Nutritional status, anthropometry, symptom burden, and health-related quality of life of chronic kidney disease of unknown etiology (CKDu) patients in Sri Lanka

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Abstract

For more than two decades, various tropical regions of the world have been experiencing increasing rates of chronic kidney disease (CKD) unrelated to conventional causes such as diabetes, hypertension, and other known etiologies. The etiology of the disease is still unclear; therefore, referred to as CKD of unknown etiology (CKDu). The disease has become a serious health problem in certain parts of Sri Lanka particularly, in North Central, Uva, and North-Western provinces.

The aims of the study were to describe and characterize the nutritional status, anthropometry, symptom burden, and health-related quality of life (HRQOL) of CKDu patients in order to examine the association of nutritional status in the development of CKDu, to study the longitudinal changes in anthropometry in CKDu, and to assess the sarcopenia prevalence, symptom burden, HRQOL, and associated factors of CKDu patients.

This was a prospective, longitudinal study that included a cohort of newly-identified CKDu patients and an individually age- and the sex-matched control group who live in the same area. A total of 120 patients with CKDu stages II-V participated in the study and followed-up for a period of one year. Demographic and health-related characteristics data were collected from all the participants, and laboratory, symptom burden, and HRQOL data of CKDu patients were also collected. Each participant underwent anthropometric and body composition measurements at each 2-month interval.

The mean age of the case and control group was 62 (SD-11), and 83 (69.2%) were men. A significantly higher proportion of CKDu patients were engaged in farming (93.3% vs. 82.5%) and had no or primary education (97.5% vs. 78.3%) compared to the control group.

Study I: All basic anthropometric measures and indices except body muscle% (BM%) were higher in the control group than the case group; however, the actual magnitude of these differences was small or non-significant. The discriminative ability of anthropometric parameters was low (area under the ROC curve $\leq$0.6).

Study II: The proportion of CKDu patients with low muscle mass, muscle strength, and physical performance was 77.5%, 70.8%, and 35.0%, respectively. The prevalence of sarcopenia was 66.7%, while 15% had severe sarcopenia. Only 5% of the CKDu patients had none of the indicators of sarcopenia. Men were more likely to be sarcopenic than

women (OR-7.735; p=0.009). The likelihood of having sarcopenia was increased by 7.9 times with central obesity (p=0.041) and reduced by 6.12% with each unit increase in body mass index (BMI).

Study III: There was a significant gain in body fat% and decline in BM% among elderly male CKDu patients over time with no significant effect on weight and BMI, which is referred to as masked obesity. Female CKDu patients demonstrated a significant gain in waist and hip circumferences; however, the effect on weight and BMI was significant only among young women.

Study IV: The majority of patients (95%) reported experiencing at least one symptom, and 55.8% of them reported having 5 or more symptoms. Bone/joint pain was the most experienced symptom. The mean symptom burden, physical component summary, mental component summary, and kidney-disease-specific component scores were 12.71 (SD-10.45), 68.63 (SD-19.58), 78.53 (SD-18.78), and 81.57 (SD-5.86), respectively. Age was a significant predictor of HRQOL, while hemoglobin level and being a farmer were significant predictors of symptom burden.

A number of important conclusions can be drawn from these results. First, this study unable to find any constructive evidence linking nutritional status to the development of CKDu. Second, evidence of a higher prevalence of sarcopenia among CKDu patients was found, even during the early stages of the disease. Third, elderly male CKDu patients demonstrated masked obesity with time, and therefore the integration of body composition measurements in addition to conventional BMI screening is recommended. Finally, CKDu patients in all stages experience symptom burden affecting all aspects of HRQOL warranting measures to relieve symptoms and improve the well-being of patients.

Key words: Chronic kidney disease of unknown etiology, Nutritional status, Physical activity, Sarcopenia, Symptom burden, Quality of life, Sri Lanka

Contents

List of Publications

The following papers have been published during my candidature.

1. Abeywickrama, H.M.; Wimalasiri, S.; Koyama, Y.; Uchiyama, M.; Shimizu, U.; Kakihara, N.; Chandrajith, R.; Nanayakkara, N. Quality of Life and Symptom Burden among Chronic Kidney Disease of Uncertain Etiology (CKDu) Patients in Girandurukotte, Sri Lanka. *Int. J. Environ. Res. Public Health* 2020, *17*, 4041. DOI:10.3390/ijerph17114041
2. Abeywickrama, H.M.; Wimalasiri, K.M.S.; Koyama, Y.; Uchiyama, M.; Shimizu, U.; Chandrajith, R.; Nanayakkara, N. Assessment of Nutritional Status and Dietary Pattern of a Rural Adult Population in Dry Zone, Sri Lanka. *Int. J. Environ. Res. Public Health* 2020, *17*, 150. DOI: 10.3390/ijerph17010150
3. Abeywickrama, H.M.; Koyama, Y.; Uchiyama, M.; Shimizu, U.; Iwasa, Y.; Yamada, E.; Ohashi, K.; Mitobe, Y. Micronutrient Status in Sri Lanka: A Review. *Nutrients* 2018, *10*, 1583. DOI: 10.3390/nu10111583

The conference publications during my candidature includes;

1) Abeywickrama, H.M.; Wimalasiri, K.M.S.; Koyama, Y.; Uchiyama, M.; Shimizu, U.; Chandrajith, R. Assessment of the nutritional status of a rural adult community in the dry zone, Sri Lanka, *20th Congress of Parenteral and enteral nutrition society of Asia*, October 2019.
2) Abeywickrama, H.M.; Koyama, Y.; Wimalasiri, K.M.S.; Uchiyama, M.; Shimizu, U.; Chandrajith, R.; Nanayakkara, N. Association between chronic kidney disease of unknown etiology (CKDu) and anthropometric measures and indices; A case-control study in Sri Lanka, *ESPEN congress*. September 2020.
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Prizes received during my candidature;

- 2020 MDPI writing prize for the submission on “My research on chronic kidney disease on unknown etiology and the United Nations sustainable development goals”

List of Figures

List of Tables

List of Abbreviations

AA	Aristolochic acid
AAN	Aristolochic acid nephropathy
ABSI	A body shape index
AER	Albumin excretion rate
AIC	Akaike's information criterion
AKI	Acute kidney injury
AUC	Area under the curve
AVI	Abdominal volume index
AWGS	Asian Working Group for Sarcopenia
BAI	Body adiposity index
BEN	Balkan endemic nephropathy
BF	Body fat
BIA	Bio impedance analysis
BM	Body muscle
BMI	Body mass index
BRI	Body roundness index
Ci	Conicity index
CI	Confidence interval
CIN	Chronic interstitial nephropathy
CINAC	Chronic interstitial nephropathy in agricultural communities
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CKDSI	Chronic kidney disease symptom index
CKDu	Chronic kidney disease of unknown etiology
CO	Central obesity
CVD	Cardiovascular diseases
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ESRD	End-stage renal disease
EWGSOP	European Working Group on Sarcopenia in Older People

FFM	Fat-free mass
FM	Fat mass
FNIH	Foundation for the National Institutes of Health
GBD	Global burden of disease
GFR	Glomerular filtration rate
GN	Glomerulonephritis
GNRI	Geriatric nutritional risk index
GS	Gait speed
Hb	Hemoglobin
HBP	High blood pressure
HC	Hip circumference
HD	Hemodialysis
HGS	Hand grip strength
HI	Hip index
HIV	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus associated nephropathy
HRQOL	Health-related quality of life
HT	Hypertension
IPAQ	International physical activity questionnaire
IQR	Inter quartile ranges
KDIGO	Kidney disease improving global outcomes
KDQOL-SF^{TM}	Kidney disease quality of life – short form
KDSC	Kidney-disease-specific component
LBW	Low birth weight
MCS	Mental component summary
MeHg	Methylmercury
MeN	Mesoamerican epidemic nephropathy
MET	Metabolic equivalent of task
MM	Muscle mass
MS	Muscle strength
MUAC	Mid-upper arm circumference
NCDs	Non-communicable diseases
NCP	North Central province

NSAIDs	Non-steroidal anti-inflammatory drugs
PA	Physical activity
PCS	Physical component summary
QOL	Quality of life
ROC	Receiver-operating characteristic
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SD	Standard deviation
SMI	Skeletal muscle index
T2DM	Type 2 diabetes mellitus
UACR	Urinary albumin creatinine ratio
UUC	Urothelial cancer
WC	Waist circumference
WHO	World health organization
WHR	Waist-to-hip ratio
WHtR	Waist-to-height ratio
YLDs	Years lived with disability
YLLs	Years of life lost

Declaration

I hereby declare that the work presented in this thesis was exclusively carried out by me, under the supervision of Prof. Yu Koyama, Department of Nursing, Graduate School of Health Sciences, Niigata University, Japan.

It describes the results of my own independent research, except where due reference has been made in the text. No part of this thesis has been submitted earlier or concurrently for any degree by me.

Signature of the candidate: ……

Hansani Madushika Abeywickrama

Date: ……..

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I hope this study will be a contribution to the health of people with or at risk of CKDu.

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Dedication

To my family for their endless love, care, and firm belief in me, which kept me going on this journey

CHAPTER 1

Background

1.1. Chronic Kidney Disease

Chronic kidney disease (CKD) is a worldwide public health concern that contributes greatly to morbidity and mortality from non-communicable diseases (NCDs). According to the global burden of disease (GBD) study 2017(1), the prevalence of CKD was estimated to be 9.1% with an estimated 697.5 million individuals affected worldwide. In 2017, around 1.2 million people died because of CKD, resulting in a 41.5% increase in all-age mortality from CKD since 1990. In a best-case scenario, the number of deaths due to CKD projected to rise by 1 million and up to 4 million in a worst-case scenario, by 2040 (2). In 1990, CKD was the 27th leading cause of death which rose to the 18th leading cause of death in 2010 (3). In 2017, CKD ranked as the 12th leading cause of death (1). CKD is also associated with substantial morbidity. Worldwide, CKD accounted for 7.3 million years lived with disability (YLDs), 28.5 million years of life lost (YLLs), and 35.8 million disability-adjusted life years (DALYs) (1). The age-standardized CKD prevalence was 1.29 times higher in females than males. In contrast, the global age-standardized mortality rate of CKD 1.3 times higher among males than females. Incidence, prevalence, and progression of CKD vary across different countries by ethnicity and social determinants of health. People in the lowest socio-demographic quartile have a higher risk of CKD compared to those in the highest quartile (4).

1.1.1. Definition and classification of CKD

The definition and classification of CKD have evolved, and the current international consensus by kidney disease improving global outcomes (KDIGO) (5) define CKD as abnormalities of kidney structure or function present for at least 3 months with health implications. The criterion of CKD includes either of the following presents for >3 months;

1. Glomerular filtration rate (GFR) <60ml/min/1.73m^2
2. markers of kidney damage (1 or more)

- Albuminuria (Albumin excretion rate (AER) ≥30mg/24h; urinary albumin creatinine ratio (UACR) ≥30mg/g

- Urine sediment abnormalities
- Electrolyte and other abnormalities due to tubular disorders
- Abnormalities detected by histology
- Structural abnormalities detected by imaging
- History of kidney transplantation

KDIGO recommends that CKD is classified based on the cause (C), GFR (G), and albuminuria (A) categories, which is collectively known as CGA classification. Cause (C) classification of CKD is based on the presence or absence of underlying systemic diseases and location within the kidney of observed or presumed pathologic-anatomic findings (Table 1.1).

Table 1.1: CKD classification based on the anatomic location within the kidney and presence or absence of systemic disease

Location	**Examples of systemic diseases affecting the kidney**	**Examples of primary kidney diseases**
Glomerular diseases	Diabetes mellitus (DM); Systemic autoimmune diseases; Systemic infections; Drugs; Neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative glomerulonephritis (GN); Focal or segmental glomerulosclerosis; Membranous nephropathy; Minimal change disease
Tubulointerstitial diseases	Systemic infections; Drugs; Autoimmune; Sarcoidosis; Urate; Environmental toxins (lead, aristolochic acid (AA)); Neoplasia (myeloma)	Urinary-tract infections; Stones; Obstruction
Vascular diseases	Atherosclerosis; Hypertension (HT); Ischemia; Cholesterol emboli; Systemic vasculitis; Thrombotic microangiopathy; Systemic sclerosis	Associated renal limited vasculitis; Fibromuscular dysplasia

Cystic and congenital diseases	Polycystic kidney disease; Alport syndrome; Fabry disease	Renal dysplasia; Medullary cystic disease; Podocytopathies

Source: KDIGO 2012 clinical practice guidelines for the evaluation and management of CKD (5)

CKD categories are assigned based on GFR (G categories G1 through G5), and on albuminuria (A categories A1 through A3). An increase in categories is associated with increased risk of disease progression, all-cause mortality, cardiovascular death, and acute kidney injury (AKI) (Table 1.2 and Table 1.3).

Table 1.2: GFR categories in CKD

Category	**GFR level (ml/min/1.73m^2)**	**Terms**
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Source: KDIGO 2012 clinical practice guidelines for the evaluation and management of CKD (5)

Table 1.3: Albuminuria categories in CKD

Category	**AER**	**UACR***		**Terms**
	(mg/ 24 hrs)	**(mg/mmol)**	**(mg/g)**	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased
A3	>300	>30	>300	Severely increased

*Approximate equivalent to UACR

Source: KDIGO 2012 clinical practice guidelines for the evaluation and management of CKD (5)

CGA categories are also used in predicting risk for the outcome of CKD. The following heat map represents the risk of prognosis of CKD according to GFR and albuminuria categories (Figure 1.1).

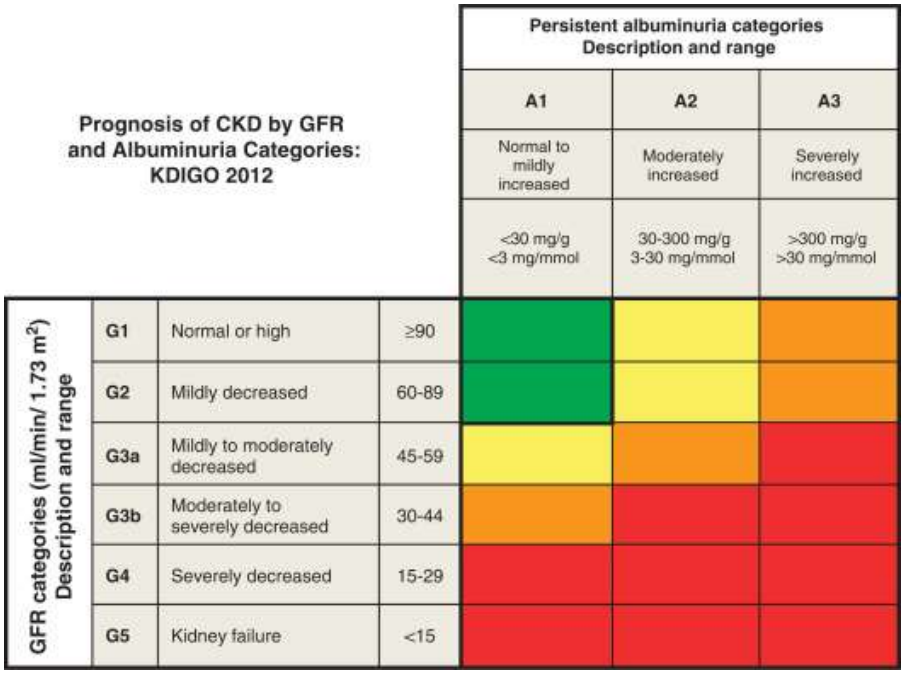

Figure 1.1: Predicting prognosis of CKD by GFR and albuminuria categories

Green - low risk; Yellow - moderately increased risk; Orange - high risk; Red - very high risk

Source: KDIGO 2012 clinical practice guidelines for the evaluation and management of CKD (5)

1.1.2. Causes and risk factors of CKD

CKD shares common risk factors with other NCDs such as cardiovascular diseases (CVD) and DM, and those risk factors can be categorized in several ways. Risk factors can be modifiable or non-modifiable/ fixed. Family history or genetic predisposition (6), increasing age (7), gender-specific differences (8), previous kidney disease or injury (9), low birth weight (LBW) (9) are some non-modifiable risk factors. Modifiable risk factors can be behavioral (smoking (10), physical inactivity (11,12), poor nutrition (13,14)), or biomedical (HT (15), CVD (16), overweight and obesity (17), DM (18), systemic infections (19). Identification of modifiable risk factors as early as possible is important to devise strategies for preventing and limiting the progression of CKD.

Risk factors can also be categorized as development factors and progression factors. Development factors include susceptibility factors and initiation factors. Susceptibility factors increase susceptibility to kidney damage which includes older age, genetic predisposition, and LBW/ low kidney mass. Factors that directly cause kidney damage such as autoimmune diseases (20,21), DM, HT, systemic infections, and toxins (22) are known as initiation factors. Progression factors worsen kidney damage and cause a rapid decline in GFR, and examples include high blood pressure (HBP), poor DM control, smoking, and CVD. However, with sustained exposure, certain factors may fall into more than one of these categories (23).

According to GBD study 2017, impaired fasting plasma glucose, HBP, high body mass index (BMI), a diet high in sodium (Na), and lead (Pb) accounted for 57.6%, 43.2%, 26.6%, 9.5%, and 3.6% of the age-standardized rate of CKD DALYs. HBP was the leading risk factor for CKD burden in East Asia, Eastern Europe, tropical Latin America, and Western Sub-Saharan Africa, whereas high fasting plasma glucose accounted for the largest proportion of CKD in all other regions (1).

DM and HT are the major causes of CKD worldwide. According to the GBD 2017, DM was the largest contributor to the number of CKD DALYs (30.7%) with CKD due to type 1 and type 2 DM (T2DM) resulting in 2.9 million, and 8.1 million DALYs, respectively. Among the many causes of CKD, only T2DM showed a significant increase in the age-standardized DALYs rate (9.5%) from 1990 to 2017. However, CKD due to causes other than HT, DM, and GN resulted in the highest age-standardized rate of DALYs in 2017 (Figure 1.2) (1). Etiological factors of CKD have also divided as vascular, glomerular, tubulointerstitial, and obstructive (23).

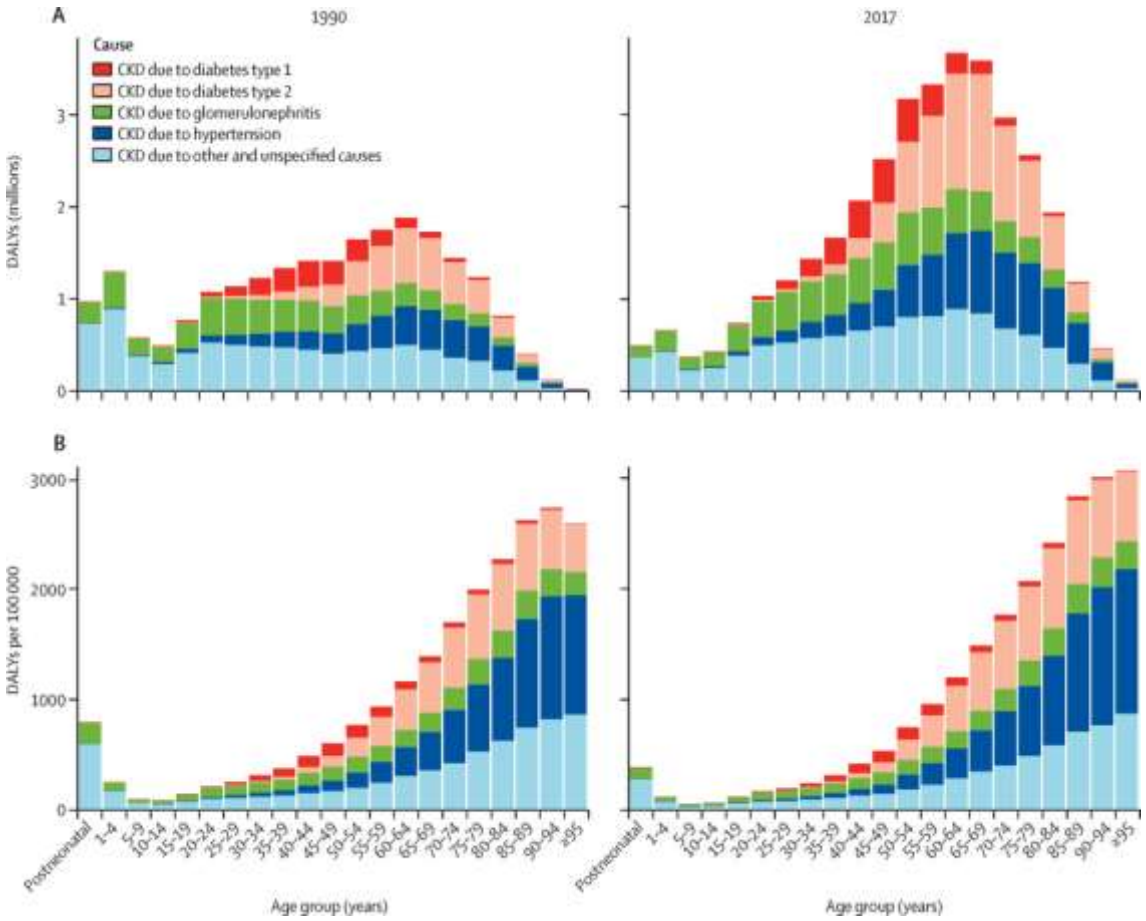

Figure 1.2: Global DALYs number (A) and rate (B) for CKD by different etiology in 1990 and 2017

Source: Global, regional, and national burden of CKD, 1990-2017 (1)

1.1.3. Clinical manifestations and complications of CKD

Many people are often asymptomatic of their CKD and are diagnosed after the disease is well advanced or after chance findings from screening tests such as routine medical check-ups. However, some people show symptoms directly depending on the cause of CKD. As kidney function becomes less effective, uraemic retention products accumulate in the body, affecting nearly all body systems and organs. Figure 1.3 illustrates the possible symptoms and signs of CKD (4).

