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Original Research

Frailty, Health-Related Quality of Life, Cognition, Depression, Vitamin D and Health-Care Utilization in an Ambulatory Adult Population with Type 1 or Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Cross-Sectional Analysis

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Key Messages

- No previous studies have examined the prevalence of frailty in people with diabetes and chronic kidney disease in relation to vitamin D status.
- The factors influencing the onset of frailty and the impact on health-care utilization have not been studied.

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ABSTRACT

Objectives: Frailty can cause increased vulnerability to adverse health outcomes, such as falls, fractures, depression and reduced health-related quality of life (HRQoL). This cross-sectional study compared the differences in body composition, HRQoL, mental health and cognitive and vitamin D (vitD) status with health-care utilization by frail and nonfrail adults with diabetes mellitus (type 1 and type 2) and with chronic kidney disease (stages 1 through 5).
Methods: We studied adults with type 1 and type 2 diabetes and chronic kidney disease stages 1 through 5 who were participating in a longitudinal follow-up study (41 to 83 years of age; n=41). Body composition (dual-energy x-ray absorptiometry); vitD status (serum 25[OH]D_3); frailty (Edmonton Frail Scale); depression (Major Depression Inventory); HRQoL (Short Form Health Survey-36); and cognitive status (Mini Mental State exam) were measured using validated tools. Participants who were on dialysis and had body weights >136 kg, and coinciding comorbidities known to influence vitD metabolism were excluded.
Results: Frailty occurred in 17% of participants (n=7). Frail participants had lower lean body mass, lower HRQoL scores (individual and composite scores), more depression (p=<0.05) and higher numbers of health visits (total, inpatient and emergency) compared with nonfrail participants (p<0.05). No differences in health-care visit types or vitD status were noted between frail and nonfrail participants (p>0.05).
Conclusions: Frailty in an ambulatory population of adults with chronic kidney disease and diabetes is associated with low lean body mass, low HRQoL, greater depression and higher numbers of health-care visits.

Mots clés :
diabète sucré
fragilité
utilisation des soins de santé
santé mentale et cognitive
qualité de vie
vitamine D

RÉSUMÉ

Objectifs : La fragilité peut accroître la vulnérabilité aux événements indésirables tels que les chutes, les fractures, la dépression et diminuer la qualité de vie liée à la santé (QVLS). La présente étude transversale a permis de comparer les différences de la constitution corporelle, la QVLS, la santé mentale et cognitive, et le statut en vitamine D (vit D) à l'utilisation des soins de santé par les adultes fragiles et les adultes non fragiles atteints de diabète sucré (de type 1 ou de type 2) et de néphropathie chronique (de stades 1 à 5).

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Méthodes : Les adultes (de 41 à 83 ans; n=41) atteints de diabète de type 1 ou de type 2 et de néphropathie chronique de stades 1 à 5 qui participaient à une étude de suivi longitudinale ont fait l'objet de notre étude. Nous avons mesuré au moyen d'outils validés la constitution corporelle (absorptiométrie à rayons X à énergie double), le statut en vit D (la concentration sérique de 25[OH]D_3), la fragilité (l'échelle Edmonton Frail Scale), la dépression (le Major Depression Inventory), la QVLS (le questionnaire sur l'état de santé SF-36) et l'état cognitif (mini-examen de l'état mental). Nous avons exclu les participants qui suivaient une dialyse et avaient un poids corporel>136 kg, et qui présentaient des maladies concomitantes connues pour influencer le métabolisme de la vit D.
Résultats : La fragilité était présente chez 17 % des participants (n=7). Les participants fragiles avaient des masses maigres plus faibles, des scores de QVLS plus élevés (scores individuels et composites), davantage de dépression (p=<0,05) et un nombre plus élevé de consultations (totales, en milieu hospitalier et à l'urgence) par rapport aux participants non fragiles (p<0,05). Nous n'avons noté aucune différence dans les types de consultations ou le statut de la vit D entre les participants fragiles et les participants non fragiles (p>0,05).
Conclusions : La fragilité chez une population d'adultes sur pied atteints de néphropathie chronique et de diabète est associée à une masse maigre faible, une faible QVLS, davantage de dépression et un nombre élevé de consultations.

