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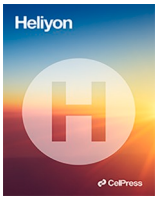

Research article

Ketoanalogue use is associated with a lower risk of worsening frailty among patients with diabetic kidney disease of advanced stage: A retrospective cohort study

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ABSTRACT

Background: Patients with diabetes kidney disease (DKD) are at risk of developing frailty, leading to functional impairment and poor outcomes. Medications are potential modifiers of such risk. Ketoanalogues have been shown to delay dialysis initiation in DKD patients. We investigated whether ketoanalogues use influenced the risk of worsening frailty in this population.
Methods: From 840,000 patients with diabetes, we identified those with DKD but without full-fledged frailty, and divided them into those with and without receiving ketoanalogue, followed by propensity score matching in 1:4 ratio. Worsening frailty was defined as ≥1 positive FRAIL item increase compared to baseline status (0, 1, or 2 items) during follow-up. We used Cox proportional hazard regression to estimate the probability of worsening frailty, adjusting for demographics, comorbidities, glycemic control, renal function, treatments and medications.
Results: Totally 183 and 732 ketoanalogue users and matched non-users were identified, respectively. The mean age of included patients was 57.4 years, with 91.3 % having non-dialysis stage 5 chronic kidney disease. Approximately two-thirds had pre-frailty (1 o2 items). After 3.72 years, 16.6 % patients had worsening frailty. Multivariate analyses, adjusting for confounders disclosed that ketoanalogue users (≥14 days) had a significantly lower risk of worsening frailty than non-users (hazard ratio (HR) 0.52, 95 % confidence interval (CI) 0.32–0.87). Sensitivity analysis including those received ketoanalogue ≥28 days showed even greater benefits (HR 0.45, 95 % CI 0.26–0.78).

Abbreviations: aDCSI, adapted diabetes complication severity index; CCI, Charlson comorbidity index; CI, confidence interval; CKD, chronic kidney disease; DKD, diabetic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; ICD-9-CM, International Classification of Disease, 9th version Clinical Modification; LCDP, longitudinal cohort of diabetes patients; SMD, standardized mean differences.

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Conclusions: Patients with DKD receiving ketoanalogues were less likely to have worsening frailty over time than non-users. Our findings uncover a new potential strategy of ameliorating frailty progression in this population carrying a high risk of accelerated aging.

1. Introduction

The number of patients with chronic kidney disease (CKD), especially those with diabetic kidney disease (DKD), is on the rise globally due to populational aging, increasing comorbidity burdens and polypharmacy risk, aggravated by their tendency to developing acute kidney injury [1]. CKD patients are at risk of developing a variety of complications, ranging from anemia, osteodystrophy, bleeding diathesis, to atypical ones such as ectopic calcification involving vascular tissues and fertility impairment [2]. Emerging studies suggest that having CKD also renders patients susceptible to malnutrition, sarcopenia, and frailty, a distinctive class of degenerative trait prevalent among older adults. The presence of diabetes mellitus (DM) further intensifies this tendency to have bodily degeneration. The term "frailty" therefore illustrates an intrinsic vulnerability to adverse stimuli coming from ambient environment or host endogenously. Operationalizing frailty requires physical measurements or counting a diverse spectrum of cumulative deficits according to different conceptual construct. Among those with CKD, a meta-analysis incorporating 1,675,482 patients revealed that 34.5 % and 39.4 % had frailty and prefrailty (a precursor stage of frailty), respectively [3]. The presence of frailty, either in the form of higher frailty index or greater numbers of positive frail phenotypes, increases the risk of all-cause, cardiovascular mortality and end-stage kidney disease (ESKD) among survivors [4,5]. Frailty in patients with DKD further raises the probability of musculoskeletal complications, neurologic malfunctioning, and subsequent functional impairment [6]. How to ease this degenerative process among patients with DKD has gradually surfaced as an important therapeutic goal for providing holistic care in this population.