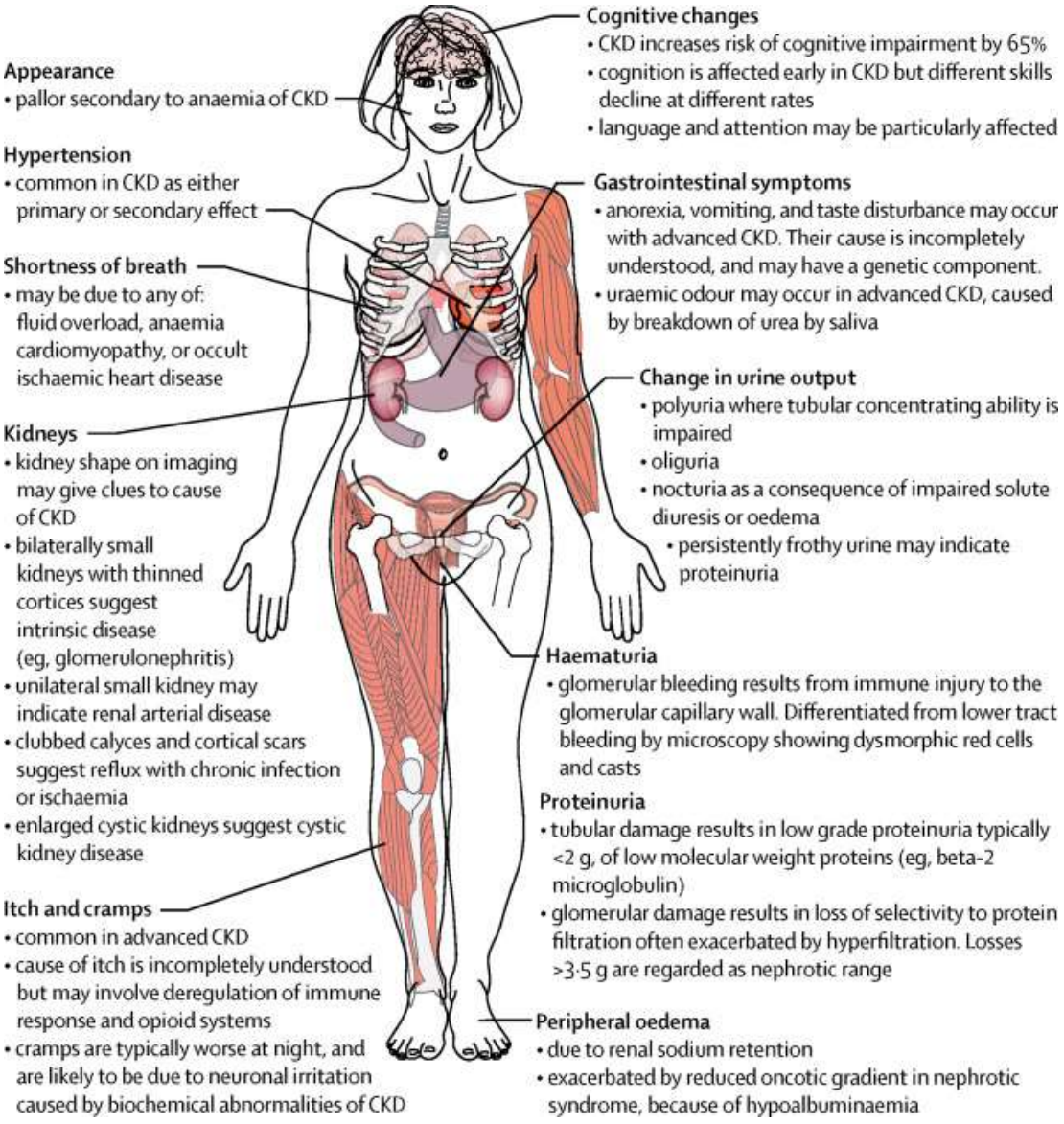

Figure 1.3: Signs and symptoms of CKD

Source: Chronic kidney disease, 2017 (4)

CKD is a major risk factor for other chronic diseases and mortality, and this interaction is entwined with complications of CKD (4). CKD is associated with several complications, including anemia, metabolic bone disease, CVD, cancer, hyperlipidemia (4,24). Progression to end-stage renal disease (ESRD) is a complication of CKD itself, which result in increased disability and mortality (25). The premature death of CKD patients is 5 - 10 times more likely than progress to ESRD. The risk of death increase exponentially with a progressive decline of kidney function and this is largely attributable to CVD mortality (4).

1.1.4. CKD in Sri Lanka

Even though there are no completely reliable numbers for the full extent of CKD incidence, prevalence, mortality, and trends in Sri Lanka, health statistics, and published studies have reported a steady increase of patients with CKD. Annual health statistics report on hospitalizations and deaths in the public sector hospitals in the country do not specifically provide data for CKD but report diseases of the urinary system. According to the annual health statistics in 2017, diseases of the urinary system was the 6th leading cause of hospitalization, accounting for 4.7% of total hospital admissions. In 2015, 4.4% of hospital admissions were due to diseases of the urinary system and is ranked as the 7th leading cause of hospitalization. The rate of hospital deaths by diseases of the urinary system was 12.9 per 100,000 population in 2017 and ranked as the 8th leading cause of death from 2014 to 2017. Nevertheless, there is substantial variation in hospital admissions and deaths due to urinary system diseases when disaggregated by districts in the country. In 2017, diseases of the urinary system were the leading cause of death in Polonnaruwa and Vavunia districts, while it was ranked as the 4th and 5th leading causes of hospitalization in Mullativu, Monaragala, Badulla, Polonnaruwa, and Kilinochchi districts (26).

In 2019, Ranasinghe *et al*. (27) published the first large-scale cross-sectional survey from Sri Lanka which described the incidence, prevalence, and trend of CKD in the North Central Province (NCP) of the country. The study included 30,566 CKD patients who had been diagnosed from 2003 to 2017. The incidence of CKD showed a steady increase from 2009 to 2012, a sharp increase from 2013 to 2016, and a slight decrease in 2017. The prevalence was more than 70%, 40%, and 33% in patients over 50, 60, and 70 years of age, respectively. Male farmers were the most affected, while the majority of patients were in CKD stage I (69.6%). The point prevalence of CKD in high incidence areas of NCP ranged from 2.44 – 4.35, while the 5-year survival rate was 71.2%. Within the 5 years of diagnosis, 21.4% of CKD patients were dead. Among the CKD deaths 23.2%, 67.6%, and 82.8% occurred within 1, 3, and 5 years of diagnosis.

1.1.5. Clusters of CKD around the world

In addition to HT and DM, so-called traditional causes of CKD, non-traditional causes such as infections, nephrotoxic drugs, herbal medications, and environmental toxins have been associated with a high prevalence of CKD. Further, the distribution of CKD sometimes follows a geographical cluster, affecting particular segments of the population. For instance, renal failure attributable to glomerular sclerosis caused by T2DM was a major cause of morbidity and mortality among Pima Indians of Arizona, however, the overall incidence of ESRD has decreased since 1990, possibly due to the widespread use of angiotensin-converting enzyme inhibitors to slow the disease progression (28). Higher rates of preterm birth and LBW was associated with an increased risk of developing renal failure in adult life among indigenous Australians, as a result of smaller kidney volume and nephron deficiency (29,30). Human immunodeficiency virus (HIV) patients of African ancestry show a high susceptibility to develop HIV-associated nephropathy (HIVAN) which leads to renal enlargement and rapid progression to kidney failure (31,32).

In some populations, environmental toxins, such as heavy metals, mycotoxins, have been identified as causes of CKD. Nephropathy due to methylmercury (MeHg) poisoning along the Minamata Bay in Japan, associated with the ingestion of fish and shellfish contaminated by MeHg discharge in wastewater from a chemical plant (33). Itai-Itai disease is caused by cadmium (Cd) exposure that was first reported in the Jinzu river basin of Toyama prefecture, Japan. The main characteristic of the disease is osteomalacia accompanied by severe bone pain, and renal tubular nephropathy (34). Contaminated food with ochratoxin A, a nephrotoxic mycotoxin, has been linked to an increased prevalence of chronic interstitial nephropathy (CIN) of unknown cause in Tunisia (35).

AA nephropathy (AAN), is a rapidly progressive interstitial nephritis leading to ESRD, was initially reported in a group of patients in Belgium who had ingested slimming pills containing a Chinese herb known as *Aristolochia Fangchi*, which is rich in AA. Later new cases of AAN were regularly reported worldwide including France, Germany, Spain, UK, US, China, Japan, India, and Hong-Kong (36). Balkan endemic nephropathy (BEN) is chronic tubulointerstitial nephropathy which was first described in 1956 among residents of farming villages located along tributaries of the Denbu river in Bosnia-

Herzegovina, Croatia, Macedonia, Serbia, Bulgaria, and Romania. The disease is characterized by an insidious onset, familial clustering, gradual progression to ESRD, and close association with upper urothelial cancer (UUC). Studies conducted over decades have provided a strong case that the BEN and UUC are stemming from chronic dietary exposure to AA, a principle component of *Aristolochia clematitis* which grows as a weed in the wheat fields of the endemic regions (37).

From the 1990s, a rapid increase in CKD prevalence was observed in several tropical regions in the world, including Central America (El-Salvador, Guatemala, Nicaragua, and Costa Rica), South Asia (Sri Lanka and India), and Africa (Egypt). This form of CKD cannot be attributed to any known etiologies and has different epidemiological characteristics than traditional CKD, hence known as CKD of unknown etiology (CKDu) (38).

1.2. Chronic kidney disease of unknown etiology (CKDu)

CKDu is defined as an impairment of kidney function in which the cause cannot be attributed to any known etiology such as DM, chronic HT, snake bite with systemic envenomation, chronic GN, or obstructive nephropathy (39). Different nomenclature has been used to describe CKDu in the literature: CIN in agricultural communities (CINAC), CKD of unknown origin, agrochemical nephropathy. The disease is also named after the region or country of its origin: Central American nephropathy, Salvadoran agricultural nephropathy, Mesoamerican epidemic nephropathy (MeN), chronic tubule-interstitial kidney disease of Central America and Udhanam endemic nephropathy in India, or Sri Lankan agricultural nephropathy (40). There is no acceptable global definition for CKDu, however, a case definition was developed by the Ministry of Health, Sri Lanka in 2016 (41). Later, the Sri Lanka Society of nephrology refined this definition through a consensus of experts and agreed upon a new case definition for CKDu which is based on 3-tiers of diagnosis;

(i) suspected CKDu which is relevant to the primary care level,
(ii) probable CKDu which is for epidemiologic surveillance, and
(iii) confirmed CKDu for clinical diagnosis (Table 1.4).

Table 1.4: Case definition of CKDu Sri Lanka 2018 update (42)

Suspected CKDu
Essential criteria
GFR <60 ml/min per 1.73 m^2 using CKD epidemiology collaboration (CKD-EPI) equation OR albuminuria ≥ 30 mg/g creatinine OR proteinuria ≥ 150 mg/g creatinine
Exclusion criteria to identify suspected CKDu among those satisfying the above criteria
Urine protein: creatinine ratio > 3000 mg/g creatinine
DM based on self-report of diagnosis OR being on treatment OR capillary random plasma glucose ≥ 200 mg/dl
HT based on treatment with more than 2 drugs OR untreated blood pressure of >160/100 mmHg
AKI that required dialysis in the past based on the history or documented evidence
Age > 70 years
Probable CKDu
Essential criteria
GFR < 60 ml/min per 1.73 m^2 using CKD-EPI equation OR UACR ≥ 30 mg/g creatinine OR urine protein: creatinine ratio ≥ 150 mg/g creatinine On repeat assessment after 12 weeks AND satisfying the criteria for suspected CKDu
Exclusion criteria to identify probable CKDu among those satisfying the above criteria
DM based on the presence of any of the standard criteria for diagnosis (fasting plasma glucose ≥126 mg/dl, 2-h plasma glucose ≥200 mg/dl on oral glucose tolerance test, HbA1c ≥6.5%)

Clinical OR laboratory OR ultrasound evidence of other causes of CKD such as;

- Polycystic kidney disease
- Congenital malformations
- Autoimmune diseases
- Glomerular diseases

Ultrasound evidence of;

- Unequal kidney sizes with a discrepancy of >1.5 cm
- Obstructive nephropathy
- Kidney stones of any of the following features
    - An obstructive stone
    - A non-obstructive single stone >10 mm
    - A non-obstructive multiple stones >5 mm in either or both kidneys

Confirmed CKDu

Confirmed with histopathology consistent with CKDu

All the above-mentioned criteria for probable CKDu

AND (in addition) histopathological features consistent with CKDu on biopsy

Confirmed clinically in the absence of histopathology

All the above-mentioned criteria for probable CKDu

AND (in addition) renal biopsy not possible

1.2.1. Epidemiology of CKDu

High prevalence of CKDu has mainly been reported in low- and middle- income countries in Central America and Asia. The estimates in the two regions difficult to compare mainly due to differences in case definitions. The highest prevalence of CKDu has been reported in Nicaragua where 10-20% of the adult population are affected (43). On the other hand, prevalence rates in South Asia are around 1.5-4% (27). In both regions, CKDu predominately affects men who are typically around the age of 40-60 years and engaged in agriculture such as rice paddy farmers in Sri Lanka and sugar cane farmers in Nicaragua (44). However, there are emerging reports of CKDu in women and children who live in the same environment (39,45).

In Sri Lanka, CKDu burden is most prominent in NCP and the disease has spread to adjacent farming areas in Uva, North Western, and Eastern provinces. According to the statistics in NCP, the etiology was unknown in 70.2% of the newly diagnosed CKD patients from 2009 to 2011, with more than 60000 estimated patients and 20000 deaths annually (44). A recent study reported that 10% of the population of certain administrative divisions in NCP have had medical care for CKDu (46).

1.2.2. Clinical profile and histopathology of CKDu

CKDu is a slow, progressive condition and the majority of patients are asymptomatic during the early stages of the disease. Arthralgia, asthenia, decreased libido, muscle cramps, and faintishness are some of the general symptoms reported at early stages. Urinary symptoms such as nocturia, dysuria, post-void dribbling, urinary hesitancy, and foamy urine are also reported. These symptoms appear in stage II and increase with the progression of the disease. As for markers of renal damage, the urine sediment shows no significant abnormalities, proteinuria is rare, and tubular markers such as β2-microglobulin are elevated in the urine. The studies have reported that at the advanced stage of the disease renal ultrasound shows increased echogenicity, decreased cortico-medullary ratio, and irregular margins (44).

The morphological pattern of CKDu has been described as chronic tubulointerstitial nephritis in studies conducted in both Sri Lanka and El-Salvador. A retrospective renal histopathology analysis carried out in Sri Lanka reported interstitial fibrosis as the main pathological feature in renal biopsies of CKDu patients, with varying degrees of interstitial inflammation, tubular atrophy, and glomerulosclerosis (47,48). Severe interstitial fibrosis and tubular atrophy and less glomerulo-megaly were found among sugarcane workers with CKDu compared to non-sugarcane agricultural workers and non-agricultural workers in El-Salvador (49).

1.2.3. Etiology of CKDu

Although multiple hypotheses have been formulated on potential risk factors for CKDu in Sri Lanka and other countries, the definitive cause/s of the disease is still unknown. Data from published literature strongly suggest that the CKDu origin is multifactorial rather than due to a single cause, and most of the studies conducted so far have focused

on occupational, environmental, lifestyle, and genetic factors. The causes related to agriculture such as heat stress and dehydration, infection/ inflammation, and contaminated water with heavy metals and/ or pesticides have been proposed. Heat stress and dehydration are the favored explanations in Central America as the possibility of recurrent heat exposure with physical exertion, excessive sweating, and inadequate water and mineral replacement can result in CKDu (50).

Although the available evidence and circumstances do not completely rule out heat stress and dehydration as the possible causes of CKDu in South Asia, various environmental contaminants such as heavy metals, silica, pesticides have received particular attention. Tubulointerstitial pathology suggests a potential toxin involvement in the causation of CKDu, and given the link with agricultural communities and the fact that many pesticides are known human nephrotoxins, pesticides have been widely studied. However, recent systematic review found that pesticides were an unlikely cause of CKDu (50). Metals and other contaminants in water and food such as arsenic, Cd, fluoride, aluminum, and silica have also received much attention, however, studies conducted in Sri Lanka and Central America have found either low levels of these contaminants in water, food, and/ or urine, or findings were not consistent when repeated (39,51). Hardness and fluoride in drinking water is one of the most commonly proposed etiological factor in recent years (52,53). A recent review concluded excess fluoride in drinking water and in the locally grown food in the affected areas in Sri Lanka as the causative factor of CKDu (54).

Mycotoxins such as aflatoxins, ochratoxins, and fumonisins and bacterial toxins present in food and drinking water are usually nephrotoxins and have been characterized for CKDu. Some viral and bacterial infections including leptospirosis, Malaria, leprosy, and hantavirus are thought to play a role in the development of CKDu as they are known to cause AKI which may progress to CKDu. Genetic susceptibility was identified as a risk factor for CKDu, and a recent study found a genome-wide significant association with CKDu for a single nucleotide polymorphism. Evidence regarding other postulated causes such as non-steroidal anti-inflammatory drugs (NSAIDs), ayurvedic medicines, alcohol consumption, smoking, malnutrition, LBW, intake of fructose-rich soft drinks, selenium deficiency is largely anecdotal, hence there is a need for these hypothesis to be either confirmed or rejected (39,50,51).

CHAPTER 2

Objectives

2.1. Rationale of the study

Numerous studies on CKDu have been undertaken from biochemical and epidemiological perspectives. However, the main objective of many of these studies has been to identify the etiology of the disease, and a few studies have sought to address the characteristics and experiences of those already affected by the disease. Anthropometric profile and nutritional characteristics of patients are important in predicting complications and determining treatment strategies. Despite its scientific and clinical importance, most healthcare professionals and researchers in Sri Lanka are unaware of the prevalence and impact of sarcopenia in patients. Symptoms experienced by patients are multidimensional and characterized by prevalence, distress, severity, and frequency. Assessment of all those characteristics is important to capture the impact of the disease and direct treatment. Quality of life (QOL) represents the impact of the disease or its' treatment on the subjective feeling of the patient about their physical, mental, emotional, social, and functional wellbeing. As many CKDu patients are from rural, socio-economically disadvantaged communities, it is imperative to ensure that they have the best QOL when being managed. For these reasons, it is important that research is conducted to provide health care professionals with evidence of the profile and experiences of patients. Evaluation of these factors among CKDu patients can add new insight into the management of the disease as it enables adjustment of medical decisions and patient management interventions to the physical, emotional, and social needs of patients.

2.2. Significance of the study

The studies in this thesis are the first attempts to (1) systematically document the profile of CKDu patients in terms of anthropometry, nutritional status, and physical activity (PA), (2) assess the prevalence of sarcopenia among a patient group in Sri Lanka, and (3) describe the multidimensional experiences and perspectives of patients with the diagnosis of CKDu in terms of symptom burden and QOL. It was hoped that the findings of this study will inform health care providers about better management of CKDu patients by identifying areas that clinical interventions and health education should focus on.

2.3. General and specific objectives

2.3.1. General objective

The overall objective of this study was to describe and characterize the nutritional status with a focus on anthropometry and PA, symptom burden, and health-related quality of life (HRQOL) of CKDu patients to enhance the understanding of the disease condition and to expand the disease-related knowledge.

2.3.2. Specific objectives

Four studies form the basis of this thesis, and the specific objectives for each study were as follows.

Study I: Association of nutritional status with CKDu: a case-control study

- to examine the associations of anthropometric parameters and PA with CKDu
- to determine the use of anthropometric variables in the risk prediction of CKDu

Study II: Prevalence and associated factors of sarcopenia among CKDu patients

- to determine the prevalence of sarcopenia in CKDu patients who are not on renal replacement therapy (RRT)
- to examine the demographic, lifestyle, anthropometric, and clinical factors associated with sarcopenia

Study III: A longitudinal study of the anthropometric changes in CKDu

- to describe longitudinal changes in anthropometric parameters of CKDu patients in comparison to non-CKDu subjects
- to explore the effects of age and sex on anthropometric changes in CKDu

Study IV: Symptom burden and HRQOL among CKDu patients

- to assess the prevalence, severity, and burden of symptoms, and HRQOL of CKDu patients who are not on RRT
- to determine the socio-demographic, anthropometric, and PA correlates

CHAPTER 3

Methods and materials

3.1. Research design

This study used a prospective, longitudinal design in a cohort of patients with CKDu and a group of age- and sex-matched controls.

3.2. Study area and population

CKDu patients were recruited from the renal clinic in District Hospital, Girandurukotte, Sri Lanka from January 2019 to March 2019. The patients who were recently diagnosed to have CKDu by a consultant nephrologist and not on RRT formed the study group.

The control (non-CKDu) group consisted of age- ($\pm$3 years) and sex-matched individuals selected from the community who had not been diagnosed with CKD/ CKDu. All subjects were inhabitants of the Girandurukotte area.

3.3. Sample size

A list of patients registered at the renal clinic in District hospital, Girandurukotte, Sri Lanka from June 2018 to January 2019 was obtained. After excluding those with CKD and other renal problems, 178 CKDu patients were approached, and finally, 120 patients were eligible and agreed to participate in the study.

After each case was enrolled, individuals who were confirmed of not having CKD/CKDu and best match with age ($\pm$3 years) and sex of cases were identified using the records of the most recent screening program. Those who satisfy the inclusion criteria were invited to participate in the study by an individual visit.

3.4. Inclusion and Exclusion criteria

The inclusion and exclusion criteria for cases and controls are described in Table 3.1.

Table 3.1. The inclusion and exclusion criteria of CKDu and non-CKDu groups

	Inclusion criteria	Exclusion criteria
CKDu group	· Patients who were diagnosed to have CKDu in the last ≤6 months · Patients who were not receiving or planned to receive RRT · Patients who gave their consent to participate	· Subjects with psychiatric/ cognitive disorders · Subjects with language barriers (hearing or speech impairment) · Subjects who are extremely debilitated
Non-CKDu group	· Individuals who had not been diagnosed with CKD/CKDu · Subjects who were individually matched with age and sex of patients · Individuals who agreed to participate	

3.5. Procedure

3.5.1. Ethics

The study was approved by;

- Ethical Review Committee, Graduate School of Health Sciences, Niigata University, Japan.
- Ethical Review Committee, Faculty of Allied Health Sciences, University of Peradeniya, Sri Lanka.

The study conformed fully with the Principles of the Declaration of Helsinki. Informed written consent (Annexure 1) was obtained from all the subjects before data collection.

3.5.2. Procedure of subject recruitment

When the CKDu patients and non-CKDu individuals were invited to participate in the study, they were informed about the study and its purpose, data collection methods, time taken for data collection, and confidentiality of personal information through an information sheet (Annexure 2). The recruitment of the study subjects was done per the inclusion and exclusion criteria described above.