Introduction

Frailty is a physiologic condition in which decreased physiologic reserves and altered bodily functions cause increased vulnerability to adverse health outcomes, such as falls and fractures, and reduced health-related quality of life (HRQoL) (1,2). The term *physiologic reserve* refers to an organ's ability to adapt to metabolic and environmental stressors. This means that patients with frailty have decreased abilities to handle physiologic stress (1–3) and have increased difficulty in regaining homeostasis after an insult. There is no universal clinical definition of frailty, but various tools have been created to assess frailty (3–5). Frailty includes both physical (body composition) and psychosocial components (HRQoL, mental health [MH], cognitive function) in its definition, including significant reductions in lean mass, altered abilities to perform activities of daily life (ADLs), and reduced cognition and MH (1,6). Lifestyle may influence the onset and progression of frailty, but the major factor influencing the risk for frailty in adults is the presence of chronic diseases, such as chronic kidney disease (CKD) (7) and diabetes mellitus. Diabetes is a condition that occurs in up to 9% of Canadians, so examination of the potential onset of comorbid conditions such as frailty are important to consider because they may have a direct impact on morbidity and mortaliy (8–12). CKD is a common comorbid condition in diabetes, occurring in 30% to 50% of adults with type 1 and type 2 diabetes (13). The prevalence of frailty with CKD appears to be dependent on kidney function, with the highest prevalence (~70%) occurring in patients with stage 5 CKD who are undergoing dialysis (3,14,15). Hence, examining factors that may influence both the onset and the progression of frailty in this vulnerable population is important.

Frailty has been associated with increased morbidity, hospitalization and mortality in patients who have diabetes and CKD, but the longitudinal evolution of this disorder has not been well described, particularly in relation to potential lifestyle factors that may contribute to this disorder (8,16,17). Lifestyle and health factors, such as low muscle mass, reduced MH, low HRQoL and some nutrient deficiencies such as vitamin D (vitD) are factors that have been associated with the presence of frailty in adults with chronic health conditions (5,17–21). Patients with diabetes and CKD are especially vulnerable to vitD deficiency due to metabolic changes in vitD metabolism and dietary restrictions that ensure electrolyte and glycemic control, which often include foods and beverages high in vitD (20). This is particularly relevant in adults living in northern climates such as Alberta, where cutaneous synthesis of vitD may be severely impacted (22). Therapy for frailty is aimed at treatment of the causes of underlying disease and rehabilitation of physical functionality and overall diet quality to ensure that all nutritional requirements of individuals are met.

The study's objective was to compare the differences in body composition, HRQoL, MH, vitD status and health-care utilization between frail and nonfrail ambulatory adults with diabetes and CKD (stages 1 through 5). We hypothesized that frailty would be associated with suboptimal vitD status, lower cognition, lower HRQoL, lower MH, reduced lean body mass and higher health-care utilization in adults with CKD and diabetes (type 1 and type 2).

Methods

This was a descriptive cross-sectional study that included 41 ambulatory adults (41 through 83 years of age) with type 1 (n=3) or type 2 (n=38) diabetes mellitus and CKD (stages 1 through V) who had previously been enrolled in a randomized controlled trial (n=120) between 2012 and 2014 that examined the effects of 2 modes of vitD supplementation (2,000 IU/day vs. 40,000 IU/month) and who were undergoing longitudinal annual evaluation (23). Patients were recruited from the Northern Alberta Renal Program (24). Patients were excluded from the original randomized controlled trial if they were on dialysis (estimated glomerular filtration rate <10 mL/min/1.73 m^2), had body weights that precluded the ability to perform body composition measurements (>136 kg) according to dual-energy x-ray absorptiometry and/or were taking medications known to influence vitD metabolism and/or had coinciding comorbidities known to influence vitD status (e.g. malabsorption, untreated celiac disease) and/or who were on strict exercise regimens to promote weight loss (23,24). Included in this cross-sectional analysis were patients who had completed annual longitudinal visits and who had had frailty assessments performed during these visits (n=41) at either the year 4 or the year 5 follow up.

No significant differences in demographics, anthropometrics, CKD stages or diabetes types or durations were observed between those who consented to participate in the longitudinal follow-up study and those who had participated in the original randomized controlled trial (p>0.05). The dependent variable included frailty assessment using the Edmonton Frail Scale (EFS). The independent variables included body composition (measured by dual-energy x-ray absorptiometry); cognition (Mini Mental State Examination [MMSE]); HRQoL (Short Form Health Survey [SF-36]); depression assessment (Major Depression Inventory); physical activity (International Physical Activity Questionnaire); and health-care utilization. No significant differences in anthropometrics, CKD stages or demographic variables were observed between the participants receiving frailty assessments at year 4 or at year 5 (p>0.05).

