Vitamin D Status and Health-care Outcomes in an Ambulatory Population of Patients with Diabetes and Chronic Kidney disease: A Five-year Follow-up.

by

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Abstract

Vitamin D (VitD) deficiency is a prevalent condition in Canada, especially in northern latitudes where sunlight exposure is limited (1-3). Elderly patients especially those with chronic conditions such as Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD) have a higher risk of developing vitD deficiency (1, 4, 5). Elderly patients with CKD also have a higher risk of developing other conditions like decreased bone health, decreased health related quality of life (HRQoL), depression and frailty (6, 7). The exact relationship between vitD status and the development of these other conditions is still not clear, but associations have been reported in the literature (8-10). Two studies will be described. The first is a cross sectional study (n=41) on the relationship between vitD and frailty and the second study examines the longitudinal associations of vitamin D with HRQoL, mental health, cognitive status and body composition (n=50) in an ambulatory adult population with DM and CKD over five years. The findings of these studies indicate that these patients have a high rate of vitD supplementation (1000-2000 IU/D of vitD3) with the majority of participants having sufficient vitD status defined as 25(OH)D levels above 75 nmol/l. Participants with frailty (predominantly pre-frail) had an increased number of health events, increased depression and decreased HRQoL. While most participants had lower HRQoL than Canadian norms, participants with frailty were markedly lower than those without frailty (11). Over five years, body composition (total or segmental, lean mass or fat mass), HRQoL, cognition or mental health remained stable with no significant changes. VitD sufficiency was associated with lower major depression inventory scores (less depression) as well as increased HRQoL scores in the vitality and mental health domains. Both frailty and vitD deficiency remain public health concerns, especially in populations with DM and CKD. A better understanding of the underlying mechanisms for the development of frailty, as well as the role of vitD in these mechanisms is required.

Preface

This thesis is an original work by Stephany Isabel Adame Perez. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name: "Vitamin D Supplementation and Bone Health in Adults with Diabetic Nephropathy: A follow up study", No. Pro00049292, April 20, 2014.

Chapter 3 of this thesis has been submitted for publication as Adame Perez SI*, BSc MSc (cand), Senior P, MD, Field CJ, PhD RD, Jindal K, MD, Mager DR, PhD RD, "Vitamin D Status, Health Related Quality of Life and Frailty in an Ambulatory Population with Diabetes Mellitus and Chronic Kidney Disease." to the Can J Diabetes Jan 2018 (in review), Submission no: CJD_2018_1. Stephany Adame Perez was responsible for data collection (along with Leslie Seto MSc RD), data analysis, manuscript preparation (along with DR Mager), review and approval of final manuscript. Senior P and Mager DR, were responsible for study design, supervised data collection and data analysis, data interpretation, manuscript preparation, review and approval of final manuscript. Field CJ and Jindal K contributed to contributed to data interpretation, manuscript review and approval of final manuscript. Data collection for chapter 4 of this thesis was done by Leslie Seto RD MSc and Stephany Adame Perez (Years 3-5) and the baseline data and years 1-2 were done by Stephanie Jackson MSc RD, Ping Li RD and Michelle Hoffmann MSc. The study design and grant funding were developed and obtained by the PI Dr Diana Mager PhD RD/CI: Dr Peter A. Senior. Operating funding was obtained from the Kidney Foundation of Canada and the Canadian Foundation for Dietetic Research and Practice.

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A project like this can't be done by a single person, it takes a village. There are multiple people who helped me make this possible in one way or another, and I would like to thank each one of you.

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List of Abbreviations

(Alphabetical Order)

25(OH)D: 25-hydroxyvitamin D

1,25(OH)$_2$D: 1,25-dihydroxyvitamin D

ADLs: Activities of Daily Life

AHS: Alberta Health Services

ASM: Appendicular Skeletal Muscle Mass

ASMI: Appendicular Skeletal Muscle Mass Index

BAP: Bone Alkaline Phosphatase

BMD: Bone Mineral Density

BMI: Body Mass Index

CHMS: Canadian Health Measure Studies

CKD: Chronic Kidney Disease

CVD: Cardiovascular Disease

DM: Diabetes Mellitus

DNPC: Diabetic Nephropathy Prevention Clinic

DRI: Dietary Reference Intake

DXA: Dual-energy X-ray Absorptiometry

EFS: Edmonton Frail Scale

eGFR: Estimated Glomerular Filtration Rate

FMI: Fat Mass Index

FN: Femoral Neck

F/U: Follow up

HRQoL: Health Related Quality of Life

HbA1c: Glycated Hemoglobin A1c

HDL: High Density Lipoprotein

IPAQ: International Physical Activity Questionnaire

KDOQI: Kidney Disease Outcomes Quality Initiative

LDL: Low Density Lipoprotein

MDI: Major Depression Inventory

MMSE: Mini Mental State Examination

MOS: Medical Outcomes Study

PTH: Parathyroid Hormone

RBC: Random Blood Glucose

RIC: Renal Insufficiency Clinic

SF-36: 36-Item Short Form Survey

Sup: Supplementation

T1DM: Type 1 Diabetes Mellitus

T2DM: Type 2 Diabetes Mellitus

VitD: Vitamin D

VDBP: Vitamin D Binding Protein

VDRs: Vitamin D Receptors

Presentation of Work within Thesis

Presentations

Adame Perez SI*, Mager DR. Vitamin D RCT and Follow-up Study. Presentation to Northern Alberta Renal Program (NARP) team, July 2017.

Abstracts

1) Adame Perez SI*, Seto L, Jindal K, Senior P, Mager DR. Characteristics of Vitamin D Supplement Users in an Ambulatory Population with Diabetes and Chronic Kidney Disease (CKD). ADI Research Day, October 2016. Poster Presentation.

2) Adame Perez SI*, Seto L, Jindal K, Senior P, Mager DR. Frailty Influences Risk for Depression, Reduced Quality of Life (QoL) and Risk of Hospitalization in an Ambulatory Population with Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD). ADI Research Day, October 2017. Poster Presentation.

3) Adame Perez SI*, Seto L, Jindal K, Senior P, Mager DR. Vitamin D Status, Depression, Frailty and Sarcopenia in an ambulatory population with Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD). Diabetes Canada's 20th Annual Professional Conference, November 1-4, 2017. Edmonton, Canada. Poster Presentation.

Submitted Papers

Adame Perez SI*, BSc MSc (cand), Senior P, MD, Field CJ, PhD RD, Jindal K, MD, Mager DR, PhD RD. Vitamin D Status, Health Related Quality of Life and Frailty in an Ambulatory Population with Diabetes Mellitus and Chronic Kidney Disease. Submitted to Can Journal of Diabetes, January 2018. (In review)

Chapter 1: Literature Review

1.1 Introduction

Vitamin D (VitD) is a fat-soluble vitamin responsible for many functions in the human body (1). VitD has been classically related to calcium metabolism and bone health, but recently, vitamin D receptors (VDRs) have been found in different organ systems (1, 12). The discovery of VDRs in numerous parts of the body suggests that vitD has more roles than the ones that have been traditionally studied. Some of the alternative roles of vitD include immune system regulation, muscle health and function, cognitive health, and mental health regulation (1, 9, 13, 14). VitD deficiency has been associated with poor bone health, depression, sarcopenia, increased risk for infection and overall poor health (1, 12, 15). VitD is the only vitamin that can be both acquired through food consumption and made in the body through sunlight exposure (1). Although vitD can be produced in the body, vitD deficiency is a common condition worldwide, particularly in Northern Alberta where reduced sunlight exposure, especially in the winter months, results in reduced cutaneous synthesis of vitD (1, 2, 16).

Diabetes Mellitus (DM) is one of the most common diseases and one of the leading causes of death worldwide (17). In 2013 in Canada, the prevalence of DM was approximately 10% of the Canadian population (18). The uncontrolled hyperglycemias in DM usually result in the development of comorbidities some of which are life threatening (19, 20). One of the most common comorbidities of DM is chronic kidney disease (CKD), with around 30-40% of diabetic patients also having CKD (21, 22). VitD deficiency is highly prevalent in CKD due to dietary restrictions of vitD rich foods, and impairments in renal function that lead to reduced activation of vitD into 1,25(OH) D_3 (4, 16, 23) and potentially reduced sunlight exposure. This indicates that vitD is a nutrient at risk in adults with both DM and CKD; and that routine vitD supplementation

may be needed to ensure vitD needs are met. This is important to ensure that the complications arising from vitD deficiency such as fractures, falls and poor bone health are prevented.

Frailty, which refers to a condition of increased vulnerability to endogenous and exogenous stressors caused by a decrease in physiological reserves and functions (24), is a condition in that is highly prevalent in elderly patients, especially those with chronic health conditions such as CKD (6, 25-27). Frailty causes an increased vulnerability to adverse health outcomes such as falls, increased hospitalization and increased mortality (6, 24). Patients with chronic conditions such as DM and CKD have an increased vulnerability to developing frailty due to physiological changes related to the disease (6, 28). Important physiological concerns in adults with CKD and DM include the potential impact of uremia and hyperglycemia that can result in increasing oxidative stress and inflammation that may potentially impact overall bone health and organ function such as the pancreas, kidneys, heart, lungs and liver (29-34).

It is common clinical practice to supplement patients diagnosed with DM and CKD with vitD as it is well known that vitD deficiency may increase the risk for Frailty and co-morbid risks associated with organ dysfunction and changes in overall body composition (23). There are different opinions about which vitD supplementation strategy is better suited for these patients, and what levels of 25 $(OH)D_3$ in blood should be aimed for. Different approaches and strategies have been recommended, varying in dosage and frequency. Our recent work in adults with CKD and DM illustrates that either daily dosing with 2000 IU/D or 40,000 IU/month over six months was sufficient to promote 25(OH)D concentrations > 75 nmol/l; a level that has been associated with vitD sufficiency (7, 35). However, little is known what level of VitD supplementation is needed to promote optimal HRQoL, mental health and body composition (23, 36). This is important to understand, as there is substantial literature to suggest that vitD may play an important role in these important patient outcomes. Hence, the purpose of this literature review was to

examine the evidence with regard to the role of vitD on body composition, HRQoL, mental health in adults with DM and CKD. In addition, this review examined the interrelationships between vitD status and risk for frailty in adults with DM and CKD.

1.2 Vitamin D

1.2.1 Roles of Vitamin D in the human body

1.2.1.1 Vitamin D and calcium metabolism

VitD has many roles in the body, but one of the most important and studied roles is calcium absorption and regulation (1, 37, 38). Because of its close relationship with calcium, vitD also plays a fundamental element in bone health and regulation. When vitD is activated to its active form in the kidneys ($1,25(OH)_2 D_3$), it travels to the intestine and bones in order to exert its calcium-regulating role (1). In the intestine, vitD binds to the vitD receptors (VDRs) located on the intestinal absorptive cells, which in turn activate genes that increase calcium absorption (1, 39). On the other hand, if there is a calcium deficiency in the diet, vitD will act in the bone and interact with osteoblasts, stimulating the production of osteoclasts (1, 36). Osteoblasts are bone-forming cells, and osteoclasts are bone-reabsorbing cells, which, with the help of vitD help regulate bone health (1). The activation of osteoclasts results in calcium stores being removed from the bone, and then deposited in the blood to maintain calcium homeostasis, which is essential for life and physiologic functions in the body (1, 38).

1.2.1.2 Non-skeletal roles of Vitamin D

The various non-skeletal roles of vitD in the body are presented in **Table 1.1.** Several research studies have illustrated that VDRs are found in many tissues and that vitD exerts its effects through intracellular signaling of a variety of proteins within the cell (12, 40-43). VitD has been shown to have a positive effect on muscle mass and strength (1, 14, 44, 45). This lower muscle

strength is possibly related to the decrease of type 2 muscle fibers that has been found in vitD deficiency, as well as the presence of infiltration of fat in interfibrillar spaces (44). Low vitD levels have been associated with decreased cardiovascular health, mainly through the action of VDRs in the renin angiotensin system, which may influence risk for hypertension (15, 40, 46). Insulin secretion is dependent on calcium levels in the blood, making vitD indirect modulator of insulin secretion and glucose control (1, 47, 48). The active form of vitD, $1,25(OH)_2D_3$ is an important immunomodulator, as some immune cells, like dendritic cells, have VDRs and T and B cells express VDR when active (1, 49, 50). The discovery of VDRs in areas of the brain associated with mood regulation and cognition suggest that vitD deficiency could have a role in their regulation (1, 3, 9, 42).

Table 1.1 Non-Skeletal Roles of Vitamin D

Vitamin D Role	Action
a) Muscle health (1, 14, 44, 45)	-Increased muscle mass -Increased muscle quality (increase number of type 2 muscle fibers) -Increased muscle strength
b) Cardiovascular health (15, 40, 46)	-Blood pressure control (renin-angiotensin system)
c) Immune system regulator (1, 3, 49, 50)	- Regulation of immune response
d) Insulin secretion and reduced insulin resistance (1, 47, 48)	-Indirect regulation through calcium regulation -Improvement of insulin resistance caused by inflammation
e) Mental health (1, 3, 9, 42)	-Increased cognition (minimizes cognition loss) -Decreased depression -Neuronal Transmission

1.2.2 Vitamin D Metabolism

1.2.2.1 Vitamin D synthesis and absorption

VitD is a unique vitamin because it can be consumed in the diet, but it can also be produced by the body through metabolic pathways (1, 39). VitD is also known as the sunshine vitamin because it is produced in the skin through sunlight exposure. With sufficient sunlight exposure, endogenous vitD production accounts for 80-90% of vitD in the body, while nutritional intake accounts for 10-20% (1, 3, 16). VitD, from both endogenous production or from the diet, can be either stored in adipose tissue, or metabolized in the liver (1, 39). The process by which vitD is produced and activated in the body involves different steps that take place in different organs in the body, mainly the skin, the liver and the kidneys (1, 39) **figure 1.1**.

VitD can also be found in foods, which contain either ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D3) (1, 3, 16). VitD in either of its forms is absorbed in the intestine and then hydroxylated into its active form though the same pathways as endogenous vitD (1, 39). Aging can cause a reduction in endogenous vitD production due to a decreased concentration of 7-dehydrocholesterol in the skin, which causes elderly people to be more dependent on dietary/supplemental vitD (1).

1.2.2.2 Vitamin D activation pathways

VitD must be activated for it to be able to perform its roles in the body (1). VitD is hydroxylated into 25-hydroxyvitamin D_3 by the liver, and then it is converted into its active form, calcitriol (1,25 $(OH)_2$ D_3), by the kidneys (1, 16). The 1-hydroxylation takes place in the kidney's proximal tubule and it is positively regulated by parathyroid hormone (PTH) and negatively regulated by Fibroblast Growth Factor 23 (FGF-23) (1, 16, 39). There are other elements involved in the regulation of 1,25 $(OH)_2$ D_3 activation, such as hypocalcemia, hypophosphatemia, and calcitonin (39). The process of VitD metabolism and activation is shown in **figure 1.1**.