3.5.3. Data Collection and Tools

3.5.3.1. Socio-demographic and health-related data

The socio-demographic variables collected were sex, age, education level, marital status, occupation, number of household members and level of income. In addition, the presence of NCDs and health-related habits such as alcohol consumption, cigarette smoking and betel chewing were also assessed using an interviewer-administered questionnaire (Annexure 3). Clinical and biochemical information of patients was extracted from their clinic books, investigation reports, and diagnostic cards if available. The latest available GFR level within 3 months was used to determine the stage of the disease. According to the KDIGO paper, GFR $\geq$90, 60-89, 30-59, 15-29, <15 ml/min/1.73m^2 were defined as stage I, II, III, IV, and V, respectively (55). The most recent hemoglobin (Hb) level was recorded referring to patients' investigation reports within 3 months. In accordance with world health organization (WHO) guidelines, anemia was defined as Hb <12.0 g/dl in women and Hb <13.0 g/dl in men (56).

3.5.3.2. PA Data

The long form of the international physical activity questionnaire (IPAQ) was translated into native language and the pre-tested questionnaire was used in data collection. The questionnaire covered four domains of PA: work-related, domestic and yard, transportation-related and leisure time. In addition, the IPAQ also included questions about the time spent sitting. For each domain, the number of days over the last 7 days the participant spent more than 10 minutes walking, moderate and vigorous PA and duration per day were collected (Annexure 4). All IPAQ data were cleansed and processed referring to the IPAQ scoring protocol (57). Continuous measurements were expressed as metabolic equivalent of task (MET) minutes/week (MET-min/week) and individuals were classified as having 'high', 'moderate' or 'low' PA, based on their categorical score.

3.5.3.3. Measurements

For all participants, anthropometric and body composition measures were collected by the same trained operator. Height was measured to the nearest 0.1 cm with an upright portable stadiometer (Seca 213; seca Deutschland, Hamburg, Germany) while the participant was in a standing position without footwear, looking straight ahead at the Frankfort plane. Weight and body composition measurements: body fat% (BF%) and

body muscle% (BM%), were obtained using a body composition monitor (Model HBF-220; Omron Healthcare Co. Ltd, Kyoto, Japan) by instructing participants with minimal clothing and dry feet to step on the monitor after entering the participant's gender, age and height into the machine. Here, BF% and BM% is assessed by bioimpedance analysis (BIA) Guest mode was used throughout the period of study and values automatically displayed on the monitor were recorded for each participant. Waist circumference (WC), hip circumference (HC), and mid-upper arm circumference (MUAC) were determined using a non-stretchable measuring tape (Seca 201, seca Deutschland, Hamburg, Germany) to the nearest 0.1 cm according to standard guidelines. WC was measured at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest. HC was measured at the widest circumference of the buttocks (58). MUAC was measured at the midpoint between the acromion process and olecranon process when the forearm is hanging loose at the side (59). Blood pressure was measured using a digital blood pressure monitor (Model MP-126, Berlin, Germany).

A systolic blood pressure (SBP) of ≥ 140 mmHg and/or a diastolic blood pressure (DBP) of ≥ 90 mmHg were considered as the cut-off levels for the presence of HT (60). Hand grip strength (HGS) was measured with a ZAZ electronic hand dynamometer (Zakka-town, Kumagaya, Japan) with participants seated in a chair with their hips flexed at 90^0 and feet resting on the floor without arm support. The shoulder of the rest arm was abducted and neutrally rotated, elbow was flexed to 90^0 and the forearm was in neutral position. Following a demonstration, the dynamometer was placed vertically in line with the forearm and participant was asked to squeeze the handle with as much force as possible for 3 seconds (61). Three repeated measurements were recorded for the right hand with a rest period of at least 15 seconds between trials and the maximum value of the 3 trials was used in the analysis. The gait speed (GS) of patients was based on the measurement of average time taken for the participants to walk along a six-meter distance at their usual walking speed (62). There were a walk-in and a walk-out phase of 1 meter, before and after the six-meter distance, respectively. Measurements were recorded in a data sheet (Annexure 5).

3.5.3.4. Symptom burden of CKDu patients

Prevalence, severity and burden of symptoms were assessed using the locally developed and validated CKD symptom index – Sri Lanka (CKDSI) (63). The instrument assessed the prevalence during the 7 days prior to the time of inquiry. Severity of the symptoms was assessed using the following response options; 'very mild', 'mild', 'moderate', 'severe', and 'very severe', scored from 1-5 (Annexure 6). Allocating score of zero for the symptoms did not experienced by the patient during the above mentioned time frame, and summing up the severity scores for all symptoms, the possible symptom burden score for each patient was ranged from zero to 125.

3.5.3.5. HRQOL of CKDu patients

HRQOL was assessed using the kidney disease quality of life – short form (KDQOL-SF^{TM}) version 1.3 questionnaire, developed by RAND cooperation (64), which has been culturally adapted, modified, and translated into Sinhala language by Senanayake *et al*. (65). This version of the questionnaire has confirmed as a valid and reliable instrument to assess HRQOL of CKD patients in Sri Lanka. The instrument basically consists of two components; kidney disease specific component and SF-36. Forty-three items in kidney disease specific components assess 11 domains including; symptoms/ problems (12 items), effects of kidney disease (8 items), burden of kidney disease (4 items), work status (2 items), cognitive function (3 items), quality of social interaction (3 items), sexual function (2 items), sleep (4 items), social support (2 items), dialysis staff encouragement (2 items), and patient satisfaction (1 item). SF-36 measures four domains in physical health including physical function (10 items), role limitations caused by physical problems (4 items), pain (2 items), general health perceptions (5 items); four domains in mental health including role limitations caused by emotional problems (3 items), social function (2 items), emotional well-being (5 items), energy/ fatigue (4 items), and overall health rating (1 item). Answer options are different between questions which usually range from 2 to 7, except for the overall health item, which ranges from 0 to 10 (Annexure 7). Scores of the different domains and subscales were calculated according to KDQOL-SF^{TM} scoring manual (66). First, raw pre-coded numeric values for responses in each item were transformed to a 0 to 100 possible range, where higher scores always reflect better QOL. Subsequently, items in the same domain or subscale were averaged together to give domain/ scale scores ranges from 0-100, where higher scores indicate better HRQOL.

3.6. Nutritional Status Indicators

Various anthropometric indices were calculated and used as index of general obesity (BMI) and indices of abdominal adiposity (WC, WHR, and WHtR) and gluteofemoral adiposity (HC, HI). In addition, different WC-based anthropometric indices were calculated for comparison. Skeletal muscle index (SMI) was calculated to use in sarcopenia screening.

Anthropometric indices were calculated as follows:

(I) A body shape index (ABSI) (67)

$$\text{ABSI} = 1{,}000 * \text{WC (m)} * \text{Weight (kg)}^{-2/3} * \text{Height (m)}^{5/6}$$

ABSI was multiplied by 100 to derive numbers that would be more intuitive to use than the original values, which are < 0.1.

(II) Abdominal volume index (AVI) (68)

$$\text{AVI} = \frac{2 * [\text{WC (cm)}]^2 + 0.7\ [\text{WC (cm)} - \text{HC (cm)}]^2}{1000}$$

(III) Body adiposity index (BAI) (69)

$$\text{BAI} = \frac{\text{HC (cm)}}{[\text{Height (m)}]^2} - 18$$

(IV) Body mass index (BMI)

$$\text{BMI} = \text{Weight (kg)}/\text{Height (m)}^2$$

(V) Body roundness index (BRI) (70)

$$\text{BRI} = 364.2 - 365.5 * \{1 - [(0.5 * \text{WC (m)}/\pi)^2/(0.5 * \text{Height (m)})^2]\}^{0.5}$$

(VI) Conicity index (Ci) (71)

$$\text{Ci} = \frac{\text{WC (m)}}{[0.109 * \sqrt{\text{Weight (kg)}/\text{Height (m)}}]}$$

(VII) Hip index (HI) (72)

$$\text{HI} = \text{HC (m)} * \text{Weight (kg)}^{-0.482} * \text{Height (m)}^{0.310}$$

(VIII) Waist-to-hip ratio (WHR)

$$\mathrm{WHR} = \mathrm{WC}/\mathrm{HC}$$

(IX) Waist-to-height ratio (WHtR)

$$\mathrm{WHtR} = \mathrm{WC}/\mathrm{Height}$$

(X) Skeletal muscle index (SMI) (73)

$$\mathrm{SMI} = \mathrm{Skeletal\ \ muscle\ \ mass\ \ (kg)}/\mathrm{Height\ \ (m)}^2$$

Then, individuals were categorized based on the BMI cut-off values recommended for Asian populations by WHO expert consultation (74), as underweight (< 18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23-27.5 kg/m^2) and obese (> 27.5 kg/m^2). Central obesity (CO) was defined according to WC, WHR, and WHtR. Men with a WC ≥ 90 cm and women with a WC ≥ 80 cm were identified as having CO, in accordance with the cut-off values for South Asians (75). CO was also determined as a WHR ≥ 0.9 in men and ≥ 0.85 in women, according to the WHO criteria (58) and a WHtR of > 0.5 (76).

In addition, nutritional risk of CKDu patients was assessed using geriatric nutritional risk index (GNRI), which is calculated by serum albumin level and BMI. GNRI is a simple objective index of malnutrition and found be an appropriate tool for nutrition screening and a prognostic predictor among patients with no dialysis stage III-V CKD (77). The GNRI was calculated as reported by Bouillanne *et al*. (78) using the following formula.

$$\mathrm{GNRI} = 14.89 + \mathrm{Serum\ \ albumin\ \ (g/dl)} + [41.7 * (\mathrm{body\ \ weight/ideal\ \ body\ \ weight})]$$

The ideal body weight was defined as the value calculated from the height and a BMI of 22 kg/m^2 instead of the value calculated using the Lorentz formula in the original GNRI equation because of its validity (77,79). Body weight/ideal body weight was set to 1 when the patient's body weight exceeded the ideal body weight. As proposed by Bouillanne et al. (78) CKDu patients were categorized as; major-risk group (GNRI: <82), moderate-risk (GNRI: 82–<92), low-risk group (GNRI: 92–98), no-risk group (GNRI: >98).

3.7. Sarcopenia screening

Sarcopenia was measured by the updated diagnosed criteria recommended by Asian Working Group for Sarcopenia (AWGS) in 2019 (73), which included following three elements:

- Low muscle mass (MM) measured using BIA and defined as SMI <28 kg for men and <18 kg for women
- Low muscle strength (MS) measured using HGS and defined as HGS <28 kg for men and <18 kg for women
- Low physical performance measured using usual GS and defined as 6-m walk <1.0 m/s

Based on AWGS 2019 sarcopenia categories were defined as follows;

- Possible sarcopenia - either low MS or low physical performance
- Sarcopenia - low MM with either low MS or low physical performance
- Severe sarcopenia - presence of low MM, low MS and low physical performance
- No sarcopenia - none of the aforementioned conditions

3.8. Longitudinal study

Study measurements were recorded from the study participants at 2 months apart during a 1-year follow-up period. Follow-up time began on the date of entry into the cohort. The end date of the follow-up was March 31, 2020. During this period, 5 CKDu patients died, 1 patient was referred for hemodialysis (HD), and 14 dropped out. In control group, 2 individuals died and 5 dropped out. A flowchart of the study is presented in Figure 3.1.

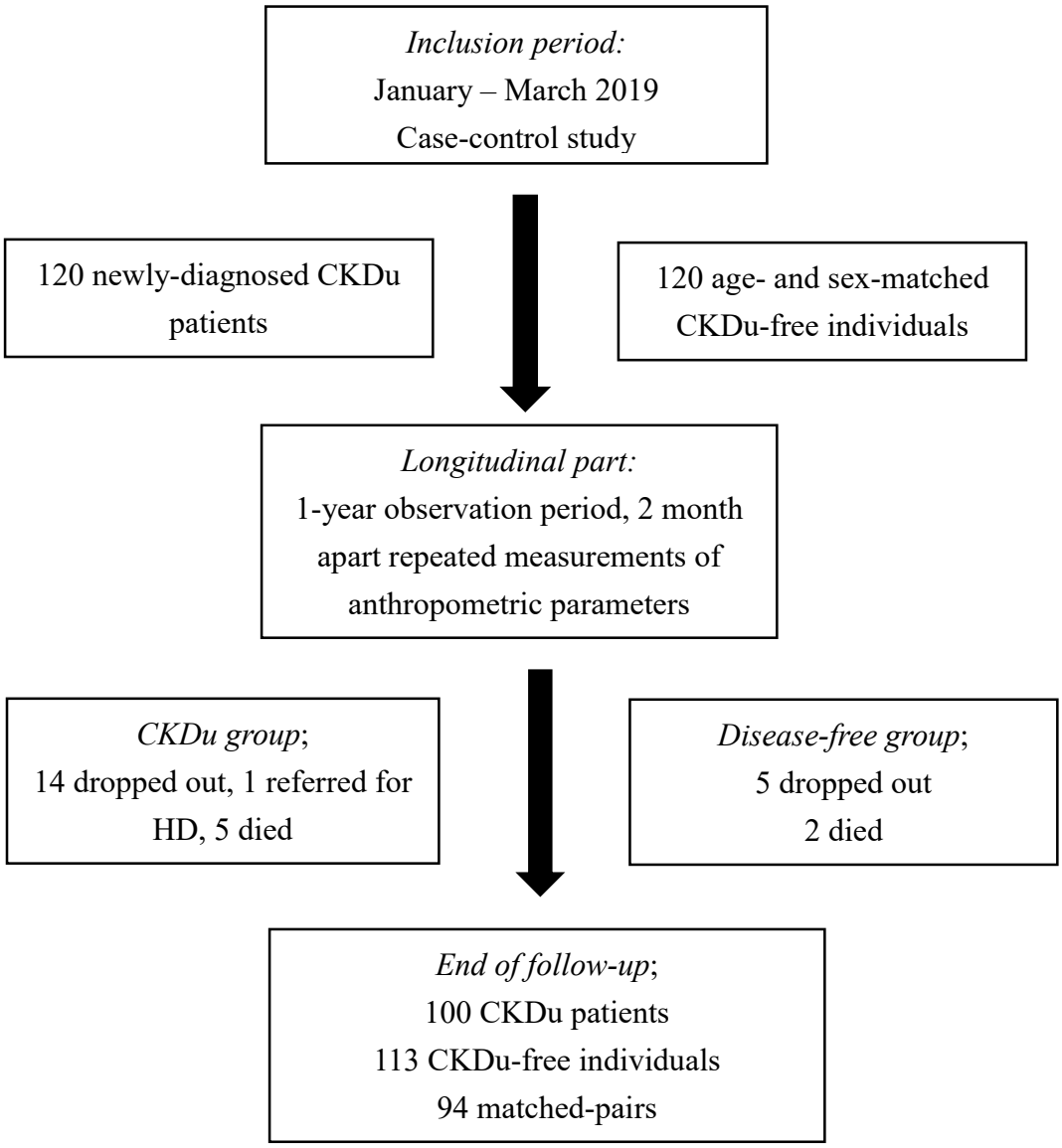

Figure 3.1. Flow diagram of the longitudinal study

3.9. Statistical Analyses

Continuous data were checked for normal distributions using the Shapiro-Wilk test and visual inspection of the group histograms and summarized as means and standard deviation (SD), or medians and inter quartile ranges (IQR) depending on the normality of the distributions. Categorical variables were summarized as absolute and percent frequencies. A two-sided p value <0.05 was recorded statistically significant and IBM SPSS statistics 24 was used for all the statistical analyses except for Bhapkar test (performed using MS excel).

Study I:

Differences in continuous variables between cases and controls were assessed by the paired t-test or Wilcoxon rank-sum test for normal and skewed distributions, respectively. Comparisons of categorical variables between the two groups were performed by Wilcoxon rank-sum test (ordinal data), McNemar (dichotomous data), and Bhapkar test (nominal data). Predictive performance of the anthropometric parameters was assessed by generating receiver-operating characteristic (ROC) curves. Only the complete matched pairs for each outcome were used in analyses.

Study II:

Comparative analysis between the sarcopenic and non-sarcopenic groups was carried out using the Student t-test and Mann-Whitney U test, according to the data distribution verified by the Shapiro-Wilk test, for the quantitative variables and the chi-square test for the categorical variables. Associations between independent variables and sarcopenia (dependent variable) were determined by multivariate binary logistic regression analysis. Variables which derived a probability value of less than 0.2 in the bivariate analysis were included as independent variables. Nagelkerke's R^2 was used to assess the variability explained by the model. The Hosmer and Lemeshow test ($p > 0.05$) was applied to analyse the degree of model fit. ROC curves was constructed to determine the cut-off points of the anthropometric indicators as discriminators of sarcopenia.

Study III:

Longitudinal data were plotted by individuals to examine for trends and trends and outliers. The longitudinal changes in the body composition was examined using linear-mixed effects models, which model both fixed and random effects and account for unequal sampling intervals and missing data. Following previous methods (80), random intercepts as well as random slopes for the effect of time (months since baseline), and a hierarchical approach was used for model fitting. First, a random intercept model (Model 1) was fitted adjusting for CKDu status reflecting individual differences at baseline. Then this model was extended with both random slope and random intercept (Model 2) reflecting individual rate of changes. The covariance matrix was modeled as unstructured. The restricted maximum likelihood method was used for the estimation of regression coefficients. Akaike's information criterion (AIC) value was used to identify the best-

fitting model by choosing the model with the lowest AIC. These models provide estimates of the average linear trajectories over time while accounting for correlation among repeated measurements from the same participants. Next, in order to examine the influence of age and sex on change in body composition, fixed indicator intercepts of age (<60 years vs. >60 years) and sex were introduced to the model. The effect of age and sex in CKDu patients further estimated using slopes from the models, and the point estimate and 95% confidence interval (CI) were used to generate forest plot.

Study IV:

Significant differences in proportions between groups were calculated by the chi-square test. For the continuous variables, the Student t-test or the Mann–Whitney U test was used to compare two groups, depending on the normal/skewed distribution of a particular data set. Three summary scores in KDQOL-SF^{TM}; physical component summary (PCS), mental component summary (MCS), and kidney-disease-specific component (KDSC) score were calculated. Simple and multiple linear regression analyses were then performed to identify the independent predictors for the KDQOL-SF^{TM} summary scores and symptom burden score among patients with CKDu. The variables analyzed were age, gender, education level, having a significant other, number of family members, income level, occupation, presence of co-morbidities, family history of CKDu, PA level, CKDu stage, years since diagnosis of CKDu, BMI, BF%, BM%, HGS, SBP, DBP, GFR, and Hb level. Statistically significant independent variables identified in the simple linear regression were included in the stepwise multiple regression model for determinants of HRQOL and symptom burden. Preliminary analyses were performed to ensure there was no violation of the assumptions of normality, linearity and multicollinearity.

CHAPTER 4

Study I
Associations of nutritional status with CKDu: a case-control study

4.1. Introduction

An increasing body of evidence is accumulating for an etiologic role of anthropometric factors for CKD (81–83). Obesity is an independent risk factor for T2DM and HT (84,85), the major factors that accounted for the largest proportion of CKD burden worldwide (1). Epidemiological studies have shown that adiposity may directly attribute to the incidence and progression of CKD (86,87). Likewise, dietary intake and PA that are both determinants of nutritional status, also appear to have an association with CKD risk (88,89). While the role of nutritional status and PA on CKD is well-established in the literature, their associations with CKDu needs to be clarified as CKDu is not associated with known related factors such as HT or DM. In a preliminary study on the nutritional status of the general population Girandurukotte area, we found a higher prevalence of general obesity (35.8% were overweight and 13.3% were obese) and CO (59.2% by WC and 74.2% by WHtR); however, 68% of the study population was women. Interestingly, 11.7% were underweight, and 55% of them reported high PA (90). Therefore, this study was sought to (I) examine the associations of anthropometric parameters and PA with CKDu in an age- and sex-matched case-control population, and (II) determine the use of anthropometric variables in the risk prediction of CKDu. It was hypothesized that in comparison with healthy controls, those with CKDu would have unfavorable body anthropometry and composition and PA.

4.2. Results

4.2.1. Socio-demographic and health-related characteristics of cases and controls

The study comprised 120 case-control pairs. The mean (SD) age (years) of cases and controls was 61.86 (11.31) and 61.55 (11.01), respectively. Both in cases and controls, 83 (69.2%) were males. All the participants were Buddhists in religion and Sinhala in ethnicity. The socio-demographic and lifestyle characteristics and of cases and controls are shown in Table 4.1. There was a statistically significant difference in the proportions of cases and controls with regard to education level and occupation. McNemar post-hoc

tests with Bonferroni adjustment revealed that the proportions of cases and controls were significantly different only for having primary and secondary/tertiary education. Self-reported past and/ or present tobacco smoking was found to be more prevalent among the non-CKDu group. No significant differences were recorded in the rest of the parameters assessed between the two groups.

Table 4.1: Socio-demographic and health-related characteristics of cases and controls

Parameters	Cases n (%)	Controls n (%)	*p*-value
Age[a]			
30 – 49	14 (11.7)	15 (12.5)	
50 – 69	71 (59.2)	71 (59.2)	
>70	35 (29.2)	34 (28.3)	
Education[b]			0.048*
No education[c]	25 (20.8)	31 (25.8)	0.405
Primary education[c]	92 (76.7)	63 (52.5)	<0.001[#]
Secondary or higher education[c]	3 (2.5)	26 (21.7)	<0.001[#]
Marital status[d]			0.279
Married	111 (92.5)	115 (95.8)	
Divorced/ widowed	7 (5.8)	5 (4.2)	
Never married	2 (1.7)	0	
Number of family members[b]			0.569
1 or 2	27 (22.5)	33 (27.5)	
3 or 4	50 (41.7)	43 (35.8)	
5 or more	43 (35.8)	44 (36.7)	
Occupation[d]			0.035*
Farming[c]	112 (93.3)	99 (82.5)	<0.001[#]
Employed/ self-employed[c]	4 (3.3)	10 (8.3)	<0.001[#]
Retired/ not working[c]	4 (3.3)	11 (9.2)	<0.001[#]
Monthly income (Sri Lankan Rupees)[b]			0.247
<10000	42 (35)	35 (29.2)	
10000 - 20000	71 (59.2)	77 (64.2)	
>20000	7 (5.8)	8 (6.6)	

Health-related habits[e]			
Tobacco smoking	4 (3.3)	23 (19.2)	<0.001*
Betel chewing	72 (60.0)	72 (60.0)	1.000
Alcohol consumption	12 (10.0)	13 (10.8)	1.000
Family history of CKD[e]	25 (20.8)	37 (30.8)	0.090
Blood pressure			
SBP (Mean, SD)[f]	144.51 (21.50)	147.92 (19.44)	0.178
DBP (Mean, SD)[f]	95.11 (14.29)	98.01 (13.60)	0.091
% with HBP[e]	80 (66.7)	85 (70.8)	0.568

[a] Participants were matched 1:1 by age (±3 years allowed).

[b] Wilcoxon Signed-rank test; [c] McNemar's post-hoc test; [d] Bhapkar chi-square test for paired nominal data; [e] McNemar's test; [f] Paired t-test.