Study visits were conducted in the Clinical Research Unit of the Alberta Diabetes Institute at the University of Alberta. Blood for assessment of vitD status (25[OH]D_3) was collected at the time of routine clinical blood work, which included estimated glomerular filtration rates and glycated hemoglobin, random blood glucose, urea, creatinine, albumin and parathyroid hormone levels (25). Serum 25(OH)D_3 was measured in the Core Laboratory of the University of Alberta Hospital according to standard methodologies (24). VitD status was classified using the following serum concentrations as cutoffs: <75 nmol/L (insufficient) and ≥75 nmol/L (sufficient) (26). Serum 25(OH)D_3 <50 nmol/L was classified as deficient (26). Demographics (age, gender, height, weight, body mass index [kg/m^2]) were collected during the study visit by trained personnel using validated methodologies and clinical information (medication use, comorbidities, diabetes type, duration of diabetes, CKD stage) were collected from the medical health records. CKD stages were defined according to Kidney Disease Outcomes Quality Initiative guidelines: stages 1 to 2, ≥60 mL/min/1.73 m^2; stages 3 to 4, 15 to 59 mL/min/1.73 m^2; stage 5, <15 mL/min/1.73 m^2) (27). Ethics approval was obtained from the Human Research Ethics Board at the University of Alberta (Pro00049292). Informed consent was obtained prior to enrollment in the study.

Frailty and cognition

Frailty was assessed using a modified version of the self-reported EFS (28,29). The EFS is based on 9 different domains, including concepts addressing cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and self-reported performance. Scoring for the EFS ranges from not frail (0 to 5); apparently vulnerable (6,7); mildly frail (8,9); moderately frail (10,11); and severely frail (12 to 18) (28,29). Because of the smaller sample size in this study, frailty was analyzed as plus-frail (scores of 6 to 18) and minus-frail (scores ≤5). The EFS was modified to include the drawing component of the MMSE instead of the traditional clock test (30). This change was made to reduce the length of the study visits and to reflect emerging evidence that the traditional clock test may not reflect higher-order cognitive function accurately in some patient populations (31). Cognition was assessed by using the MMSE, which consists of 11 items, including both questions and tasks (scores <24 are considered abnormal) (30).

Body composition

Body composition (BC) was assessed using the GE Lunar Prodigy High-speed Digital Fan Beam dual-energy x-ray absorptiometry (v. 10.5; GE Healthcare, Madison, Wisconsin, United States). BC parameters included whole-body and regional (arms, legs, trunk, android, gynoid and total mass) fat mass, lean mass (LM), total tissue and bone mineral content. The fat mass index (FMI) was calculated by using the following formula: total fat/height^2 (m^2). Appendicular skeletal muscle was obtained through the addition of the LM of the arms and legs in kilograms. Appendicular skeletal muscle mass index (ASMI) was calculated by using the following formula: ASM/height^2 (m^2). Low LM was defined as an ASMI more than 2 SD below the sex-specific means of a normal reference population (7.26 kg/m^2 for men and 5.45 kg/m^2 for women) (32).

HRQoL, mental health and physical activity

HRQoL was assessed using the validated self-reported SF-36 (33). The SF-36 consists of 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and MH) and 2 component summaries (physical component summary and mental component summary) (33–35). A score ranging from 0 to 100 was calculated for each domain; higher scores were representative of greater HRQoL. Comparison of individual domain and composite scores was made to age-matched normative data (35).

Depression was assessed using the validated, self-reported Major Depression Inventory (scores ≥20 are considered abnormal) (36). Physical activity was assessed using the International Physical Activity Questionnaire (37,38), which was scored to determine the total amount of metabolic equivalents (METs) in minutes per week and the total number of sedentary hours per participant (37).

Health-care utilization

A chart review was conducted using electronic medical records to assess cumulative individual health-care events (numbers and types) between 2012 and 2017. Types of health-care visits were categorized according to the International Classification of Diseases-10-Canada diagnosis codes associated with each health-care visit and then subcategorized into the following categories: nephrology, diabetes, ophthalmology, musculoskeletal, cardiovascular and other (23).

Statistical analysis

Data analysis was completed using the SAS 9.0 statistical software (v. 9.4; SAS Institute, Cary, North Carolina, United States). Data were expressed as mean ± SD (parametric) or median + interquartile range (nonparametric). Nonparametric variables were log transformed. Frailty was assessed as a categorical (yes/no) variable only; scores ≤5 were indicative of frailty. Independent t tests (parametric) and Mann-Whitney (nonparametric) analyses were conducted to assess the differences in continuous outcome variables (vitD status, HRQoL, BC, health-care utilization, cognition, physical activity, laboratory values, comorbidities) between frail and nonfrail participants. In contrast, the Fisher exact test (low expected frequency data) was used to assess for differences in categorical variables: frailty (plus or minus); depression (plus or minus); reduced lean body mass (plus or minus); sex (male or female); diabetes type (1 or 2); vitD (≥ or <75 nmol/L). Multivariate logistic regression analysis was conducted to assess the relationships among frailty and body composition, vitD status, HRQoL and MH. Data were adjusted for potential confounding variables (CKD stage, gender) where necessary. A p value ≤0.05 was considered significant.