The pathogenesis and risk factors for frailty in patients with DKD remains under active exploration. DKD *per se* is associated with accelerated biologic aging through various mechanisms such as senescence, epigenetic alterations and stem cell wearing, partially underlying the origin of frailty in this population [7]. A literature summary discovered that lifestyle factors (smoking), comorbidity, psychiatric illnesses, and endocrinologic insufficiency were important risk factors for frailty in patients with CKD, especially those with DKD [6]. On the other hand, medications are also an important modifier of frailty risk. Chi et al. recently showed that the constituents of glucose-lowering regimen could alter the risk of frailty progression, with a greater risk among insulin users while lower risk among users of monotherapy with oral anti-diabetic medications [8]. In patients with DKD, Lee et al. also demonstrated that higher doses of muscle relaxant use paralleled the subsequent increase in the risk of incident frailty [9]. Interestingly, the same group of researchers showed that frailty itself might modify the associations between medications and their outcome influences [10]. These findings exemplify the potential role of medications as frailty risk modifiers in patients with DKD.

Ketoanalogues are nutritional supplements that, combined with low protein diet, can retard renal function deterioration and improve metabolic perturbations in patients with severe DKD [11]. Through improving nitrogen recycling and preserving carbonic structure for energy generation, ketoanalogues have been proposed to reduce uremic toxin production. A meta-analysis involving 12 clinical trials demonstrated that restricted protein diet with ketoanalogue supplementation could significantly delay dialysis initiation among patients with CKD, without causing malnutrition [12]. These findings similarly apply to those with DKD. Despite the benefits outlined above, however, very few studies examined whether ketoanalogue use led to changes in the risk of developing frailty in this population. None addresses the issue whether ketoanalogues influence the risk of worsening frailty over time. Therefore, we hypothesized that ketoanalogue use might reduce the risk of frailty in patients with DKD of advanced stage. We used a well-maintained cohort of patients with DKD to investigate this issue.

2. Method

2.1. Identification of study patients

We retrospectively analyzed the Longitudinal Cohort of Diabetes Patients (LCDP), a prospectively collected cohort of patients with DM in Taiwan. The details of this cohort and studies published based on LCDP analysis are available elsewhere [13]. In brief, 840,000 patients with at least one time of DM diagnosis (International Classification of Disease, 9th version Clinical Modification (ICD-9-CM)) were randomly selected from the entire Taiwanese population between Jan 1, 2004 and Dec 31, 2011 and incorporated into LCDP. Clinical variables, including demographic profile, clinical diagnosis, comorbidities, treatment variables, and medications were all retrieved from the nationwide reimbursement dataset for the documentation purpose. We used adapted diabetes complications severity index (aDCSI) to estimate the severity of diabetic complications, a surrogate of glycemic control status. aDCSI has been shown to outperform Charlson comorbidity index (CCI) regarding prognosis and cardiovascular risk prediction [14]. The use of any medication, apart from the index one of interest (ketoanalogues), was defined according to the presence of any prescription record during the follow-up period. Follow-up of cohort patients was done on an annual basis.

In this study, we further increased the specificity of DM through requiring at least 3 times of out-patient or 1 time of in-patient diagnosis. We defined the index date as the day from which patient follow-up started, according to the time when the DM and CKD diagnoses was satisfied. Clinical variables were ascertained prior to the index date in line with prior reports [15]. Exclusion criteria consisted of the following conditions; we excluded pediatric cases (age $\leq$20 years), those with missing demographics, with pre-existing relevant outcome of interest (e.g. full-fledged frailty, definition shown in the next section), and those with insufficient duration for

clinical variable ascertainment (prior to January 1st, 2004) or insufficient follow-up duration (after June 30th, 2011). To identify those with DKD, we further excluded those without pre-existing non-dialysis CKD according to ICD-9-CM diagnostic codes utilized and validated previously in Taiwanese cohorts [16]. The index date was defined as the date during which the first ketoanalogue prescription was noted. All the identified patients were followed up until death, development of the outcome of interest, or December 31st, 2011, whichever occurred first. The current study follows the STROBE guideline, and a STROBE checklist has been attached in the supplementary file.