*Statistically significant at $p<0.05$.

#Statistically significant at Bonferroni adjusted significant criterion of $p<0.016$.

4.2.2. Anthropometric and PA profile of CKDu and non-CKDu groups

Table 4.2 shows the mean (SD) values of the basic anthropometric measures in cases and controls and the relative differences (case-control/ control) in percent for the total sample and sex-categories. All basic anthropometric measures evaluated were higher among the non-CKDu group except for BM%; however, only in the case of MUAC and WC, the differences were statistically significant. Male CKDu patients, as opposed to female patients, had higher BM% while the difference between case and control groups was statistically significant only for MUAC of men. All the measures were higher among women in the control group, while none of the differences was statistically significant.

Various anthropometric indices were used in the analysis and all were higher among the non-CKDu group. However, the differences were statistically significant only for WHtR, ABSI, Ci, AVI, BRI, and HI. In both sex categories, the subjects with CKDu reported significantly different average ABSI and Ci than those without CKDu. As opposed to male CKDu patients, the mean ABSI was significantly higher among female CKDu patients. Even though WHtR, AVI and BRI were significantly different between the total case and control group, the differences were not significant when the analysis was stratified by gender (Table 4.3).

Table 4.2: Mean (SD) of basic anthropometric measures and relative differences between CKDu cases and matched controls

	Weight (kg)	**Height (cm)**	**MUAC (cm)**	**WC (cm)**	**HC (cm)**	**BF%**	**BM%**	**HGS**
Total; n=120								
Cases	53.123 (10.020)	157.571 (8.080)	25.096 (2.542)	83.279 (9.854)	85.325 (9.491)	26.587 (8.406)	28.051 (4.730)	21.692 (7.376)
Controls	54.066 (10.925)	158.175 (8.580)	25.955 (3.002)	86.050 (10.732)	87.504 (10.062)	28.193 (7.847)	27.607 (3.633)	22.369 (6.556)
Relative difference %	-1.744	-0.382	-3.310	-3.220	-2.490	-5.697	1.608	-3.027
p-value	0.480[a]	0.468[a]	**0.016*[a]**	**0.037*[a]**	0.090[a]	0.070[a]	0.380[b]	0.330[a]
Men; n=83								
Cases	54.336 (9.985)	161.054 (6.474)	24.837 (2.510)	81.669 (8.751)	83.337 (8.590)	23.025 (6.724)	29.637 (4.733)	23.680 (7.641)
Controls	55.516 (11.854)	161.813 (7.325)	25.790 (3.125)	84.096 (11.026)	85.705 (10.618)	24.994 (6.485)	28.877 (3.432)	24.029 (6.557)
Relative difference %	-2.126	-0.469	-3.695	-2.886	-2.763	-7.878	2.632	-1.452
p-value	0.483[a]	0.491[a]	**0.022*[a]**	0.136[a]	0.139[a]	0.074[a]	0.209[b]	0.688[a]
Women; n=37								
Cases	50.400 (9.683)	149.757 (5.439)	25.676 (2.550)	86.892 (11.276)	89.784 (10.009)	34.576 (5.978)	24.492 (2.030)	17.232 (4.846)
Controls	50.814 (7.667)	150.014 (4.709)	26.324 (2.709)	90.432 (8.675)	91.541 (7.324)	35.368 (5.592)	24.757 (2.177)	18.646 (4.853)
Relative difference %	-0.815	-0.171	-2.462	-3.915	-1.919	-2.239	-1.070	-7.583
p-value	0.850[a]	0.817[a]	0.343[a]	0.129[a]	0.416[a]	0.597[b]	0.597[a]	0.220[a]

[a] *p*-value by Paired t-test; [b] *p*-value by Wilcoxon Signed-Rank test. *Significant differences between cases and controls at $p<0.05$.

Table 4.3: Mean (SD) of different anthropometric indices and relative differences between CKDu cases and matched controls

	BMI	**WHR**	**WHtR**	**ABSI[#]**	**Ci**	**BAI**	**AVI**	**BRI**	**HI**
Total; n=120									
Cases	21.318 (3.277)	0.976 (0.032)	0.530 (0.066)	8.665 (0.610)	1.321 (0.095)	25.327 (5.742)	14.072 (3.351)	4.014 (1.354)	0.146 (0.011)
Controls	21.556 (3.616)	0.983 (0.038)	0.546 (0.075)	8.876 (0.621)	1.356 (0.099)	26.232 (6.276)	15.047 (3.634)	4.362 (1.522)	0.148 (0.010)
Relative difference %	-1.104	-0.712	-2.930	-2.377	-2.581	-3.450	-6.480	-7.978	-1.351
p-value	0.581[a]	0.100[b]	**0.036*[a]**	**0.003*[a]**	**0.002*[a]**	0.130[a]	**0.030*[a]**	**0.024*[a]**	**0.016*[a]**
Men; n=83									
Cases	20.858 (3.123)	0.980 (0.020)	0.507 (0.050)	8.528 (0.536)	1.296 (0.078)	22.805 (3.999)	13.495 (2.902)	3.542 (0.964)	0.142 (0.009)
Controls	21.100 (3.703)	0.981 (0.033)	0.520 (0.067)	8.694 (0.553)	1.323 (0.088)	23.706 (5.220)	14.392 (3.698)	3.827 (1.296)	0.144 (0.009)
Relative difference %	-1.147	-0.102	-2.250	-1.909	-2.041	-3.797	-6.233	-7.447	-1.389
p-value	0.640[a]	0.404[b]	0.165[a]	**0.035*[a]**	**0.010*[b]**	0.215[a]	0.099[a]	0.112[a]	**0.040*[a]**
Women; n=37									
Cases	22.350 (3.420)	0.967 (0.049)	0.580 (0.070)	8.973 (0.659)	1.379 (0.106)	30.985 (4.999)	15.368 (3.929)	5.072 (1.509)	0.155 (0.009)
Controls	22.579 (3.231)	0.988 (0.048)	0.603 (0.058)	8.285 (0.572)	1.429 (0.082)	31.898 (4.521)	16.516 (3.049)	5.564 (1.299)	0.157 (0.007)
Relative difference %	-1.014	-2.126	-3.814	8.304	-3.499	-2.862	-6.951	-8.843	-1.274
p-value	0.774[a]	0.078[a]	0.172[b]	**0.031*[a]**	**0.019*[a]**	0.480[b]	0.155[a]	0.105[a]	0.225[a]

[a] *p*-value by Paired t-test; [b] *p*-value by Wilcoxon Signed-Rank test. *Significant differences between cases and controls at $p<0.05$.

[#]The original ABSI values which were <0.1, multiplied by 100 to derive numbers that would be more intuitive to use.

The prevalence of underweight, overweight, and obesity were comparable between the cases and controls. Thirty-seven (30.9%) of CKDu patients and 45 (37.5%) of controls had BMI higher than normal. The proportions with CO defined using WC and WHtR were higher among the control group; however, there were no significant differences. A higher proportion of patients had a lower PA level than that of the control group (Table 4.4). The findings remained non-significant when the analysis was done using sex-categories (Data not shown).

Table 4.4. Distribution based on BMI, CO, PA level among cases and controls

Variable	Cases *n* (%)	Controls *n* (%)	*p*-value
BMI category[a]			
Underweight	21 (17.5)	26 (21.7)	0.811
Normal	62 (51.7)	49 (40.8)	
Overweight	32 (26.7)	37 (30.8)	
Obese	5 (4.2)	8 (6.7)	
CO[b]			
By WC	47 (39.2)	61 (50.8)	0.055
By WHtR	76 (63.3)	88 (73.3)	0.112
Self-reported PA level[a#]			0.012*
Low[c]	53 (52.0)	35 (34.3)	0.018
Moderate[c]	25 (24.5)	30 (29.4)	0.458
High[c]	24 (23.5)	37 (36.3)	0.055

[a] Wilcoxon Signed-rank test; [b] McNemar's test; [c] McNemar's post-hoc test.

*Statistically significant at $p<0.05$.

[#]Self-reported PA data was available only for 102 case-control pairs.

As there was a significant association between low PA level and CKDu status, different PA scores between cases and controls were compared. In general, all self-reported PA scores (MET-min/week) and the time spent sitting (min/week) were higher among the non-CKDu group. All of the scores were comparable except for higher moderate PA level and the time spent sitting observed among the male control group. Interestingly, none of the women in both case and control groups reported vigorous PA (Table 4.5).

Table 4.5: Self-reported PA scores of CKDu cases and control groups*

	Cases Median (IQR)	Controls Median (IQR)	*p*-value[a]
Walking domain score (MET-min/ week)			
Total	0.00 (0.00-321.75)	0.00 (0.00-693.00)	0.201
Men	0.00 (0.00-396.00)	0.00 (0.00-693.00)	0.510
Women	0.00 (0.00-198.00)	0.00 (0.00-408.38)	0.227
Moderate domain score (MET-min/ week)			
Total	495.00 (0.00-1485.00)	1260.00 (0.00-2928.75)	**0.002**[#]
Men	151.25 (0.00-1197.50)	652.50 (0.00-3217.50)	**0.006**[#]
Women	1027.50 (481.88-2137.50)	1740.00 (630.00-2527.50)	0.133
Vigorous domain score (MET-min/ week)			
Total	0.00 (0.00-0.00)	0.00 (0.00-4320.00)	0.442
Men	0.00 (0.00-5400.00)	0.00 (0.00-5760.00)	0.483
Women	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.705
Total score (MET-min/ week)			
Total	712.50 (49.50-2826.00)	1890.00 (356.63-7379.25)	0.097
Men	487.50 (0.00-6645.00)	949.50 (173.25-8343.75)	0.162
Women	1689.00 (536.25-2418.75)	1890.00 (813.38-2700.00)	0.349
Total sitting time (min/ week)			
Total	780.00 (420.00-1380.00)	960.00 (690.00-1560.00)	**0.017**[#]
Men	832.50 (420.00-1380.00)	1050.00 (690.00-1680.00)	**0.034**[#]
Women	735.00 (326.25-1215.00)	945.00 (607.50-1207.50)	0.261

*102 matching case-control pairs completed the IPAQ questionnaire, which consisted of 72 male and 30 female pairs.

[a] Difference between two groups by Wilcoxon Signed-Rank test.

[#]Significant differences between cases and controls at $p<0.05$.

4.2.3. ROC curves of anthropometric parameters as predictors of CKDu

To ascertain which indicator was better among those that showed a significant association in the univariate analysis, the ROC curve was estimated (Figure 4.1). The area under the curve (AUC) for all the parameters assessed was less than or closer to 0.6 and summarized in Table 4.6. AUC was best for Ci (0.604), followed by MUAC (0.598), WC (0.588), and AVI (0.588).

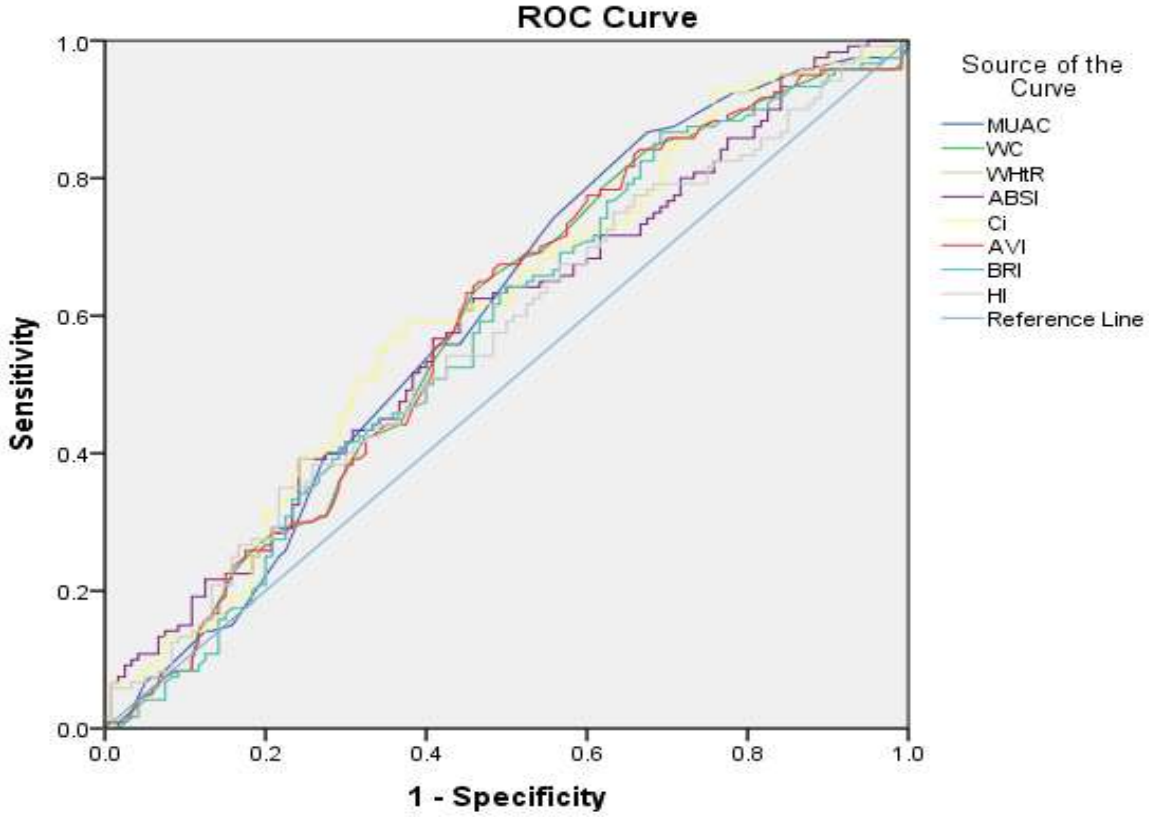

Figure 4.1. ROC curves for anthropometric parameters of CKDu status

Table 4.6: Area under the ROC curves for anthropometric parameters of CKDu status

Variable		MUAC	WC	WHtR	ABSI	Ci	AVI	BRI	HI
AUC		0.598	0.588	0.573	0.584	0.604	0.588	0.573	0.568
95% CI	Lower	0.526	0.515	0.501	0.512	0.533	0.516	0.501	0.496
	Upper	0.670	0.660	0.646	0.656	0.676	0.660	0.646	0.640

4.3. Discussion

Despite the increasing prevalence of CKDu among farming communities in Sri Lanka and several tropical countries in Central America, there are no studies with robust evidence on the nutritional risk factors of CKDu. Thus, this study addressed one of the identified gaps in the epidemiologic literature, namely, the effect of obesity and body composition on the risk of CKDu. Controls were slightly taller, heavier with higher BF% than did the cases. Although some of the differences were statistically significant in the bivariate analysis, the actual magnitude of the difference was small, suggesting no clinically relevant difference existed between the cases and controls for any of these parameters. Two statistically significant differences with relatively larger magnitude were found for AVI and BRI; however, those differences were not significant when the analysis was stratified by gender. Similar null findings were observed when examined by ROC, as none of the variables assessed had acceptable discriminative accuracy (AUC<0.6). The findings of this study revealed that family history of CKD and tobacco smoking did not show a significant association with CKDu status; however previous studies have been shown as risk factors (91,92). This study found a lack of education to be highly associated with CKDu. This may be associated with being a paddy farmer, which is an established risk factor of CKDu (44).

As we recruited patients who were recently diagnosed with the disease, it was assumed that their anthropometry and lifestyle have not significantly changed due to the diagnosis and can be used to make inferences for their previous nutritional status. Both general and abdominal obesity were found to be higher among the non-CKDu group than the CKDu group, even though there were no significant differences. There can be a number of reasons for this observation. First, although cases were recently diagnosed, a considerable proportion of them was in the advanced stages and this may have resulted in the lower values among patients. Second, as CKDu is not associated with common obesity-associated risk factors such as DM and HT, there may be a protective effect. Whilst obesity has been identified as a risk factor for new-onset of CKD (93), the evidence on the association between obesity and outcomes in the CKD population is complex and controversial. A cohort study conducted in the United States observed a consistent, U-

shaped association between BMI and the outcomes of kidney disease progression and mortality, with the best outcomes observed in overweight and mildly obese subjects (94). Another retrospective cohort study conducted by Davis *et al.* (95), reported an association between overweight BMI and reduced risks of kidney disease progression and all-cause mortality in stage III-IV CKD. This risk factor paradox has been referred to as "reverse causation", implying the beneficial effects of increased fat mass (96).

This study found a high level of PA among those without CKDu. Low PA level among CKDu patients may be a result of the disease itself, comorbidities, or subsequent fatigue as a majority of the patients were in advanced stages of the disease. Interestingly, time spent sitting was also higher in the control group. In the present study, PA was self-reported rather than objectively measured; which is associated with over- and under-estimation. PA is widely accepted as an important modifiable risk factor for several NCDs including CKD. In the Singapore Chinese Health Study, those engaged in any PA had a lower risk of ESRD, and a dose-response relationship with the intensity of PA was reported (97). A recent study found a reduced risk of ESRD with higher levels of PA, among those with preserved kidney function. The authors also reported that sedentary time was not associated with increased ESRD risk except in participants with low baseline GFR (98).

4.4. Strengths and limitations

One of the strengths of the present study is matching the CKDu patients to non-CKDu controls on two of the strongest unmodifiable risk factors: age and sex (men have a higher risk of CKDu than women), which enabled to carefully examine the other characteristics as potentially contributing factors to the pathogenesis of CKDu. The clearly defined recruitment criteria of the cases and controls enabled the selection of the controls in an unbiased manner. Further, both cases and controls belong to a homogeneous base subpopulation, they were not only matched by age but also proceeded from the same healthcare system, and they exhibited similarities concerning most sociodemographic variables. Another strength is the use of standardized anthropometric factors and standardized tools. Still, some potential limitations should also be considered. First, a

larger sample size might be desirable to have enough statistical power as the magnitude of many of the observed associations were low. Second, there is a possibility of information bias, particularly with regard to self-reported PA and health-related habits. For example, there is a possibility of under-reporting smoking by patients, which could be driven by the feeling of guilt or social implications. Third, the inability to compare the results those of similar study is a limitation, which is a common issue in initial studies.

4.5. Conclusion

In conclusion, this investigation has provided no constructive evidence that anthropometric measurements are related to CKDu risk. This lack of association may be attributable, in part, to study methods and to the weak, underlying association. Given that CKDu etiology is complex, multifactorial, and poorly understood at present, additional investigations will be needed to clarify the roles of personal factors, including anthropometric characteristics, in CKDu pathogenesis.

CHAPTER 5

Study II
Prevalence and associated factors of sarcopenia among CKDu patients

5.1. Introduction

Sarcopenia is a broader term that describes the loss of MM and MS and low physical performances due to aging or other conditions (99). The AWGS defined sarcopenia as "age-related loss of MM, plus low MS, and/or low physical performance"(73). Although originally defined as a condition related to aging, various international societies currently recognize the role of catabolic diseases in the etiology of sarcopenia (100–103). Muscle loss is a prevalent condition in CKD, mainly among ESRD patients who are on HD (104). The etiologic factors of muscle loss in CKD are diverse and occur as a result of the accelerated protein catabolism from the disease and the dialysis procedure, independently of age (99). Recent studies have reported increased prevalence rates with the progression of the disease (105). Further, sarcopenia is associated with worse clinical outcomes in CKD patients, including poor QOL and higher hospitalization, morbidity, and mortality rates (106–109). Screening for sarcopenia in vulnerable populations including CKD patients has been recommended. However, there is a scarcity of studies on the CKD population, and they are mostly limited to HD patients. In Sri Lanka, studies on sarcopenia are still limited. In the context of the prevailing epidemic of CKDu among rural agricultural communities in Sri Lanka, the patients are at higher risk for malnutrition not only because of metabolic derangements inherent to the disease but also because of social and economic hardships and gaps in available knowledge. To our knowledge, no study has systematically evaluated the nutritional status of this population yet. Given the convincing relationship between sarcopenia, CKD, and adverse clinical outcomes, identifying the prevalence and associated factors is imperative as it could assist health care professionals in patient care and management. As such, the objectives of this study were to determine the prevalence of sarcopenia in non-dialysis-dependent CKDu patients and determine the demographic, lifestyle, anthropometric, and clinical factors associated with sarcopenia.

5.2. Results

5.2.1. Sarcopenia components and categories

The prevalence of sarcopenic phenotypes among non-dialysis CKDu patients is presented in Table 5.1. The sarcopenia indicators of low MM, MS, and GS were present in 77.5%, 70.8%, and 35.0% of CKDu patients, respectively. According to the AWGS suggested algorithm, the prevalence of sarcopenia in men and women was 73.5% and 51.4%, respectively. The prevalence of possible sarcopenia and sarcopenia was significantly higher in men than in women. Only 5% of patients did not have any of the indicators of sarcopenia, while 15% had severe sarcopenia.

Table 5.1. Summary of sarcopenia components and categories stratified by gender in CKDu patients

	Total (N=120)	**Men (N=83)**	**Women (N=37)**	***p*-value**
SMI[a]	5.916 (1.022)	6.137 (1.102)	5.421 (0.566)	**<0.001***
HGS[a]	21.692 (7.376)	23.680 (7.461)	17.232 (4.846)	**<0.001***
GS[b]	1.279 (0.538)	1.246 (0.519)	1.353 (0.578)	0.198
Low MM[c]	93 (77.5%)	67 (80.7%)	26 (70.3%)	0.205
Low MS[c]	85 (70.8%)	63 (75.9%)	22 (59.5%)	0.067
Low GS[c]	42 (35.0%)	33 (39.8%)	9 (24.3%)	0.102
Low MM and MS[c]	67 (55.8%)	51 (61.4%)	16 (43.2%)	0.064
Low MM and GS[c]	31 (25.8%)	25 (30.1%)	6 (16.2%)	0.108
Low MS and GS[c]	26 (21.7%)	21 (25.3%)	5 (13.5%)	0.148
No sarcopenia[c]	6 (5.0%)	2 (2.4%)	4 (10.8%)	0.051
Possible sarcopenia[c]	101 (84.2%)	75 (90.4%)	26 (70.3%)	**0.005***
Sarcopenia[c]	80 (66.7%)	61 (73.5%)	19 (51.4%)	**0.017***
Severe sarcopenia[c]	18 (15.0%)	15 (18.1%)	3 (8.1%)	0.158

[a] Independent sample t-test; [b] Mann-Whitney U test; [c] Chi-square test

*Significant differences between sexes at $p<0.05$.

Data are presented as mean (SD) or n (%).