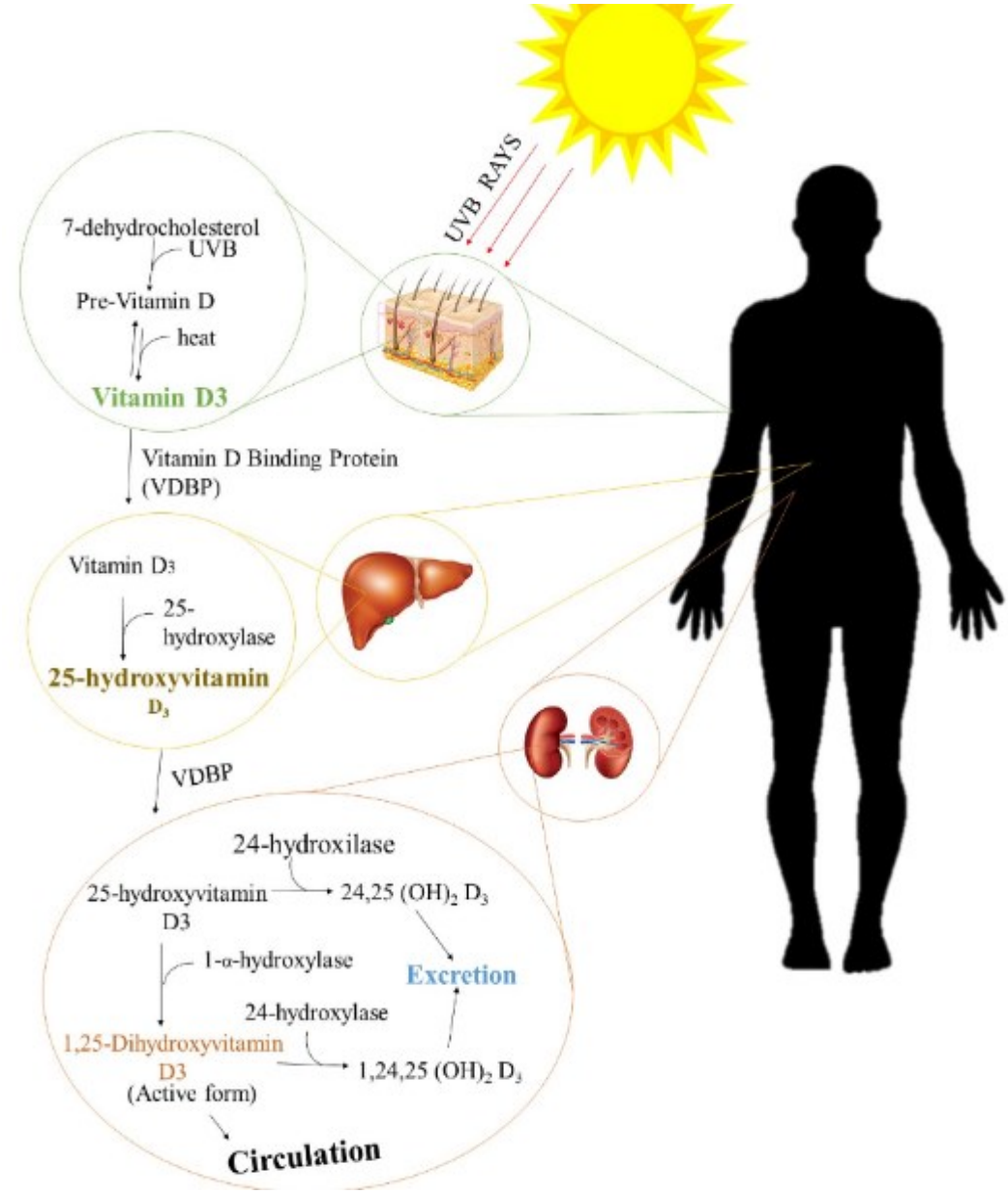

Figure 1.1 Vitamin D metabolism in the body. By author, Adame 2018.

1.2.3 Vitamin D Intake

1.2.3.1 Dietary Reference Intake of Vitamin D

The Dietary Reference Intakes (DRI) for vitD were updated by the U.S. Institute of Medicine (IOM) in 2010 (1, 36, 51). The DRIs for vitD aim to maintain skeletal health and are set

using the assumption of minimal sunlight exposure (36). The DRIs for vitD and the Tolerable Upper Intake Level are shown in **Table 1.2.**

Table 1.2 Vitamin D DRI.

Age	Recommended Dietary Allowance per day	Tolerable Upper Intake Lever per day
0-6 Months	400 IU (10 mcg)	1000 IU (25 mcg)
7-12 Months	400 IU (10 mcg)	1500 IU (38 mcg)
1-3 years	600 IU (15 mcg)	2500 IU (63 mcg)
4-8 years	600 IU (15 mcg)	3000 IU (75 mcg)
9-70 years	600 IU (15 mcg)	4000 IU (100 mcg)
>70 years	800 IU (20 mcg)	4000 IU (100 mcg)

Adapted from Health Canada (51).

1.2.3.2 Forms of Vitamin D

VitD supplementation is different from the supplementation of other vitamins, because it is meant to compensate for low sunlight exposure as the food supply is very low in vitamin D (1, 3, 49). VitD supplements are available both as cholecalciferol (D_3) and ergocalciferol (D_2) (1, 3). Cholecalciferol, or vitD_3 is a form of vitD that can be found in animal tissue (3). Cholecalciferol is supposed to have a better effect on 25(OH)D levels than ergocalciferol (52). It is thought that the liver's hydroxylases have a higher affinity for vitD_3, giving vitD_3 a metabolic advantage over vitD_2 (1). Ergocalciferol is a plant-based form of vitD and is found mainly in UVB irradiated mushrooms and yeast (1). The structural difference between vitD_2 and vitD_3 is shown in **figure 1.2**.

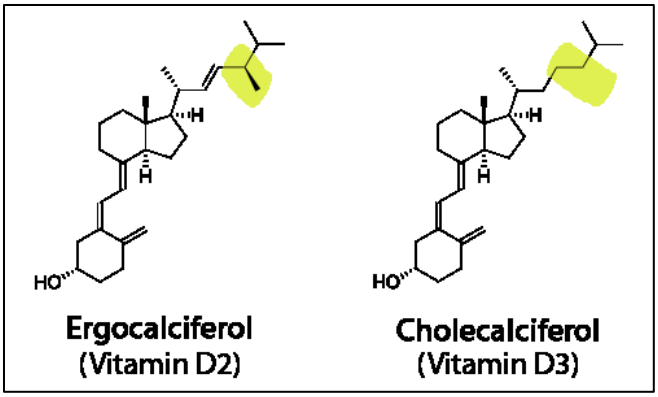

Figure 1.2 Molecular Structure of Vitamin D_2 and Vitamin D3

Most commonly, in Canada and in the US, over the counter supplements of vitD are $vitD_3$ varying in doses (200-1000 IU/capsule), while prescription preparations are done using $vitD_2$, generally 50,000 IU or 8,000 IU for pediatric patients (1).

1.2.3.3 Dietary Sources of Vitamin D

VitD can be found in food either as vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) (1, 3, 51). A limited amount of foods contains vitD naturally, but some commercial products are supplemented with vitD (1). Some vitD rich foods include egg yolk, oily fish like salmon and sardines, and oil from the liver of some fish like cod and tuna (1, 3, 49, 51). Some examples of fortified foods include milk, margarine, breakfast cereals, bread products, orange juice, yogurts and cheeses (1, 3, 49, 51). **Table 1.3** shows the amount of vitamin D contained in some common foods.

Table 1.3 Examples of Vitamin D containing foods

Food	Amount	Vitamin D
Fortified orange juice	125 ml or ½ Cup	50 IU
Soy beverage fortified with vitamin D	250 ml or 1 Cup	88-123 IU
Fortified milk (3.3%, 2%, 1% skim, chocolate)	250 ml or 1 Cup	103-105 IU

Fortified skim milk powdered	24 g	103 IU
Yogurt (plain, fruit bottom), fortified with vitamin D	175 g or ¾ Cup	58-71 IU
Egg, yolk, cooked	2 Large	57-88 IU
Beef liver, cooked	75 g or 2.5 oz	36 IU
Salmon (all types)	75 g or 2.5 oz	181-699 IU
Whitefish, lake, cooked	75 g or 2.5 oz	369 IU
Mackerel, Pacific, cooked	75 g or 2.5 oz	342 IU
Sardines, Pacific, canned	75 g or 2.5 oz	144 IU
Tuna, albacore, raw or cooked	75 g or 2.5 oz	82-105 IU
Tuna, white, canned with water	75 g or 2.5 oz	60 IU
Cod liver oil	5 ml	427 IU

*****Adapted from Dietitians of Canada "Food Sources of Vitamin D".

1.2.3.4 Vitamin D Status

VitD status is determined by the amount of 25(OH) D_3 present in the blood (1, 3, 36). Even though 1,25$(OH)_2$ D_3 is the active form of vitD, it is not considered a good indicator of vitD status due to its short half-life (39). Another reason why 1,25$(OH)_2D_3$ is not considered a reliable reflection of nutritional vitD status is its tight regulation by elements such as serum PTH, calcium and phosphorus (1, 53). Serum 1,25$(OH)_2D_3$ levels will remain stable even in the presence of low 25(OH)D as long as there is a normal kidney function or until the development of a severe vitD deficiency (1). In patients with CKD alterations in serum PTH, calcium and phosphorus are common (54). Due to these alterations in laboratory values and the decrease in kidney function, alterations in renal production of 1,25 $(OH)_2$ D_3 are likely to occur in CKD (37, 54). There is extra renal production of 1,25 $(OH)_2$ D_3 in diverse cells in the body (eg. monocytes and skin cells) and this is a non PTH-regulated mechanism (1, 55, 56). Extra renal activation 1,25 $(OH)_2$ D_3 seems to

be substrate dependent, with an increased production in higher 25(OH)D levels (55-57). Although extra renal activation may aid in the production of 1,25 $(OH)_2$ D_3, this is mainly for local cellular and tissue utilization (55, 56). While extra-renal production of 1,25 $(OH)_2$ D3 may contribute to serum concentration, this is insufficient to compensate for reduced renal vitD activation. This means that patients with CKD will likely have a decreased 1,25 $(OH)_2$ D_3 status, even in the presence of extra renal activation. In contrast, in renal disease 25(OH)D levels can be altered due to urinary secretion of VDBP in the presence of proteinuria (58, 59). Even though 25(OH)D can be altered in CKD, it is still considered the most valid measure of vitD status.

The exact reference values to diagnose vitD deficiency vary depending on the organization. The Institute of Medicine determined vitD deficiency to be serum 25(OH)D <30 nmol/l, based on to the risk of rickets and negative health effects (60). The Canadian Society of Endocrinology and Metabolism consider vitD deficiency as 25 (OH) D_3 values <50 nmol/l, vitD insufficiency as levels between 50 and 75 nmol/l and vitD sufficiency as levels >75 nmol/l (36). A 25(OH) D_3 level >75 nmol/l is considered adequate to prevent the development of conditions such as osteoporosis and secondary hyperparathyroidism, as well as to optimize other non-skeletal roles of vitD (1, 3, 36). VitD status is an important element to consider in the management of CKD (23, 36). The National Kidney Foundation (NKF) states that 25(OH) D_3 levels should be greater than 30 ng/mL (75 nmol/l) in patients with CKD stage 3-4, and that if the levels are lower than that, the patient should receive vitD supplementation in order to prevent secondary hyperparathyroidism (23). The NKF also mentions that in normal patients over 60 years of age, the lower limit for 25(OH) D_3 levels is 15 ng/mL (23).

1.2.3.5 Vitamin D dosage, frequency and toxicity

The RDA is 600 IU per day for adults and 800 IU per day for adults over 70 years old (51). Recent studies have shown that more vitD than the RDA might be required in the elderly and some

clinical populations, in order to prevent the development of non-skeletal complications related to vitD status (15, 36, 61). Supplementation strategies aiming to cover the RDA might be adequate for individuals with a normal physiology or who have sufficient sunlight exposure to promote optimal cutaneous synthesis of vitD, but some patients might need higher doses of vitD due to dietary restrictions or the presence of some clinical conditions that may impact vitD absorption (e.g cystic fibrosis) and/or vitD metabolism (kidney disease) or who may have dietary restrictions that impact the ability to consume vitD rich foods (15, 61). Patients with CKD often have diets restricted in protein, phosphorus and potassium, which limits the amount of many vitD containing foods they can consume (e.g vitD fortified cow's milk which is high in phosphorus) (23). Patients with CKD also have an impaired VitD activation, as the kidneys are the main area for VitD activation (39). The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that patients with chronic kidney disease receive vitD supplementation, especially after stage 3 (23). The KDOQI guidelines indicate than if a patient's 25 (OH) D level is < 75 nmol/l, supplementation with $vitD_2$ should be initiated, though it also mentions that $vitD_3$ could be used (23). The recommended approach is to give 50,000 IU of D_2 monthly for 6 months in patients who are deficient in vitD and once the patient is replete, treatment should continue with a multivitamin containing $vitD_2$ or $vitD_3$ (23). However, recent work in our group suggests that patients with both DM and CKD can achieve vitD levels >75 nmol/l with either daily $vitD_3$ dosing of 2000 IU/D or 40,000 IU/month without evidence of adverse effects (7). The importance of achieving 25(OH) concentrations of vitD > 75 nmol/l is to minimize the risk for secondary hyperparathyroidism, which can increase the risk significant for the development of osteodystrophy in patients with end-stage renal failure (37, 62, 63).

According to Health Canada, the tolerable upper intake level in healthy individuals is 4,000 IU (51). Other studies consider that the tolerable safe upper intake level should be 10,000 IU per

day for adults (1). The recent work in our group suggests that patients with CKD (stage 2-4) can consume monthly doses up to 40,000 IU/month or 2000 IU/D without any potential signs of toxicity (e.g hypercalcemia) (7). VitD toxicity can cause non-specific symptoms such as anorexia, weight loss, polyuria, and heart arrhythmias, but the most clinically important signs of vit D toxicity in the renal patient is the potential for hypercalcemia (1). Hypercalcemia in renal patients may cause vascular and tissue calcification, and damage to the heart, blood vessels, and kidneys (64). Although there is some controversy in the literature about what represents a 'toxic' level of 25(OH)D in the blood, most agree that levels >500 nmol/l are considered to be potentially toxic (1).

1.2.5 Vitamin D, Diabetes Mellitus and Chronic Kidney Disease

1.2.5.1 Vitamin D and Diabetes Mellitus and CKD.

VitD deficiency in DM and CKD has been reported to range between 30-60% of the population; particularly in adults with more advanced CKD (stages 4-5) and in individuals living in northern climates like Alberta where reduced cutaneous synthesis leads to a high rate of vitD deficiency (65-68). A variety of factors influence overall vitD status in this population, including reduced renal conversion to the active vitD form in more advanced CKD and potentially reduced vitD intake due to therapeutic dietary restrictions of vitD rich foods that also contain nutrients (electrolytes and carbohydrate) that may exacerbate pre-existing electrolyte abnormalities and glycemic intolerance (1, 16, 23, 69). Another important factor is the reduced sunlight exposure that individuals in Northern Alberta experience, particularly in the winter months. Recent work by our group has shown that vitD supplementation in the order of 2000 IU/D or 40,000 IU/month of $vitD_3$ is needed in order to maintain serum 25(OH)D concentrations > 75 nmol/l (7, 35, 70).

1.2.5.2 Body Composition Changes in DM and CKD.

There are several studies that indicate that reduced lean body mass in the presence of obesity (sarcopenic obesity), is highly prevalent in individuals with both DM and CKD (71-76). In DM alone, obesity is highly prevalent; above 50% of individuals with T2D (77-79). In particular, insulin resistance can stimulate substantial changes in lipogenic enzymes (Sterol regulatory element binding protein (SREBP) resulting in increased skeletal muscle lipogenesis and increased protein turnover in the skeletal muscle. This may lead to an increased risk for fat infiltration (myosteatosis) in the muscle and reduced lean body mass (31, 80, 81). In addition, the presence of chronic uremia can lead to a state of chronic acidosis which causes abnormal muscle protein metabolism leading to lean mass depletion (29, 30, 82, 83). The metabolic acidosis caused by chronic uremia in CKD induces increased protein degradation which may lead to an increased risk for sarcopenia in patients with CKD (29, 30, 82, 83); even in the presence of obesity.