Results

Demographic, anthropometric and laboratory variables

Anthropometric, demographic and laboratory data according to frailty are presented in Table 1A and B. The majority of patients (90%; n=37) were older than 60 years of age. None of the patients younger than 60 (41 to 59 years; n=4) were frail, and no significant differences in anthropometric or demographic variables were observed between this group of 4 patients and those in the nonfrail group (n=30) (p>0.05). Frailty occurred in 17% (n=7) of participants; 6 (85%) of these participants fell within the apparently vulnerable or mildly frail categories, while 1 participant was categorized as moderately frail. Participants were taking, on average, 11±4 medications (prescribed or over the counter), and the number of comorbid conditions (median, range) they presented in addition to diabetes and CKD was 5 (1 to 10) (23). Frail participants had a higher number of comorbid conditions than nonfrail participants (6±2 [frail] and 4±2 [nonfrail]; p=0.03). A total of 21 (51%) participants were taking oral hypoglycemic agents, 30 (73%) participants were taking insulin therapy and 12 (29%) were taking combined therapies. There was no difference in therapies (oral hypoglycemic agents, insulin)

Table 1
A. Demographic, anthropometric and clinical data. B. Laboratory data

A

Variable	Total (n=41)	By frailty		
		Frail (n=7)	Not frail (n=34)	p value
Male, n (%)	26 (63)	4 (57)	22 (65)	0.69
Age (years)	70 (65–74)	70 (67–74)	70 (65–76)	0.87
Weight (kg)	88.8±17.0	79.4±18.8	90.7±16.3	0.12
Height (m)	1.68±0.08	1.68±0.1	1.69±0.08	0.80
Body mass index (kg/m^2)	31±5.5	28±5.7	31±5.3	0.12
Type 2 diabetes, n (%)	38 (92)	5 (71)	33 (97)	0.07
Diabetes duration (years)	16±13	21.4±14.6	19.4±9.9	0.65
Comorbidities	5 (4–6)	6 (6–10)	5 (4–6)	0.03*
Chronic kidney disease, stage 3 through 5, n (%)	26 (63)	7 (100)	19 (56)	0.03*
Oral hypoglycemic agents, n (%)	24 (58)	3 (42)	21 (61)	0.42
Insulin therapy, n (%)	28 (68)	6 (85)	22 (64)	0.39
Vitamin D >75 nmol/L, n (%)	28 (70)	3 (42)	25 (75)	0.16
Vitamin D >50 nmol/L, n (%)	36 (90)	6 (85)	30 (90)	0.55
Vitamin D supplementation, n (%)	31 (76)	6 (86)	25 (74)	0.66
Vitamin D supplementation (IU)	2,000 (1,000–2,000)	1,000 (1,000–1,000)	2,000 (1,000–2,000)	0.06

B

Variable	Total (n=41)	By frailty			Normal range
		Frail (n=7)	Not frail (n=33)	p value	
eGFR (mL/min/1.72 m^2)	44±29	18±9	50±29	0.007*	>59.0
25(OH)D_3 (nmol/L)	88 (71–115)	74 (54–103)	89 (77–115)	0.43	>50
A1C (%)	7.3±1.1	7.5±1.3	7.3±1.1	0.73	4.3–6.1
Random blood glucose (mmol/L)	8.4 (7–11.7)	8.3 (6.8–13.6)	8.5 (7.1–11.1)	0.62	3.3–11
Albumin (g/L)	40±2.9	38±2.7	41±2.8	0.04*	35–50
PTH (pmol/L)	5.4 (3.2–15.9)	17.3±12.1	11.4±17.6	0.40	1.4–6.8
Urea (mmol/L)	9.5 (6.5–19.3)	15.5 (13.8–19.6)	8.4 (6.2–19.0)	0.13	2.5–8.0
Creatinine (umol/L)	139 (86–230)	299 (160–408)	115 (82–227)	<0.05*	50–105
Calcium (mmol/L)	2.33±0.14	2.24±0.18	2.36±0.13	0.05	2.10–2.60
Phosphorus (mmol/L)	1.2 (1.1–1.4)	1.3±0.4	1.2±0.2	0.14	0.80–1.45
C-reactive protein (mg/dL)	2.2 (1.3–6.3)	6.3 (4.1–7.0)	1.8 (0.9–5.9)	0.38	<8.0

25(OH)D_3, vitamin D status; *A1C,* glycated hemoglobin; *eGFR,* estimated glomerular filtration rate; *PTH,* parathyroid hormone.
Notes for A: Data are expressed as n (percentage) or mean ± standard deviation or median (interquartile range). A t test was conducted to assess the difference in means among groups. A Fisher exact test was used to assess relationships among categorical variables (gender, stage of chronic kidney disease, vitamin D supplementation, type of diabetes, vitamin D >75 nmol/L). Comorbidities were gathered from the patients' charts using physician ICD-10 codes and were counted using direct count. Vitamin D levels were unavailable for 1 participant due to difficulties with venous access, which precluded the ability to obtain a sample.
Notes for B: Data are expressed as mean ± standard deviation or median (interquartile range). A t test was conducted to assess the difference in means among groups. Laboratory data were missing for 1 participant (nonfrail group) due to difficulties with phlebotomy, which precluded the performance of routine blood work. Normal ranges were obtained from Alberta Health Services.
* p≤0.05 was considered significant.