5.2.2. Socio-demographic, health-related, and anthropometric characteristics of sarcopenic and non-sarcopenic CKDu patients

The participants' characteristics according to the presence or absence of sarcopenia are summarized in Table 5.2. The mean age of CKDu patients with and without sarcopenia was 63.71 (10.12) and 58.18 (12.72), respectively. The majority of those with sarcopenia were men. All basic anthropometric measures were lower in the sarcopenic group except for height. Interestingly, there was no significant difference in BM% and HGS in the two groups. Significantly lower values were recorded for BMI, WHtR, AVI, BAI, and BRI in patients with sarcopenia compared to those without sarcopenia. In the sarcopenic group, 22.5% were underweight, while 18.8% were overweight. None of the sarcopenic patients were obese. In contrast, more than half of the non-sarcopenic group had general and CO.

Table 5.2: Socio-demographic, lifestyle, and anthropometric characteristics of CKDu patients with and without sarcopenia

Characteristics	Sarcopenia (N=80)	No sarcopenia (N=40)	*p*-value
Socio-demographic and lifestyle			
Age[a]	63.71 (10.12)	58.18 (12.72)	**0.011***
Sex[b]			
Male	61 (76.3%)	22 (55.0%)	**0.017***
Female	19 (23.8%)	18 (45.0%)	
Education status[b]			
No education	17 (21.3%)	8 (20.0%)	
Primary	62 (77.5%)	30 (75.0%)	0.463
Secondary	1 (1.3%)	2 (5.0%)	
Marital status[b]			
Married	75 (93.8%)	36 (90.0%)	
Divorced/ widowed	4 (5.0%)	3 (7.5%)	0.750
Never married	1 (1.3%)	1 (2.5%)	

Characteristics	Sarcopenia (N=80)	No sarcopenia (N=40)	*p*-value
Number of family members[b]			
1 or 2	18 (22.6%)	9 (22.5%)	
3 or 4	32 (40.0%)	18 (45.0%)	0.834
5 or more	30 (37.5%)	13 (32.5%)	
Occupation[b]			
Farming	75 (93.8%)	37 (92.5%)	
Employed/ self-employed	1 (1.3%)	3 (7.5%)	0.077
Retired/ not working	4 (5.0%)	0 (0.0%)	
Monthly income (Sri Lankan Rupees)[b]			
<10000	35 (43.8%)	7 (17.5%)	
10000 - 20000	42 (52.5%)	29 (72.5%)	0.051
>20000	3 (3.8%)	4 (10.0%)	
Health-related habits[b]			
Tobacco smoking	2 (2.5%)	2 (5.0%)	0.600
Betel chewing	48 (60.0%)	24 (60.0%)	1.000
Alcohol consumption	8 (10.0%)	4 (10.0%)	1.000
Family history of CKD[b]	14 (17.5%)	11 (27.5%)	0.204
Anthropometric measures			
Height[a]	157.700 (8.545)	157.313 (7.153)	0.806
Weight[a]	50.941 (9.347)	57.485 (10.005)	**0.001***
MUAC[c]	24.506 (2.184)	26.275 (2.812)	**0.002***
WC[a]	81.375 (8.831)	87.088 (10.770)	**0.002***
HC[a]	83.350 (8.718)	89.275 (9.845)	**0.001***
BF%[c]	25.848 (6.498)	28.065 (11.256)	**0.040***
BM%[c]	27.546 (3.189)	29.060 (6.791)	0.883
HGS[c]	21.143 (7.478)	22.790 (7.133)	0.222

Characteristics	Sarcopenia (N=80)	No sarcopenia (N=40)	*p*-value
Nutritional status indicators			
BMI[a]	20.376 (2.734)	23.202 (3.487)	**<0.001***
WHR[c]	0.976 (0.021)	0.975 (0.048)	0.295
WHtR[a]	0.517 (0.059)	0.555 (0.072)	**0.003***
ABSI[c]	8.719 (0.630)	8.558 (0.559)	0.126
AVI[c]	13.403 (2.856)	15.412 (3.870)	**0.011***
BAI[a]	24.278 (5.343)	27.425 (5.999)	**0.004***
Ci[a]	1.320 (0.096)	1.324 (0.095)	0.821
BRI[c]	3.752 (1.157)	4.539 (1.567)	**0.014***
HI[a]	0.145 (0.011)	0.146 (0.009)	0.638
BMI category[b]			
Underweight	18 (22.5%)	3 (7.5%)	**<0.001***
Normal	47 (58.8%)	15 (37.5%)	
Overweight	15 (18.8%)	17 (42.5%)	
Obese	0 (0.0%)	5 (12.5%)	
CO by WC[b]	26 (32.5%)	21 (52.5%)	**0.034***
CO by WHtR[b]	48 (60.0%)	28 (70.0%)	0.284

Data are presented as mean (SD) or n (%).

[a] Independent sample t-test; [b] Chi-square test; [c] Mann-Whitney U test

*Significant differences between the groups at $p<0.05$.

5.2.3. Clinical and functional characteristics of sarcopenic and non-sarcopenic CKDu patients

The relationship between sarcopenia status and clinical and functional factors in CKDu patients is shown in Table 5.3. Between the sarcopenic and non-sarcopenic groups, there were no significant differences in CKDu stage, blood pressure, PA, symptom burden, nutritional risk, and biochemical characteristics. However, there were significant differences in QOL with regard to MCS and KDSC.

Table 5.3: Clinical and functional characteristics of CKDu patients with and without sarcopenia

Characteristics	**Total (N=120)**	**Sarcopenia (N=80)**	**No sarcopenia (N=40)**	***p*-value**
		CKDu stage[a]		
Early stages	47 (39.2%)	32 (40.0%)	15 (37.5%)	
Stage IV	49 (40.8%)	35 (43.8%)	14 (35.0%)	0.328
Stage V	24 (20.0%)	13 (16.3%)	11 (27.5%)	
		Blood pressure		
SBP (mmHg)[b]	144.51 (21.50)	143.93 (22.62)	145.68 (19.27)	0.434
DBP (mmHg)[b]	95.11 (14.29)	94.80 (15.06)	95.73 (12.76)	0.544
% with HBP[a]	80 (66.7)	51 (63.7)	29 (72.5)	0.338
		PA scores[#]		
Walking domain (MET-min/wk)[b]	0.00 (0.00-280.50)	0.00 (0.00-445.50)	0.00 (0.00-0.00)	**0.009***
Moderate domain (MET-min/wk)[b]	480.00 (0.00-1425.00)	487.50 (0.00-1685.63)	165.00 (0.00-1110.00)	0.318
Vigorous domain (MET-min/wk)[b]	0.00 (0.00-0.00)	0.00 (0.00-3240.00)	0.00 (0.00-0.00)	0.100
Total score (MET-min/wk)[b]	675.00 (0.00-2619.50)	712.50 (129.00-4215.00)	525.00 (0.00-1890.00)	0.069
Sitting time (min/ wk)[b]	825.00 (420.00-1380.00)	802.50 (420.00-1380.00)	840.00 (360.00-1260.00)	0.913
GS (m/s)[b]	1.28 (0.54)	1.30 (0.60)	1.25 (0.40)	0.610
PA categories[a]				
Low	56 (53.3)	37 (52.9)	19 (54.3)	
Moderate	25 (23.8)	14 (20.0)	11 (31.4)	0.226
High	24 (22.9)	19 (27.1)	5 (14.3)	

Characteristics	Total (N=120)	Sarcopenia (N=80)	No sarcopenia (N=40)	*p*-value
		***Symptom burden*[b]**		
No. of symptoms	5.00 (3.00-7.00)	5.00 (3.00-7.00)	5.50 (3.00-7.75)	0.607
Symptom burden score	10.00 (6.00-17.75)	9.00 (6.00-18.00)	11.00 (6.50-17.00)	0.841
		***HRQOL scores*[b]**		
PCS score	75.31 (52.81-85.47)	73.44 (50.16-83.59)	78.13 (62.34-87.50)	0.077
MCS score	85.81 (62.70-94.38)	83.25 (59.22-93.94)	89.63 (74.38-95.53)	**0.046***
KDSC score	82.37 (78.97-84.97)	81.26 (78.36-84.45)	83.91 (80.73-85.22)	**0.040***
		Nutritional risk		
GNRI score[c]	103.97 (7.46)	103.32 (7.01)	105.27 (8.23)	0.179
GNRI risk categories[a]				
No risk	93 (77.5%)	62 (77.5%)	31 (77.5%)	
Low risk	22 (18.3%)	14 (17.5%)	8 (20.0%)	0.782
Moderate risk	5 (4.2%)	4 (5%)	1 (2.5%)	
		***Biochemical characteristics*[b]**		
GFR (ml/min/1.73 m^2)	25.65 (17.38-38.35)	25.85 (18.00-41.48)	23.65 (11.78-34.45)	0.206
Hb (g/dl)	11.90 (10.93-13.00)	11.80 (11.00-12.98)	12.00 (10.90-13.25)	0.666
Serum albumin (g/dl)	4.30 (4.10-4.68)	4.35 (4.20-4.50)	4.20 (4.00-4.80)	0.328
Serum cholesterol (mg/dl)	167.25 (145.48-191.38)	168.30 (145.48-197.48)	165.55 (144.45-181.25)	0.441

Characteristics	Total (N=120)	Sarcopenia (N=80)	No sarcopenia (N=40)	*p*-value
Sodium (mEq/L)	143.00 (139.65-144.38)	143.05 (139.88-144.98)	142.55 (138.85-144.08)	0.382
Potassium (mEq/L)	4.43 (3.85-5.17)	4.41 (3.81-5.13)	4.56 (3.90-5.31)	0.515
Phosphate (mg/dl)	3.58 (3.09-3.97)	3.60 (3.08-4.01)	3.54 (3.11-3.96)	0.964
Calcium (mg/dl)	10.13 (9.60-10.47)	10.19 (9.72-10.50)	10.09 (9.20-10.43)	0.139
Serum creatinine (mg/dl)	2.58 (1.93-3.90)	2.58 (1.85-3.87)	2.56 (1.99-4.53)	0.391
Serum uric acid (mg/dl)	6.39 (5.34-7.55)	6.29 (5.21-7.46)	6.57 (5.82-7.86)	0.126

#For PA data, Total N=105; Sarcopenia N=70; No sarcopenia N=35.

Data are presented as mean (SD), median (IQR), or n (%).

[a] Chi-square test; [b] Mann-Whitney U test; [c] Independent sample t-test

*Significant differences between the two groups at $p<0.05$.

5.2.3. Factors associated with sarcopenia

The multivariate analysis of factors related to sarcopenia is shown in Table 5.4. Due to the multi-collinearity among anthropometric measures and indices, only BMI categories and CO by WC were included in the study. The logistic regression model was a good fit with $\chi^2(8) = 2.630$, $p=0.955$. The model explained 46.7% (Nagelkerke R^2) of the variance in sarcopenia and correctly classified 82.9% of cases. Men were 7.7 times more likely to exhibit sarcopenia than women ($p=0.009$). Being overweight or obese was associated with a reduction in the likelihood of having sarcopenia (OR-0.021, $p=0.009$). With each unit increase in BMI, the odds of sarcopenia was reduced by 6.12% (B= -0.612, SE=0.177, $p=0.001$) when BMI was included as a continuous variable in the regression model. However, CO by WC increased the likelihood of having sarcopenia by 7.9 times in CKDu patients ($p=0.041$).

Table 5.4: Multiple logistic regression analysis on factors associated with sarcopenia among CKDu patients

Factors	B	SE	Wald	Adjusted OR	95% CI	*p*-value
Age	0.033	0.032	1.042	1.033	0.970-1.101	0.307
Sex						
Men	2.046	0.778	6.920	7.735	1.685-35.517	**0.009***
Women	Ref					
Occupation						
Farming	-1.218	1.325	0.845	0.296	0.022-3.969	0.358
Other	Ref					
Monthly income						
<10000 SLR	0.883	0.644	1.883	2.419	0.685-8.544	0.170
>10000SLR	Ref					
BMI category						
Underweight	Ref					
Normal	-0.602	0.979	0.378	0.548	0.080-3.734	0.539
Overweight/ obese	-3.857	1.485	6.751	0.021	0.001-0.388	**0.009***
CO by WC	2.068	1.013	4.167	7.909	1.086-57.608	**0.041***
Total MET score	0.000	0.000	3.122	1.000	1.000-1.000	0.077

The model was adjusted for GNRI score, HRQOL scores, serum calcium, and serum uric acid. *$p<0.05$.

As many of the anthropometric factors were associated with the sarcopenic status, their predictive accuracy was assessed using ROC. Table 5.5 shows the AUC of anthropometric factors with the respective CI. The AUC was highest for BMI (AUC-0.715, 95% CI 0.611-0.818, p <0.001), followed by weight (AUC-0.677, 95% CI 0.578-0.776) and MUAC (AUC-0.672, 95% CI 0.565-0.778). Only BMI had an AUC higher than 0.7, representing acceptable discrimination, and Figure 5.1 displays the ROC for BMI as a predictor of sarcopenia. The respective cut-off point, sensitivity, and specificity were ≤22.4 kg/m^2, 75%, and 60%.

Table 5.5: Area under ROC curves of the anthropometric indicators to discriminate sarcopenia in CKDu patients

Anthropometric parameter	AUC	95% CI	*p*-value
Weight	0.677	0.578 - 0.776	0.002
MUAC	0.672	0.565 - 0.778	0.002
WC	0.639	0.532 - 0.746	0.013
HC	0.663	0.559 - 0.768	0.004
BF%	0.615	0.493 - 0.738	0.040
BMI	0.715	0.611 - 0.818	0.000
WHtR	0.638	0.533 - 0.743	0.014
AVI	0.642	0.536 - 0.749	0.011
BAI	0.651	0.548 - 0.753	0.007
BRI	0.638	0.533 - 0.743	0.014

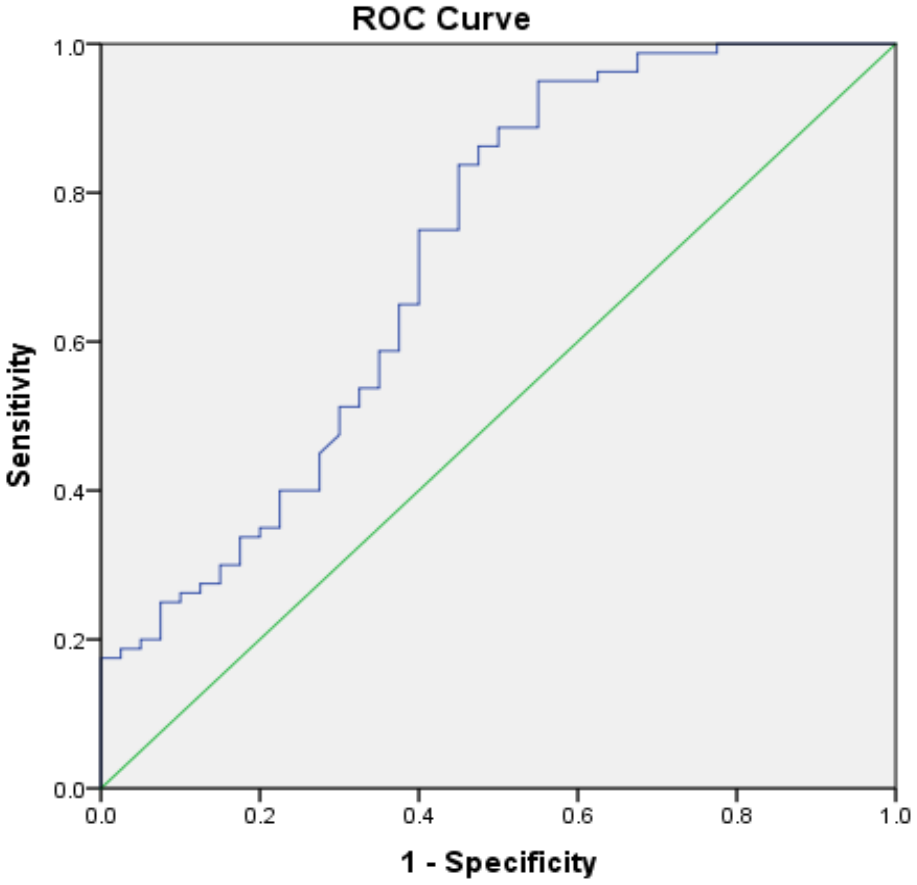

Figure 5.1. ROC curve of BMI as a predictor of sarcopenia in CKDu patients

5.3. Discussion

To the best of our knowledge, this study is the first investigation to address the prevalence of sarcopenia among CKDu patients. In fact, relatively limited evidence is available regarding the prevalence of sarcopenia in Sri Lanka. A recent study in Sri Lanka reported the prevalence of pre-sarcopenia, sarcopenia, and severe sarcopenia among middle-aged women as 3.0%, 2.2%, and 0.7%, respectively (110). The present study indicates that sarcopenia is common (66.7%) in non-dialysis dependent CKDu patients, while 15% had severe sarcopenia. Herein, we observed a higher prevalence of sarcopenia (68%) among patients in the early stages of CKDu, indicating the need for early diagnosis of sarcopenia in renal patients to establish measures to prevent its progression and its related complications.

Numerous studies have addressed the prevalence of sarcopenia in various populations, particularly the elderly population. In CKD, the majority of the studies on sarcopenia have evaluated HD patients, and few studies have investigated the early stages of CKD. The evidence on sarcopenia is still evolving in the literature, and different diagnostic criteria are used in research and clinical practice proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) (102), Foundation for the National Institutes of Health (FNIH) sarcopenia Project (103), and the AWGS (73). The prevalence rates of sarcopenia in CKD patients were found to be varied according to the diagnostic criteria applied (111). Hence, it is difficult to compare the results from different studies because of the various measurement methods, diagnostic criteria, and study populations. This study applied the AWGS criteria to define sarcopenia and measured the MM with BIA and physical performance with a 6-m walk test.

In the present study, sarcopenia was found to be widespread in elderly male CKDu patients, and there was no association with the degree of renal function impairment and the biochemical parameters studied. These findings were in keeping with those of D'Alessandro *et al.* (112), who reported a prevalence of 55% and 12.5% among older and younger seniors in the early stages of CKD using EWGSOP criteria. In contrast, there is evidence of correlations between the worsening renal function and the high prevalence of

sarcopenia (113). Another study demonstrated 33.7% of sarcopenia prevalence among elderly patients with ESRD, with 37% and 29.3% prevalence rates in men and women, respectively (114). They also reported no association between nutritional surrogates such as BMI and serum albumin. However, in the present study, the anthropometric variable best associated with sarcopenia was BMI, and the prevalence rate among men was much higher (76.3%).

Using EWGSOP criteria, 2 studies reported 5.9% (111) and 11.9% (115) prevalence of sarcopenia in patients with CKD who are not on dialysis. A study that used the AWGS criteria categorized 9.5% of CKD patients as sarcopenic and 55.9% of the patients as pre-sarcopenic (116). Another study conducted in Japan reported a 40% prevalence among patients undergoing HD, with 37% and 45% prevalence in men and women, respectively (117). Zhou *et al*. (118) reported a 14% presence of sarcopenia using MM and MS in CKD patients who are not on RRT and varied prevalence rates with the use of different indicators. They further reported a higher prevalence in men than in women irrespective of the criteria used. Unexpectedly, no association of sarcopenia with PA was found, in contrast to the findings of several studies (113,115). In the present study, CKDu patients with sarcopenia had lower QOL scores, which were significantly less for MCS and KDSC. Depression has been reported as a strong predictor of a rapid decline in MM and strength and thereby can be a causative factor for sarcopenia in patients with a decreased physical capacity by chronic conditions such as CKD (119–121).

This study demonstrated an association between many anthropometric indicators and sarcopenia among CKDu patients. Generally, sarcopenic patients had lower mean values of anthropometric measurements than non-sarcopenic patients, however, only BMI was found to have an acceptable predictive and discriminatory power. The cut-off point that provided the best balance between sensitivity and specificity was ≤ 22.4 kg/m2. Several studies have shown the usefulness of various anthropometric parameters for the screening of sarcopenia. However, few studies have investigated a CKD population. BMI was a strong predictor of skeletal MM in healthy men and women over the age of 65 years (122). Another study showed BMI and arm circumference as the indicators with the highest

ability to discriminate older adults of both sexes with sarcopenia (123). They reported cut-off values of $\leq 24.8\ kg/m^2$ and $\leq 24.5\ kg/m^2$ for men and women, respectively. Anthropometric indicators can be easily applied to primary health care centers as a part of a follow-up process. Therefore, taking together the information from the present study and the updated recommendations from AWGS and EWGSOP, it is recommended to screen for sarcopenia in the early-stage CKDu population in Sri Lanka to identify those who are with the condition and those who are at risk.

5.4. Strengths and limitations

Some limitations of this study should be acknowledged. First, although we adjusted for many regular confounders in this study, unmeasured factors (medications and interventions, dietary intake) may bias the study results. Second, we excluded patients who receive dialysis as well as those who are too debilitated which may result in an underestimation of sarcopenia in this population. Third, this was a small, single-center study that had a relatively short observation period. However, this study had several strengths. We used a definition of sarcopenia that included the components of low MM combined with low MS and physical performance. Furthermore, we used a direct physical function test to estimate MS. However, I believe that the limitations mentioned above do not compromise the quality of the study and hopefully, these observations can contribute to improve the understanding of CKD sarcopenia and stimulate further insight into CKDu.

5.5. Conclusions

In conclusion, sarcopenia was common in patients with non-dialysis dependent CKDu in this study, even during the early stages of the disease. Men were more likely to have sarcopenia compared to women, and BMI is the best predictor for sarcopenia. While general obesity reduced the likelihood of having sarcopenia, CO increased the odds of sarcopenia among CKDu patients. However, these findings should be explored with prospective studies with a larger and diverse sample.

CHAPTER 6

Study III
A longitudinal study of the anthropometric changes in CKDu patients

6.1. Introduction

The analysis of body composition in CKD patients has gained interest in recent years as a risk factor for morbidity and mortality (124). Particularly, BMI was reported to have a distinct association with survival of CKD patients which is different from that of the general population (96). The association of BMI with survival is usually described as having a J or U shape, with higher mortality at both extremes, in the general population. CKD Patients with low BMI are at a higher risk of mortality than those with a normal BMI, however in contrast to the general population high BMI is not associated with higher mortality among patients with ESRD (96). Moreover, there are emerging reports on the protective effect of increased fat mass not only in dialysis patients but also in those who are not in RRT (96,125). A recent study reported the associations between high lean/ fat tissue index with better outcomes in non-dialysis-dependent CKD patients (125). In CKD patients, body composition is frequently altered, with obesity and muscle wasting common and sometimes occurring simultaneously (126). These body composition changes were found to be influenced by age and sex (80) and have important implications for QOL, morbidity, and mortality (126). However, the patterns of body composition changes in CKDu patients might be different from that of the CKD patients due to its non-association with obesity related etiology. Therefore, this study sought to understand the alterations of body composition patterns among non-dialysis dependent CKDu patients in comparison to non-CKDu subjects. It was hypothesized that in comparison with healthy controls, those with CKD would have accelerated changes in body composition, which will be modified by age and sex.

