis showed that IGF-1 tertile was significantly associated with hospitalization for infection (Fig. 3B). However, this association was no longer significant when analyzed using Cox models adjusted for the major demographic factors (Table 3).

Of the 169 patients with hospitalization for infection, 47 patients died after infection. Based on the direct cause of death, 13 patients died from cardiovascular causes (sudden death, N=5; heart failure, N=5; ischemic heart disease, N=2; and stroke, N=1) and 29 patients died from non-
### Table 1. Baseline characteristics of the hemodialysis cohort by tertile of IGF-1

| Characteristics | No. of participants with data | Overall N = 516 | IGF-1 tertile | P across tertiles |
|-----------------|------------------------------|----------------|---------------|------------------|
| IGF-1 (ng/mL)   | 516                          | 147 (107–187)  | 94 (77–108)  | 147 (137–158)  | 212 (187–257)  | < 0.001 |
| Age (years)     | 516                          | 61 (54–68)     | 65 (59–72)   | 61 (53.8–67)   | 56 (51–63)    | < 0.001 |
| Sex (%male)     | 516                          | 63             | 70           | 55              | 64             | 0.01    |
| Dialysis duration (year) | 516                     | 9.2 (3.8–15.9) | 9.5 (3.5–17.5) | 11.4 (5.5–16.9) | 6.8 (3.1–12.8) | 0.003   |
| Diabetic kidney disease (%) | 516                      | 21             | 22           | 15              | 28             | 0.02    |
| Pre-existing CVD (%) | 516                        | 33             | 43           | 27              | 29             | 0.002   |
| Hypertension (%) | 516                          | 41             | 87           | 85              | 87             | 0.76    |
| Smoker (%)      | 516                          | 86             | 43           | 41              | 39             | 0.79    |
| HDL-C (mg/dL)   | 516                          | 44 (36–54)     | 46 (36–56)   | 45 (37–57)     | 41 (35–50)    | 0.02    |
| Non-HDL-C (mg/dL) | 516                    | 115 (91–138)   | 106 (86–131) | 116 (90–144)   | 121 (100–147) | < 0.001 |
| Dyslipidemia (%) | 516                          | 50             | 45           | 49              | 56             | 0.10    |
| BMI (kg/m²)     | 516                          | 21.6 (19.6–23.4) | 20.7 (19.1–22.5) | 21.3 (19.4–23.2) | 22.7 (20.8–24.4) | < 0.001 |
| Serum albumin (g/dL) | 516                     | 3.7 (3.5–3.9)  | 3.6 (3.4–3.8) | 3.7 (3.5–3.9)  | 3.8 (3.6–4.0) | < 0.001 |
| CRP (mg/dL)     | 516                          | 0.14 (0.05–0.41) | 0.14 (0.06–0.46) | 0.14 (0.05–0.41) | 0.13 (0.04–0.31) | 0.23 |
| Calcium (mg/dL) | 516                          | 9.1 (8.6–9.8)  | 9.0 (8.3–9.7) | 9.2 (8.6–9.9)  | 9.2 (8.6–9.8) | 0.04    |
| Phosphate (mg/dL) | 516                      | 5.8 (5–6.6)    | 5.5 (4.7–6.4) | 5.8 (5.2–6.8)  | 5.9 (5.1–6.8) | < 0.001 |
| Intact PTH (pg/mL) | 516                        | 118 (41–215.8) | 118 (55–194) | 135 (42.8–258) | 106 (34–191) | 0.39    |
| Use of VDRA (%) | 516                          | 36             | 42           | 33              | 34             | 0.18    |
| Hematocrit (%)  | 516                          | 30.7 (28.6–32.4) | 30.6 (28.5–32.5) | 30.3 (28.3–32.2) | 31 (29–32.5) | 0.18    |
| ESA dose (units/wk) | 516                     | 9000 (7500–9000) | 9000 (7500–9000) | 9000 (7500–9000) | 9000 (6000–9000) | 0.18    |
| Use of IV iron (%) | 516                        | 58             | 62           | 62              | 50             | 0.02    |
| Hypothyroidism (%) | 516                        | 11             | 14           | 14              | 4              | 0.002   |

The table gives medians (interquartile ranges) for continuous variables and percentages for categorical variables. $P$ values by Kruskal-Wallis test or $\chi^2$ test.