1.2.5.3 Vitamin D and body composition.

There is a large body of evidence that indicates that vitD status may be impacted by body composition (14, 84-86). This includes evidence that shows that overweight and obese adults may have lower serum 25(OH)D_3 levels than adults with body weights within normal reference ranges (84-86). In addition, weight loss in obese individuals has been associated with significant increases in serum 25(OH) D_3 levels (87-89). Whether the lower vitD status in obese individuals is due to increased sequestration of vitD in adipose tissue stores or reduced release of endogenous stores of vitD into the serum or reduced intake or reduced rates of cutaneous synthesis is unclear. Recent evidence shows that low vitD intakes in Canada are endemic and are not directly related to body weights (1-3). In fact, most Canadians experienced low cutaneous vitD synthesis due to low sunlight exposure, regardless of body habitus and can only maintain serum 25(OH)D_3 levels > 75 nmol/l with vitD supplementation in excess of the current RDA (>600 IU/D) (1, 3, 36). Hence, alterations in vitD status in obese individuals are likely related to all of the above factors, with

potentially the contribution of increased sequestration/reduced endogenous release from adipose tissue stores increasing the risk for vitD deficiency.

The presence of intracellular VDR in skeletal muscle also suggest that vitD may play an important role in skeletal muscle function and skeletal muscle mass (44, 90). Low lean body mass, accompanied by reduced muscle strength, in the presence of vitD deficiency has been shown to be highly prevalent in the elderly and in patients with CKD, diabetes and cancer with sarcopenia (44, 45, 90, 91). Several studies in animal models and in humans have shown that vitD supplementation can result in improvements in insulin sensitivity in both healthy subjects and in those with DM; resulting in improved glycemic tolerance, decrease in myosteatosis through reductions in lipogenic pathways and decreased activation of nuclear factor kappa-light-chain-enhancer (NF-κβ) and TNF-α (31, 92-96). Taken all together these data indicate that vitD supplementation may inhibit a variety of pathways (including SREBP cleaving activating protein (SCAP)/SREBP and NF-κB) to protect skeletal muscles against metabolic derangements of chronic diseases such as DM and insulin resistance, thereby optimizing overall muscle strength, muscle composition and muscle functionality (13, 14, 31, 44, 45, 97, 98). This is particularly relevant to patients with DM and CKD, where myosteatosis induced by insulin resistance and chronic uremia may result in muscle breakdown and reductions in muscle strength (29, 31, 74, 75, 99).

Recent work by our group and others has shown that vitD status is related to higher fat mass in adults with both DM and CKD (14, 35, 44, 70, 84, 90). Patients with DM and advanced CKD tend to have low lean body mass and increased adiposity, with a lower lean body mass found in more advanced CKD (30, 75, 76).

1.3 Health Related Quality of Life

1.3.1 Term Description

Health Related Quality of Life (HRQoL) is a measure of physical and social functioning, as well as of perceived and mental well-being (100). HRQoL also considers concepts that relate to the individual's ability to perform activities of daily activities of life (ADL), psycho-social factors, mental health and overall sense of well- being (101-103). All of these factors can directly influence the individual's ability to function independently (100-102, 104). The presence of co-morbidities in individuals with chronic diseases such as DM and CKD can significantly influence overall HRQOL and are important factors to consider in the overall evaluation of HRQoL (101, 104-106). The assessment of HRQoL in clinical practice as well as its consideration in treatment plans would promote a multidimensional and wholesome treatment for chronic conditions.

1.3.2 HRQoL and DM and CKD

Several studies have examined HRQOL in adults with DM and CKD, illustrating that HRQOL is impacted by the presence of these chronic diseases (7, 9, 103-107). In particular, there is evidence that patients with CKD stages 3-5 have significantly lower HRQoL than those with milder CKD (stages 1-2) and that HRQoL can be significantly lower than age-gender matched healthy controls in the community (102, 103, 105, 108-110). This may be further exacerbated by co-morbid conditions such as DM, which have also been shown to reduce HRQoL (7, 101, 104, 106, 107). Differences in perceived HRQoL between groups may be related to increasing age, number of co-morbid conditions, marital status, gender and education (100, 101, 111, 112). One of the main challenges with assessing HRQoL in DM and CKD and other clinical populations is the choice of tool used to assess HRQoL (**Table 1.4**) (100, 101, 113, 114). Many of these tools rely on self-report of the individual participant and hence can impacted significantly by the presence of dementia or general cognitive decline (100, 112). The presence of depression may also

influence overall perceptions by the individual (110, 112). Patients with DM and CKD have a higher risk of developing dementia, depression and general cognitive dysfunction (110, 115-119) and hence the lower HRQoL experienced by these populations is not unexpected. Risk for depression in patients with DM and CKD have been reported to be as high as 30% and 39% percent, respectively (117, 119-121). This appears to worsen with increasing co-morbid burden and advancement of CKD (121).

1.3.3 Vitamin D, HRQOL, Mental Health and Depression

There are studies that have evaluated the associations between vitD, HRQOL and mental health in healthy and clinical populations (7, 9, 122-126). VitD deficiency has been associated with an increased risk for reduced HRQoL in several cross-sectional studies; but limited data are available regarding the associations between vitD status and HRQoL over the longer term or whether or not routine vitD supplementation may elicit improvements in overall HRQOL. This may be due to the heterogeneity of study designs used (cross sectional, RCT), sample size, dosing frequency (daily vs monthly vs weekly), doses used (400 IU – 500,000 IU) and type of vitD (D_3 vs D_2) (7, 123, 125-129). A recent systematic review by our group found that vitD supplementation may have a small to moderate effect on quality of life when used on a short-term basis in diseased populations, but no data were available regarding the relationship over the longer term (126). No major impact of vitD supplementation in healthy populations was noted (126). A recent six-month RCT by our group examined the impact of two vitD supplementation strategies (2000 IU/D vs 40,000 IU/D) of vitD_3 in adults with CKD and DM and detected modest improvements in physical functioning domains when 25(OH)D_3 concentrations were > 75 nmol/l but no other changes were found in overall HRQoL (7).

Studies examining the association between mental health, depression and vitD deficiency are highly prevalent within the literature (9, 15, 115, 130, 131). Most of the research on vitD

deficiency in CKD has been conducted in patients with advanced CKD, with little to no effects of vitD supplementation on improving or resolving overall depression scores (132-134). In contrast, some studies have demonstrated that women with T2D experience significant improvement in mental health/depression when receiving vitD supplementation (130), while others have shown no associations with vitD deficiency/vitD supplementation in adults with DM (135). Overall these studies have the same methodological differences as the body of literature related to vitamin D supplementation and HRQoL making conclusions regarding the interrelationships between vitD status, vitD supplementation and mental health/depression difficult to determine. Few RCTs have been done; and no studies examining these associations over the longer term (>6 months) have been done in adults with both CKD and DM.

1.3.4 HRQoL Tools

A description of different generic and disease specific (DM and CKD) tools for assessing HRQoL is presented in **Table 1.4**. Within the renal literature, most researchers either use the SF-36 or SF-12 (short form) to assess overall HRQoL. These tools have been validated for use and have been used consistently within these populations to assess the impact of CKD on these functions (101, 113, 114, 136, 137). The main strengths and limitations are listed in **Table 1.4**.

Table 1.4 Generic and disease specific HRQoL tools

Name of Tool	Target population	Domains	Strengths	Limitations
SF-36	General Population	• Physical Functioning • Role-Physical • Bodily Pain	• Can be used in different populations, with and without	• Relies on self-reporting. • Lack of objective,

		• General Health • Vitality • Social Functioning • Role-Emotional • Mental Health	clinical conditions. • Multidimensional, includes element of physical, mental and social functioning. • Easy to apply. • Can be self-administered.	quantitative measures. • Long and taxing to answer. • Uses some terms that can be confusing to some users. • Encompasses a 4-week period, so results can be biased by recent events.
SF-20	General Population	• Physical Functioning • Role functioning • Social Functioning • Mental Health • Current Health Perceptions • Pain	• Can be used in different populations, with and without clinical conditions. • Multidimensional, includes element of physical, mental and social functioning. • Easy to apply. • Can be self-administered. • Encompasses a 3-month period. • Shorter than SF-36.	• Relies on self-reporting. • Lack of objective, quantitative measures.

SF-12	General Population	• Current Health Perceptions • Physical Functioning • Mental Health	• Can be used in different populations with chronic conditions. • Multidimensional, includes element of physical, mental and social functioning. • Easy and fast application.	• Relies on self-reporting. • Lack of objective, quantitative measures. • It is short and relies on a limited number of questions in order to extrapolate diagnosis in different domains.
Diabetes Quality of Life (DQoL)	Disease Specific-Diabetes	• Satisfaction with treatment • Impact of treatment • Worry about the future effects of diabetes • Worry about social/vocational issues	• Involves the assessment of elements inherent to diabetes, making it more specific. • Both for type 1 and type 2 DM • Simple to answer, no previous training needed.	• Might not reflect some non-diabetes related elements that could affect quality of life. • Self reported.
Audit of Diabetes-Dependent Quality of Life (ADDQoL)	Disease Specific-Diabetes	• Leisure activities • Working life • Local or long-distance journeys • Holidays • Physical health	• Considers a wholesome and multidimensional assessment of quality of life specific to	• Self-reported. • Could be complicated for elderly patients due to the formatting.

		• Family life • Friendships and social life • Close personal relationships • Sex life • Physical appearance • Self-confidence • Motivation to achieve things • People's reactions • Feelings about the future • Financial situation • Living conditions • Dependence on others • Freedom to eat and freedom to drink.	patients with diabetes. • Both for type 1 and type 2 DM. • Shows the effects of diabetes-related complications in quality of life. • Addresses patient's concerns regarding their condition.	
Diabetes-39	Disease Specific-Diabetes	• Energy and Mobility • Diabetes Control • Anxiety and Worry • Social Burden • Sexual Functioning • Diabetes Medication.	• Considers a wholesome and multidimensional assessment of quality of life specific to patients with diabetes. • Both for type 1 and type 2 DM.	• Self-reported. • Analogue response scale.

			• Can be filled out by patient.	
Kidney Disease Quality of Life (KDQoL)	Disease Specific-Chronic Kidney Disease	• Symptom/problems • Effects of kidney disease on daily life • Burden of kidney disease • Cognitive function • Work status • Sexual function • Quality of social interaction • Sleep	• Includes the core of SF-36 questionnaire plus kidney disease-specific elements. • Includes a list of symptoms and conditions related to kidney disease. • Includes elements for pre-dialysis, hemodialysis and peritoneal dialysis. • Simple to answer, patient-friendly.	• Self-reported. • Encompasses a 4-week period. • Long • Might be biased towards different degrees if the disease (ie patients with stage 5 will get lower scores than those with stage 1)

Description of health-related quality of life assessment tools by target population. Target populations included: general population, diabetes and kidney disease. Stage 1 kidney disease is defined as a GFR >90, stage 5 kidney disease is defined as a GFR <15. GFR=glomerular filtration rate. (101, 113, 114, 136, 137)

1.4 Frailty

1.4.1 Frailty in the elderly

While there is no universal definition for frailty, it is generally accepted that frailty refers to a condition of increased vulnerability to endogenous and exogenous stressors caused by a decrease in physiological reserves and functions (24). Physiological reserves are an organ's capacity to function under stress. These decreased physiological reserves and functions expose the

individual to a higher risk of negative health-related outcomes such as increased hospitalizations, increased falls, increased depression and increased mortality (138, 139). The components of frailty are shown in **Figure 1.3**. Pre-frailty is described as a physiological condition that represents a threshold between robustness and frailty (140, 141). In pre-frailty, patients have some of the characteristics known for frailty, which makes them vulnerable to adverse health outcomes, but they don't have enough deficits to be considered fully frail (140, 141).

With the recent advances in health research and health care, people are living longer, which is increasing the number of elderly individuals in the world's population (24, 25, 138, 142). Elderly individuals have an increased risk of developing conditions like frailty, especially in the presence of chronic conditions (6, 26, 80, 138). These individuals have an increased need of health services due to their increased risk of morbidity, as well as an increased need of social support, causing a significant burden in the health care system (27, 138, 142, 143). There is a growing interest on the development of preventive measures that help diminish the development of conditions like frailty in order to promote healthy aging.

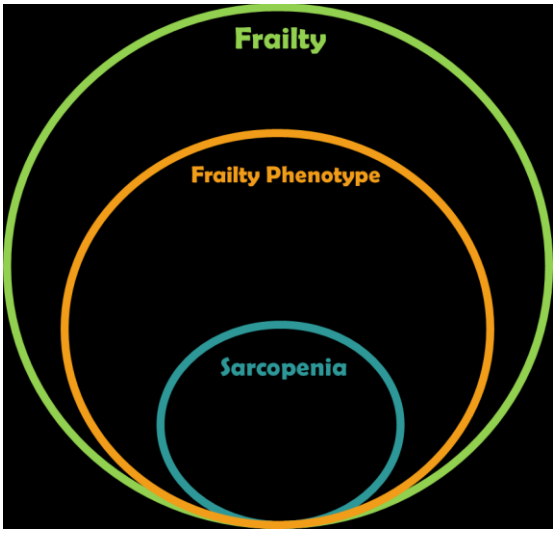

Figure 1.3 Components of frailty (Created by Author, Adame 2018)

There is variability in the literature concerning the clinical signs and elements that should be considered for the diagnosis of frailty. Frailty has been traditionally described as a physical condition and evaluated using tests for the assessment of lean body mass and physical functionality (strength, speed, endurance, activities of daily life) (6, 24, 144). Recently, frailty has evolved into a more multidimensional concept, which includes not only physical health and performance, but psychosocial elements such as depression, cognition and social support as well (25, 27, 143, 145). This means that frailty is a condition with a multidimensional vulnerability, and not only physical. Frailty has been associated with older age, the presence of chronic conditions such as DM and CKD, comorbidities and being female (6, 25-27, 142). Higher risk of frailty has also been found in individuals with lower socio-economic status, limited education and poverty (25, 27).

1.4.2 Frailty and DM

The presence of some chronic conditions such as DM has been related with an increased risk of developing frailty (25, 26, 80, 142). Poor glucose and lipid control have been associated with an increased risk of developing comorbidities and inflammation, which have been associated with frailty (27, 80, 142, 146). Uncontrolled hyperglycemia has been associated with the development of low lean body mass, which is one of the main physical components of frailty (31, 80, 147). Patients with diabetes have been shown to have a higher risk of developing conditions like depression or cognitive decline, which are psychosocial components that have been highly associated with frailty (9, 130). This shows that patients with DM, especially those with worse glycemic control, have a higher risk of developing conditions like sarcopenia, depression or cognitive decline, and that places them at an increased risk of developing frailty.

1.4.3 Frailty and Chronic Kidney Disease

Patients with CKD have an altered physiology due to the kidney's malfunctioning, which can be severe depending on the CKD stage the patient is in. Patients with CKD seem to be more

vulnerable to developing frailty, especially in the more advanced stages of the disease (6, 28, 148). The incidence of frailty in CKD patients ranges from 7% in non-dialyzed patients to around 67% in patients in dialysis (28, 148, 149). There is still not a complete and definite understanding of why patients with CKD have a higher incidence of frailty, but it is most likely caused by the physiological changes found in CKD. Some of the factors that could be driving the increased presence of frailty in these individuals are the chronic inflammation, the loss of protein and lean body mass, the systemic acidosis and hormonal disturbances present in CKD (6, 29, 30). Some of the hormonal disturbances that occur in CKD are related to bone metabolism, like increased PTH and decreased vitD, which in turn make bones fragile, muscle weaker and alters mood (9, 12, 115, 130). This places patients at higher risk of fractures, falls, sarcopenia, depression and other adverse health conditions related to vitD deficiency (3, 8, 44, 115, 150).

1.4.4 Frailty Tools

A comparison between some of the most common tools used to assess frailty in the literature is shown in **Table 1.5**.