2.2. Exposure characterization

We investigated the influence of ketoanalogue use on the outcome of interest. In Taiwan, ketoanalogue was reimbursed by Taiwan National Health Insurance (NHI) Bureau since 2004, on condition that patients had stage 5 pre-dialysis CKD for at least 3 months [17], whereas those with earlier CKD stage received such medications without reimbursement. So, the majority of patients receiving ketoanalogue identified in this cohort were expected to have stage 5 CKD without dialysis or kidney transplantation, which was identified based on the use of Taiwan NHI reimbursed erythropoietin in patients with kidney failure. According to Taiwan NHI regulations, erythropoietin could be reimbursed only if patients had a serum creatinine higher than 6 mg/dL (roughly equivalent to an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2) according to prior studies [17]. Identified patients with DKD were divided into those without and with ketoanalogue use, defined as at least 14 days of use during the follow-up period, similar to the threshold adopted by other pharmacoepidemiology analyses in Taiwan [18]. Non-users were identified if they never received any ketoanalogue during the study period. The issue of immortal time bias was minimized by matching the index date between ketoanalogue users and non-users, ensuring that each individual had a similar start time for follow-up.

2.3. Outcome determination

The primary outcome of interest in this study was the worsening of frailty, defined as having $\geq$1 FRAIL item increase compared to baseline assessment during the follow-up period. For frailty assessment at baseline and during follow-up, we used the FRAIL scale, whose acronym consisted of Fatigue, Resistance, Ambulation, Illness, and Loss of body weight. Details of how to assess the five FRAIL items are available elsewhere [15]. In brief, a validated combination of diagnostic codes and physical status characterization was assigned to operationalize the five FRAIL items above. Although this operationalization scheme may have limitation in item sensitivity, its application in registry-based studies has been shown to correlate highly with clinical outcomes and various degenerative features, especially in patients with CKD [15]. FRAIL scale has been recommended as a simple and rapid approach for assessing frailty at primary care setting, and performs as well as the Fried phenotype and Study of the Osteoporotic Fractures (SOF) scale [19]. In patients with DM and/or CKD, results from FRAIL scale also exhibited tight associations with mortality, healthcare consumption, and other health-related outcomes [15,20]. Full-fledged frailty was defined as having $\geq$3 positive FRAIL item according to the original classification scheme [21]. At baseline, the frailty assessment results were assessed once, and those with full-fledged frailty were excluded. During follow-up, the primary outcome, or worsening frailty, was recognized if they had $\geq$1 increase of positive FRAIL item compared to their baseline status. An increase in FRAIL items has been shown to be a surrogate for changing frail severity and correlated with poorer outcomes dose-responsively [15]. Another study in patients with DM revealed that more positive FRAIL item counts were correlated with aggravated glycemic control [8], supporting the utility of this approach.

2.4. Statistical analysis

For continuous and categorical variables, we described them in means $\pm$ standard deviations (normally distributed) or medians with inter-quartiles (non-normally distributed) and numbers with percentages, respectively. We compared normally and non-normally distributed continuous variables using Student's *t*-test and Mann-Whitney *U* test, respectively. Chi-square test was used to compare categorical variables. We first removed those who received ketoanalogue for less than 14 days. We then performed propensity score matching in a 1:4 ratio between ketoanalogue users and matched non-users who did not receive any ketoanalogues during the study period. Matching was based on demographic profile, comorbidities, treatment variables, medications, and numbers of FRAIL items, using the nearest propensity scores within a range of 0.01. Standardized mean differences (SMDs) were used to described differences. The kidney function among non-users were similar to users after matching, as most of them had stage 5 CKD. Kaplan-Meier survival analysis was done to illustrate the event-free probability between users and non-users, followed by comparison using a log-rank test. Finally, Cox proportional hazard regression was used to estimate the risk of worsening frailty associated with ketoanalogue use in this cohort. Sensitivity analyses were also done by varying the duration of ketoanalogue use, from at least 14 days to at least 28 days. A competing risk analysis that included mortality as a competing event was also conducted. All analyses were done by the SAS software (SAS institute, NC, USA). A two-tail p value < 0.05 was considered statistically significant.

3. Result

During the study period, 840,000 patients with DM were screened. After applying the exclusion criteria, we identified 165,156 patients with DKD, from whom 188 ketoanalogue users were grouped (Fig. 1). After propensity score matching, we identified 732 matched non-users from 164,959 patients with DKD and analyzed accordingly. Minimal SMDs were noted between all matching variables. Among all, only 22 (2.4 %) had a concurrent diagnosis of any glomerular diseases. The mean duration of ketoanalogue use in

the user group was 132.66 ± 150.42 days.