Abbreviations: IGF-1, insulin-like growth factor 1; T, tertile; CVD, cardiovascular disease; HDL, high-density lipoprotein; BMI, body mass index; CRP, C-reactive protein; PTH, parathyroid hormone; VDRA, vitamin D receptor activator; ESA, erythropoiesis-stimulating agent; IV-iron, intravenous iron preparation.

Conversion factors for units: HDL-C and Non-HDL-C in mg/dL to mmol/L, $\times$ 0.02586; phosphorus in mg/dL to mmol/L, $\times$ 0.3229.
cardiovascular causes (infection, N=22; uremia, N=2; and others, N=5), whereas the direct cause was unknown for the remaining 5 patients. The Kaplan–Meier analysis showed that a lower IGF-1 level was significantly associated with a higher risk of death after infection (Fig. 4B). This association remained significant when analyzed using a Cox model adjusted for the possible confounders (Table 4).
also predicted cardiovascular and non-cardiovascular deaths. IGF-1 level did not have an independent association with new CVD events, whereas a lower IGF-1 was significantly associated with death after a new CVD event. Additional analyses showed that IGF-1 was not independently associated with hospitalization for infection, whereas a low IGF-1

Discussion

We started this study to examine the associations between IGF-1 and the preplanned key outcomes, namely, all-cause mortality, new CVD events, and death after new CVD events. A low IGF-1 level was an independent predictor of all-cause death, and it
hemodialysis. In our study, a lower IGF-1 predicts both cardiovascular and non-cardiovascular deaths based on the direct causes of death. Then, one may speculate that a lower IGF-1 could predict both cardiovascular and non-cardiovascular events. However, IGF-1 was not an independent predictor of either new CVD events or hospitalization for infection. Nonetheless, a lower IGF-1 was significantly predictive of shorter survival after CVD events and infection.

How can we understand these results? The relative risk of cardiovascular death in patients treated with a lower IGF-1 level predicted death after hospitalization for infection. These results may indicate that a low serum IGF-1 concentration is closely related with vulnerability to fatal outcomes in the case of stressful conditions such as cardiovascular and infectious events in patients undergoing hemodialysis.

Previous studies by Jia et al. [12] and Nilsson et al. [20] reported that a lower IGF-1 level was an independent predictor of all-cause mortality in patients with kidney failure starting hemodialysis or peritoneal dialysis. These previous studies are consistent with our results in patients on maintenance hemodialysis. In our study, a lower IGF-1 predicts both cardiovascular and non-cardiovascular deaths based on the direct causes of death. Then, one may speculate that a lower IGF-1 could predict both cardiovascular and non-cardiovascular events. However, IGF-1 was not an independent predictor of either new CVD events or hospitalization for infection. Nonetheless, a lower IGF-1 was significantly predictive of shorter survival after CVD events and infection.

How can we understand these results? The relative risk of cardiovascular death in patients treated

**Fig. 4.** Kaplan–Meier curves of death after new CVD events and death after infection

The left panel (A) shows that a lower IGF-1 level was associated with a higher risk of death after CVD events in an unadjusted model. The right panel (B) shows the similar association between IGF-1 and the risk of death after hospitalization for infection. Abbreviations: CVD, cardiovascular disease; IGF-1, insulin-like growth factor 1; T, tertile.