Table 1.5 Comparison between frailty assessment tools

Name of Tool	Variables Considered	Strengths	Limitations	Validation
Frailty Phenotype	Weight loss, weakness (handgrip strength), exhaustion, walking speed, physical activity.	-Has both functional tests (weakness, walking speed) and self-reported elements. -Is considered to be more accurate	-Requires access to specialized equipment in order to assess certain aspects (hand-grip strength).	

		than other self-reported tools due to its quantitative tests.	-Requires previous training for the interviewer. -Doesn't consider psychosocial elements.	
Frailty Index	Considers a list of deficits (at least 50), and makes an index depending the amount the patient presents at the moment.	-Takes into consideration severity of disease and number of conditions presented.	-Lack of quantitative functional measures. -Can be long, as the list of deficits has >50 items.	
Edmonton Frail Scale	Cognition, General Health Status, Functional Independence, Social Support, Medication Use, Nutrition, Mood, Incontinence, Functional Performance	-Can be completed quickly in a clinical setting without the need for specialized equipment. -Addresses both functional and psychosocial elements. -Includes some tests for cognition (clock test)	-Lack of quantitative functional measures.	

FRAIL Scale	Fatigue, Resistance, Aer0obic capacity, Illness, Loss of weight.	-The test is self-reported, can be done in a clinical environment without any extra equipment. -No specialized training needed.	-Lack of quantitative functional measures. -Doesn't consider psychosocial elements.	
Clinical Frailty Scale	Physical Activity, presence of disease, activities of daily life.	-Rapid and simple assessment. -No specialized tools/instruments are required.	-Can be potentially subjective, as the interviewer assesses and chooses the category based on observation. -The differences between diagnostic categories are sometimes slight and could cause misclassification.	
Groningen Frailty Indicator	Physical, Cognitive, Social, Psychological.	-Assesses a multidimensional definition of frailty considering physical, cognitive and	-Self-reported assessment, no functional measures.	

		psychosocial elements.		
G8 Questionnaire	Loss of appetite, weight loss, mobility, neuropsychological problems, body mass index, medication use, self-perceived health, age.	-Involves both physical and psychosocial elements. - Multidimensional assessment of frailty.	-Self-reported -Lack of functional measures.	

Comparison of the most common tools used to assess frailty. Domains, strengths and limitations are considered. Frailty Phenotype defined frailty as the presence of 3 or more out of the 5 elements considered. The frailty index provides a continuous value that can be re assessed to measure the progression or regression of frailty but has no official categorical value. The Edmonton Frail Scale defines a score of 05 as non-frail, 6-7 as apparently vulnerable, 8-9 as mildly frail, 10-11 as moderate frailty and 12-18 as severely frail. The FRAIL scale defines robustness as 0/5 deficits present, pre-frailty as 1-2/5 and frailty as >3/5. The clinical frail scale includes 9 different diagnoses that go from very fit to terminally ill and considers frailty as limitations in the development of activities of daily life. The Groningen frailty indicator considers a score >3 as frail. The G8 questionnaire considers a score ≤14 as abnormal. (139, 151-155).

The Edmonton Frail Scale (EFS) has been validated for use in the clinical setting and has shown a 75% sensitivity and a specificity of 88% for detecting frailty when compared to other tools such as the Fried's Frailty Phenotype (152, 155, 156). Fried's Frailty Phenotype is considered one of the most accurate diagnostic tools for physical frailty, asit includes functional measures like handgrip strength and walking speed (141). The EFS's performance was also assessed by Perna et al by assessing 366 hospitalized patients and then associating the results with the results of other diagnostic tests and clinical data (155). The tests and clinical data used by Perna et al to assess the EFS'S performance included the Mini-Mental State Examination (MMSE) for cognitive status,

number of diseases, number of drugs taken daily, Barthel Index and Activities Daily Living for functional independence, Mini Nutritional Assessment, Geriatric Depression Scale, Skeletal Muscle Index for sarcopenia, bone health and handgrip strength (155). They found associations with independence, drug intake, mood, mental health, functional status and nutrition (155).

1.4.5 Vitamin D and Frailty Vitamin D status/role of supplementation and frailty.

Studies have shown that suboptimal vitD status (<75 nmol/l) was related to increased risk for frailty in different populations (10, 157-160). Some of the more direct factors that have been hypothesized to be related to the association of vitD and frailty are vitD's role in muscle health, bone health and mental health (44, 115, 160, 161). VitD supplementation has been proposed as a viable prevention strategy for frailty in CKD (91, 162, 163). This is particularly relevant in adults with CKD who live in northern climates because both renal conversion and cutaneous vitD synthesis are severely impaired (1-3). VitD deficiency has been associated with increased risk for frailty in CKD with proposed threshold for increasing frailty risk associated with serum $25(OH)D_3$ concentrations <75 nmol/l (10, 91, 157, 158, 162). However, no studies have evaluated the associations between frailty and vitD in adults with CKD, particularly in the longer term (longer than six months). None of these studies have examined the efficacy of routine vitD supplementation on health care utilization related to frailty incidence. Research examining these interrelationships is warranted since frailty has been related to significant health care utilization in the elderly.

1.5 Conclusion

VitD is an important micronutrient that is responsible for many vital functions in the human body (1, 9, 15, 44). Even though vitD can be acquired through the diet and be produced by the body through metabolic pathways, there is still a high prevalence of vitD deficiency in the general population within Canada (1, 3, 36, 49). One of the major risk factors in Canada for vitD deficiency is reduction in cutaneous vitD synthesis due to poor sunlight exposure (1-3, 164). In addition, vitD intake in the Canadian public is uniformly low because there are few sources of vitD in our food supply (e.g vitD fortified cow's milk, fatty fish) that are routinely consumed by the general public (164, 165). This makes it challenging for Canadian adults to meet their daily vitD needs without vitD supplementation. Adults with both DM and CKD also have additional challenges meeting vitD needs due to the restrictive therapeutic diets they typically consume which may be low in vitD (23, 39). It is especially concerning for patients with CKD due to the reduced renal conversion to the active form (39, 166, 167). Hence routine vitD supplementation in excess of the RDA is required to ensure vitD needs are met, particularly as vitD deficiency has been associated with reduced HRQoL, onset and expression of co-morbid conditions such as fracture, falls, frailty and overall mental health in some clinical populations (7, 8, 14, 61, 123, 168). Very little is known regarding the efficacy of routine vitD supplementation on these important outcomes in adults with DM and CKD, particularly in the longer term. This is important to understand as this population has a high co-morbid burden, which may contribute to reduced HRQoL, overall survival and health care utilization. The thesis objective was to examine the associations between vitD status and vitD supplementation on HRQoL, mental health, body composition and risk for frailty in an ambulatory population of adults with CKD and DM.

By studying and understanding vitD and its effects on the body, and quality of life, new and better treatment strategies can be developed for patients with clinical conditions. These

strategies will translate into better health care, and possibly, they might reduce the burden on health services.

Chapter 2. Research plan

2.1 Study Rationale

Vitamin D (vitD) is an essential vitamin due to its many roles in the human body mainly in bone, muscle, mental (cognition, mood) and immune health (1, 7, 169). There is a high incidence of vitD deficiency in Canada due to lack of sunlight exposure and limited dietary sources of vitD (1, 2). Elderly patients and patients with chronic health conditions tend to have an increased risk for developing vitD deficiency due to changes in physiology (decreased 7-dehydrocholesterol levels, decreased activation), suboptimal vitD intake and reduced sunlight exposure (1). This is of particular concern in northern communities where reduced cutaneous vitD synthesis results in a high prevalence of vitD deficiency in the general population (1, 2). Patients with diabetes mellitus (DM) and chronic kidney disease (CKD) have a special vulnerability to vitD deficiency due to impairments in vitD synthesis associated with declining renal function and recommendations to avoid vitD rich foods that may contribute to impaired glycemic control and electrolyte abnormalities (166). Hence the use of vitD supplementation is an important strategy to ensure that adults with DM and chronic CKD can meet their vitD requirements (7).

VitD deficiency has been associated with numerous negative health effects, which include decreased bone health, increased susceptibility to infection, decreased cognition, increased depression, reduced health related quality of life (HRQoL) and decreased skeletal muscle health (strength/quality) (9, 13, 126, 130, 159). In addition, there is some literature to indicate that vitD deficiency contributes to frailty in the elderly (10, 159). Frailty is a condition in which decreased physiological reserves and functions cause an increased susceptibility to adverse health outcomes such as fractures and falls, placing patients with this condition at increased risk for increased morbidity and mortality (24). The frailty definitions typically encompass both physiological (reduced lean mass/altered muscle functionality) as well as components of cognitive, mental health

and overall HQOL. Some of the elements of frailty like decreased muscle strength, altered mental health and cognition and reduced HRQOL could be related to vitD deficiency (9, 10, 126, 161). While frailty has been documented in up to 70% of adults with CKD (6, 28), little is known regarding the interrelationships between vitD status and frailty in adults with both DM and CKD. Even less is known about the longitudinal evolution of frailty and its associations with vitD status and whether or not vitD supplementation plays a role in the prevention and/or treatment of frailty in adults with DM and CKD. Understanding the incidence, longitudinal changes in components of frailty (body composition, mental health, HRQOL, cognitive status) are important to ensure that effective preventative and treatment strategies can be developed in this population.

The overall objective for this thesis was to study the associations between vitD status, frailty prevalence, body composition, HRQOL, and mental health and cognitive status in adults with DM and CKD.

2.2 Hypotheses and Objectives

2.2.1 Study 1: *Vitamin D Status, Health Related Quality of Life and Frailty in an Ambulatory Population with Diabetes Mellitus and Chronic Kidney Disease (Chapter 3).*

Objective: Compare body composition, HRQoL, mental health, vitD status and health care utilization between frail and non-frail adults with DM and CKD (stages 1-5).

Hypothesis: We hypothesized that frailty would be associated with suboptimal vitD status (as defined by serum 25(OH)D < 75 nmol/l), lower cognition, lean body mass, HRQoL, mental health, and higher health care utilization in adults with CKD and DM.

This chapter has been submitted to the Canadian Diabetes Journal for peer review in Jan 2018.

2.2.2 Study 2: *Longitudinal assessment of the associations between vitamin D and clinical outcomes (body composition, HRQoL, mental health) over five years in an cohort of ambulatory adults with diabetes mellitus and chronic kidney disease (stages 1-5). (Chapter 4).*

Objective # 1: Examine the longitudinal changes in body composition, HRQoL, cognition and depression on a group of adults with diabetic nephropathy over a period of 5 years.

Objective #2: Determine the vitD status (serum 25 (OH)D and 1,25 (OH) D) and its association with body composition, HRQoL, cognition and depression on a group of adults with diabetic nephropathy over a period of 5 years.

Hypothesis #1: There will be increased fat mass, decreased lean mass, decreased HRQoL, increased depression, and decreased cognition over time.

Hypothesis #2. Participants with suboptimal vitD status (serum $25(OH)D_3$ <75 nmol/l) will have worse health outcomes (lower lean body mass, higher fat mass, lower HRQoL and lower mental health and cognition) than those with vitD status >75 nmol/l.

Chapter 3: Vitamin D Status, Health Related Quality of Life and Frailty in an Ambulatory Population with Diabetes Mellitus and Chronic Kidney Disease.

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Abstract

Background. Frailty can cause an increased vulnerability to adverse health outcomes such as falls, fractures, depression and reduced health related quality of life (HRQoL). Vitamin D (vitD) deficiency, a common condition within northern populations and patients with diabetes mellitus (DM), has been associated with an increased risk for frailty in the elderly. The study objective was to compare body composition, HRQoL, cognitive status, mental health, VitD status and health care utilization between frail and non-frail adults with CKD (stages 1-5) and to assess the interrelationships between vitD status and these factors.

Methods and Participants: Body composition (Dual-Energy-X-ray-Absorptiometry), vitD status (serum 25(OH)D3), frailty (Edmonton Frail Scale), depression (Major Depression Inventory) and HRQoL (SF-36) in an ambulatory population of adults (>18 years) with DM and CKD (stage 1-5) were studied (n=41).

Results: Frailty occurred in 17% of participants. Frail participants had lower lean body mass, and HRQOL scores ($p=\leq 0.05$), more depression ($p=\leq 0.05$) and higher numbers of health visits (total, inpatient and emergency) ($p=\leq 0.05$) compared with non-frail participants. No differences in health care visit types or vitD status was noted between frail and non-frail participants ($p>0.05$).

Conclusions: Frailty in adults with CKD and DM is associated with low lean body mass, low HRQoL, more depression, and increased health care visits.

Key words: vitamin D, frailty, pre-dialysis, diabetes mellitus, health care utilization, quality of life, mental health.

3.1 INTRODUCTION

Frailty is a physiological condition in which decreased physiological reserves and altered bodily functions cause an increased vulnerability to adverse health outcomes such as falls and fractures and reduced health related quality of life (HRQoL) (6, 24). The term physiological reserve refers to an organ's ability to adapt to metabolic and environmental stressors. This means that patients with frailty have a decreased ability to handle physiologic stress (6, 24, 139), and have increased difficulty regaining homeostasis after an insult. While lifestyle may influence the onset and progression of frailty, the major factors influencing the risk for frailty in adults is the presence of chronic diseases such as chronic kidney disease (CKD) (170) and diabetes mellitus (DM) (26, 146, 148, 149). The prevalence of frailty in CKD appears to be dependent on kidney function, with patients with a more advanced disease having a higher prevalence with up to 70% in patients with stage 5 CKD undergoing dialysis (28, 139, 171). Therapy for frailty is aimed at treatment of underlying disease etiology and rehabilitation of physical functionality and overall diet quality to ensure all nutritional requirements of the individual are met. Frailty has been associated with increased morbidity, hospitalization and mortality in CKD, but the longitudinal evolution of this disorder has not been well described, particularly in relation to potential lifestyle factors that may contribute to it (172).

Vitamin D (vitD) deficiency has been one of the nutrient deficiencies associated with frailty in the elderly with chronic health conditions (10, 95). However, the relationship between vitD deficiency and frailty in patients with DM and CKD has not been established. This is important to understand as vitD deficiency is highly prevalent within the general population in northern climates such as Alberta (2). Elderly patients with DM and CKD are especially vulnerable to vitD deficiency due to metabolic changes in vitD metabolism and dietary restriction often includes foods/beverages highest in vitD to ensure electrolyte and glycemic control (95). VitD deficiency

has been related with decreased health and functioning of various bodily systems, some of them being musculoskeletal health and cognitive health (1, 10, 116). VitD has numerous roles in human physiology, mediated through the action of the VitD receptors (VRDs), which are present in different cells and tissues (1, 10). The importance of vitD to skeletal muscle might be a key factor in conditions involving decreased musculoskeletal health, such as frailty.

The study objective was to compare body composition, HRQoL, mental health, vitD status and health care utilization between frail and non-frail adults with DM and CKD (stages 1-5). We hypothesized frailty would be associated with suboptimal vitD status (as defined by serum 25(OH)D < 75 nmol/l), lower cognition, lean body mass, HRQoL, mental health, and higher health care utilization in adults with CKD and DM.

3.2 METHOD

This is a cross-sectional study that included 41 ambulatory adults (>18 years) with type 1 (T1D) (n=3) or type 2 (T2D) (n=38) diabetes mellitus (DM) and CKD stages 1-5. Participants in this cross-sectional study participated in a vitD supplementation RCT and were later enrolled in a longitudinal study (vitamin D follow-up) examining vitD status and health care outcomes (7).