The mean age of study patients was 57.4 years, with more males than females and an overall low prevalence of smoking/alcoholism (Table 1). The most common morbidity among this cohort was non-dialysis stage 5 CKD (91.3 % prevalence), expectable based on the local insurance reimbursement policy, followed by hypertension (89.1 %), hyperlipidemia (46.4 %), and osteoarthritis (29.9 %) (Table 1). Their mean CCI and aDCSI scores were 4.1 and 1.8, respectively. Approximately three-fourths received angiotensin receptor blockers and beta-blockers, while half received statin and benzodiazepines. As for glucose-lowering drugs, sulfonylurea was the most commonly used ones (44.5 %), followed by meglitinide (33.8 %) and insulin (30.9 %) (Table 1). Patients with DKD receiving ketoanalogue had similar age and sex distribution to non-users (Table 1). Ketoanalogue users were well balanced with non-users with regard to CCI, glycemic control status, each comorbidity prevalence, and the proportion of anti-hypertensives, anti-lipidemics, anti-platelets, anti-coagulants, uric acid-lowering agents, anti-depressants, anti-psychotics, benzodiazepines, glucose-lowering drugs, and anti-inflammatory agents (Table 1).

For frailty status at baseline, 33.3 %, 52.5 %, and 14.2 % patients did not have any, had 1, and 2 positive FRAIL items, respectively (Table 1). The most common positive FRAIL item among patients was Illness (63.1 %), followed by Fatigue (14.9 %) and Loss of weight (1.6 %). There were no significant differences between ketoanalogue users and non-users regarding FRAIL item counts and positive items (Table 1).

After a median 3.72 years of follow-up, 152 (16.6 %) patients had worsening frailty (Table 2). The incidence of worsening frailty among ketoanalogue non-users and users was 48.43 and 27.47 per 1000 patient-year, respectively. Kaplan-Meier analyses revealed that ketoanalogue users had significantly lower probability of developing worsening frailty compared to non-users ($p = 0.02$; Fig. 2). Univariate analysis using Cox proportional hazard regression showed that ketoanalogue use correlated with a lower risk (hazard ratio (HR) 0.57, 95 % confidence interval (CI) 0.35–0.92). After accounting for mortality as the competing event, ketoanalogue was still associated with a significantly lower risk of worsening frailty (HR 0.54, 95 % CI 0.32–0.92) (Table 2). Multivariate analyses, adjusting for demographic profile, comorbidities, aDCSI, CCI, treatment variables, frail status, and medication usages disclosed that ketoanalogue users still had a significantly lower risk of worsening frailty than non-users (HR 0.52, 95 % CI 0.32–0.87). A sensitivity analysis including only those received ketoanalogue ≥28 days showed even greater benefits associated with ketoanalogue use (HR 0.45, 95 % CI 0.26–0.78) (Table 3).

4. Discussion

In this study, we used a well-maintained cohort of patients with DKD to answer our research question, whether ketoanalogues influenced the risk of worsening frailty. Clinical features were well balanced between matched ketoanalogue users and non-users. Patients with DKD receiving ketoanalogues exhibited a significantly lower risk of worsening frailty during follow-up compared to non-users; this association was independent of demographic variables, comorbidities, glycemic control, renal function, treatments and medications. Our findings help identify a new strategy of ameliorating frailty progression in patients with CKD, who already carries a high risk of accelerated aging.