**Table 4.** Multivariable-adjusted associations of IGF-1 with death after new CVD events and death after infection

| Outcome                        | Models | Adjustment                                                                 | HR (95%CI) per 1 SD higher IGF-1 | P value |
|--------------------------------|--------|----------------------------------------------------------------------------|----------------------------------|---------|
| Death after new CVD events     | 1 Unadjusted         |                                                                              | 0.53 (0.38–0.73)                 | < 0.001 |
|                                | 2 Age and sex        |                                                                              | 0.59 (0.41–0.82)                 | 0.002   |
|                                | 3 Model 2 + DKD or not, duration of HD, and prior CVD |                                                                              | 0.60 (0.42–0.85)                 | 0.003   |
|                                | 4 Model 2 + BMI, serum albumin, and Log-CRP |                                                                              | 0.61 (0.42–0.87)                 | 0.006   |
|                                | 5 Model 2 + Hypothyroidism |                                                                              | 0.59 (0.41–0.83)                 | 0.002   |
| Death after infection          | 1 Unadjusted         |                                                                              | 0.50 (0.33–0.74)                 | < 0.001 |
|                                | 2 Age and sex        |                                                                              | 0.54 (0.35–0.81)                 | 0.002   |
|                                | 3 Model 2 + DKD or not, duration of HD, and prior CVD |                                                                              | 0.61 (0.40–0.91)                 | 0.02    |
|                                | 4 Model 2 + BMI, serum albumin, and Log-CRP |                                                                              | 0.66 (0.42–1.02)                 | 0.06    |
|                                | 5 Model 2 + Hypothyroidism |                                                                              | 0.54 (0.35–0.81)                 | 0.002   |

The table gives HRs (95% CIs) per 1 SD higher IGF-1 for death after new CVD events and death after hospitalization for infection. Abbreviations: HR, hazard ratio; 95%CI, 95% confidence interval; SD, standard deviation; IGF-1, insulin-like growth factor 1; CVD, cardiovascular disease; DKD, diabetic kidney disease; HD, hemodialysis; BMI, body mass index; and CRP, C-reactive protein.
with hemodialysis was reported in the range of 10–30 as compared with the general population. Although the risks for incident acute myocardial infarction and incident stroke in hemodialysis patients are higher than those in the general population, the elevated risk for incident CVD events does not fully explain the extremely high risk for cardiovascular death in this population. Importantly, hemodialysis patients have a lower survival rate after myocardial infarction and stroke. Thus, the extremely elevated risk for cardiovascular mortality can be explained by the synergistic effects of a high risk for the occurrence of CVD events and a high risk for subsequent death.

Going back to the interpretation of our results, if we can divide the pathway to cardiovascular event-related death into two steps, namely, the occurrence of a CVD event (first step) and death after the CVD event (second step), a lower IGF-1 can be regarded as a factor preferentially associated with the second step.

At least two previous studies examined the predictors of death after incident CVD event among hemodialysis patients. These studies reported that a higher age, higher level of CRP, and lower BMI were among the independent factors associated with death after the composite of myocardial infarction and stroke. These reports may indicate that the so-called “malnutrition–inflammation–atherosclerosis syndrome,” “malnutrition–inflammation complex syndrome,” and PEW are the factors closely related to the second step to cardiovascular death. In the present study, we showed that a lower IGF-1 was predictive of death after a new CVD event independent of age, sex, dialysis duration, diabetic kidney disease or not, and prior CVD history. When adjustment was done for BMI, serum albumin, and CRP, the association between IGF-1 and death after CVD events remained significant. Thus, a lower IGF-1 appears to represent risk of poor survival after CVD events independent of PEW.

We found that a lower IGF-1 level was independently associated with not only death after new CVD events but also death after infection. Taken together, a lower IGF-1 level could represent vulnerability to fatal outcomes when the patient is exposed to some stressful conditions. According to Fried et al., geriatricians define frailty as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes. Therefore, a lower IGF-1 can be regarded as a biomarker of frailty by this definition. In the absence of a gold standard criteria for frailty, it is usually diagnosed using the phenotypes including shrinking, weakness, self-reported exhaustion, slowness, and low physical activity level. In the elderly general population, IGF-1 was associated with muscle weakness, decreased tongue pressure, and functional deterioration after hospitalization. Also, in patients treated with hemodialysis, a lower IGF-1 was associated with a lower muscle strength. Taken these findings into consideration, a lower serum IGF-1 level may serve as a biomarker of frailty in hemodialysis patients, although we did not have information for the phenotypic criteria for frailty in this study.