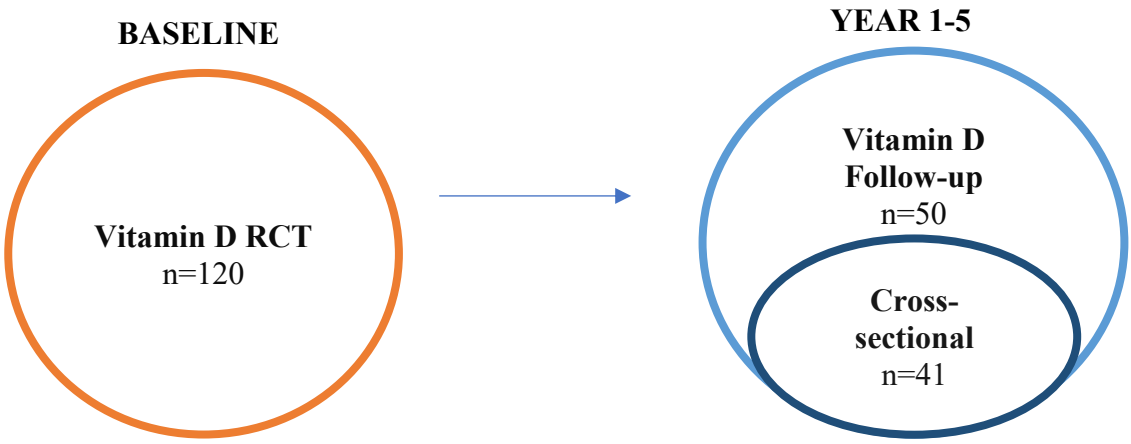

Figure 3.1 Participant distribution between RCT, longitudinal and cross-sectional studies. Participants in the longitudinal study were recruited from the RCT at the end of the study for a 1-5 year longitudinal study. The cross-sectional study is a subset analysis of participants from the follow up study who had a frailty assessment done between 2016-2017.

Vitamin D RCT

Patients were recruited for the vitD RCT from Northern Alberta Renal Program (NARP) clinics at Alberta Health Services (AHS) in Edmonton, Alberta between November 2011 and December 2013. These clinics included the Renal Insufficiency Clinic (RIC) and the diabetic Nephropathy Prevention Clinic (DNPC).

Potential participants were approached by a member of the clinical team (e.g. RD or RN) and asked if a research team member could discuss this study with them. If verbal consent was provided, then a research team member contacted the patient, explained the study to them and determined their eligibility for participation in the RCT; if eligible and agreed by the patient, informed consent was signed, and the baseline study appointment was booked.

Inclusion criteria for the VitD RCT included: Adult (18– 80 years) patients diagnosed with diabetes (Type 1 and Type 2) and stage 1–4 CKD (Glomerular Filtration Rate (GFR) 15–89 mL/min/ 1.73 m^2). Exclusion criteria for the RCT included: 1) Patients with co-morbid conditions known to affect vitD metabolism including gastrointestinal, liver, rheumatoid or bone disorders (e.g. hyperthyroidism, untreated celiac disease, cancer, Paget's disease, sarcoidosis, malabsorption, etc.). Individuals with severe, permanent vision impairment will be excluded as this will preclude them from reading supplement labels accurately and safely. Pregnant women will be excluded as Dual-energy X-ray Absorptiometry (DXA) scans are not recommended during pregnancy. Patients weighing >136 kg will be excluded as the DXA table cannot accommodate this weight. 2) Patients on drug therapy known to interfere with vitD (e.g. oral glucocorticoids, cholestyramine, colestipol, mineral oil, Orlistat, digoxin). 3) Patients on other forms of active D metabolites (e.g. calcitriol, vitamin D2). 4) Patients with stage 5 CKD (GFR <15 mL/min/1.73 m2), receiving dialysis or on a kidney transplant list. 5) Patients with pre-existing hypercalcemia (>2.75 mmol/L), hyperphosphatemia (>2.0 mmol/L), severe secondary hyperparathyroidism (PTH

>66 pmol/L), and serum 25(OH)D >200 nmol/L. 6) Patients with serum 25(OH)D <37.5 nmol/L at time of screening to control for correction of vitamin D deficiency. 7) Patients undergoing strict heavy exercise for weight control and/or those who used sunscreen lotion on a regular basis. (173)

Frailty Study (Cross-sectional study)

Participants in the current study were longitudinally followed between Years 1-5 post RCT enrollment (173). Yearly follow-ups were booked by phone within a 3-month window of the yearly mark. The cross-sectional study is a subset analysis of those participants (n=41) who agreed to the longitudinal F/U study and who had a frailty assessment done between 2016-2017.

Inclusion criteria for this cross sectional included: 1) Ambulatory adults (>18 years) with Type 1 or Type 2 Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD). 2) Participated in a Vitamin D supplementation RCT and are part of the vitD F/U Study. 3) Had a frailty assessment completed between 2016-2017. Exclusion criteria included: 1) Participants who did not participate in the vitD F/U Study. 2) Participants without a frailty assessment. 3) Pregnant women. 4) Patients with co-morbid conditions known to affect vitamin D metabolism including gastrointestinal, liver, rheumatoid or bone disorders. 5) Patients weighing >136kg. 6) Patients on drug therapy known to interfere with vitamin D metabolism.

The study design and data gathered per year is described in **figure 3.1**. Primary outcome data included vitD status (serum 25(OH)D_3), frailty assessment (Edmonton Frail Scale), Appendicular Skeletal Muscle Mass Index (ASMI), Fat Mass Index (FMI) and body composition. Secondary outcome data included cognition (Mini Mental State Examination), HRQoL (SF-36), depression assessment (Major Depression Inventory), physical activity (International Physical Activity Questionnaire), and health care utilization. Diet (3-day food records), bone density, sunlight exposure, and season were assessed per year, but are not reported in this thesis.

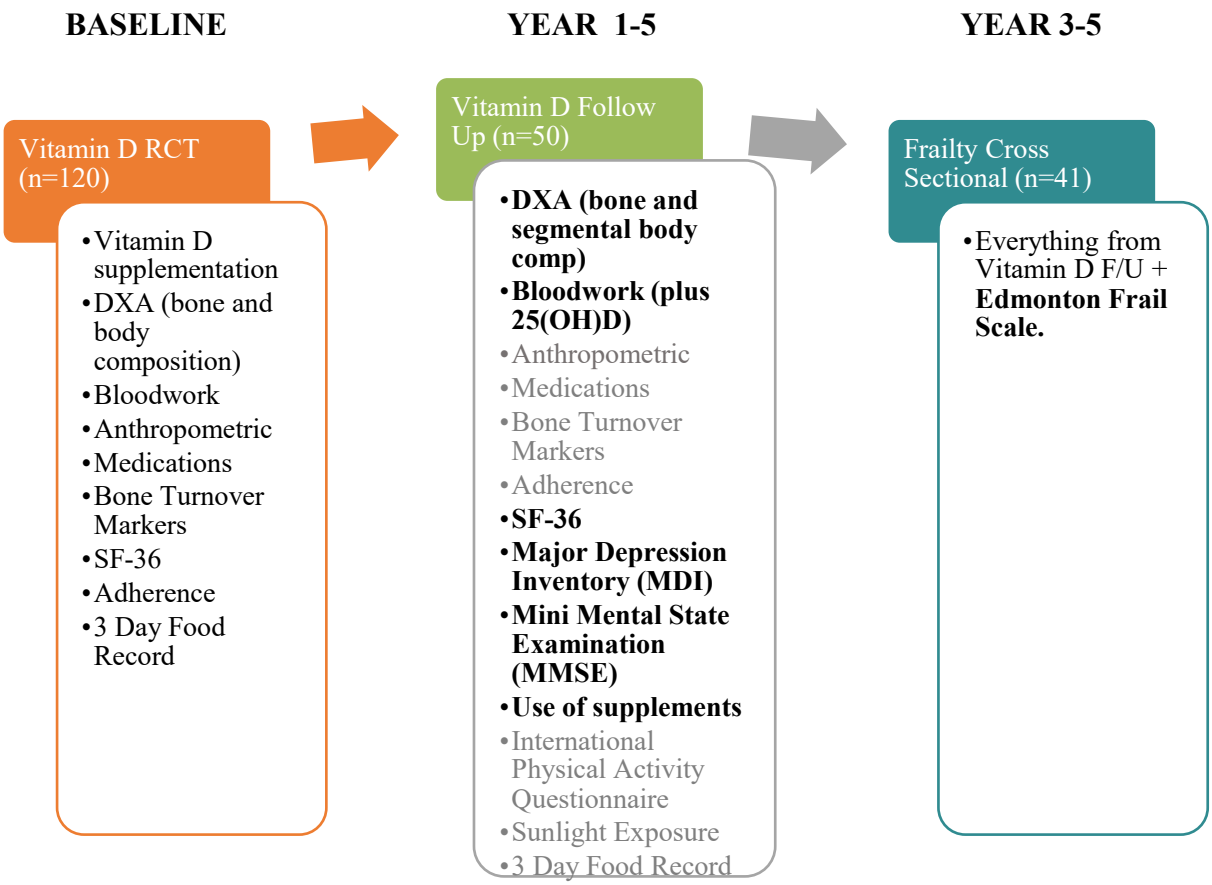

Figure 3.2 Variables assessed in this cross-sectional analysis (Frailty). Variables in black and bold font were analyzed in this cross-sectional study. Frailty assessment was added at the 3rd year of the follow up. The cross-sectional study is a subset analysis analyzing the participants who had a frailty assessment.

Study visits were conducted in the Clinical Research Unit of the Alberta Diabetes Institute at the University of Alberta, Canada. Blood for assessment of vitD status (25(OH)D3) was collected at the time of routine clinical blood work (estimated Glomerular Filtration Rate (eGFR), Glycated Hemoglobin A1c (A1c), Random Blood Glucose, Urea, Creatinine, Albumin, Parathyroid Hormone (174)). Serum 25(OH)D_3 was measured in the Core Laboratory of the University of Alberta Hospital according to standard methodologies (173). VitD status was classified using the following serum concentrations as cut-offs: <75 nmol/l (insufficient) and ≥75 nmol/l (sufficient) (36). Serum 25(OH)D_3 <50 nmol/l was classified as deficient (36). Demographic (height, weight, age, gender), anthropometric (height, weight, Body Mass Index

(BMI) (kg/m^2)) and clinical information (medication use, comorbidities, DM type, duration of DM, CKD stage) were collected. Ethics approval was obtained from the Human Research Ethics Board (HREB) at the University of Alberta, Canada (Pro00049292). Informed consent was obtained prior to study enrollment.

3.2.1 Frailty and Cognition

Frailty was assessed using a modified version of the self-reported Edmonton Frail Scale (EFS) (152, 155). The EFS is based on 9 different domains, including concepts addressing Cognition, General Health Status, Functional Independence, Social Support, Medication Use, Nutrition, Mood, Continence and Self-Reported Performance (scores > 5 indicative of frailty). The EFS was modified to include the drawing component of the Mini Mental State Exam (MMSE) instead of the traditional clock test (175). Cognition was assessed using the Mini Mental State Examination (MMSE), which consists of 11 items, which include both questions and tasks (scores< 24 abnormal) (175).

3.2.2 Body composition

Body composition was assessed using the LUNAR Prodigy High-speed Digital Fan Beam DXA (version 10.5, GE Healthcare, Madison, Wisconsin, USA). Body composition parameters included whole body and regional (Arms, Legs, Trunk, Android, Gynoid and Total Mass) Fat Mass, Lean Mass, Total Tissue and Bone Mineral Content. Fat Mass Index (FMI) was calculated with the formula Total Fat/height^2 (m). Appendicular Skeletal Muscle (ASM) was obtained through the addition of the lean mass of the arms and legs in kg. Appendicular Skeletal Muscle Mass Index (ASMI) was calculated with the formula ASM/height^2 (m). Low lean body mass was defined as an ASMI more than 2 standard deviations (s.d) below sex-specific means of a normal reference population (7.26 kg/m^2 for men and 5.45 kg/m^2 for women) (176).

3.2.3 Health related quality of life, mental health and physical activity

HRQOL was assessed using the validated self-reported Short Form Health Survey (SF-36) (137). The SF-36 consists of 8 domains (Physical functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, Role Emotional and Mental Health) and 2 component summaries (Physical Component Summary and Mental Component Summary). A score from 0 to 100 was calculated for each domain; a higher score was representative of higher HRQoL.

Depression was assessed using the validated, self-reported Major Depression Inventory (MDI) (scores ≥20 are considered abnormal) (177). Physical Activity was assessed using the International Physical Activity Questionnaire (178) (179). IPAQ was scored to determine the total amount of MET min/week and the total amount of sedentary hours per participant (178). Data from IPAQ in which activity time added to >960 min was excluded as per guidelines (178).

3.2.4 Health Utilization

A chart review was conducted using electronic medical records to assess individual cumulative health events/health event types from 2012 to 2017. Health care event history was categorized as inpatient, outpatient, emergency and total health utilization events using the classification included in the records. Health visit type was categorized into the following categories: nephrology, diabetes, ophthalmology, musculoskeletal, cardiovascular and other. This classification was based on the most common comorbidities observed in this population (7).

3.2.5 Statistical analysis

Data analysis was completed using the SAS 9.0 statistical software (SAS, Version 9.4; SAS Institute Inc., Cary, NC, USA). Data was expressed as mean ± standard deviation (parametric) or median + interquartile range (non-parametric). Non-parametric variables were log transformed. Frailty (+/-), depression (+/-), low lean body mass (+/-), sex (male/female), DM type (type 1 or

type 2 DM) were treated as categorical values. VitD was treated both as categorical ($25(OH)D_3$ <75 and ≥75 nmol/l) and as a continuous variable, in order to assess the relationship of vitD status with primary outcomes. Chi-square analysis were conducted in order to assess the relationship between categorical variables (Frailty (+/-), depression (+/-), low lean body mass (+/-), sex (male/female), DM type (type 1 or type 2 DM)) .Multi-variate analyses were conducted to assess the relationship between Frailty and vitD status with Body Composition, HRQoL and Mental Health with adjustment for potential confounding variables (age, sex, DM duration/type, CKD stage) but these were not reported in this thesis if not significant. A p value ≤ 0.05 was considered significant.

3.3 RESULTS

3.3.1 Demographic, anthropometric and laboratory variables

Anthropometric, demographic and laboratory data by frailty and vitD status are presented in **Table 3.1** and **Table 3.2**. Frailty occurred in 17% (n=7) participants; 6 (85%) of these participants fell within the apparently vulnerable/mildly frail categories, while 1 participant was categorized as moderately frail. Participants were taking on average 11 ± 4 medications (prescribed/over-the-counter) and the number of co-morbid conditions (median, range) they presented in addition to DM and CKD was 5 (1-10) (7). Frail participants had a higher number of comorbid conditions than non-frail participants (6 ± 2 (frail) and 4 ± 2 (non-frail); p≤0.05). A total of 21 (51%) participants were on oral hypoglycemic agents (OHA), 30 (73%) participants were on insulin therapy and 12 (29%) were on combined therapies. There was no difference in therapies (OHA, insulin) between frail and non-frail participants. In total, 70% (n=28) of participants had sufficient vitD levels (>75 nmol/l), while 10% (n=4) had deficient levels (<50 nmol/l). There was a 76% prevalence of vitD supplementation. There were no differences in sex, age, weight, height, BMI, DM duration, vitD supplementation, vitD levels or glycemic control (A1c or RBG)

between participants with and without frailty (p>0.05). Participants with frailty were more likely to have advanced CKD compared to those without frailty (p=0.03). All participants had MMSE scores indicative of normal cognitive status (>24) for age and gender. There was no relationship between cognitive scores and frailty (p>0.05), nor with vitD status (p>0.05).