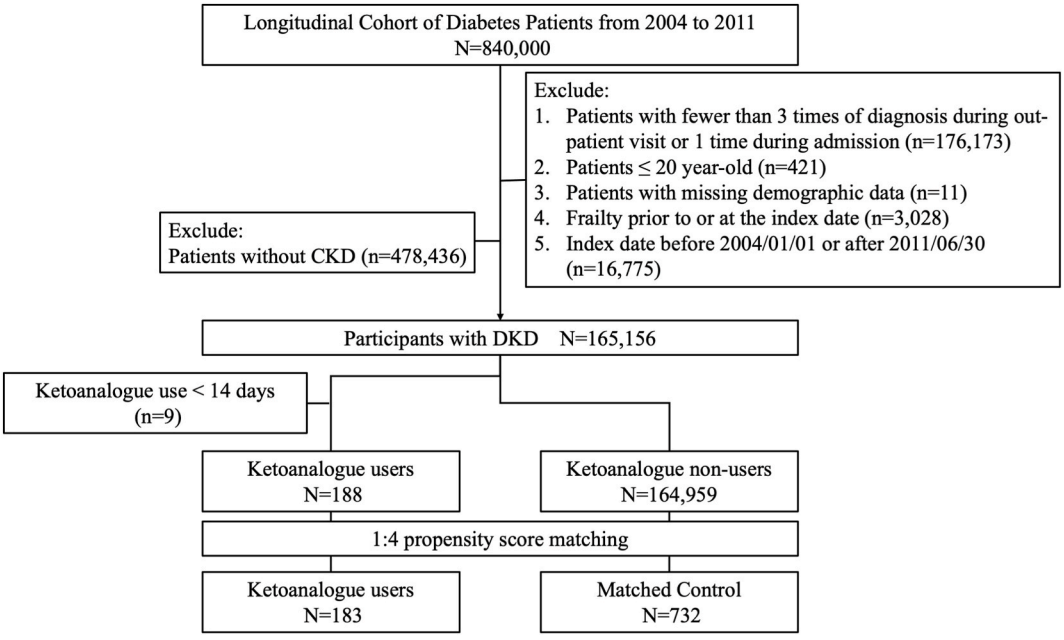

Fig. 1. The flow chart of patient selection in this study.
CKD, chronic kidney disease; DKD, diabetic kidney disease.

Table 1
Clinical features of participants with advanced diabetic kidney disease according to keto-analogue users or non-users.

	ketoanalogue		*p-value*	*SMD*
	Users (n = 183)	**Non-users (n = 732)**		
Demographic and physical condition				
Age (years)	57.3 ± 13.2	57.4 ± 13.6	*0.90*	*−0.01*
Sex (Female %)	81 (44.3)	304 (41.5)	*0.50*	*0.01*
Obesity (%)	3 (1.6)	17 (2.3)	*0.57*	
Substance use history				
Smoking (%)	2 (1.1)	10 (1.4)	*0.77*	*−0.02*
Alcoholism (%)	1 (0.6)	5 (0.7)	*0.84*	*−0.02*
Baseline number of FRAIL component			*1.00*	*<0.01*
None	61 (33.3)	244 (33.3)		
One	96 (52.5)	384 (52.5)		
Two	26 (14.2)	104 (14.2)		
Baseline FRAIL component prevalence				
Fatigue (%)	26 (14.2)	110 (15.0)	*0.78*	*−0.02*
Resistance (%	2 (1.1)	6 (0.8)	*0.72*	*0.03*
Ambulation (%)	1 (0.6)	3 (0.4)	*0.80*	*0.02*
Illness (%)	116 (63.4)	461 (63.0)	*0.92*	*0.01*
Loss of weight (%)	3 (1.6)	12 (1.6)	*1.00*	*<0.01*
Charlson comorbidity index	4.1 ± 1.9	4.1 ± 2.3	*0.99*	*<0.01*
aDCSI	1.9 ± 1.4	1.8 ± 1.3	*0.42*	*0.07*
Comorbidity profile				
Hypertension (%)	161 (88.0)	654 (89.3)	*0.60*	*−0.04*
Hyperlipidemia (%)	81 (44.3)	344 (47.0)	*0.51*	*−0.05*
Cerebrovascular disease (%)	34 (18.6)	130 (17.8)	*0.80*	*0.02*
Acute coronary syndrome (%)	41 (22.4)	162 (22.1)	*0.94*	*0.01*
Congestive heart failure (%)	29 (15.9)	108 (14.8)	*0.71*	*0.03*
Atrial fibrillation (%)	25 (13.7)	96 (13.1)	*0.85*	*0.02*
Peripheral vascular disease (%)	6 (3.3)	21 (2.9)	*0.77*	*0.02*
Stage 5 chronic kidney disease (%)	167 (91.3)	668 (91.3)	*1.00*	*<0.01*
Cancer (%)	17 (9.3)	74 (10.1)	*0.74*	*−0.03*
Chronic liver disease (%)	45 (24.6)	183 (25.0)	*0.91*	*−0.01*
COPD (%)	20 (10.9)	88 (12.0)	*0.68*	*−0.03*
Gout (%)	48 (26.2)	194 (26.5)	*0.94*	*−0.01*
Parkinsonism (%)	3 (1.6)	13 (1.8)	*0.90*	*−0.01*
Psychiatric illnesses (%)	28 (15.3)	94 (12.8)	*0.38*	*0.07*
Osteoarthritis (any site) (%)	55 (30.1)	219 (29.9)	*0.97*	*<0.01*
Treatment prior to follow-up initiation				
Cardiac catheterization (%)	2 (1.1)	7 (1.0)	*0.87*	*0.01*
Cardiac surgery (any) (%)	5 (2.7)	24 (3.3)	*0.71*	*−0.03*
ICU admission (%)	20 (10.9)	80 (10.9)	*1.00*	*<0.01*
Hospital admission (%)	84 (45.9)	338 (46.2)	*0.95*	*−0.01*
Medication usage				
Anti-hypertensives				
ACEI (%)	79 (43.2)	306 (41.8)	*0.74*	*0.03*
ARB (%)	142 (77.6)	589 (80.5)	*0.39*	*−0.07*
β-blockers (%)	144 (78.7)	580 (79.2)	*0.87*	*−0.01*
Anti-lipidemics				
Statin (%)	103 (56.3)	431 (58.9)	*0.52*	*−0.05*
Fibrate (%)	45 (24.6)	178 (24.3)	*0.94*	*0.01*
Anti-platelets				
Aspirin (%)	79 (43.2)	362 (49.5)	*0.13*	*−0.13*
Clopidogrel (%)	25 (13.7)	97 (13.3)	*0.88*	*0.01*
Anti-coagulants				
Warfarin (%)	7 (3.8)	28 (3.8)	*1.00*	*<0.01*
Uric acid-lowering agent				
Allopurinol (%)	29 (15.9)	107 (14.6)	*0.68*	*0.03*
Anti-depressants (%)	41 (22.4)	154 (21.0)	*0.69*	*0.03*
Anti-psychotics (%)	55 (30.1)	232 (31.7)	*0.67*	*−0.04*
Benzodiazepine (%)	106 (57.9)	427 (58.3)	*0.92*	*−0.01*
Glucose-lowering drugs				
Biguanide (%)	41 (22.4)	183 (25.0)	*0.47*	*−0.06*
Sulfonylurea (%)	75 (41.0)	332 (45.4)	*0.29*	*−0.09*
Meglitinide (%)	59 (32.2)	250 (34.2)	*0.62*	*−0.04*
Alpha-glucosidase inhibitor (%)	41 (22.4)	168 (23.0)	*0.87*	*−0.01*
Thiazolidinedione (%)	26 (14.2)	110 (15.0)	*0.78*	*−0.02*
DPP4 inhibitors (%)	29 (15.9)	108 (14.8)	*0.71*	*0.03*