6.2. Results

There were a total of 240 participants in the study who collectively had 1326 records for each body composition measurement and among those CKDu patients had 687 measurements for each parameter. The mean number of measurements per participant was 5.53 (1.39) while it was 5.33 (1.59) and 5.73 (1.12) for cases and control, respectively. The distribution of the number of records for each parameter for cases was as follows: one measurement in 10 (8.3%), two in 5 (4.2%), three and four in 2 (1.7%), five in 1 (0.8%) and more than six in 100 (83.3%). In the control group, 113 (94.2%) had six records for each parameter, while 2 (1.7%) and 5 (4.2%) had two and one records, respectively.

The estimates of body composition measurements (Weight, WC, HC, BF%, BM%, and BMI) without considering the time variable (random intercept model; Model 1) and then considering it as an explanatory variable (the combined random intercept and random slopes model; Model 2) is summarized in Table 6.1. The considerable improvement of AIC with Model 2 for each parameter suggests that it is better than Model 1. The constant value represents the mean value of the anthropometric parameter for the non-CKDu group at the index visit. The slope represents the average gain/ loss in anthropometric parameters for each visit for the control group. The CKDu intercept and slope estimates represent the difference in intercept and slope in CKDu patients compared to controls.

The results of the models that take into account the CKDu status, age, and sex are summarized in Table 6.2. CKDu patients had lower weight, WC, HC, BF%, and BMI and greater BM% compared to controls. Except for BM%, all the other measures increased with time in CKDu patients. Importantly, loss of BM% in CKDu patients was significantly higher compared to controls. Older age was a strong determinant of lower anthropometric values; however, it was not a determinant of changes in any anthropometric parameters. Unsurprisingly, male gender was a strong determinant of higher weight and BM% and lower WC, HC, BF%, and BMI. There was a significant loss in WC and gain in BF% with time among men.

Table 6.1. Hierarchical development of mixed model for each anthropometric measure with and without considering time variable

Parameter	Weight		WC		HC		BF%		BM%		BMI	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Constant (IQR)	53.599 (1.385)	54.214 (1.615)	85.644 (1.531)	86.161 (1.553)	87.662 (1.269)	87.568 (1.385)	27.982 (1.056)	28.341 (1.315)	27.720 (0.475)	27.673 (0.606)	21.405 (0.468)	21.631 (0.537)
CKDu intercept (IQR)	-0.517 (0.842)	-1.314 (1.431)	-1.939 (0.932)	-2.264 (1.591)	-1.491 (0.811)	-1.798 (1.388)	-0.644 (0.730)	-1.542 (1.240)	0.288 (0.327)	0.828 (0.550)	-0.162 (0.282)	-0.420 (0.479)
p-value	0.228	0.072	**<0.001***	**0.005***	**<0.001***	**0.011****	0.084	**0.015****	0.084	**0.003***	0.260	0.086
Slope (IQR)		-0.251 (0.334)		-0.225 (0.417)		0.032 (0.334)		-0.144 (0.291)		0.015 (0.131)		-0.092 (0.112)
p-value		0.141		0.290		0.850		0.332		0.826		0.107
CKDu slope (IQR)		0.328 (0.481)		0.146 (0.538)		0.141 (0.468)		0.373 (0.417)		-0.226 (0.185)		0.105 (0.162)
p-value		0.182		0.594		0.554		0.079		**0.017****		0.200
Log likelihood	9430	8737	9698	9064	9319	8737	9021	8087	6893	5877	6533	5949
AIC	9434	8759	9702	9086	9323	8759	9025	8109	6897	5899	6537	5971

Model 1: Random intercept model; Model 2: Combined random intercept and random slope model

*p<0.01; **p<0.05

Table 6.2. Mixed model estimates of anthropometric measures

Parameter	Weight	WC	HC	BF%	BM%	BMI
Constant	54.251	84.993	91.933	36.124	24.683	23.251
IQR	3.025	2.870	2.656	1.604	0.864	1.010
CKDu intercept	-1.282	-2.317	-1.847	-1.529	0.845	-0.425
IQR	1.431	1.590	1.384	1.197	0.555	0.480
p-value	0.079	**0.004***	**0.009***	**0.012****	**0.003***	0.083
Elderly intercept	-5.244	-0.345	-1.022	-0.656	-0.204	-1.380
IQR	2.775	2.597	2.413	1.394	0.765	0.926
p-value	**<0.001***	0.792	0.401	0.353	0.599	**0.004***
Male intercept	4.390	-5.188	-5.381	-10.585	4.446	-1.148
IQR	2.870	2.704	2.561	1.474	0.811	0.956
p-value	**0.003***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**0.019****
Slope (per visit)	-0.181	0.534	0.420	-0.947	0.176	-0.088
IQR	0.577	0.671	0.558	0.659	0.226	0.194
p-value	0.538	0.119	0.140	0.005	0.128	0.373
CKDu slope	0.326	0.162	0.157	0.357	-0.237	0.107
IQR	0.482	0.536	0.465	0.407	0.187	0.162
p-value	0.184	0.554	0.510	0.085	**0.013****	0.193
Elderly slope	-0.070	-0.081	-0.149	0.090	-0.077	0.001
IQR	0.493	0.579	0.476	0.593	0.193	0.168
p-value	0.780	0.784	0.539	0.765	0.435	0.987
Male slope	-0.029	-1.014	-0.423	1.062	-0.163	-0.006
IQR	0.524	0.613	0.507	0.616	0.206	0.176
p-value	0.913	**0.001***	0.102	**0.001***	0.120	0.944
Log likelihood	9399	9661	9287	8959	6786	6528
AIC	9407	9669	9295	8967	6794	6536

*p<0.01; ** p<0.05

Parameter	Age	Sex	n	Estimate	95% CI	*p* -value
Weight (kg)	<60	Female	15	0.408	0.358	**0.030**
	>60	Female	22	-0.057	0.220	0.595
	<60	Male	34	-0.073	0.169	0.396
	>60	Male	49	0.116	0.319	0.470
WC (cm)	<60	Female	15	1.107	0.492	**<0.001**
	>60	Female	22	0.784	0.380	**<0.001**
	<60	Male	34	-0.343	0.342	**0.049**
	>60	Male	49	-0.573	0.284	**<0.001**
HC (cm)	<60	Female	15	0.757	0.419	**0.001**
	>60	Female	22	0.621	0.395	**0.004**
	<60	Male	34	0.021	0.349	0.902
	>60	Male	49	-0.416	0.256	0.256
BF%	<60	Female	15	0.209	0.625	0.475
	>60	Female	22	-0.259	0.469	0.276
	<60	Male	34	0.252	0.305	0.104
	>60	Male	49	0.432	0.323	**0.010**
BM%	<60	Female	15	0.107	0.554	0.705
	>60	Female	22	-0.139	0.207	0.186
	<60	Male	34	-0.286	0.333	0.089
	>60	Male	49	-0.327	0.258	**0.013**
BMI (kg/m^2)	<60	Female	15	0.173	0.155	**0.032**
	>60	Female	22	-0.024	0.097	0.612
	<60	Male	34	-0.027	0.066	0.417
	>60	Male	49	0.061	0.149	0.418

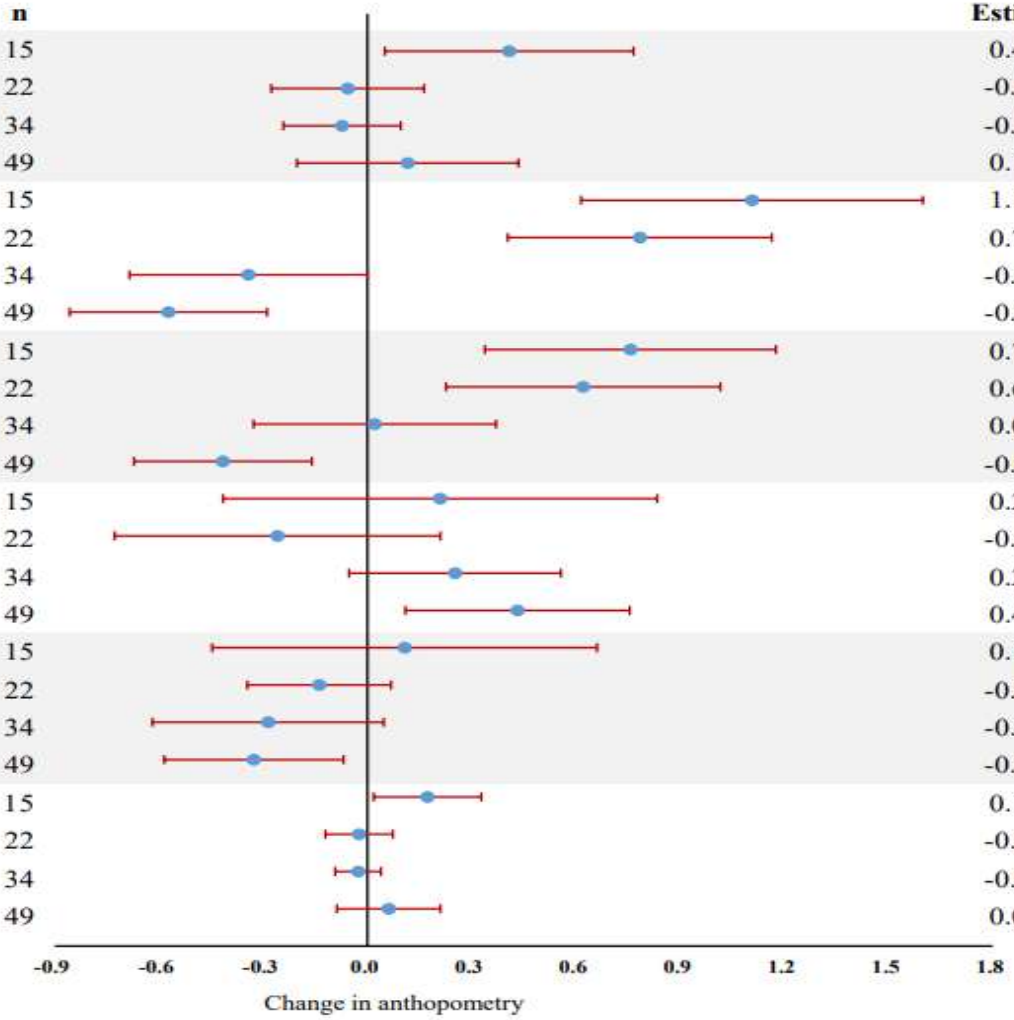

Figure 6.1: Estimates of change in anthropometric measures over time in CKDu patients

The effect of age and sex on body composition in CKDu was assessed and the estimates with 95% CIs are shown in Figure 6.1. Among younger women, all the parameters gained over time, while those changes were significant for weight, WC, HC, and BMI. Among elderly women, there was a significant increase in WC and HC. Among younger men, the loss of WC stands out while the decline in weight appears to be a result of BM% loss than BF% gain. Prominent changes in BF% and BM% can be seen among elderly men, while those changes did not affect their weight or BMI.

6.3. Discussion

To our knowledge, this is the first report of longitudinal changes in anthropometric measures among CKDu patients. The findings of this study can be summarized as follows. (i) Compared with non-CKDu controls, patients with CKDu had a lower weight, WC, HC, BF%, and BMI, and a greater BM%. However, the loss of BM% with time was significantly higher in patients. (ii) Independent of CKDu status, age >60 years was a strong determinant of lower weight and BMI, but not BF% or BM%. Age was also not a strong determinant of changes in body parameters, which could be a result of symmetric changes in BF% or BM%. (iii) Although compared with women, men had a higher BM%, the loss of BM% was not significant. Conversely, compared with women, men had a significantly low BF%, but the accumulation of BF was significantly higher in men. Therefore, compared with women, the BF% that was lower in men at baseline accumulates over time. Although there were significant changes in other parameters (weight, WC, HC, and BMI) between men and women at baseline, the changes over time were not modified by gender except for WC. (iv)The changes in body composition among CKDu patients were influenced by age and sex. Particularly, elderly men had significant changes in BF% and BM% with little changes in body weight or BMI.

Younger men had a relatively similar pattern of changes in anthropometric measures, although those changes were not significant. This similar pattern suggests the prevalence of masked obesity among men with CKDu. Masked obesity is a condition where bodyweight stays constant, but there is a loss of MM and a gain of fat mass (80). Thus, the use of conventional nutritional assessment methods such as body weight, BMI, and circumferences (WC, HC), may not be sufficient to detect changes associated specifically with CKDu. A recent study also emphasized the importance of body composition assessment (BF and BM) in CKD patients (80). In contrast, it appears that young women with CKDu have overt obesity, with increased weight, WC, HC, and BF%, with little changes in BM%. However, the number of women with CKDu in this study was relatively low to make conclusive comments. Despite baseline differences, there was a significant loss of WC among male patients, as opposed to female patients who demonstrated a significant increase with time. Compared to older women, the rate of WC gain was higher among younger women. Conversely, the rate of WC loss was higher among older men in comparison to younger men.

The studies that evaluate changes in anthropometric measures in CKD patients who are not on RRT is limited. A recent study reported the longitudinal changes in stage I-IV CKD patients by assessing the body composition using air-displacement plethysmography for up to 6 years (80). In contrast to the findings of the current study, patients with CKD had greater weight, BMI, and BF% than the healthy controls. Further, this study reported a significant loss of weight, BMI, fat mass (FM), and fat-free mass (FFM) among elderly CKD patients over time. Specifically, there was an accelerated loss of FFM in elderly black male patients. The author also described the occurrence of masked obesity in CKD patients who are young, male, and black. A study that assessed the changes in body composition of HD patients reported a significant reduction in BMI (-0.1259), triceps skinfold thickness (-0.4376), mid-arm muscle circumference (-0.2066), FM index (-0.1467), FFM index (-0.1459), and phase angle (-0.1018) over 24 months (127). Several studies report associations between anthropometric parameters, complications, and mortality in CKD patients (95,128–130).

6.4. Strengths and limitations

Several important limitations of this study should be acknowledged. First, the small sample size was relatively small limiting the sensitivity to detect subtle changes in the natural history of the disease or subtle influences of age and sex on these changes. Second, it is possible that anthropometric parameters might not change appreciably within the limited follow-up period. Third, there is a possibility of residual confounding due to the limited adjustment of the models. Finally, only CKDu patients who were not on RRT studied in this study, limiting the generalizability of results to patients who are receiving dialysis. Taking these limitations into considerations these results are only hypothesis-generating and therefore the researchers' goal is to continue the present study with a larger sample size and longer follow-up period. The major strength of this study was the use of a linear mixed model in the analysis of longitudinal data, which provides high statistical power and adjusts for follow-up measurement of each individual according to the baseline measurement.

6.5. Conclusions

In summary, this study shows the diverse changes in anthropometric measures in CKDu patients while some measures appear to be more sensitive to change than others. Detection of masked obesity among men with CKDu emphasizes the importance of body composition measures (BF% and BM%) in addition to conventional nutritional status measures (weight, BMI, WC, HC). Bioelectrical impedance analysis is easily performed in a clinical setting and provides an inexpensive, objective assessment of body composition. Future studies to analyze the prognostic implications of these findings are recommended.

CHAPTER 7

Study IV
Symptom burden and HRQOL among CKDu patients

7.1. Introduction

Symptom burden has been defined as a subjective, quantifiable prevalence, frequency, and severity of symptoms placing a physiological burden on patients and resulting in multiple negative physical and emotional responses (131,132). As symptom burden focuses on multiple concurrent symptoms and multidimensional attributes of symptoms, it provides a clear picture of the patient's experience of the disease (133). The majority of the studies so far have focused on cancer patients (134), and, recently, attention has been paid to other chronic diseases as well (135). CKD patients experience a multitude of physical and emotional symptoms, such as fatigue, pain, pruritis, shortness of breath, irritability, anxiety, nausea, anorexia, muscle cramps, sexual difficulty, sleep disturbances, and depression due to both the disease and its treatment. These symptoms occur in clusters rather than in isolation (136). There is growing evidence that reports a high symptom burden among CKD patients at all stages, exerting a negative impact on their QOL (136,137). HRQOL is an important aspect which demonstrates the patients' perceptions of their functioning in different domains including physical, psychological, and social well-being (138). Compared to in the general population, HRQOL is found to be lower among CKD patients (139), leading to adverse health outcomes (140). Assessments of symptom burden and HRQOL have been recognized as useful predictors of clinical condition and disease progression of pre-dialysis patients, and their use has been recommended for clinical decision making (136,140,141).

Living with a chronic disease such as CKDu requires a variety of adaptations and changes to daily lifestyle and habits, which in turn challenge both the psychological and social wellbeing of patients. As the disease has disproportionately affected rural, poor, male farming communities, financial constrains due to disability, work loss, and out-of-pocket expenditure have had a big impact on both their socio-economic status and psychological wellbeing (142). Senanayake *et al*. (2017) assessed the symptom burden and self-perceived severity of symptoms among CKD patients living in Anuradhapura district, Sri Lanka, and found that patients in all stages of CKD experience high symptom burden (143). Another study which assessed the QOL and symptom burden of CKD patients receiving hemodialysis in Sri Lanka found low QOL, and more than half of the study population reported feelings of worry and sadness (144). Unfortunately, less is known about the prevalence, severity, and impact of symptoms on the HRQOL of CKDu patients. Therefore, we believe that an understanding of symptom burden, HRQOL, and potential contributing factors in patients with CKDu would be helpful to plan and provide appropriate and timely patient-centered care and to improve the HRQOL of this population. A recent study in Sri Lanka identified level of education, employment status, stage of CKD, dialysis treatment, and presence of co-morbidities as significant predictors

of symptom burden (143), and low income and physical and psychological burden as independent predictors of low HRQOL (145) in a CKD/CKDu population. On account of the various negative impacts of CKDu on the physical, psychological, and social wellbeing of patients, the disease can be a cause of devastation not only in patients but also their families and relevant agricultural societies. Therefore, this study aimed to assess the prevalence, severity, and burden of symptoms, and HRQOL of CKDu patients and their correlation with socio-demographic, disease-related, anthropometric, and PA characteristics.

7.2. Results

7.2.1. Prevalence, intrusiveness and burden of symptoms

The median number of symptoms reported by patients was 5 (IQR; 3–7), and the mean (SD) was 5.59 (3.73). The majority of patients (n = 96, 80%) experienced 1–9 symptoms, with only 5% of patients reporting no symptoms at all. Three (2.5%) patients described having 15 or more symptoms. Prevalence of symptoms among the study population during the period of one week by sex and by stages of CKDu are listed in Table 7.1. The most prevalent symptoms were bone/joint pain (67.5%; 95% CI 58.3-75.8), loss of appetite (50.8%; 95% CI 41.6-60.1), and lack of energy (47.5%; 95% CI 38.3-56.8). The least prevalent symptoms were changes in skin color and feeling sad (2.5%, 95% CI 0.5-7.1), weight loss (5.8%, 95% CI 2.4-11.6), and hiccups and impotence (6.7%, 95% CI 2.9-12.7). Statistically significant differences between prevalence of symptoms among men and women were found for nausea (M-15.7%, F-32.4%, p=0.037), vomiting (M-2.4%, F-24.3%, p<0.001), and difficulty sleeping (M-42.2%, F-21.6%, p=0.030). There were no significant differences between prevalence of symptoms among CKDu stages.

In general, perceived severity was ‘mild’ or ‘moderate’ for many symptoms (Table 7.2). Feeling irritable, difficulty in keeping legs still, muscle cramps, and bone/joint pain were perceived as ‘moderate’ by 16 (38.10%), 17 (37.78%), 16 (34.78%), and 28 (34.75%) of those who experienced the symptoms, while 10 out of 43 patients who experienced difficulty sleeping rated it as ‘severe’. Mean (SD), median (IQR) and range of symptom burden scores were 12.71 (10.45), 10.00 (6.00-17.75), and 0-62, respectively.