What is the relationship between low IGF-1, PEW, and frailty? In this study, a low IGF-1 level was associated with all-cause mortality independent of the PEW-related factors (BMI, serum albumin, and CRP). In the same model, these PEW-related factors were also significant predictors of all-cause mortality (data not shown), suggesting that both low IGF-1 and PEW were associated with vulnerability to adverse outcomes. Similarly, a lower IGF-1 level was associated with death after a new CVD event and death after hospitalization for infection independent of these PEW-related factors. Presumably, IGF-1 and PEW play different roles in the pathogenesis of vulnerable clinical course. IGF-1 is a growth factor that promotes cell proliferation and tissue repair, whereas protein-energy store is used for tissue repair processes. Therefore, we interpret our data to indicate that both sufficient IGF-1 and protein-energy store are required for better survival after a stressful condition, such as CVD and infection. In other words, the results suggest that a low IGF-1 level, in addition to PEW, is a key factor that predisposes patients to frailty.

Then, what causes decreased IGF-1 levels in these patients? First, since hepatic IGF-1 secretion is stimulated by GH, the suppression of GH secretion from the pituitary gland can be one of the reasons. Metabolic acidosis in kidney failure was shown to suppress GH secretion. Second, hepatic dysfunction may cause low IGF-1. Because hepatitis C viral (HCV) hepatitis was highly prevalent among hemodialysis patients in 1990s, we looked for HCV antibody data in 2004 in medical records; however, it was only available for the 284 patients of this cohort, and 14% of these patients were HCV(+). Thus, the role of HCV(+) in low IGF-1 cannot be ruled out. Third, endocrine disorders other than pituitary hormones may affect IGF-1 level. Among these, hypothyroidism is known to be causally related to low IGF-1 level. In our patients, the presence of hypothyroidism was found to be an independent factor associated with a lower IGF-1 level (Supplemental Table 2). Finally, a higher age is the
most powerful factor associated with a lower IGF-1 level (Supplemental Table 2). Importantly, however, the inverse associations of low IGF-1 with all-cause mortality, death after CVD event, and death after infection remained significant when the models were adjusted for confounding factors, including hypothyroidism and age (Tables 2, 3, 4).

This study has several limitations. First, because this study included only patients undergoing maintenance hemodialysis in Japan, we are not sure that the results of this study are applicable to other populations. Second, because the results of this study were based on a single measurement of serum IGF-1, the associations between IGF-1 and clinical outcomes may be underestimated or overestimated. Third, due to lack of data for the phenotypic criteria for frailty, we were unable to examine the possible relationship between serum IGF-1 and frailty as assessed by the commonly used phenotypic criteria. Fourth, although IGF-1 promotes cell proliferation and a higher level of IGF-1 is known to be associated with increased risk of some cancers such as breast cancer, we have no data on the prevalence of cancer at baseline. However, it is difficult to explain the observed inverse association between IGF-1 and mortality risk by cancer risk associated with high IGF-1. Finally, because of the observational nature of this study, the observed associations do not necessarily indicate causality.

**Conclusion**

In conclusion, a lower IGF-1 level was an independent predictor of all-cause mortality, and it also predicted poor survival after new CVD events and infection in a cohort of hemodialysis patients. These findings may indicate serum IGF-1 as a biomarker of frailty in this population. Clearly, further studies are needed to confirm our observations in other settings and test the value of IGF-1 with the simultaneous assessment of frailty using widely used criteria.