(*continued on next page*)

Table 1 (*continued*)

	ketoanalogue		*p-value*	*SMD*
	Users (n = 183)	**Non-users (n = 732)**		
Insulin (%)	54 (29.5)	229 (31.3)	*0.64*	*−0.04*
Anti-inflammatory agents				
COX2 inhibitors (%)	38 (20.8)	145 (19.8)	*0.77*	*0.02*
Median follow-up duration (with IQR) (years)	3.76 (2.1, 5.3)	3.71 (2.0, 5.3)	*0.87*	*0.01*

ACEI, angiotensin-converting enzyme inhibitor; aDCSI, adapted diabetes complication severity index; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; COX2, cyclo-oxygenase 2; ICU, intensive care unit; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; SMD, standardized mean difference.

Table 2
Risk of worsening frailty according to ketoanalogue use or not.

Variables	Number of events	Total population	Person-year	Incidence density[a]	Crude		Adjusted model[b]		Competing model[c]	
					HR	95 % CI	HR	95 % CI	HR	95 % CI
Worsening frailty										
Non-users	133	732	2746.5	48.43	1.00		1.00		1.00	
Users	19	183	691.8	27.47	0.57	0.35–0.92[d]	0.52	0.32–0.87[d]	0.54	0.32–0.92[d]

CI, confidence interval; HR, hazard ratio.
[a] per 1000 patient-year.
[b] Incorporating variables in Table 1.
[c] Mortality as a competing event.
[d] $p < 0.05$.