between frail and nonfrail participants (p>0.05). No differences in hypoglycemic or hyperglycemic episodes were noted between groups (p>0.05). In total, 70% (n=28) of the participants had sufficient vitD levels (>75 nmol/L), while 10% (n=4) had deficient levels (<50 nmol/L). Of the participants, 76% (n=31) consumed a daily vitD supplement. There were no differences in sex (p=0.69), age (p=0.87), weight (p=0.11), height (p=0.84), body mass index (p=0.12), diabetes duration (p=0.65), vitD supplementation (p=0.06), vitD levels (p=0.43) or glycemic control (A1C [p=0.73] or random blood glucose [p=0.63]) between participants with and without frailty.

Frailty, vitD and body composition

Frail participants had lower ASMI and lower LM in some body segments (trunk, gynoid and android) compared to nonfrail participants (p≤0.05). There was no difference in total FMI, total FM, %FM or %LM in the various compartments between frail and nonfrail participants (Table 2). When adjusted for the potential confounding effects of sex, frail participants had lower ASMI than nonfrail participants (p<0.05).

Frailty, HRQoL, MH, cognition and physical activity

Overall, there was a 20% incidence of depression in this cohort. Frail participants had a higher incidence (83% frail vs. 6% nonfrail) of depression (p=0.005) than those without frailty (Figure 1A). Participants with frailty scored a median (range) of 31 (13 to 54) points lower in HRQoL scores when compared to nonfrail participants (p≤0.05) (Figure 1B). With the exception of the MH domain (p=0.08) and the mental component summary, participants with frailty had significantly lower HRQoL (domains, composite scores) (Figure 1B). However, when adjusted for differences in CKD stage, only physical functioning (p=0.004), blood pressure (p=0.001), role physical (p=0.003) and the physical component summary (p=0.002) remained significantly lower in the frail vs. the nonfrail participants. When compared against Canadian normative data for age and gender, participants with frailty scored a median (range) of 40 (10 to 64) points lower than age- and gender-matched healthy norms (32), representing a clinically significant difference (>5 points) (35). All participants had MMSE scores indicative of normal cognitive status (>24 points) for age and gender (28±1) (30). There was no difference in cognitive scores between frail and nonfrail participants (p=0.14).

No significant differences in total METs between frail (1,134±1,119 METs min/week) and nonfrail (2,756±2,966 METs min/week) participants were observed (p=0.16). Frail participants spent, on average, 6.7±1.7 h sitting during weekdays and 6.4±2.2 h during the weekends, whereas nonfrail patients spent 5.8±2.6 h (p=0.36) and 5.4±3.0 h sitting, respectively (p=0.42). There was no difference in sedentary hours (weekday or weekend) between frail and nonfrail participants (p>0.05).

Table 2
Body composition data

Variable	Total (n=41)	By frailty		
		Frail (n=7)	Not frail (n=34)	p value
BMI (kg/m^2)	31±5.5	28±5.7	31±5.3	0.12
FMI (kg/m^2)	11.6±4.05	11.1±4.1	11.7±4.1	0.72
ASMI (kg/m^2)	7.6±1.04	6.8±1.0	7.7±0.9	0.02*
Low lean body mass, n (%)	9 (21.9)	4 (57.1)	5 (14.7)	0.01*
Percent of fat				
Arms (%)	35±10.5	38±9.3	34±10.8	0.46
Legs (%)	31±13.9	39±11.3	32±11.2	0.14
Trunk (%)	42±7.1	42±7.8	42±7	0.84
Android (%)	46±7.3	46±6.8	46±7.5	0.78
Gynoid (%)	37±12.4	41±10.1	37±8.9	0.3
Total (%)	38±7.8	40±7.4	37±7.9	0.4
Fat mass				
Arms (g)	2,902±1,082	3,075±1,104	2,866±1,091	0.64
Legs (g)	7,643±6,022	9,460±3,627	8,737±4,829	0.71
Trunk (g)	20,363±6,629	17,752±7,202	20,900±6,488	0.25
Android (g)	4,031±2,488	3,490±1,487	4,179±1,449	0.26
Gynoid (g)	4,834±2,361	4,848±1,693	5,218±2,128	0.66
Total (g)	32,979±11,118	31,128±10,375	33,360±11,375	0.63
Percent lean body mass				
Arms (%)	64±10.5	61±9.3	65±10.8	0.46
Legs (%)	68±13.8	60±11.3	67±11.2	0.14
Trunk (%)	58±7.1	57±7.8	58±7	0.84
Android (%)	53±7.3	53±6.8	54±7.5	0.78
Gynoid (%)	62.8±12.4	58±10.1	62±8.9	0.3
Total (%)	62±7.8	59±7.8	62±7.9	0.4
Lean body mass				
Arms (g)	5,216±1,192	4,890±877	5,284±1,248	0.43
Legs (g)	16,531±3,095	14,562±3,893	16,936±2,805	0.06
Trunk (g)	27,134±4,750	23,049±5,180	27,975±4,267	0.01*
Android (g)	4,528±952	3,741±835	4,690±902	0.01*
Gynoid (g)	7,690±1,365	6,637±1,596	7,906±1,230	0.02*
Total (g)	52,229±8,761	45,493±10,187	53,616±7910	0.02*
Total mass				
Arms (g)	8,119±1,428	7,966±1,346	8,150±1,463	0.75
Legs (g)	25,391±5,665	24,023±5,029	25,673±5,817	0.48
Trunk (g)	47,499±9,987	40,798±11,067	48,878±9,336	0.04*
Android (g)	8,590±2,199	7,231±2,223	8,870±2,119	0.07
Gynoid (g)	12,735±2,674	11,485±2,295	12,993±2,704	0.17
Total (g)	85,209±15,940	76,622±17,071	86,977±15,368	0.11