Table 7.1. Prevalence of symptoms among CKDu patients and prevalence by sex and stage in the disease

Symptom	Frequency (*N* = 120)	Percentage (95% CI)	Prevelance by Sex *n*(%)		Prevelance by Stages of CKDu *n*(%)		
			Male (*N* = 83)	Female (*N* = 37)	Early Stages (*N* = 47)	IV (*N* = 49)	V (*N* = 24)
Loss of appetite	61	50.8 (41.6–60.1)	42 (50.6)	19 (51.4)	20 (42.6)	26 (53.1)	15 (62.5)
Nausea	25	20.8 (14–29.2)	13 (15.7)	12 (32.4)	9 (19.1)	9 (18.4)	7 (29.2)
Vomiting	11	9.2 (4.7–15.8)	2 (2.4)	9 (24.3)	1 (2.1)	7 (14.3)	3 (12.5)
Diarrahea	26	21.7 (14.7–30.1)	20 (24.1)	6 (16.2)	9 (19.1)	9 (18.4)	8 (33.3)
Lethargy	44	36.7 (28.1–45.9)	30 (36.1)	14 (37.8)	16 (34.0)	17 (34.7)	11 (45.8)
Changes in skin colour	3	2.5 (0.5–7.1)	1 (1.2)	2 (5.4)	1 (2.1)	0	2 (8.3)
Swelling of arms and legs	22	18.3 (11.9–26.4)	14 (16.9)	8 (21.6)	6 (12.8)	12 (24.5)	4 (16.7)
Difficulty in breathing	24	20 (13.3–28.3)	19 (22.9)	5 (13.5)	11 (23.4)	5 (10.2)	8 (33.3)
Hiccups	8	6.7 (2.9–12.7)	5 (6)	3 (8.1)	2 (4.3)	4 (8.2)	2 (8.3)
Difficulty keeping legs still	45	37.5 (28.8–46.8)	28 (33.7)	17 (45.9)	17 (36.2)	18 (36.7)	10 (41.7)
Numbness/tingling of hands and feet	24	20 (13.3–28.3)	17 (20.5)	7 (18.9)	8 (17.0)	10 (20.4)	6 (25.0)
Lack of energy	57	47.5 (38.3–56.8)	39 (47)	18 (48.6)	24 (51.1)	21 (42.9)	12 (50.0)
Trouble with memory	22	18.3 (11.9–26.4)	15 (18.1)	7 (18.9)	9 (19.1)	7 (14.3)	6 (25.0)
Weight loss	7	5.8 (2.4–11.6)	4 (4.8)	3 (8.1)	2 (4.3)	2 (4.1)	3 (12.5)
Bone/joint pain	81	67.5 (58.3–75.8)	55 (66.3)	26 (70.3)	32 (68.1)	33 (67.3)	16 (66.7)
Muscle cramps	46	38.3 (29.6–47.6)	31 (37.3)	15 (40.5)	18 (38.3)	19 (38.8)	9 (37.5)
Difficulty concentrating	9	7.5 (3.5–13.8)	4 (4.8)	5 (13.5)	4 (8.5)	3 (6.1)	2 (8.3)
Dry skin	12	10 (5.3–16.8)	8 (9.6)	4 (10.8)	5 (10.6)	2 (4.1)	5 (20.8)
Itching	21	17.5 (11.2–25.5)	14 (16.9)	7 (18.9)	7 (14.9)	7 (14.3)	7 (29.2)
Feeling sad	3	2.5 (0.5–7.1)	2 (2.4)	1 (2.7)	2 (4.3)	1 (2.0)	0
Difficulty sleeping	43	35.8 (27.3–45.1)	35 (42.2)	8 (21.6)	15 (31.9)	18 (36.7)	10 (41.7)
Feeling irritable	42	35 (26.5–44.2)	31 (37.3)	11 (29.7)	16 (34.0)	17 (34.7)	9 (37.5)
Loss/ decreased libido	13	10.8 (5.9–17.8)	10 (12)	3 (8.1)	7 (14.9)	4 (8.2)	2 (8.3)
Impotence	8	6.7 (2.9–12.7)	5 (6)	3 (8.1)	4 (8.5)	4 (8.2)	0
Heartburn	14	11.7 (6.5–18.8)	9 (10.8)	5 (13.5)	8 (17.0)	3 (6.1)	3 (12.5)

Table 7.2. Intrusiveness of symptoms perceived by CKDu patients

Symptom	*n*	Very mild *n* (%)	Mild *n* (%)	Moderate *n* (%)	Severe *n* (%)	Very Severe *n* (%)
Loss of appetite	61	11 (18.03)	34 (55.74)	10 (16.39)	5 (8.20)	1 (1.64)
Nausea	25	12 (48.0)	9 (36.0)	2 (8.0)	1 (4.0)	1 (4.0)
Vomiting	11	3 (27.27)	6 (54.55)	2 (18.18)	0	0
Diarrahea	26	5 (19.23)	18 (69.23)	3 (11.54)	0	0
Lethargy	44	12 (27.27)	16 (36.36)	13 (29.55)	2 (4.55)	1 (2.27)
Changes in skin colour	3	2 (66.67)	0	1 (33.33)	0	0
Swelling of arms and legs	22	5 (22.73)	12 (54.55)	3 (13.64)	2 (9.09)	0
Difficulty in breathing	24	9 (37.50)	12 (50.00)	2 (8.33)	1 (4.17)	0
Hiccups	8	3 (37.50)	2 (25.00)	2 (25.00)	1 (12.50)	0
Difficulty keeping legs still	45	5 (11.11)	21 (46.67)	17 (37.78)	2 (4.44)	0
Numbness/tingling of hands and feet	24	4 (16.67)	11 (45.83)	7 (29.17)	1 (4.17)	1 (4.17)
Lack of energy	57	13 (22.81)	26 (45.61)	16 (28.07)	2 (3.51)	0
Trouble with memory	22	7 (31.82)	11 (50.00)	1 (4.55)	3 (13.64)	0
Weight loss	7	1 (14.29)	4 (57.14)	2 (28.57)	0	0
Bone/joint pain	81	4 (4.94)	41 (50.62)	28 (34.57)	8 (9.88)	0
Muscle cramps	46	5 (10.87)	18 (39.13)	16 (34.78)	7 (15.22)	0
Difficulty concentrating	9	0	4 (44.44)	3 (33.33)	2 (22.22)	0
Dry skin	12	2 (16.67)	5 (41.67)	2 (16.67)	3 (25.00)	0
Itching	21	3 (14.29)	13 (61.90)	4 (19.05)	1 (4.76)	0
Feeling sad	3	0	2 (66.67)	1 (33.33)	0	0
Difficulty sleeping	43	9 (20.93)	14 (32.56)	9 (20.93)	10 (23.26)	1 (2.33)
Feeling irritable	42	3 (7.14)	16 (38.10)	16 (38.10)	7 (16.67)	0
Loss/decreased libido	13	0	10 (76.92)	2 (15.38)	1 (7.69)	0
Impotence	8	2 (25.00)	4 (50.00)	2 (25.00)	0	0
Heartburn	14	1 (7.14)	9 (64.29)	1 (7.14)	3 (21.43)	0

7.2.2. QOL scores

The domain scores of the KDQOL-SF™ were calculated based on individual item responses. Mean scores of patient satisfaction (43.19±10.48), general health perceptions (53.42±18.88), work status (52.50±10.94), and overall health (52.92±14.46) were comparatively lower. Three summary scores, KDSC, PCS, and MCS, were calculated, and mean, median and dispersion scores are summarized in Table 7.3. Mean PCS was lower compared to mean scores for MCS and KDSC.

Table 7.3. Mean and dispersion for KDQOL-SF™ domain scores in CKDu patients

Domain	Mean	SD	Median	IQR	Min	Max
KDSC score	81.57	5.86	82.37	78.97–84.97	47.69	93.48
Symptoms/problems	90.63	10.63	93.18	88.64–97.73	22.73	100.00
Effects of kidney disease on daily life	95.21	6.64	96.88	93.75–100.00	63.00	100.00
Burden of kidney disease	83.39	14.35	87.50	75.00–93.75	25.00	100.00
Work status	52.50	10.94	50.00	50.00–50.00	50.00	100.00
Cognitive function	93.61	8.66	93.33	86.67–100.00	47.00	100.00
Quality of social interaction	84.94	11.93	86.67	80.00–93.33	53.00	100.00
Sexual function	90.36	16.14	100.00	75.00–100.00	0.00	100.00
Sleep	73.75	17.88	77.50	63.13–86.88	18.00	100.00
Social suppot	96.25	11.11	100.00	100.00–100.00	33.00	100.00
Hospial staff encouragement	96.35	8.64	100.00	100.00–100.00	75.00	100.00
Patient satisfaction	43.19	10.48	50.00	33.33–50.00	33.00	83.00
PCS score	68.63	19.58	75.31	52.81–85.47	16.88	97.50
Physical functioning	79.21	19.71	85.00	70.00–90.00	15.00	100.00
Role limitations due to physical health problems	70.83	43.40	100.00	6.25–100	0.00	100.00
Pain	71.04	22.64	77.50	55.00–90.00	0.00	100.00
General health perceptions	53.42	18.88	60.00	35.00–70.00	10.00	90.00
MCS score	78.53	18.78	85.81	62.70–94.38	33.25	100.00
Emotional well-being	84.67	15.37	88.00	76.00–100.00	28.00	100.00
Role limitations due to emotional health problems	75.28	41.34	100.00	66.67–100.00	0.00	100.00
Social functioning	79.79	20.57	87.50	62.50–100.00	25.00	100.00
Energy/fatigue	74.38	17.68	75.00	65.00–90.00	10.00	100.00
Overall Health	52.92	14.46	50.00	50.00–60.00	0.00	90.00

7.2.3. Independent Variables and Their Association with QOL Summary Scores

In simple linear regression, PCS scores were associated with age ($p < 0.001$), having no education (p=0.001), early stages of CKDu (p=0.049), duration of years being diagnosed (p=0.024), GFR (p=0.021), Hb (p=0.001), symptom burden score (p <0.001), and HGS (p=0.003). Simple linear regression of the MCS scores showed age (p <0.001), GFR (p=0.020), Hb (p=0.012), symptom burden score (p <0.001), BMI (p=0.010), and BF% (p= 0.023) as significant determinants. KDSC scores were associated with age ($p < 0.001$), having no education (p <0.001), and symptom burden score (p <0.001) in simple linear regression (Table 7.4). Symptom burden scores were associated with engaging in farming (B = −11.830, β = −0.284, p=0.002) and Hb (B = −1.372, β = −0.219, p=0.016) in simple linear regression.

Multiple linear regression was performed to explore how socio-demographic, health-related, and anthropometric characteristics influence HRQOL and symptom burden scores. Variables with p values less than 0.05 in simple linear regression, plus gender, were selected. Table 7.5 summarizes the final significant models obtained by stepwise linear regression. Age was identified as a significant independent predictor, negatively influencing all PCS (p <0.001), MCS (p=0.009), and KDSC (p=0.018) scores. Higher Hb was a significant predictor (p <0.05) of higher scores of PCS (β=0.177) and lower scores of symptom burden (β= −0.177). Symptom burden score independently influenced all HRQOL scores (PCS; β= −0.417, MCS; β= −0.464, KDSC; β= −0.494).

Table 7.4. Simple linear regression of socio-demographic, health-related, and anthropometric parameters with PCS, MCS, and KDSC scores in CKDu patients

Predictor	PCS					MCS					KDSC				
	USC B	SE	SC Beta	95% CI for B		USC B	SE	SC Beta	95% CI for B		USC B	SE	SC Beta	95% CI for B	
				Lower	Upper				Lower	Upper				Lower	Upper
Age	−0.872**	0.138	−0.503	−1.144	−0.599	−0.601**	0.143	−0.362	−0.883	−0.319	−0.181**	0.045	−0.350	−0.270	−0.093
Male gender	−0.376	3.886	−0.009	−8.072	7.320	−6.241	3.683	−0.154	−13.534	1.052	1.412	1.156	0.112	−0.877	3.700
Having no education	−14.053**	4.226	−0.293	−22.421	−5.685	−4.349	4.220	−0.094	−12.705	4.007	−5.446**	1.224	−0.379	−7.869	−3.022
Having a significant other	5.871	6.793	0.079	−7.580	19.322	−5.751	6.514	−0.081	−18.650	7.148	1.670	2.033	0.075	−2.356	5.697
Having <5 family members	0.417	3.743	0.010	−6.995	7.828	1.390	3.587	0.036	−5.714	8.494	1.687	1.109	0.139	−0.510	3.883
Monthly income <10000SLR	−2.418	3.756	−0.059	−9.856	5.021	−1.944	3.604	−0.050	−9.082	5.193	−0.083	1.126	−0.007	−2.313	2.147
Engage in farming	3.298	7.189	0.042	−10.937	17.533	4.868	6.886	0.065	−8.768	18.504	1.742	2.147	0.074	−2.510	5.994
Presence of co-morbidities	3.492	3.903	0.082	−4.237	11.222	6.734	3.705	0.165	−0.602	14.071	0.145	1.172	0.011	−2.175	2.466
Having family history of CKD	−7.263	4.368	−0.151	−15.914	1.388	−4.452	4.219	−0.097	−12.806	3.902	−1.549	1.315	−0.108	−4.152	1.055
Early stages of CKDu	7.179*	3.617	0.180	0.016	14.341	6.629	3.473	0.173	-0.249	13.507	0.498	1.099	0.042	−1.679	2.675
GFR	0.295*	0.126	0.211	0.046	0.543	0.284*	0.120	0.212	0.045	0.522	0.016	0.038	0.038	−0.060	0.092
Hb	3.621**	1.027	0.309	1.588	5.654	2.557*	1.008	0.227	0.561	4.553	0.530	0.319	0.151	−0.102	1.162
SBP	0.000	0.084	0.000	−0.166	0.166	−0.012	0.080	−0.014	−0.171	0.147	0.009	0.025	0.033	−0.041	0.059
DBP	0.095	0.126	0.069	−0.154	0.344	0.062	0.121	0.047	−0.177	0.302	0.016	0.038	0.040	−0.058	0.091
Low PA	−5.688	3.559	−0.146	−12.736	1.360	−4.074	3.430	−0.109	−10.866	2.718	0.295	1.076	0.025	−1.836	2.427
Symptom burden score	−0.797**	0.156	−0.425	−1.107	−0.488	−0.723**	0.151	−0.402	−1.023	−0.423	−0.301**	0.044	−0.536	−0.387	−0.215
BMI	0.698	0.548	0.116	−0.387	1.782	1.343*	0.514	0.234	0.325	2.361	0.184	0.164	0.102	−0.141	0.508
BF%	0.232	0.213	0.100	−0.190	0.655	0.463*	0.201	0.207	0.064	0.861	−0.017	0.064	−0.024	−0.144	0.110
BM%	0.102	0.381	0.025	−0.653	0.856	−0.251	0.365	−0.063	−0.973	0.472	0.112	0.114	0.090	−0.113	0.336
HGS	0.717**	0.238	0.268	0.246	1.187	0.412	0.233	0.160	−0.050	0.875	0.131	0.073	0.163	−0.013	0.275

Abbreviations: USC B-unstandardized regression coefficient; SE-standard errors of B; SC Beta-standardized coefficient. *$p < 0.05$; **$p < 0.01$

Table 7.5. Independent predictors of PCS, MCS, KDSC, and symptom burden scores

Variable	Unstandardized Coefficients		Standardized Coefficients	95% CI		*p*
	B	SE	Beta	Lower	Upper	
PCS Score (Adjusted R^2 = 0.429)						
Years of age	−0.754	0.135	−0.417	−1.022	−0.486	<0.001
Symptom burden score	−0.782	0.154	−0.383	−1.087	−0.477	<0.001
Hb	2.065	0.873	0.177	0.333	3.798	0.020
MCS Score (Adjusted R^2 = 0.360)						
Symptom burden score	−0.916	0.156	−0.464	−1.225	−0.608	<0.001
Years of age	−0.372	0.140	−0.212	−0.650	−0.094	0.009
BF%	0.451	0.172	0.205	0.109	0.793	0.010
GFR	0.240	0.105	0.179	0.031	0.449	0.025
KDSC Score (Adjusted R^2 = 0.413)						
Symptom burden score	−0.307	0.047	−0.494	−0.402	−0.213	<0.001
Having no education	−2.951	1.213	−0.203	−5.358	−0.544	0.017
Years of age	−0.109	0.046	−0.198	−0.200	−0.019	0.018
Symptom burden score (Adjusted R^2 = 0.112)						
Engaged in farming	−11.702	3.603	−0.281	−18.837	−4.566	0.002
Hb	−1.347	0.540	−0.215	−2.417	−0.277	0.014

R^2-squared multiple correlation coefficients

7.3. Discussion

To best of our knowledge, this is the first ever study to assess QOL and symptom burden which focused entirely on CKDu patients. One of the important findings of this study is the marked symptom prevalence in CKDu patients, where the vast majority of patients (95%) reported experiencing at least one symptom and 55.8% of them reported having five or more symptoms. Individual analysis of the symptoms revealed that bone/joint pain is the most commonly reported symptom, followed by loss of appetite, lack of energy, muscle cramps, and difficulty in keeping legs still. These findings are compatible with two previous studies conducted in Sri Lanka, which assessed the symptom burden of CKD patients whose etiology may or may not be known. The most commonly reported symptoms were bone/joint pain (87.6%), feeling irritable (78.6%), muscle cramps (77.5%), and lack of energy in one study (143), and tiredness and lack of energy (73.3%), shortness of breath (65.9%), swelling in legs (56.2%), muscle cramps (53.1%) and bone/joint pain (48.9%) in the other study (144). Both of these studies included patients undergoing dialysis, while there were no dialysis patients included in the present study. However, these findings are consistent with other studies which have used CKD patients managed without RRT (137,146).

In the present study, the prevalence of symptoms was similar, irrespective of the gender and stage of CKDu. The burden of symptoms in CKD patients at all stages and the importance of symptom assessment even in the early stages of the disease have been pointed out by other studies (137,143). Brown *et al*. (137) have reported that men are less likely to report symptoms compared to women and when they do report them usually describe them as less intrusive. Symptoms were frequently reported as mild or moderate in the current study, and the symptom perceived as most severe was difficulty in sleeping. In contrast, a recent study in Sri Lanka reported loss of or decreased libido as the most severe symptom among CKD patients (143). The symptom burden score of the current study is much lower than the previously reported score by Senanayake *et al*. (Mean-35.8) (143). As 77% of the sample in Senanayake *et al*.(143) were in the advanced stages of the disease and 3.4% were undergoing hemodialysis, the difference in the symptom burden scores might be largely attributed to the differences in patients' perceptions of the severity of symptoms. Although the symptom burden score was considerably lower in the current study, the fact that 95% of patients are experiencing at least one symptom indicates the importance of incorporating symptom assessment into clinical management from early stages of CKDu.

A few studies have evaluated the QOL of non-dialysis patients. This discussion used the previous studies that used the same questionnaire to assess QOL of CKD patients for comparison. The mean KDSC was the highest among QOL quality scores, followed by MCS and PCS, respectively. This points to the fact that, despite the worsening of physical health status, mental health status and kidney-disease-specific QOL aspects are relatively preserved. This may be associated with the chronic nature of the disease, where patients get adapted to the disease, its treatments, and also psychologically to their condition (147,148). The mean PCS and MCS in this study population was significantly higher compared to Kefale *et al*. (PCS-38.1; MCS-46) (148) and De Goeij *et al*. (PCS-54.4; MCS-67.8) (141). The median summary scores for CKD/CKDu patients reported in a recent study in Sri Lanka were much lower than in the current study (PCS-35.0; MCS-58.4; KDSC-58.4) (145). This may be attributed to the lower GFR in these study populations compared to the current study. Another study observed PCS of 44.4 and 43.1, and MCS of 46.0 and 47.7 among stage III and stage IV and V patients, respectively (147). Symptom burden score was negatively correlated with all QOL summary scores, suggesting the importance of symptom monitoring in CKDu patients. Symptom burden score was not associated with educational status, CKDu stage, or presence of co-morbidities, in contrast to Senanayake *et al*.(143), who reported those factors as independent predictors of symptom burden among CKD patients in Sri Lanka. Hb and being engaged in farming were the only predictor variables of symptom burden score in the present study. However, when the R^2 value is considered, these variables explain only 11.2% of the variation in symptom burden score, suggesting that it is influenced by other unrecognized factors.

Among demographic and anthropometric factors, having education, BMI, BF%, and HGS were found to be positively associated with one or more summary scores, while higher age was associated with low QOL. In multiple regression analysis, age was found to be strongly associated with all the summary scores. This finding is in accordance with studies conducted in Brazil (147) and Portugal (149) and different from a study conducted in Ethiopia (148). Similar to previous studies, this study found Hb to be a significant predictor of PCS (144-146), but not of MCS. A prospective study reported a dramatic improvement in QOL of non-dialysis CKD patients with increased Hb levels from <11 to 11–12 g/dl (150). Having at least primary education was a predictor of a high KDSC score. While relevant literature on KDSC score among non-dialysis patients is limited, this finding may probably be associated with the fact that having at least primary education enhances patients' ability to comprehend the information given by care givers, thus complying with treatments. Senanayake *et al*. (145) reported higher education level, being employed, higher income, CKD stage, depression and psychological distress as significant independent predictors of HRQOL among CKD patients in Sri Lanka. HRQOL in the current study, however, was not associated with gender, employment, family income, marital status, nutritional status, or CKD stage. Kefale *et al*. (148) found that both high family income and Hb level were significantly related to better QOL. Similarly, educational status and absence of CKD complications have also been predictors of PCS and MCS, respectively. A study by Cruz *et al*. (147) found that many socio-demographic factors, including age, ethnicity, gender, professional activity, education, and income, were associated with QOL in relation to clinical factors (co-morbidities, Hb, serum phosphorus level).

7.4. Strengths and limitations

Some limitations of the present study must be considered. Firstly, there was a relatively non-equal representation between the stages of CKDu to detect significant differences. As patients are usually at the late stages of the disease when they are diagnosed, the investigator encountered difficulties in recruiting the subjects in the initial stages of the disease. Secondly, the study was conducted at a single clinic, limiting the extrapolation of results. Finally, the quantitative nature of the data may not highlight patients' perceptions; thus, studies that consider qualitative assessments, such as interviews and focus group discussions, would have provided a clear understanding of the influence of CKDu on HRQOL. Nevertheless, this study used questionnaires that were developed specifically for CKD patients and also validated for the Sri Lankan context.

7.5. Conclusions

In the current study population, 95% of patients were suffering from at least one symptom, and high symptom burden was strongly associated with HRQOL. These findings suggest that patients in early stages of the disease and patients who are not receiving RRT suffer from a multitude of symptoms, and, therefore, focus should be given to addressing symptom burden from an earlier stage of the disease. CKDu patients with a higher age were found to have worse QOL. Hb and GFR were associated with PCS and MCS, respectively. Among anthropometric factors, only BF% was a significant predictor of MCS. Although effects of age cannot be controlled, caregivers should focus on reducing the effects of factors that can be moderated, such as Hb level and symptom burden. In general, assessment of nutritional status, symptom burden and HRQOL of CKDu patients during their routine clinic visits is highly recommended. More longitudinal studies and qualitative studies on these aspects are encouraged.

CHAPTER 8

Conclusions

This study assessed the nutritional status, symptom burden, and HRQOL of non-dialysis CKDu patients attending a renal clinic in Sri Lanka. The study results were presented and discussed in the previous chapters. This chapter presents the implications of the findings and proposes recommendations for clinical and nursing practice, education, and future research and finally summarize the conclusions of study I-IV.

8.1. Implications and recommendations for practice

The present study indicates unfavorable nutritional status and health characteristics associated with risk of NCDs, such as CO, HBP, betel chewing among both CKDu patients and non-CKDu individuals. This suggests the need for further screening and education of rural communities as well as the type, amount, and resources used for screening and education about NCDs risk by public health services in Sri Lanka. Health care providers need to be aware of; (1) sarcopenia prevalence characterized by low muscle mass and muscle strength, (3) prevalence of masked obesity among male CKDu patients characterized by loss of MM and gain of fat mass without significantly changing body weight or BMI, and (2) symptom burden characterized by a simultaneous prevalence of different symptoms with varying degree of severity even during the early stages of the disease. It is important to consider these factors when making patient management decisions by doctors and patients care plans by nurses as they have direct implications with the disease progression and prognosis as well as the HRQOL of patients.

The instruments used in this study; CKDSI-Sri Lanka and KDQOL-SF^{TM} have already been validated to Sri Lanka context, and could be used as a tool kit for fast and regular assessment of symptom burden and QOL in CKDu patients. Based on the findings of the study, regular assessment of anthropometric measures of CKDu patients, even those who are in early stages, is highly recommended. The integration of body composition (BM% and BF%) assessment in addition to conventional anthropometric measurements is recommended to detect the subtle changes in nutritional status.