Table 3.1 Demographic, anthropometric and clinical data

		By Frailty			By vitamin D status		
Variable	**Total (n=41)**	**Frail (n=7)**	**Not Frail (n=34)**	**P-value**	**>75 nmol/l (n=28)**	**<75 nmol/l (n=12)**	**P-value**
Male n (%)	26 (63%)	4 (57%)	22 (65%)	0.70	16 (57%)	9 (75%)	0.28
Age (years)	70 ± 8.9	70 (67-74)	70 (65-76)	0.87	69.8 ± 6.7	68.6 ± 11.8	0.69
Weight (kg)	88.8 ± 17.0	79.4 ± 18.8	90.7 ± 16.3	0.12	93.1 ± 15.1	79.7 ± 18.7	**0.02***
Height (m)	1.68 ± .08	1.68 ± 0.1	1.69 ± 0.08	0.80	1.68 ± 0.07	1.69 ± 0.10	0.77
BMI (kg/m^2)	31 ± 5.5	28 ± 5.7	31 ± 5.3	0.12	32.8 ± 4.6	27.8 ± 6.0	**<0.01***
DM Type 2, n (%)	38 (92%)	5 (71%)	33 (97%)	**0.01***	27 (96%)	10 (83%)	0.14
DM Duration (years)	16 ± 13	21.4 ± 14.6	19.4 ± 9.9	0.65	18.6 ± 9.1	22.9 ± 13.8	0.25
CKD Stage 3-5 n (%)	26 (63%)	7 (100%)	19 (56%)	**<0.05***	16 (57%)	10 (83%)	0.11
Vitamin D Sup n (%)	31 (76%)	6 (86%)	25 (74%)	0.49	25 (89%)	6 (50%)	**<0.01***
Vitamin D Sup (IU)	2000 (1000-2000)	1000 (1000-1000)	2000 (1000-2000)	0.06	1752 ± 710	1166 ± 408	0.06

Data expressed as mean ± standard deviation or median (interquartile range). Kg= kilogram, m = meters, n= number, BMI= Body Mass Index (kg/m^2), DM= Diabetes Mellitus, CKD = Chronic Kidney Disease, IU= International Units, Sup=supplementation. A t-test was conducted to assess the difference in means between groups. A p value ≤0.05 is considered significant.

Table 3.2 Laboratory Data

Variable	Total (n=41)	By Frailty			By vitamin D status			Normal Range
		Frail (n=7)	Not Frail (n=34)	P-value	>75 nmol/l (n=28)	<75 nmol/l (n=12)	P-value	
eGFR (ml/min/1.72m^2)	44 ± 29	18 ± 9	50 ± 29	**<0.01***	50 ± 28	33 ± 31	0.08	>59.0
25(OH)D$_3$ (nmol/l)	88 (71-115)	82 ± 29.9	89 (77-115)	0.43	108 ± 30	55 ± 15	**<0.0001***	>50
HbA1c (%)	7.3 ± 1.1	7.5 ± 1.3	7.3 ± 1.1	0.73	7.4 ± 1.1	7.2 ± 1.2	0.7	4.3 - 6.1
Random Blood Glucose (mmol/L)	8.4 (7 - 11.7)	8.3 (6.8-13.6)	8.5 (7.1-11.1)	0.62	8.9 ± 2.7	11.8 ± 6	0.05	3.3 - 11
Albumin (g/L)	40 ± 2.9	38 ± 2.7	41 ± 2.8	**<0.05***	41 ± 2.6	40 ± 3.8	0.11	35 - 50
PTH (pmol/L)	5.4 (3.2 – 15.9)	17.3 ± 12.1	11.4 ± 17.6	0.40	8.5 ± 8.9	21.8 ± 25.9	**<0.05***	1.4 - 6.8
Urea (mmol/L)	9.5 (6.5 - 19.3)	15.5 (13.8-19.6)	8.4 (6.2-19.0)	0.13	11.4 ± 6.7	14.7 ± 8.0	0.19	2.5 - 8.0
Creatinine (umol/L)	139 (86 - 230)	304 ± 146	115 (82-227)	**<0.05***	163 ± 123	278 ± 176	**<0.05***	50 - 105
Calcium (mmol/L)	2.33 ± 0.14	2.24 ± 0.18	2.36 ± 0.13	0.05	2.37 ± 0.1	2.25 ± 0.1	**<0.05***	2.10 - 2.60
Phosphorus (mmol/L)	1.2 (1.1 – 1.4)	1.3 ± 0.4	1.2 ± 0.2	0.14	1.1 ± 0.2	1.3 ± 0.3	0.05	.80 - 1.45
C-Reactive Protein (mg/dL)	2.2 (1.3- 6.3)	6.3 (4.1-7.0)	1.8 (.9- 5.9)	0.38	3.9 ± 3.8	5.1 ± 6.1	0.5	< 8.0

Data expressed as mean ± standard deviation or median (interquartile range). eGFR= estimated Glomerular Filtration Rate, HbA1c= Hemoglobin A1c, PTH = Parathyroid Hormone. A t-test was conducted to assess the difference in means between groups. A p value ≤0.05 is considered significant.

3.3.2 Frailty, vitamin D and body composition

Body composition data for frail and non-frail participants as well as by vitD status is showed in **Table 3.3.** Frail participants had lower ASMI, lower lean mass (LM) in some body segments (trunk, gynoid and android areas) compared to non-frail participants ($p \leq 0.05$). There was no difference in total FMI, total fat mass, percent of fat mass or percent of lean mass in the different compartments between frail and non-frail participants ($p > 0.05$). Participants with vitD levels <75 nmol/l had lower weight ($p = 0.02$), lower BMI ($p = 0.006$) and lower FMI ($p = 0.01$) than those with levels ≥75 nmol/l.

Table 3. 3 Body Composition Data

		By Frailty			By vitamin D status		
Variable	**Total (n=41)**	**Frail (n=7)**	**Not Frail (n=34)**	**P-value**	**>75 nmol/l (n=28)**	**<75 nmol/l (n=12)**	**P-value**
BMI (kg/m^2)	31 ± 5.5	28 ± 5.7	31 ± 5.3	0.12	33 ± 4.6	28 ± 6.0	**<0.01***
FMI (kg/m^2)	11.6 ± 4.05	11.1 ± 4.1	11.7 ± 4.1	0.72	11.1 ± 4.1	11.7 ± 4.1	0.72
ASMI (kg/m^2)	7.6 ± 1.04	6.8 ± 1.0	7.7 ± 0.9	**0.02***	7.7 ± 0.9	7.3 ± 1.1	0.17
Low lean body mass n(%)	9 (21.9)	4 (57.1%)	5 (14.7%)	**0.01***	4 (57.1%)	5 (14.7%)	**0.01***
Percent of Fat							
Arms (%)	35 ± 10.5	38 ± 9.3	34 ± 10.8	0.46	38 ± 10	30 ± 9.7	**0.01***
Legs (%)	31 ± 13.9	39 ± 11.3	32 ± 11.2	0.14	35 ± 11.7	31 ± 10.5	0.36
Trunk (%)	42 ± 7.1	42 ± 7.8	42 ± 7	0.84	44 ± 6.8	39 ± 6.2	**0.03***
Android (%)	46 ± 7.3	46 ± 6.8	46 ± 7.5	0.78	48 ± 7.1	43 ± 5.9	0.05
Gynoid (%)	37 ± 12.4	41.± 10.1	37 ± 8.9	0.3	40 ± 9.4	37 ± 8.9	0.33
Total (%)	38 ± 7.8	40 ± 7.4	37 ± 7.9	0.4	40 ± 7.7	35 ± 6.9	0.06
Fat Mass							
Arms (g)	2902 ± 1082	3075 ± 1104	2866 ± 1091	0.64	3219 ± 1052	2291 ± 820	**0.009***
Legs (g)	7643 ± 6022	9460 ± 3627	8737 ± 4829	0.71	9685 ± 4927	7296 ± 3426	0.13
Trunk (g)	20363 ± 6629	17752 ± 7202	20900 ± 6488	0.25	22227 ± 6029	16599 ± 6467	**0.01***
Android (g)	4031 ± 2488	3490 ± 1487	4179 ± 1449	0.26	4501 ± 1324	3199 ± 1348	**0.007***
Gynoid (g)	4834 ± 2361	4848 ± 1693	5218 ± 2128	0.66	5476 ± 2166	4544 ± 1670	0.19

Total (g)	32979 ± 11118	31128 ± 10375	33360 ± 11375	0.63	36015 ± 10636	26977 ± 9685	**0.01***
Percent Lean Body Mass							
Arms (%)	64 ± 10.5	61 ± 9.3	65 ± 10.8	0.46	62 ± 10	70 ± 9.7	**0.02***
Legs (%)	68 ± 13.8	60 ± 11.3	67 ± 11.2	0.14	65 ± 11.7	69 ± 10.5	0.36
Trunk (%)	58 ± 7.1	57 ± 7.8	58 ± 7	0.84	56 ± 6.8	61 ± 6.2	**0.03***
Android (%)	53 ± 7.3	53 ± 6.8	54 ± 7.5	0.78	52 ± 7.2	57 ± 5.9	**0.04***
Gynoid (%)	62.8 ± 12.4	58 ± 10.1	62 ± 8.9	0.3	60 ± 9.4	63 ± 8.4	0.33
Total (%)	62 ± 7.8	59 ± 7.8	62 ± 7.9	0.4	60 ± 7.7	65 ± 6.8	0.06
Lean Body Mass							
Arms (g)	5216 ± 1192	4890 ± 877	5284 ± 1248	0.43	5156 ± 1077	5447 ± 1469	0.48
Legs (g)	16531 ± 3095	14562 ± 3893	16936 ± 2805	0.06	16911 ± 2937	15658 ± 3532	0.25
Trunk (g)	27134 ± 4750	23049 ± 5180	27975 ± 4267	**0.01***	27932 ± 4575	25070 ± 4885	0.08
Android (g)	4528 ± 952	3741 ± 835	4690 ± 902	**0.01 ***	4764 ± 900	3999 ± 927	**0.01***
Gynoid (g)	7690 ± 1365	6637 ± 1596	7906 ± 1230	**0.02 ***	7940 ± 1285	7086 ± 1472	0.07
Total (g)	52229 ± 8761	45493 ± 10187	53616 ± 7910	**0.02 ***	53307 ± 8213	49553 ± 10122	0.22
Total Mass							
Arms (g)	8119 ± 1428	7966 ± 1346	8150 ± 1463	0.75	8375 ± 1241	7738 ± 1646	0.18
Legs (g)	25391 ± 5665	24023 ± 5029	25673 ± 5817	0.48	26596 ± 5680	22954 ± 5055	0.06
Trunk (g)	47499 ± 9987	40798 ± 11067	48878 ± 9336	**0.04 ***	50162 ± 8884	41667 ± 10581	**0.01***
Android (g)	8590 ± 2199	7231 ± 2223	8870 ± 2119	0.07	9264 ± 1928	7197 ± 2185	**0.004***
Gynoid (g)	12735 ± 2674	11485 ± 2295	12993 ± 2704	0.17	13417 ± 2641	11254 ± 2274	**0.01***
Total (g)	85209 ± 15940	76622 ± 17071	86977 ± 15368	0.11	89322 ± 14148	76531 ± 17221	**0.01***

Data expressed as mean ± standard deviation or median (interquartile range). eGFR= estimated Glomerular Filtration Rate, HbA1c= Hemoglobin A1c, PTH = Parathyroid Hormone. A t-test was conducted to assess the difference in means between groups. A p value ≤0.05 is considered significant.

3.3.3 Frailty, HRQoL, mental health and physical activity

Data for MDI and HRQoL scores is represented in **figures 3.1** and **3.2**, respectively. Participants with frailty scored a median (range) of 31 (13-54) lower in HRQoL scores when compared to non-frail participants ($p \leq 0.05$). When compared against normative data for age and gender, participants with frailty scored a median (range) of 40 (10-64) points under the Canadian norms; this is more than 5 points below, which is considered clinically significant (11). There was no relationship between vitD status and quality of life scores ($p > 0.05$). Overall, there was a 20% prevalence of depression in this cohort. Frail participants had a higher prevalence of depression ($p \leq 0.05$) than those without frailty. There was no relationship between MDI scores and vitD status ($p > 0.05$).

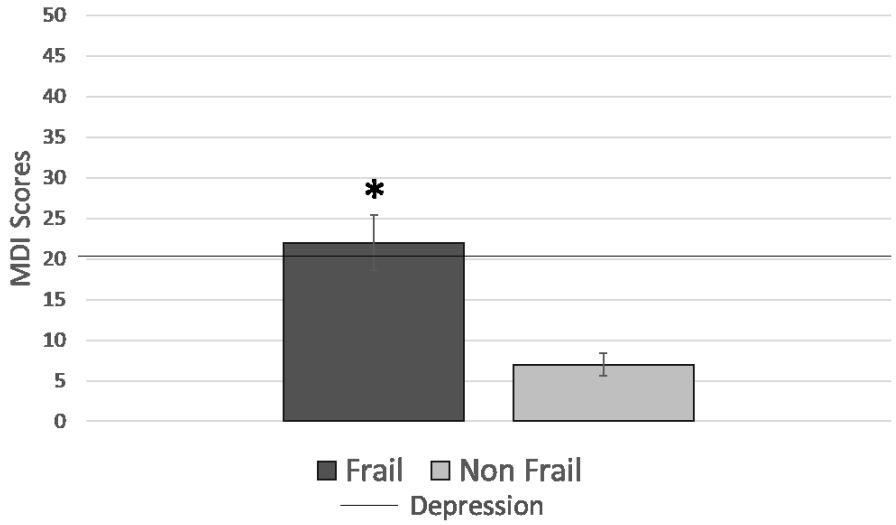

Figure 3.3 Major Depression Inventory Scores (MDI). Interrelationships between Frailty and depression (score ≥ 20 abnormal) as assessed by the Major Depression Inventory Scale. Frail (n=7), Non-Frail (n=34). Values are means ± SD. A t-test was conducted to assess the difference in means between groups. Values with an asterisk are significantly different at $p \leq 0.05$

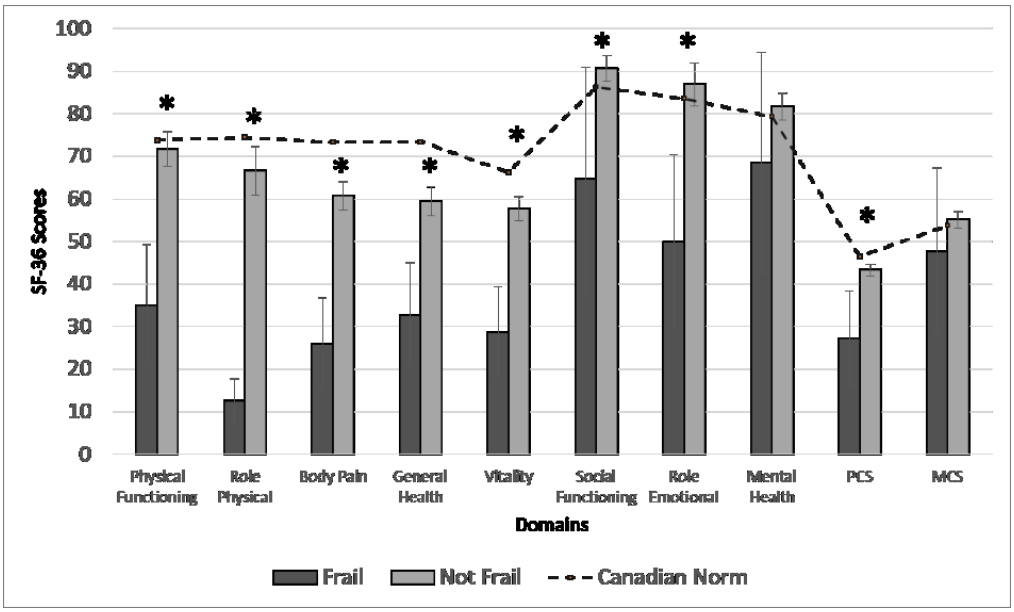

Figure 3.4 Health Related Quality of life. Interrelationships between Frail and non-frail participants. SF-36 responses were compared to Canadian normative values (dashed line) (27). Frail (n=7), Not Frail (n=34). Values are means ± SD. A t-test was conducted to assess the difference in means between groups. Values with an asterisk are significantly different at $p \leq 0.05$.