ASMI, appendicular skeletal muscle mass index; *BMI*, body mass index; *FMI*, fat mass index.
Notes: A t test was conducted to assess the difference in means among groups.
* p≤0.05 was considered significant. Data are expressed as mean ± standard deviation or median (interquartile range).

Health-care utilization

Participants with frailty had a higher cumulative number of inpatient (p<0.001), emergency (p=0.002) and total (p=0.001) health-care visits compared to nonfrail participants (Figure 1C). These remained significant even after adjustment for sex and CKD stage. No significant differences in health-care utilization type between frail and nonfrail participants (p>0.05) were noted (Figure 1D).

Discussion

The study's aim was to describe the differences in depression, HRQoL, cognition, BC, MH, vitD status and health-care utilization in an ambulatory population of frail vs. nonfrail adults with type 1 and type 2 diabetes and with CKD (stages 1 through 5). One of the major findings in this study was the relatively low frailty rate of 17%, despite the relatively high comorbid burden. Frailty has been reported to occur in up to 70% of individuals with stage 4 through 5 CKD (15). In this study, frail individuals had significantly lower lean body mass, reduced HRQoL, more advanced CKD, more depression and a higher cumulative number of health-care visits, but no relationships to vitD status or cognitive status were found. Reductions in HRQoL occurred predominantly in the domains related to physical functionality (physical functioning, role physical, blood pressure, growth hormone, vitality). These domains explore the impacts of their health on ADLs, such as being limited in the types of things they can do (walking, climbing stairs, lifting things) and activities requiring greater effort (39). These findings have important implications for physical functionality in adults with diabetes and CKD because limitations in LM may be a direct contributor to risk for falls and fractures (40). It is interesting that few or no relationships were found between perceived MH in frailty, although patients with frailty had a higher prevalence of depression. This is an important finding because it shows that frailty not only has negative associations with physical health, but it also affects the way these patients live their day-to-day lives, their functional independence and, potentially, their overall perceptions regarding their health. Frailty was associated with depression, but the incidence was significantly lower than the rates reported in diabetes (41). This may have been because the patients in this study were ambulatory, had normal cognitive status, had support for ADLs provided by caregivers and family members and/or were functionally capable of attending to their own ADLs (data not shown). Mansur et al conducted a study in Brazil that analyzed the relationship between frailty and HRQoL in patients before dialysis, and they found, on average, a 22-point difference in the physical domains between frail and nonfrail participants (42). The same was observed by Chang et al in a study that assessed the relationship between frailty and HRQoL in community-dwelling elderly people (18). Similar to previous studies, an increased incidence of frailty in those with more advanced CKD was observed (9,10,15), potentially secondary to chronic protein-energy wasting and inflammation (2). Although frailty has been related to other demographic factors, such as age, gender and physical inactivity (16), no differences were observed between frail and nonfrail participants.