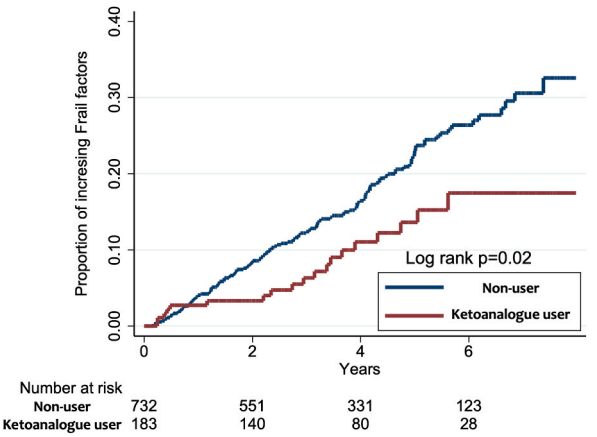

Fig. 2. Kaplan-Meier curves for the probability of worsening frailty according to ketoanalogue use or not.

Table 3
Sensitivity analysis results based on users of ketoanalogues ≥28 days.

Variables	Number of events	Total population	Person-year	Incidence density[a]	Crude		Adjusted model[b]		Competing model[c]	
					HR	95 % CI	HR	95 % CI	HR	95 % CI
Worsening frailty										
Non-users	122	676	2514.6	48.52	1.00		1.00		1.00	
Users	16	169	648.1	24.69	0.51	0.3–0.86[e]	0.45	0.26–0.78[d]	0.48	0.28–0.84[d]

CI, confidence interval; HR, hazard ratio.
[a] per 1000 patient-year.
[b] Incorporating variables in Table 1.
[c] Mortality as a competing event.
[d] $p < 0.01$.
[e] $p < 0.05$.

Prior studies revealed that approximately one-third of patients with CKD had frailty at assessment [3]. In our cohort of patients with CKD, those with frailty were excluded, and the prevalence of having precursor stage of frailty (1–2 FRAIL items) was 66.7 % (Table 1), significantly higher than estimates in the existing literature. This may result from the severity of CKD in our cohort patients (91.3 % CKD stage 5). On the other hand, the incidence of worsening frailty in our cohort (43.6 events per 1000 patient-year) was somewhat lower than findings from another study (~52 events per 1000 patient-year) [8]. It is possible that the mean age of our patients (57.4 years) was much lower than theirs (64.5 years), leading to differences in the pace of frailty worsening.

The prevalence of ketoanalogue users was relatively low in our cohort. Several reasons might be responsible for this; first, since ketoanalogues were reimbursed only for patients with stage 5 pre-dialysis CKD in Taiwan, the proportion of ketoanalogue users within the entire cohort was a surrogate for that of stage 5 CKD among all CKD patients. According to a nationwide CKD survey from Taiwan, Wen et al. showed that the proportion of stage 5 CKD patients among all CKD patients was around 0.1 % [22]. Indeed, among our cohort, the number (188/165,156) was 0.11 %, akin to that from the literature. Second, in our study, those who were prescribed ketoanalogues might be more likely to receive nephrologist follow-up and exhibited higher adherence to low protein diet recommendations, which potentially influenced the outcomes of interest. The interpretation of our findings ought to take these issues into consideration.

The association between ketoanalogue use and less probability of frailty worsening among patients with severe DKD (Table 2) may be explained by the following reasons. First and foremost, ketoanalogue supplementation in the context of dietary intervention has been shown to reduce uremic toxins, improve glycemic and blood pressure control, and potentially lower phosphorus levels in DKD patients [23]. Uremic toxins are recently pinpointed as a major driver of accelerated frailty through their multi-organ influences on patients with CKD [7]. Higher diastolic blood pressure [24] and glycative stress [25] are potential contributors to frailty development and worsening in animal and clinical studies. Hyperphosphatemia in CKD correlates with an increased frequency of osteodystrophy and vascular calcification, both of which are established predecessors of frailty [26]. In addition, ketoanalogue use is proposed to modulate the degree of gut dysbiosis and attenuate protein carbamylation [27]. An increased gut microbial alpha diversity were recently found to be associated with lower handgrip strength, sarcopenia, and potentially frailty [28]. Finally, ketoanalogue use can delay dialysis initiation and reduce eGFR decline rate [11]; better eGFR preservation may be translated into less uremic symptoms, improving quality of life, and potentially reduce subjective fatigue sensation over time [29]. Self-rated fatigue is an important element and determinant of frailty severity in kidney patients [30]. Based on the above arguments, we believe that ketoanalogue use may serve as a potential approach to reduce the risk of frailty worsening in patients with DKD (Fig. 3).