Participants with frailty reported a mean ± SD of 1134 ± 1119 MET min/week, while non-frail participants reported 2756 ± 2966 MET min/week (p= 0.16). Participants with frailty spent an average 6.7 ± 1.7 hour sitting during weekdays and 6.4 ± 2.2 hours during the weekend, while non-frail patients spent 5.8 ± 2.6 (p= 0.36) and 5.4 ± 3.0 hours respectively (p= 0.42). There was no difference in sedentary hours, either during the week or on the weekend, between frail and non-frail participants.

3.3.4 Health event history

The comparison of mean number of health events by frailty is shown in **Figure 3.4.** Participants with frailty had a higher cumulative number if health events compared to non-frail participants, ($p \leq 0.05$). The distribution of health events by type is represented in **Figure 3.5**. There was no difference in the distribution of health events when compared by types (main vs. secondary

comorbidities) between frail vs non-frail patients. Health care utilization and health event types were independent of vitD status ($p>0.05$).

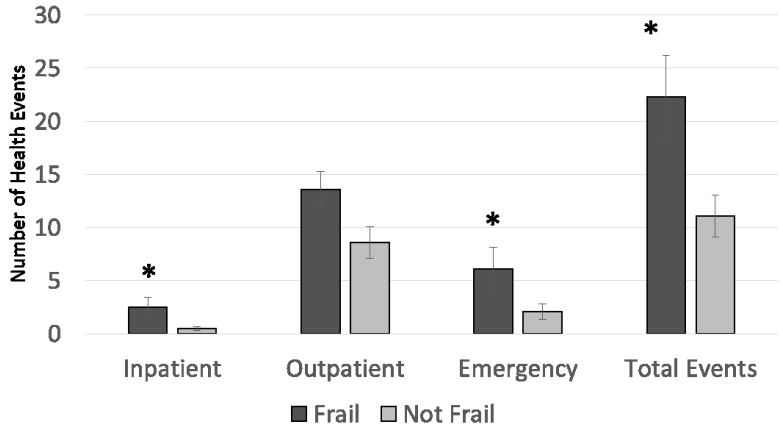

Figure 3.5 Cumulative number of health events. Interrelationships between frail and non-frail participants. Cumulative number of health events as categorized by Inpatient, Outpatient, Emergency and total health care visits between 2012-2017. Frail (n=7), Non-Frail (n=34). Values are means ± SD. A t-test was conducted to assess the difference in means between groups. Values with an asterisk are significantly different at $p \leq 0.05$.

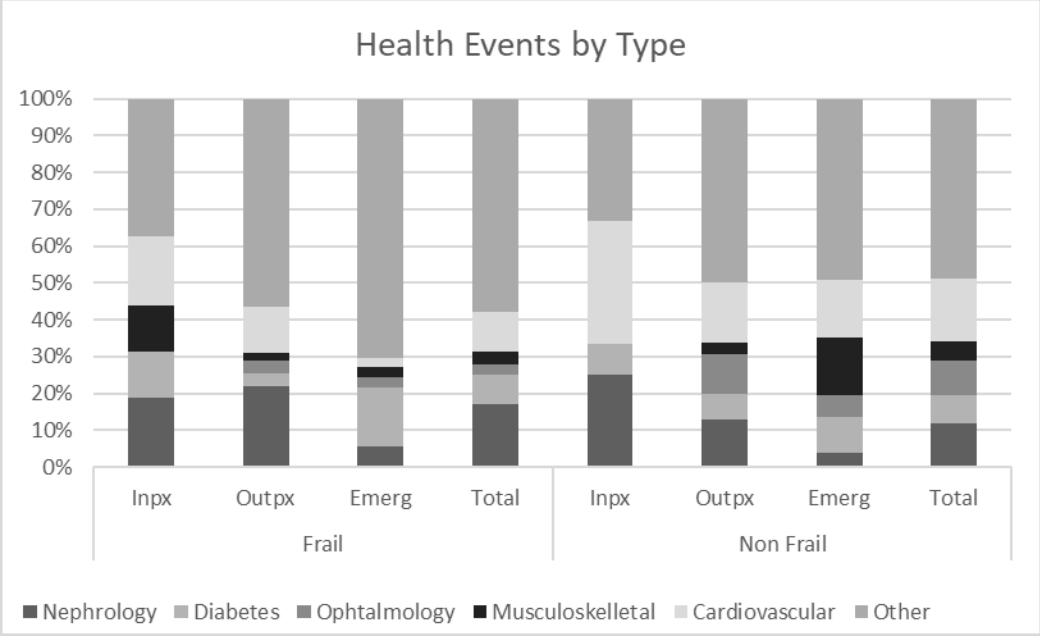

Figure 3.6 Cumulative health events by system type. Health events categorized by common co-morbid conditions. The categories used were nephrology, diabetes, ophthalmology, musculoskeletal, cardiovascular and other (events not classifiable under the previous groups, such as cancer or respiratory events). Frail (n=7), Non-Frail (n=34).

3.4 DISCUSSION

The study aim was to analyze if frail vs non-frail patients with DM and CKD had different body composition, HRQoL and vitD status and to determine relationships between vitD status and these parameters in adults with DM and CKD. One of the major findings in our study was the relatively low rate of frailty of 17%. Frailty has been reported to occur in up to 70% of individuals with stage 4-5 CKD (28). Frail individuals had significantly lower lean body mass, more advanced CKD, more depression and more cumulative number of health events. There were no differences in age, gender, vitD or overall physical status in individuals with or without frailty. This has important implications for physical functionality in adults with DM and CKD as limitations in lean body mass may be a direct contributor for risk for falls/fractures. In addition, frail participants had significantly reduced HRQOL when compared to non-frail participants, particularly in domains related to physical functionality (physical functioning, role physical, bodily pain, general health, vitality). These domains explore the impact of their health on activities of daily life (ADL) such as being limited in the types of thing they can do (walking, stairs, lifting things), or activities taking more effort. Frail participants had HRQOL scores that were more than 40 points below Canadian norms for age-gender, particularly in the domains related to physical functionality (11). This is an important finding as it shows that frailty not only has negative associations with health, but it also affects the way these patients live their day to day life, their functional independence and potentially their overall mental health. It is possible that the limitations and decreased quality of life that the patients perceive could be key underlying factors on the relationship between frailty and depression.

Mansur et al conducted a study in Brazil, analyzing the relationship of frailty and HRQoL in pre-dialysis patients and they found a 22-point difference in the physical domains between frail and non-frail participants (180). The same was observed by Chang et al in a study that assessed

the relationship between frailty and HRQoL in community dwelling elderly (143). Similar to previous studies, we found an increased incidence of frailty in more advanced CKD (6, 28, 148, 149) likely secondary to chronic protein-energy wasting and inflammation (6). Although frailty has been related to other demographic factors such as age, gender and physical inactivity (172), no differences were observed between frail vs non-frail participants. While frailty was associated with depression in this study, the prevalence was significantly lower than the typical rates reported in DM (118). This may have been due to the fact that our patients were ambulatory with supports provided for ADLs by caregivers and family members. In contrast to other studies no interrelationships between frailty prevalence and vitD status was found (10). This was likely due to the fact that our population was well supplemented with vitD (>1000 IU/d) and the majority were vitD sufficient ($25(OH)D_3$ > 75 nmol/l). This reflects the active promotion of vitD supplementation done in the clinics from which these patients were recruited. However, vitD status was inversely related to overall BMI, FMI and weight. These relationships were independent of seasonal effects and/or any recent changes in body weight, suggesting that the effects of vitD status on frailty prevalence in a well-supplemented population may be difficult to determine using $25(OH)\ D_3$ as the marker of overall vitD status.

Patients with frailty had an increased number of health events compared to non-frail participants. This difference was consistent when comparing frail participants with normative data (181). In this study, frail participants had significantly higher in-patient, emergency and total events on an annual basis than provincial averages (181). Interestingly, most of the emergency and in-patient events seemed to be related to non-DM conditions/co-morbidities (e.g respiratory, CVD, cancer) and less to DM specific events. However, results from this study indicate that health care burden and health care utilization is significantly impacted in an ambulatory population of adults with DM and CKD, all of which may significantly impact HRQOL and mental health.

This study had some limitations, mainly the lack of quantitative measures of physical functionality and muscle strength. Although this study had a small sample size, a post-hoc power analysis revealed sufficient power ($\beta>0.8$) to determine differences in primary outcomes of interest by vitD status (HRQOL, mental health and body composition). Another potential limitation was the use of the Edmonton Frail Scale, which bases its definitions of frailty on self-reported elements. Other frailty assessment tools use measures like handgrip strength and walk-tests to determine the participant's physical functioning in a more objective manner. While the EFS doesn't include functional measures, it is a validated tool that has been proved to be useful in hospitalized and ambulatory patients (152, 155). These types of tools are important as they can be used to assess frailty when quantitative functioning measures are not available. Another potential limitation includes the substitution of the 'clock exercise' skill in the EFS with the 'drawing exercise' in the MMSE tool to score for risk of frailty use the EMS tool. This may limit the extent to which higher order cognitive function can be assessed with this tool modification. Hence, this adaptation may have potentially resulted in underestimations of frailty. However, it is unlikely that this was a major factor in establishing frailty prevalence because the majority of participants perform their own ADLs including driving, buying groceries and banking and had MMSE scores within the normal range (175).

3.5 CONCLUSION

In summary, the prevalence of frailty in a cohort of adults with DM and CKD was approximately 17%. Frailty was associated with reduced lean body mass and HRQOL, more advanced CKD, depression and increased health care utilization and not to overall vitD status. However, vitD status was inversely related to fat mass, BMI and weight in both groups indicating that more work examining the interplay between body composition and vitD utilization and overall

muscle functionality is warranted. Rehabilitation strategies aimed at early identification of frailty are important to ensure effective prevention in vulnerable populations. Future studies should aim to further study the intricacies of frailty in this population, using multiple validated tools to assess frailty, in order to understand this condition better and being able to develop a plan for treatment or prevention.

AKNOWLEDGMENTS

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CHAPTER 4: Vitamin D, Body Composition, Health Related Quality of Life and Mental Health in an Ambulatory Population of Adults with Diabetic Nephropathy: A 5-year Study.

4.1 INTRODUCTION

Vitamin D (VitD) is a fat-soluble vitamin whose main sources in the body are from cutaneous synthesis and dietary intake. VitD is well known for its role in bone and calcium metabolism, but with the discovery of VitD receptors (VDR) in multiple human tissues (including the skeletal muscle) new interest has emerged on both its skeletal and non-skeletal functions (1). This includes potential effects on skeletal muscle strength and functionality, overall mental health (depression, cognition) and health related quality of life (HRQoL) (9, 13, 126, 130). VitD deficiency has also been associated with an increased risk for frailty, depression and suboptimal cognitive status in the elderly, which suggests that vitD plays an important role in the overall expression of these disorders (9, 130, 159). A recent systematic review by our group indicates that short-term vitD supplementation (in excess of 1000 IU/D) may be associated with mild improvements in HRQOL in some clinical populations in the short term (<6 months), but longer term effects of vitD supplementation on these factors has not been well established (126).

VitD deficiency is highly prevalent in North America due to reduced sunlight exposure in winter months, which means that the majority of individuals living in Canada require vitD supplements in order to meet vitD needs (1, 2). Recent studies by our group and others has shown that adults with chronic kidney disease (CKD) and diabetes mellitus (DM) have increased needs for vitD due to reduced hydroxylation of vitD to its active form in renal disease and low levels of dietary intake (7, 16, 61). VitD supplementation beyond the RDA (1000-2000 IU/D) is needed to ensure patients with both DM and CKD have adequate vitD status (serum 25(OH)D concentrations >75 nmol/l) (7, 61). Several studies in adults have also shown that obese individuals are at increased risk for vitD deficiency (84). This is thought to be due to increased vitD sequestration in

the adipose tissue and/or increased vitD utilization in obesity but may also be due to low vitD intake (1, 84). This may be further exacerbated by the presence of CKD and DM, as this clinical population are often placed on dietary restrictions of VitD rich foods due to the higher carbohydrate and electrolyte loads of these foods on the kidney (70). We have recently shown that daily supplementation of 2000 IU/D_3 or 40,000 IU/month of vitamin D_3 over six months in adults with DM and CKD (stages 2-4) was associated with improved vitD status and some markers of HRQOL (mental health domain) and bone health (7). However, this RCT did not study in detail the relationships between vitD status on cognitive and mental health and/or changes in body composition that may influence overall vitD status (7). In addition, this study was a shorter-term study (over six months) and did not explore the interrelationships between vitD status on other outcomes such as HRQOL over the longer term (> 6 months).

The study objective was to analyze the interrelationships between vitD status on body composition, HRQOL, mental health and cognitive status over five years. We studied these relationships in a subset of the original cohort of adults with CKD and DM who participated in a RCT examining the impact of two different vitD supplementation strategies (2000 IU/D vs 40,000 IU/month) on bone health and HRQOL over six months (7). We hypothesized that suboptimal VitD status (serum 25(OH)D_3 <75 nmol/l) would be associated with lower lean body mass, higher fat mass, lower HRQoL, lower cognition and higher depression in adults with DM and CKD.

4.2 METHODS

This is a longitudinal study that included 50 ambulatory adults (>18 years) with type 1 (T1D) (n= 4) or type 2 (T2D) (n=46) DM and CKD stages 1-5 who previously participated in a VitD supplementation RCT (**Figure 4.1**) (7, 173).

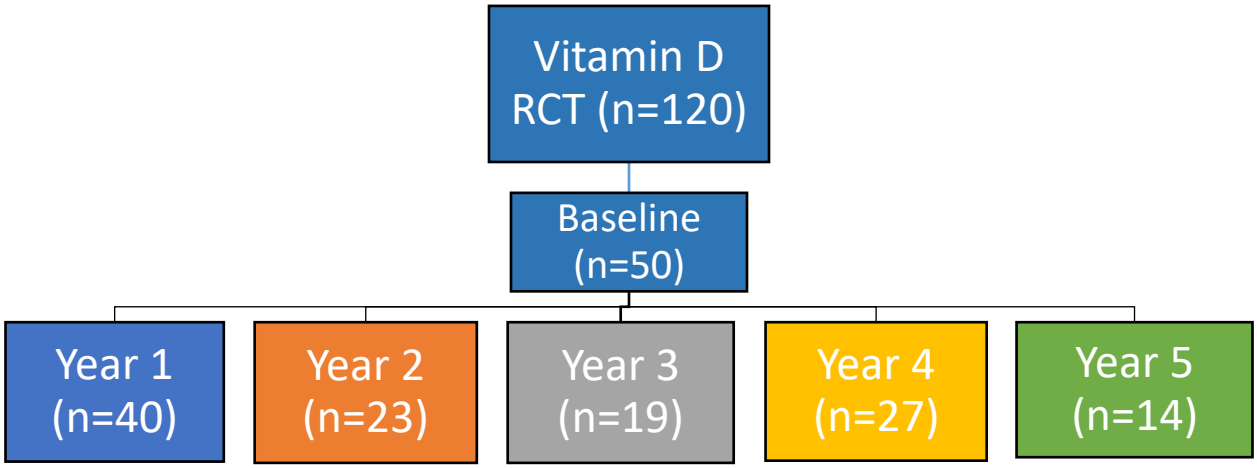


Figure 4.1 Distribution of Participants per year. Total participants in cohort =50. A total of n=13 participants assisted to all of their respective yearly follow ups up to date. A total of n=37 participants missed at least one yearly visit. All participants had baseline data (n=50). In total, n=29 participants were recruited from the Diabetic Nephropathy Prevention Clinic (DNPC), n=17 from the Renal Insufficiency Clinic (RIC) and n=4 from other clinics in Alberta Health Services. Data from the original Vitamin D RCT was considered as baseline (7).