In contrast to other studies, no interrelationships between frailty prevalence and vitD status were found (21,43,44). This was probably because our population was well supplemented with vitD (>1,000 IU/day), and the majority were vitD sufficient. This reflects the interdisciplinary focus of health-care team members on musculoskeletal health, high rates of vitD$_3$ supplementation and overall focus on comorbidity prevention (45). These relationships were independent of seasonal effects and/or any recent changes in body weight (data not shown), suggesting that the effects of vitD status on frailty prevalence in a well-supplemented population may be difficult to determine using 25(OH)D$_3$ as the marker of vitD status. Understanding of the potential underlying mechanisms of vitD in skeletal physiology in frail individuals is warranted; there is substantial evidence that vitD deficiency may contribute to risk for falls and frailty (21,43,44,46). It is interesting that few patients in this study had experienced falls (n=5 frail; n=9 nonfrail; p=0.43) and/or accessed health-care services related to broken bones over the cumulative 5-year periods examined; which further supports the premise that vitD adequacy may be an important component of fracture and frailty prevention in this population.

Patients with frailty had an increased number of health events compared to nonfrail participants. This difference was consistent when comparing the data of frail participants with normative data (47). In this study, frail participants had, on average, significantly more inpatient, emergency and total events on an annual basis than the provincial averages and the ongoing national data, which are based on much larger cohorts (47,48). Most of the emergency and inpatient events seemed to be related to nondiabetes conditions or comorbidities (e.g. respiratory issues, cardiovascular disease, cancer) rather than diabetes-specific events. These results are similar to those of a recent study by Fisher et al that indicated that across Canada, health-care utilization in adults with diabetes and 3 or more comorbid conditions is more typically related to nondiabetes