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**Conflict of Interest Statement**

All authors declared no competing interests relevant to this study.

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**Supplemental Table 1.** Definitions of CVD events in the DREAM cohort

| CVD event                          | Definition                                                                                                                                                                                                 |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ischemic heart disease (IHD)      | IHD included myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting. Angina pectoris was included in IHD only when myocardial ischemia was evident by electrocardiogram and/or stress myocardial scintigraphy. |
| Stroke                            | Stroke denoted symptomatic stroke with sudden onset of neurological deficit confirmed by magnetic resonance imaging (MRI) and/or X-ray computed tomography (CT) of the brain. Based on available information, stroke was classified into ischemic stroke, hemorrhagic stroke, and unspecified. Transient ischemic attack was not included in stroke. |
| Peripheral artery disease (PAD)   | PAD was diagnosed when the patient had history of amputation of lower limb, percutaneous transluminal angioplasty, and/or bypass grafting due to ischemic limb. We did not include intermittent claudication, leg pain at rest, or foot ulceration in PAD if none of the above-mentioned treatment was performed. |
| Congestive heart failure (CHF)    | CHF was defined by severe pulmonary edema requiring hospitalization, excluding pneumonia, but not excluding non-cardiac circulatory failure.                                                                  |
| Valve disease                     | Valve disease was diagnosed when the patient had valve replacement.                                                                                                                                      |

Sudden deaths are considered as fatal CVD events.

Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography.

**Supplemental Table 2.** Factors associated with IGF-1 levels

| Factors                                      | Standardized coefficient (β) | P value |
|----------------------------------------------|------------------------------|---------|
| Age                                          | −0.299                       | < 0.001 |
| Sex (male = 1, female = 0)                   | −0.131                       | < 0.001 |
| Diabetic kidney disease (yes = 1, no = 0)   | −0.027                       | 0.53    |
| Dialysis duration                            | −0.152                       | < 0.001 |
| Pre-existing cardiovascular disease (yes = 1, no = 0) | −0.006                       | 0.89    |
| Body mass index                              | 0.168                        | < 0.001 |
| Serum albumin                                | 0.182                        | < 0.001 |
| Log C-reactive protein                       | 0.012                        | 0.77    |
| Hypothyroidism (yes = 1, no = 0)             | −0.078                       | 0.046   |

Factors associated with IGF-1 levels were examined by a multivariable-adjusted linear regression model. Logarithmically transformed IGF-1 was entered in the model so that the residual was deemed to have normal distribution. Hypothyroidism was defined in the text.

**Supplemental Table 3.** Associations of IGF-1 with death by direct cause

| Direct cause of death | Number of cases | Unadjusted HR (per 1 SD higher IGF-1) | HR adjusted for age and sex (per 1 SD higher IGF-1) |
|-----------------------|----------------|--------------------------------------|-----------------------------------------------------|
| Cardiovascular        | 38             | 0.49 (0.31–0.74) \( P<0.001 \)       | 0.62 (0.38–0.95) \( P=0.04 \)                       |
| Non-cardiovascular    | 48             | 0.30 (0.19–0.47) \( P<0.001 \)       | 0.36 (0.22–0.57) \( P<0.001 \)                      |
| Infection             | 24             | 0.28 (0.14–0.51) \( P<0.001 \)       | 0.30 (0.15–0.57) \( P<0.001 \)                      |
| Other than infection  | 24             | 0.33 (0.17–0.59) \( P<0.001 \)       | 0.44 (0.22–0.81) \( P=0.01 \)                       |
| Unknown               | 20             | 0.58 (0.31–0.97) \( P=0.04 \)        | 0.74 (0.39–1.28) \( P=0.31 \)                       |

All-cause deaths were classified into cardiovascular death and non-cardiovascular death based on direct cause of death. The direct cause of death was unknown for 20 cases. Non-cardiovascular causes (48 cases) were further divided into infection (24 cases) and other than infection (24 cases).