Our study has its strengths and limitations. The focus of our study, the association between ketoanalogue use and the risk of worsening frailty, is rarely addressed before but carries substantial clinical implications. Strategies for mitigating frailty in patients with CKD are scant, and our findings shed light on a new approach to meet this aim. We adjusted for an extensive array of clinical variables, and the association remained significant, supporting the validity of our findings. However, there are still limitations inherent to our study. The size of our cohort was moderate only, and a greater case number as well as another independent cohort would be required to further consolidate our findings. However, the number of patients with pre-dialysis stage 5 CKD is always low in existing studies due to their intense risk of progression to dialysis-dependency within a limited time frame. From this perspective, the number of this study remained contributory to the existing knowledge. Second, we did not record dietary habits or pattern in these patients, and we could not determine the amount of dietary protein among our DKD patients. Third, we only used FRAIL scale for measuring worsening frailty. Nonetheless, this scale has been widely validated against other frail-assessing instruments in this population, with comparable results obtained. The measurement of frailty was not done in a pre-planned manner, potentially influencing the sensitivity for frailty screening. The asynchronous ascertainment of each frailty component also confers ambiguity for the precise timing of frailty onset. Nonetheless, our finding is still instrumental, in light of the rising frailty incidence in patients with DKD and the limited therapeutic options available. Fourth, we could not distinguish between the influences of ketoanalogue use, low protein diet, and/or calory intake on the observed benefits. Fifth, the use of diagnostic codes to identify those with DKD may not be always accurate. Lastly, our cohort consisted mainly of those with stage 5 CKD, and whether these findings were extrapolatable to those with earlier stage CKD remained unclear.

5. Conclusion

In conclusion, we used the LCDP cohort to test an interesting hypothesis, whether ketoanalogue use influenced the risk of worsening frailty among patients with DKD. After accounting for multiple confounders, we showed that ketoanalogue use was associated with a significantly lower risk of worsening frailty during 3.72 years of follow-up. Based on our findings, it is expected that ketoanalogue could be alternatively purposed to ameliorate frailty progression in this high-risk population. The availability of ketoanalogue and its indications in patients with CKD make it a convenient and handy medication for achieving frailty improvement in this population.

CRediT authorship contribution statement

Jui Wang: Writing – original draft, Validation, Methodology, Formal analysis, Data curation. **Szu-Ying Lee:** Writing – original draft, Validation, Methodology, Investigation, Conceptualization. **Chia-Ter Chao:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jenq-Wen Huang:** Writing – original draft, Supervision, Project administration, Investigation, Data curation. **Kuo-Liong Chien:** Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition, Conceptualization.

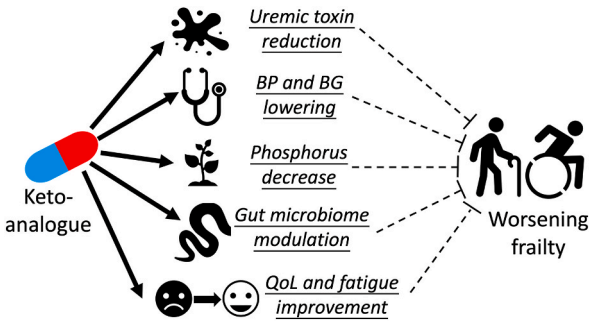

Fig. 3. A schematic diagram illustrating the potential mechanisms through which ketoanalogue use may reduce the risk of worsening frailty. BG, blood glucose; BP, blood pressure; QoL, quality of life.

Sponsor's role

The sponsors have no role in the study design, data collection, analysis, and result interpretation of this study.

Summary at a glance

Patients with diabetic kidney disease are at risk of developing frailty, for which treatments remain scant. We discovered that ketoanalogue use might be associated with less risk of worsening frailty in this population, uncovering a novel therapeutic approach.

Ethics, consent, and permission

The protocol of this study was part of a comprehensive project that studied the epidemiology and outcomes of patients with diabetes mellitus, whose protocol was approved by the institutional review board of National Taiwan University Hospital (NO. 201802063W). The overall study protocol adhered to the Declaration of Helsinki. Informed consent was waived by the institutional review board owing to the anonymized nature of dataset used in this study.

Consent for publication

Not applicable.

Availability of data and material

This raw data was unavailable due to administrative regulation imposed by the overseeing authority.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40392.

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