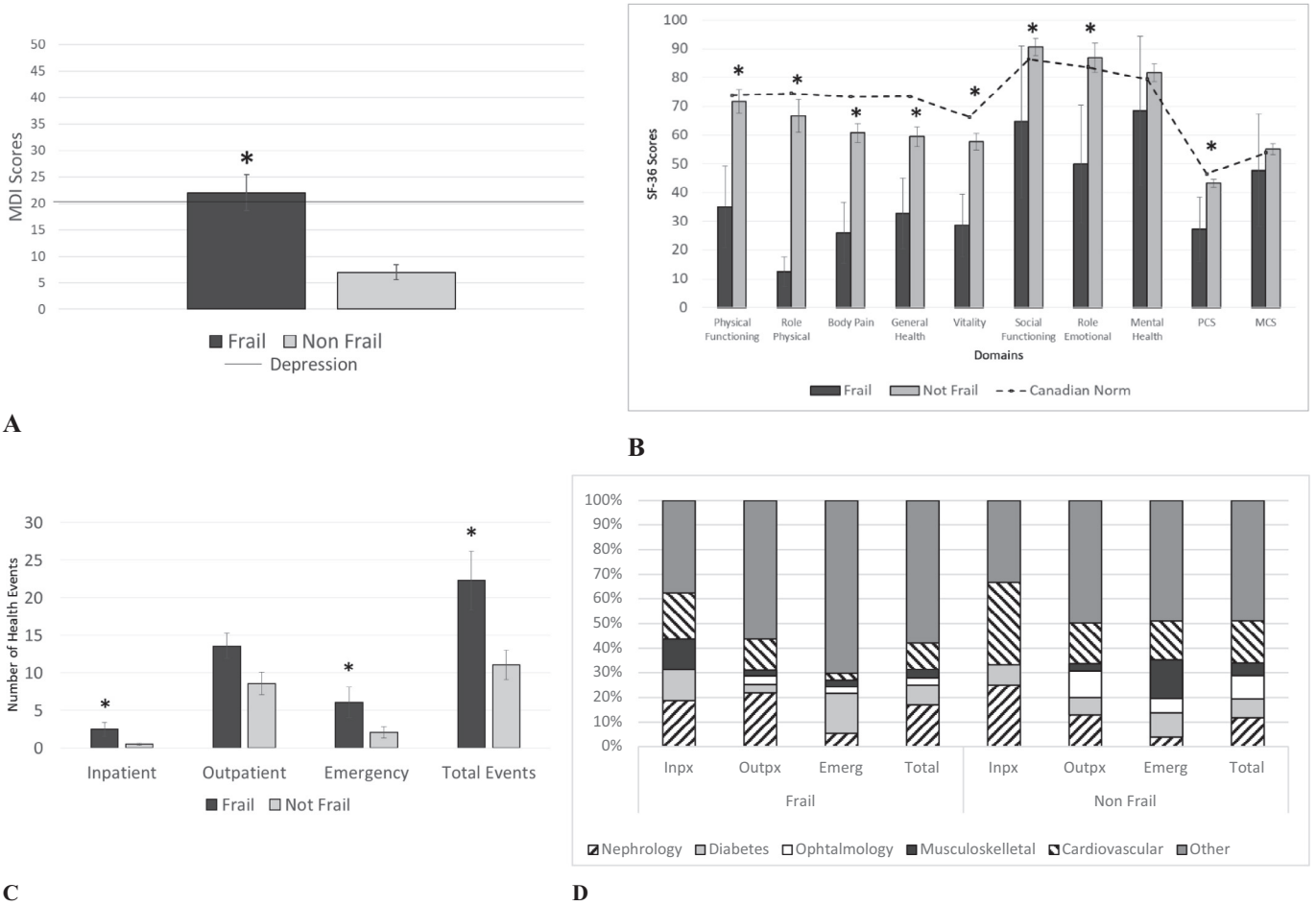

Figure 1. Comparison of frail and nonfrail adults with diabetes mellitus (type 1 or type 2) and chronic kidney disease (stages 1 through 5) with (A) Depression (as assessed by the Major Depression Inventory (MDI) Scale (p=0.0002); (B) Health-related quality of life (HRQoL) using the Short Form-36 (SF-36); (C) Cumulative number of health visits as categorized by Inpatient (Inpx), Outpatient (Outpx), Emergency (Emerg) and total health-care visits between 2012 and 2017; (D) Health Utilization by Service Type. Major Depression Inventory scores >20 indicative of depression. SF-36 is a 36-item questionnaire addressing concepts related to 8 individual domains (physical functioning, role physical, body pain, general health, vitality, social functioning, role emotional and mental health) and 2 composite scores (physical composite score [PCS] and mental composite score; health utilization by service type (% of health visits) was categorized by ICD-10 physician codes: nephrology, diabetes, ophthalmology, musculoskeletal, cardiovascular and other. The Other group represents more than 10 different service types (e.g. psychiatry, psychology, radiology and diagnostic imaging, same-day surgery, etc). Values with asterisks compare differences between frail (n=7) and nonfrail participants (n=34) at p<0.05. Dashed lines represent adult gender-matched Canadian normative values (27). Values are means ± SD, unless otherwise specified. Values with an asterisk are significantly different at p≤0.05 between frail and nonfrail participants. Frailty was assessed using the Edmonton Frail Scale (29).

conditions rather than to diabetes (48). We did not observe any differences between types of health-care services utilized by frail and nonfrail participants, but the increased use of health-care services by frail participants indicates the potential impact on health-care service access and the increasing potential for rising health-care costs associated with frailty.

This study had some limitations, mainly the lack of quantitative measures in regard to measures of physical functionality and muscle strength. The EFS is based on self-reported elements and lacks functional measures like hand-grip or walk tests that are typically used to assess participants' physical functioning. However, the EFS is a validated tool that has been proved to be useful in assessing the frailty of hospitalized and ambulatory patients (28,29). In this study, we substituted the clock exercise skill with a drawing component exercise contained in the MMSE tool to reduce the time burden of the study visit for each participant. Potentially, this could have influenced the study's ability to detect frailty, but that was unlikely to be a major factor because this task influences less than 10% of the overall scoring system of the EFS. Recent evidence has shown that these types of substitutions are appropriate for clinical populations and demonstrate a high level of agreement with EFS assessments that include the clock-drawing skill (31). Hence, this adaptation of the tool is unlikely to have contributed to underestimations of frailty. In addition, the majority of the study's participants performed their own ADLs (including driving, buying groceries and banking) and had normal MMSE scores, which is also indicative of lower frailty risk (30). The sample size in this study was relatively small, but it was sufficient to ensure that 1 SD ranges in many pertinent components of frailty assessment (body composition, HRQoL and MH status) were observed. Low frailty risk may have been more closely related to the longitudinal stability in BC (data not shown), higher levels of cognitive function and lower levels of depression when compared to other studies, which commonly report significantly more impairments in these areas (5,17,49). Although the comorbid burden of this population was high (>5 in addition to diabetes and CKD), it was related primarily to cardiovascular, gastrointestinal and respiratory comorbid conditions rather than to musculoskeletal or reduced cognitive capacity, even in patients >75 years of age. This may also explain, in part, the lower frailty prevalence in this study. Further work examining the longitudinal evolution of frailty in adults with diabetes and CKD is warranted.

Conclusions

In summary, the prevalence of frailty in an ambulatory cohort of adults with diabetes and CKD was approximately 17%. Frailty was associated with reduced lean body mass and HRQoL, depression, more advanced CKD and increased health-care utilization, but the overall prevalence of frailty was comparatively low for a population with high comorbid burdens. VitD sufficiency may be an important factor in these findings; the majority of patients were vitD sufficient. Future research examining the longitudinal evolution of frailty in this population and the impact of vitD supplementation may be important to ensure that effective prevention strategies are developed for this population.

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Author Disclosures

Conflicts of interest: None.

Author Contributions

SAP contributed to data collection, data analysis, manuscript preparation, review and approval of the final manuscript; PS and DRM contributed to study design and supervised data collection and data analysis, data interpretation, manuscript preparation and review and approval of the final manuscript; CJF and KJ contributed to study design, data interpretation, manuscript review and approval of the final manuscript.

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