8.2. Implications and recommendations for education

This study has implications for education for both CKDu patients and healthcare providers, particularly for nurses. The results of this study show the importance of nutritional counseling of CKDu patients in terms of diet, PA, sarcopenia, body composition monitoring, and the importance of regular monitoring. Patient education ought to be focused on the importance of regular follow-up, adherence with non-pharmacological interventions, seeking support, and genuine reporting of symptom burden and QOL. When providing patient education, it is important to be aware of prominent patient characteristics (higher age, male gender, low education level, and socioeconomic status) which could be associated with low levels of health literacy or

impact on understanding and adherence. Newly diagnosed CKDu patients may be more receptive to education than those who have had a longer diagnosis, as they are more likely to believe taking actions might improve their health status.

Nurses interact with patients throughout their illness trajectory. Therefore, nurses can impart information and everyday life support for patients with CKDu, thereby empowering patients to self-manage their disease. Nurses can easily administer symptom burden and HRQOL questionnaires used in this study, and assess anthropometry and body composition at each clinic visit. To be able to educate patients, and plan personalized care for patients nurses also need to be aware of sarcopenia, using body composition monitors, and administering and interpreting questionnaires in clinical and community settings. Professional education is therefore important for nurses, particularly on unaccustomed concepts for Sri Lankan nurses such as sarcopenia and body composition monitoring.

8.1.3. Implications and recommendations for research

Several implications for future research have arisen from this study. First, future research should consider further testing for these findings with a larger sample recruited from different CKDu endemic areas across Sri Lanka to increase the generalizability of these results. It would also be of interest to investigate nutritional status using biochemical tests and biological markers in a case-control population in addition to anthropometric measurements. Second, reporting all CKDu stages, RRT, years since CKDu diagnosis and their impact on anthropometric changes with time, symptom burden, and HRQOL is a worthy consideration. Third, longitudinal studies are required to determine the causal relationships between CKDu and nutritional factors. In addition, longitudinal studies to analyze the association of changes in anthropometry with time and sarcopenic status with mortality and the progression of the disease.

8.4. General conclusions

The conclusions drawn from the results of this study can be summarized as follows. First, no constructive evidence was found linking anthropometric measurements to CKDu risk. This finding might be attributed to the dissociation of CKDu etiology from common obesity-associated CKD risk factors such as DM and HT. Second, this study provides evidence for a higher prevalence of sarcopenia among non-dialysis dependent CKDu patients, even during the early stages of the disease. Sarcopenia among CKDu patients was mainly a result of muscle failure in terms of low MM and MS than low physical performance. Third, this study indicates the prevalence of masked obesity, particularly among elderly male CKDu patients. Finally, this study provide evidence for high symptom burden among non-dialysis-dependent CKDu patients. Further, burden of symptoms among patients in early stages of the disease and significant inverse association of high symptom burden with low HRQOL must be brought to the notice of the health care providers.

Annexure 1

Certificate of Consent

To be completed:

A. By the participant

1. Have you read the information sheet? YES/ NO
2. Have you had an opportunity to discuss this study and ask any questions? YES/ NO
3. Have you had satisfactory answers to all your questions? YES/ NO
4. Have you received enough information about the study? YES/ NO
5. Who explained the study to you? ……
6. Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future medical care? YES/ NO
7. Sections of your medical notes, including those held by the investigators relating to your participation in this study may be examined by other research assistants. All personal details will be treated as STRICTLY CONFIDENTIAL. Do you give your permission for these individuals to have access to your records? YES/ NO
8. Have you had sufficient time to come to your decision? YES/ NO
9. Do you agree to take part in this study? YES/ NO

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Name of Participant: _____

Signature of Participant: _____

Date: _____ (Date/ Month/ Year)

If illiterate:

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____ (Date/ Month/ Year)

B. By the investigator

I have explained the study to the above volunteer and he/ she has indicated her willingness to take part.

Name of investigator: _____

Signature of investigator: _____

Date: _____ (Date/ Month/ Year)

Annexure 2

Information Sheet

Information sheet for research on "Association between nutritional status and dietary pattern with CKDu in Girandurukotte area, Sri Lanka"

I am Hansani Madushika Abeywickrama, a Graduate student of Niigata University, Japan. We are conducting a research on 'Association between nutritional status and dietary pattern with CKDu in Girandurukotte area, Sri Lanka'. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. There may be some words that you may not understand. Please ask me to stop as I go through the information and I will take time to explain. If you have questions later, you can ask them from me or other collaborators.

Purpose of the research:

CKDu – Chronic Kidney Disease of uncertain etiology has become one of the major health issue in Sri Lanka over the past two decades and predominant in certain parts of Sri Lanka including North Central province, Uva province and a few areas of the North Western Province. Number of studies has been conducted on the subject by different researchers and they have pointed out that there is a threat for this condition to reach epidemic proportions. Etiology of the disease is believed to be multifactorial and some of the suggested etiologies are high concentration of fluoride in water, use of aluminum utensils for cooking, chronic dietary intake of cadmium, environmental toxins and occupational exposure to toxic chemicals. Even though, strong association between these factors and the occurrence of CKDu has been observed, none of the researchers were able to draw an acceptable scientific relationship between/ among above factors and the disease condition. Therefore, Sri Lanka is in a serious need for a comprehensive study of CKDu and the effect of diet and nutrition is poorly explained by the literature. Therefore, it is a national importance to assess whether nutritional status having an impact on the kidneys that predispose the persons to the disease condition. There is a high tendency of food getting contaminated and receiving insufficient nutrients, which led us to study the food patterns and nutritional status of a CKDu affected area to explore possibilities of remedial measures that can be provided.

Procedures of Research:

This research finds out the dietary pattern, nutritional status, and physical activity level among CKDu patients and people without CKDu in a CKDu endemic area. If you agree to participate then I will ask some general questions regarding your demographic, socio-economical information and health condition at the first day. I will take some information from your clinic book and diagnosis card only if it is necessary. There will also be questions that assess certain habits like tobacco smoking and betel chewing. This

questionnaire will take maximum 15 minutes to complete. I will also ask you to recall what you ate and drank in the previous day and list it out for me with estimated quantities. This dietary recall data will collect from you every two months from January, 2019 for a period of one year and will take 10-15 minutes each time. Also, I will collect information regarding your physical activity level using a brief questionnaire at two occasions. In addition, I will take some measurements such as weight, height, mid upper arm circumference, hip and weight circumference. Also, I will measure your hand grip strength. These are non-invasive and do not take much time to measure. In addition, I will ask some questions about quality of life and symptom burden only from CKDu patients.

Participant selection and voluntary participation:

We will recruit recently diagnosed patients with CKDu residing in Girandurukotte area for at least 10 years for this study. Also we will select healthy subjects with have no history of hypertension, diabetes mellitus or renal diseases, and are not on treatment for If you are a CKDu patient, diagnosed previously and already change your diet due to the diagnosis or undergo peritoneal or hemodialysis you will not be able to participate in the study. Also, if you are a healthy person with a family member who is diagnosed with CKDu, you will not be able to participate in the study. Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this hospital/clinic will continue and nothing will change. If you choose not to participate in this research project, please do not hesitate to let us know of your decision. You may change your mind later and stop participating even if you agreed earlier.

Duration:

Data will be collected in every two months starting from January, 2019 for a period of one year. You do not have to spend extra time for the study and we will use small time in 6 days during this year. During this time, we expect to gather data related to your dietary pattern, nutritional status, and physical activity.

Risks/ Hazards/ Discomforts:

No any risks or hazards or discomfort associated with participating in this study.

Potential Benefits:

There are no (direct) benefits for you by participating in this research, but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.

Reimbursement:

We are unable to reimburse you for your participation in this research either monetarily or any other form of gift(s). However, we are grateful for your participation and highly appreciate your contribution.

Confidentiality:

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except the study staff.

Right to refuse or withdraw:

You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect services you receive at this clinic in any way. You will still have all the benefits that you would otherwise have. You may stop participating in the research at any time you wish without losing any of your rights. It is your choice and all your rights will still be respected.

Whom to contact:

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of us through following contact details.

1) Name: Hansani Madushika Abeywickrama

   Address: No. 8A, Millaththawa, Girandurukotte, Sri Lanka.
   Telephone number: 071-8806521
   Email address: hansanimadushika87@gmail.com

This research proposal has been reviewed and approved by the Ethics Review Committee of the Faculty of Allied Health Sciences.

Annexure 3

Questionnaire on socio-demographic and health-related data

Date: ☐ Reference Number: ☐

Note: Be honest to give your answers.
Instructions: Read the questions carefully and put a (√) inside the appropriate box

(I) <u>Demographic/ Socioeconomic data</u>

1. Age: …….. years

2. Sex:
   a. Male ☐
   b. Female ☐

3. Religion:
   a. Buddhist ☐
   b. Hindu ☐
   c. Islam ☐
   d. Catholic ☐
   e. Other ☐ Please Specify …….

4. Level of education:
   a. No proper education ☐
   b. Primary ☐
   c. Secondary ☐
   d. Higher ☐

5. Marital status
   a. Married ☐
   b. Divorced ☐
   c. Widowed ☐
   d. Single ☐

6. Number of household members
   a. Only 2 ☐
   b. 3 or 4 ☐
   c. 5 or more ☐

7. Level of income per month (in Sri Lankan Rupees)
   a. Less than 5000 ☐
   b. 5001-10000 ☐
   c. 10001-20000 ☐
   d. 20001-30000 ☐
   e. 30001-50000 ☐
   f. More than 50000 ☐

8. Occupation: ……

(II) Health-related data

9. Presence of any Non-communicable diseases
    a. Hypertension ☐
    b. Diabetes mellitus ☐
    c. Hypercholesterolemia ☐
    d. Heart diseases ☐
    e. Asthma or chronic respiratory diseases ☐
    f. Cancer ☐
    g. Other ☐ Please Specify ……

10. Previous and present habits

	Past	Present	Frequency (Per day)
Smoking			
Betel chewing			
Alcohol use			

11. Do you have a family member/s who has been diagnosed with CKDu?
    a. Yes ☐ b. No ☐

(III) Health-related data of CKDu patients

12. Biochemical results (from clinic book and investigation reports)

Parameter	Unit	value
GFR		
Hemoglobin		
Serum albumin		

THANK YOU…

Annexure 4

International physical activity questionnaire (IPAQ)

The following questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport. Here, **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.
Note: Think about only those activities that you did for at least 10 minutes at a time.

PART 1: JOB-RELATED PHYSICAL ACTIVITY
This section is about your work that includes paid jobs, farming, course work, and any other unpaid work that you did outside your home. Do not consider unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family, as those will be asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?
   Yes ☐
   No ☐ ⟶ **Skip to PART 2: TRANSPORTATION**

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**?
   _____ days per week
   ☐ No vigorous job-related physical activity ⟶ ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?
   _____ hours per day _____ minutes per day

4. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not consider walking.
   _____ days per week
   ☐ No moderate job-related physical activity ⟶ ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?
   _____ hours per day _____ minutes per day

6. During the **last 7 days**, on how many days did you **walk as part of your work**? Please do not count any walking you did to travel to or from work.

_____ days per week

☐ No job-related working ⟶ **Skip to PART 2: TRANSPORTATION**

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ hours per day _____ minutes per day

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, shops, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a bus, motor bike, three-wheeler, or car?

_____ days per week

☐ No traveling in a motor vehicle ⟶ ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a bus, motor bike, or other kind of motor vehicle?

_____ hours per day _____ minutes per day

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** to go **from place to place**?

_____ days per week

☐ No bicycling from place to place ⟶ ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle**?

_____ hours per day _____ minutes per day

12. During the **last 7 days**, on how many days did you **walk** to go **from place to place**?

_____ days per week

☐ No walking from place to place ⟶ ***Skip to PART 3: HOUSEWORK, HOUSE MAINTAINANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ hours per day _____ minutes per day

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ days per week

☐ No vigorous activity in garden or yard ⟶ ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ hours per day _____ minutes per day

16. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ days per week

☐ No moderate activity in garden or yard ⟶ ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ hours per day _____ minutes per day

18. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ days per week

☐ No walking from place to place ⟶ ***Skip to PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ hours per day _____ minutes per day

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not consider any activities you have already mentioned.

20. Not counting any walking, you have already mentioned, during the **last 7 days**, on how many days did you **walk in your leisure time**?

_____ days per week

☐ No walking in leisure time ⟶ ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ hours per day _____ minutes per day

22. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ days per week

☐ No vigorous activity in leisure time ⟶ ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ hours per day _____ minutes per day

24. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ days per week

☐ No moderate activity in leisure time ⟶ ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ hours per day _____ minutes per day

PART 5: TIME SPENT SITTING

These questions are about the time you spend sitting while at work, at home, and during leisure time. This may include time spent sitting at a desk, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ hours per day _____ minutes per day

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ hours per day _____ minutes per day

This is the end of the questionnaire, thank you for participating.

Annexure 5

Data recording sheet

Index no: ☐

No.	Anthropometric measurement	Measurements			Mean Value
		1st	2nd	3rd	
1.	Weight (kg)				
2.	Height (cm)				
3.	Mid upper arm circumference (cm)				
4.	Waist circumference (cm)				
5.	Hip circumference (cm)				
6.	Body fat%				
7.	Body muscle%				
8.	Hand grip strength				
9.	Gait speed				

Blood pressure: ……..

Annexure 6

Chronic Kidney Disease Symptom Index – Sri Lanka

Below is a list of problems that people with chronic kidney failure may have. All patients will not have all the problems and the perception of the severity of those problems varies with the individual. For each symptom, please indicate if you had the problem during the past week by circling "yes" or "no." If "yes", please rate the severity of each in a scale of "Very mild", "Mild", "Moderate", "Severe" and "Very Severe" by circling the appropriate number.

During the past week: *Did you experience this problem?*			**If "Yes", How severe was the problem?**				
			Very mild	**Mild**	**Moderate**	**Severe**	**Very severe**
1	Loss of appetite	No					
		Yes	1	2	3	4	5
2	Nausea	No					
		Yes	1	2	3	4	5
3	Vomiting	No					
		Yes	1	2	3	4	5
4	Diarrahea	No					
		Yes	1	2	3	4	5
5	Lethargy	No					
		Yes	1	2	3	4	5
6	Changes in skin colour	No					
		Yes	1	2	3	4	5
7	Swelling of arms and legs	No					
		Yes	1	2	3	4	5
8	Difficulty in breathing	No					
		Yes	1	2	3	4	5
9	Hiccups	No					
		Yes	1	2	3	4	5
10	Difficulty keeping legs still	No					
		Yes	1	2	3	4	5
11	Numbness/tingling of hands and feet	No					
		Yes	1	2	3	4	5

12	Lack of energy	No					
		Yes	1	2	3	4	5
13	Trouble with memory	No					
		Yes	1	2	3	4	5
14	Weight loss	No					
		Yes	1	2	3	4	5
15	Bone/joint pain	No					
		Yes	1	2	3	4	5
16	Muscle cramps	No					
		Yes	1	2	3	4	5
17	Difficulty concentrating	No					
		Yes	1	2	3	4	5
18	Dry skin	No					
		Yes	1	2	3	4	5
19	Itching	No					
		Yes	1	2	3	4	5
20	Feeling sad	No					
		Yes	1	2	3	4	5
21	Difficulty sleeping	No					
		Yes	1	2	3	4	5
22	Feeling irritable	No					
		Yes	1	2	3	4	5
23	Loss/decreased libido	No					
		Yes	1	2	3	4	5
24	Impotence	No					
		Yes	1	2	3	4	5
25	Heartburn	No					
		Yes	1	2	3	4	5

Annexure 7

Kidney disease Quality of Life – Short form (KDQOL-SF™)

1. In general, would you say your health is:

Excellent	*Very good*	*Fair*	*Good*	*Poor*
☐	☐	☐	☐	☐

1. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐	☐	☐	☐	☐

2. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	*Yes, limited a little*	*No, not limited at all*
• Vigorous activities, such as running and lifting heavy objects	☐	☐	☐
• Moderate activities, such as cleaning the garden	☐	☐	☐
• Lifting or carrying groceries	☐	☐	☐
• Climbing several flights of stairs	☐	☐	☐
• Climbing one flight of stairs	☐	☐	☐
• Bending, kneeling, or stooping	☐	☐	☐
• Walking more than a mile	☐	☐	☐
• Walking more than 100 yards	☐	☐	☐
• Walking about 100 yards	☐	☐	☐
• Bathing or dressing yourself	☐	☐	☐

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	*No*
• Cut down the amount of time spent on work or other activities	☐	☐
• Accomplished less than you would like	☐	☐
• Were limited in the kind of work or other activities	☐	☐
• Had difficulty performing the work or other activities (for example, it took extra effort)	☐	☐

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	*No*
• Cut down the amount of time spent on work or other activities	☐	☐
• Accomplished less than you would like	☐	☐
• Didn't do work or other activities as carefully as usual	☐	☐

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

   How much of the time during the past 4 weeks;

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
• Did you feel full of Pep?	☐	☐	☐	☐	☐	☐
• Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
• Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
• Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
• Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
• Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
• Did you feel worn out?	☐	☐	☐	☐	☐	☐
• Have you been a happy person?	☐	☐	☐	☐	☐	☐
• Did you feel tired?	☐	☐	☐	☐	☐	☐

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	*Most of the time*	*Some of the time*	*A little of the time*	*None of the time*
☐	☐	☐	☐	☐

11. Please choose the answer that best describes how true or false each of the following statements is for you.

	Definitely true	*Mostly true*	*Don't know*	*Mostly false*	*Definitely false*
• I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
• I am as healthy as anybody I know	☐	☐	☐	☐	☐
• I expect my health to get worse	☐	☐	☐	☐	☐
• My health is excellent	☐	☐	☐	☐	☐

Your Kidney Disease

12. How true or false is each of the following statements for you?

	Definitely true	*Mostly true*	*Don't know*	*Mostly false*	*Definitely false*
• My kidney disease interferes too much with my life	☐	☐	☐	☐	☐
• Too much of my time is spent dealing with my kidney disease	☐	☐	☐	☐	☐
• I feel frustrated dealing with my kidney disease	☐	☐	☐	☐	☐
• I feel like a burden on my family	☐	☐	☐	☐	☐

13. These questions are about how you feel and how things have been going during the past 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…	*None of the time*	*A little of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
• Did you isolate yourself from people around you?	☐	☐	☐	☐	☐	☐
• Did you react slowly to things that were said or done?	☐	☐	☐	☐	☐	☐
• Did you act irritable toward those around you?	☐	☐	☐	☐	☐	☐
• Did you have difficulty concentrating or thinking?	☐	☐	☐	☐	☐	☐
• Did you get along well with other people?	☐	☐	☐	☐	☐	☐
• Did you become confused?	☐	☐	☐	☐	☐	☐

14. During the past 4 weeks, to what extent were you bothered by each of the following?

	Not at all bothered	*Some what bothered*	*Moderately bothered*	*Very much bothered*	*Extremely bothered*
• Muscle aches and pains	☐	☐	☐	☐	☐
• Chest pain	☐	☐	☐	☐	☐
• Cramps	☐	☐	☐	☐	☐
• Itchy skin	☐	☐	☐	☐	☐
• Dry skin	☐	☐	☐	☐	☐
• Shortness of breath	☐	☐	☐	☐	☐
• Faintness or dizziness	☐	☐	☐	☐	☐
• Lack of appetite	☐	☐	☐	☐	☐
• Washed out or drained	☐	☐	☐	☐	☐
• Numbness in hands or feet	☐	☐	☐	☐	☐
• Nausea or upset stomach	☐	☐	☐	☐	☐
• Problems with your access site (Hemodialysis patient only)	☐	☐	☐	☐	☐

Effects of Kidney Disease on Your Daily Life

15. Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease bother you in each of the following areas?

	Not at all bothered	*Some what bothered*	*Moderately bothered*	*Very much bothered*	*Extremely bothered*
• Fluid restriction?	☐	☐	☐	☐	☐
• Dietary restriction?	☐	☐	☐	☐	☐
• Your ability to work around the house?	☐	☐	☐	☐	☐
• Your ability to travel?	☐	☐	☐	☐	☐
• Being dependent on doctors and other medical staff?	☐	☐	☐	☐	☐
• Stress or worries caused by kidney disease?	☐	☐	☐	☐	☐
• Having sexual relationships with your partner?	☐	☐	☐	☐	☐
• Your personal appearance?	☐	☐	☐	☐	☐

The next three questions are personal and relate to your sexual activity, but your answers are important in understanding how kidney disease impacts on people's lives.

16. Have you had any sexual activity in the past 4 weeks?

Yes ☐ *No* ☐ *(If no, please skip to Q.17)*

How much of a problem was each of the following in the past 4 weeks;

	Not a problem	*A little problem*	*Somewhat of a problem*	*Very much a problem*	*Severe problem*
• Enjoying sex?	☐	☐	☐	☐	☐
• Desire for sexual activity?	☐	☐	☐	☐	☐

17. For the following question, please rate your sleep using a scale ranging from 0 representing "very bad" to 10 representing "very good." If you think your sleep is half-way between "very bad" and "very good," please mark the box under the number 5. If you think you sleep is one level better than 5, mark the box under 6. If you think your sleep is one level worse than 5, mark the box under 4 (and so on). On a scale from 0 to 10, how would you rate your sleep overall?

Very bad *Very good*

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

18. How often during the past 4 weeks

	None of the time	*A little of the time*	*Some of the time*	*A good bit of the time*	*Most of the time*	*All of the time*
• Awaken during the night and have trouble falling asleep again?	☐	☐	☐	☐	☐	☐
• Get the amount of sleep you need?	☐	☐	☐	☐	☐	☐
• Have trouble staying awake during the day?	☐	☐	☐	☐	☐	☐

19. Concerning your family and friends, how satisfied are you with...

	Very dissatisfied	*Somewhat dissatisfied*	*Somewhat satisfied*	*Very satisfied*
• The amount of time you are able to spend with your family and friends	☐	☐	☐	☐
• The support you receive from your family and friends	☐	☐	☐	☐

20. During the past 4 weeks, did you work at a paying job?

☐ *Yes* ☐ *No*

21. Do you have to stay away from your job due to your ill health?

☐ *Yes* ☐ *No*

22. Overall, how would you rate your health?

Worst possible (as bad or worse than being dead)				Half-way between worst and best						Best possible
0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Satisfaction with Care

23. Think about the care you receive for kidney disease. In terms of your satisfaction, how would you rate the friendliness and interest shown in you as a person?

Very poor	*Poor*	*Fair*	*Good*	*Very good*	*Excellent*	*The best*
1	*2*	*3*	*4*	*5*	*6*	*7*
☐	☐	☐	☐	☐	☐	☐

24. How true or false is each of the following statements?

	Definitely true	*Mostly true*	*Don't know*	*Mostly false*	*Definitely false*
• Hospital staff encourage me to be as independent as possible	☐	☐	☐	☐	☐
• Hospital staff support me in coping with my kidney disease	☐	☐	☐	☐	☐

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