Vitamin D RCT

Patients were recruited from Northern Alberta Renal Program (NARP) clinics at Alberta Health Services (AHS) in Edmonton, Alberta between November 2011 and December 2013. Participants were recruited from two types of clinics: Diabetic Nephropathy Prevention Clinics (DNPC) and the Renal Insufficiency Clinics (RIC). The DNPC clinics are interdisciplinary clinics lead by nursing/registered RD teams and endocrinologist. The focus of the DNPC is to prevent complications related to DM (bone health, declining renal function) by both lifestyle (including diet and micronutrient supplementation) and medical management (182). Typically, patients from these clinics have milder CKD (stage 1-3). In contrast the RIC are interdisciplinary clinics run by nephrologists where the main focus is the treatment of progressing/advanced CKD. Hence the focus is on medical management of declining renal function in a population with a variety of CKD

(in addition to DM induced) that typically demonstrate more severe expressions of renal function (CKD stage 2-5) (182).

Potential participants were approached by a member of the clinical team (e.g. RD or RN) and asked if a research team member could discuss this study with them. If verbal consent was provided, then a research team member contacted the patient, explained the study to them and determined their eligibility for participation in the RCT; if eligible and agreed by the patient, informed consent was signed, and the baseline study appointment was booked.

Inclusion criteria for the VitD RCT included: Adult (18– 80 years) patients diagnosed with diabetes (Type 1 and Type 2) and stage 1–4 CKD (Glomerular Filtration Rate (GFR) 15–89 mL/min/ 1.73 m^2). Exclusion criteria for the RCT included: 1) Patients with co-morbid conditions known to affect vitD metabolism including gastrointestinal, liver, rheumatoid or bone disorders (e.g. hyperthyroidism, untreated celiac disease, cancer, Paget's disease, sarcoidosis, malabsorption, etc.). Individuals with severe, permanent vision impairment will be excluded as this will preclude them from reading supplement labels accurately and safely. Pregnant women will be excluded as Dual-energy X-ray Absorptiometry (DXA) scans are not recommended during pregnancy. Patients weighing >136 kg will be excluded as the DXA table cannot accommodate this weight. 2) Patients on drug therapy known to interfere with vitD (e.g. oral glucocorticoids, cholestyramine, colestipol, mineral oil, Orlistat, digoxin). 3) Patients on other forms of active D metabolites (e.g. calcitriol, vitamin D2). 4) Patients with stage 5 CKD (GFR <15 mL/min/1.73 m2), receiving dialysis or on a kidney transplant list. 5) Patients with pre-existing hypercalcemia (>2.75 mmol/L), hyperphosphatemia (>2.0 mmol/L), severe secondary hyperparathyroidism (PTH >66 pmol/L), and serum 25(OH)D >200 nmol/L. 6) Patients with serum 25(OH)D <37.5 nmol/L at time of screening to control for correction of vitamin D deficiency. 7) Patients undergoing strict heavy exercise for weight control and/or those who used sunscreen lotion on a regular basis. (173)

Vitamin D Longitudinal Follow-up Study (Years 1-5 post RCT enrollment).

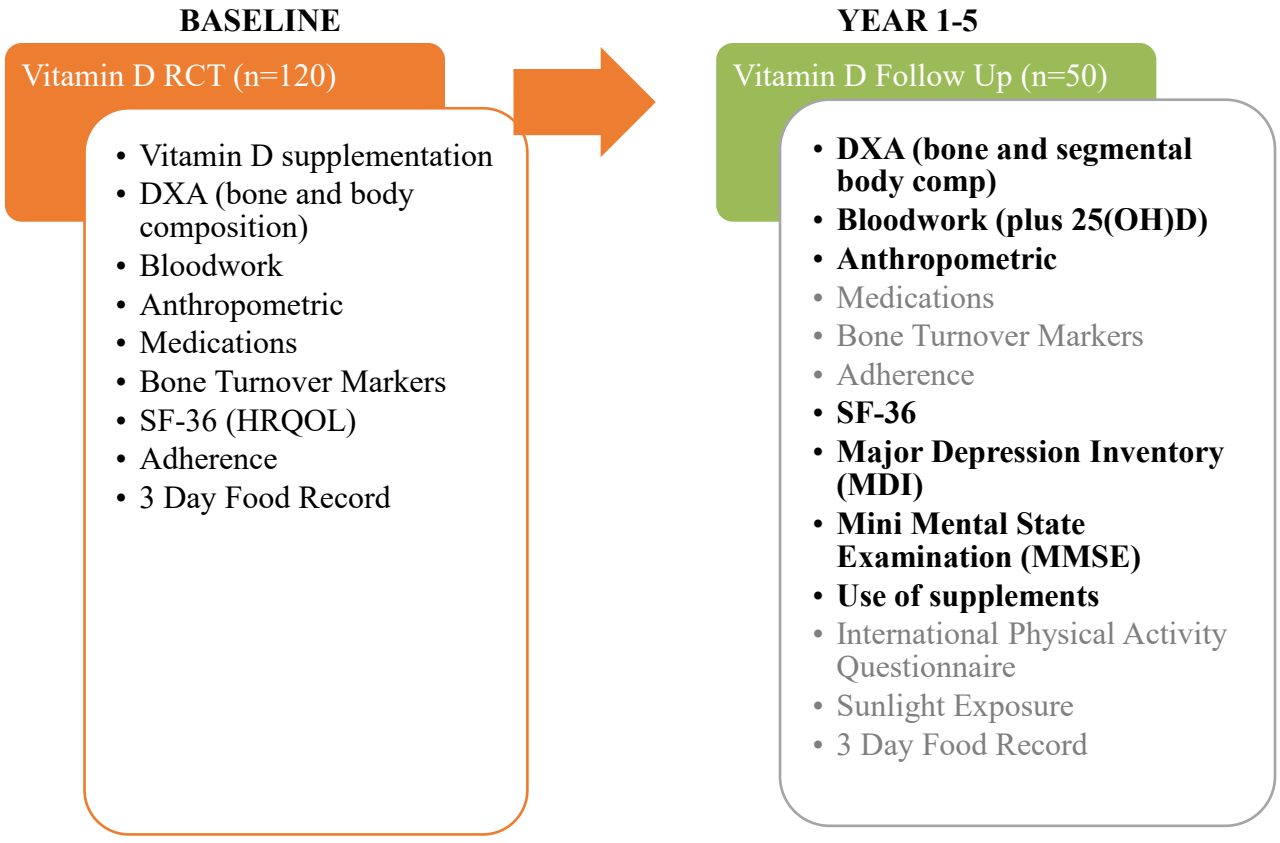
Participants were approached at the end of the RCT to discuss the follow up study, if eligible and agreed by the patient, informed consent was signed (173). Yearly follow-ups were booked by phone within a 3-month window of the yearly mark.

Inclusion criteria for the follow-up study included: 1) Ambulatory adults (>18 years) with Type 1 or Type 2 Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD). 2) Participated in a VitD supplementation RCT (7). Exclusion criteria included: 1) Participants who did not participate in the vitamin D F/U Study. 2) Pregnant women. 3) Patients with co-morbid conditions known to affect vitamin D metabolism including gastrointestinal, liver, rheumatoid or bone disorders. 4) Patients weighing >136kg. 5) Patients on drug therapy known to interfere with vitamin D metabolism.

The following additional assessments were added to the study protocol for the follow-up study: Mini-Mental State Examination (MMSE), Major Depression Inventory (MDI) and additional blood work (C- reactive protein (CRP), lipid panel). These were performed year 1- year 5. The methodology for body composition (total, segmental, Appendicular Skeletal Muscle Mass (ASMI), Fat Mass Index (FMI)), HRQoL, MMSE and MDI has been described elsewhere in this thesis (**chapter 3**). Percent change for fat mass and lean mass was calculated for each participant using the following formula: ((value year y- value year x) * 100) / value year x. Comparison of HRQoL (SF-36) to normative Canadian data was done as described previously (**chapter 3**). Ongoing data recruitment for year 5 is in progress. This thesis reports on n=50 participants with repeated measures (**Figure 4.1**). Not all participants attended each annual assessment for reasons including: lack of availability or ability to contact participant at yearly assessment, participant refusal and/or illness.

Study Design and variables assessed per year are shown in **Figure 4.2**. Primary outcomes included vitD status ($25(OH)D_3$), body composition (total/segmental, total fat/total lean, FMI, ASMI), HRQoL and mental health (cognitive, depression). Secondary variables included demographic (gender, age), disease specific (DM type/duration, CKD stage/duration), laboratory parameters (serum glucose, hemoglobin A1C, PTH, urea, creatinine, $1,25\ (OH)_2\ D_3$, calcium, magnesium, phosphorus, eGFR, lipid panel and CRP) and anthropometric (BMI, weight, height). Diet (3-day food records), bone density, sunlight exposure, and season were assessed per year, but are not reported in this thesis. Ethics approval was obtained from the Human Research Ethics Board (HREB) at the University of Alberta, Canada (Pro00049292). Informed consent was obtained prior to study enrollment.

Figure 4.2 Variables assessed per year.



Variables in bold were analyzed in this study. VitD RCT was considered baseline data. A total of 50 participants from the vitD RCT were followed longitudinally in the VitD follow up study.

Study visits were conducted in the Clinical Research Unit of the Alberta Diabetes Institute at the University of Alberta, Canada. Blood for assessment of VitD status ($25(OH)D_3$) was collected at the time of routine clinical blood work, which also included estimated glomerular filtration rate (eGFR), glycated hemoglobin A1c (A1c), random blood glucose (RBG), urea, creatinine, albumin, alkaline phosphatase (ALP), parathyroid hormone (PTH), C-reactive protein (CRP), cholesterol, triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL). Serum $25(OH)D_3$ was measured in the core laboratory of the University of Alberta Hospital according to standard methodologies (173). VitD status was classified using the following serum concentrations as cut-offs: <75 nmol/l (insufficient), ≥75 nmol/l (sufficient) (36). Serum $25(OH)D_3$ <50 nmol/l were classified as deficient (36). Demographic (height, weight, age, gender) anthropometric (height, weight, Body Mass Index (BMI) (kg/m^2)) and clinical information (medication use, comorbidities (number/type), DM type, duration of DM, CKD stage) were collected.

4.2.1 Statistical analysis

Data analysis was completed using the SAS 9.0 statistical software (SAS, Version 9.4; SAS Institute Inc., Cary, NC, USA). Data were expressed as means ± standard deviation (parametric) or medians + interquartile range (non-parametric). Non-parametric variables were log transformed prior to analysis using parametric statistics. Clinic (RIC/DNPC), year (baseline- year 5) CKD stage (1-5), depression (+/-), sex (male/female), DM type (type 1 or type 2 DM) and vitD supplementation (+/-) were treated as categorical variables. VitD was treated both as categorical ($25(OH)D_3$ <75 and ≥75 nmol/l) and as a continuous variable, in order to assess the relationship of VitD status with primary outcomes. A repeated measures analysis of variance with time was

performed between primary outcomes of interest (HRQOL, body composition and mental health) and vitD. Chi-square was used to assess the relationship between categorical variables (vitD sufficiency (+/-), sex (male/female), vitD supplementation (+, -) year (1-5). The relationship between clinics (DNPC and RIC) and primary outcomes was also assessed using a repeated measures analysis of variance. We also performed repeated measures analysis of variance with time on secondary outcomes (anthropometric, laboratory, clinical and demographic data) to determine if these changed over time while addressing the individual subject effect. Multivariate analyses were conducted to assess the relationship VitD status with Body Composition, HRQoL and Mental Health with adjustment for potential confounding variables (age, sex, DM duration/type, CKD stage). A p value ≤ 0.05 was considered significant unless otherwise specified.

4.3 RESULTS

4.3.1 Demographic, clinical, anthropometric and laboratory variables.

Demographic, clinical, anthropometric and laboratory data for the whole cohort are presented in **Table 4.1** and **Table 4.2**. Number of participants varied between years, but the outcome means remained stable over time. There were no differences in sex, weight, height, BMI, DM type (type 1 or type 2 DM), DM duration (years since diagnosis), CKD stage (1-5 stages) or VitD supplementation between years ($p>0.05$). Participants had, on average, 5 ± 2 comorbid conditions (e.g., cardiovascular disease) besides DM and CKD. The number of co-morbid conditions remained constant through the study ($p>0.05$). Year 5 PTH levels were higher compared to previous years ($p\leq0.05$). There was no effect of time on A1c, urea, creatinine, eGFR, albumin, ALP, lipid panel or vitD levels (25(OH)D and $1,25(OH)_2D_3$) ($p>0.05$). $1,25(OH)_2D_3$ concentration was positively associated with eGFR ($p\leq0.05$). Demographic, clinical, anthropometric and laboratory data for participants in RIC and DNPC are presented in **Table A.3**. Participants from RIC had lower weight, lower BMI, longer DM duration, lower eGFR, higher PTH, higher

creatinine and higher urea compared to participants from DNPC ($p \leq 0.05$). There was no difference in number of comorbidities between participants recruited from RIC and participants from DNPC ($p > 0.05$).

Participants from the follow-up study who completed all measures and attended all follow-up visits (n =13) vs those that attended some visits had lower eGFR (42 vs 51 units) (p=0.03), lower weight (86 vs 93 kg) (p=0.01), higher vitD status (100 vs 87 units) (p=0.01) and were older (69 vs 65 years) (p=0.001) than those who did not. However, no other significant differences in demographic, anthropometric or other variables (HRQOL, MMSE or depressions scores, laboratory or number of co-morbidities) were observed, $p > 0.05$).

The prevalence of vitD supplementation was 74% (n=33) in baseline, 84% (n=32) year 1, 82% (n=19) year 2, 63% (n=12) year 3, 88% (n=24) ear 4 and 78% (n=11) year 5, respectively. The mean levels of vitD supplementation ranged between a mean ± SD of 1420 ± 640 in baseline and 1720 ± 500 IU/day in year 5. The distribution of vitD supplementation doses per year is represented in a box and whisker plot shown in **Figure A.4**. The prevalence of vitD insufficiency (<75nmol/l) was of 23% (n=9) in year 1, 26% (n=6) in year 2, 31% (n=6) in year 3, 22% (n=6) in year 4 and 29% (n=4) in year 5. VitD supplementation was associated with vitD levels >75 nmol/l ($p < 0.0001$). Participants with vitD levels >75 nmol/l had higher weight (p=0.02) and BMI (p=0.0002) than those with levels <75 nmol/l. VitD status was not associated with sex, age, DM type, DM duration, CKD stage or laboratory variables ($p > 0.05$).

Participants from the Diabetic Nephropathy Prevention Clinic (DNPC) had a trend towards higher vitD concentration (91 ± 18 vs 76 ± 41 nmol/l) than patients from the Renal Insufficiency Clinic (p=0.08). This was likely secondary to the lower proportion of individuals that used (43%) vitD supplements in the RIC vs 93% in DNPC patients. Of those that supplemented with vitD, there was no difference in levels of vitD supplementation (IU/day) between RIC and DNPC

patients (1170 vs 1440) ($p>0.05$). Participants recruited from RIC had, in average, more inpatient (1.5 vs 0.6) ($p=0.03$) and emergency (4.5 vs 2.1) ($p=0.04$) health events since baseline than those recruited from DNPC (**Figure A.3**).

Table 4.1 Demographic, clinical and anthropometric data per year

Variable	**Baseline** (n=50)	**Year 1** (n=38)	**Year 2** (n=23)	**Year 3** (n=19)	**Year 4** (n=27)	**Year 5** (n=14)	p value
Age (years)	65 (60-69)	66 (62-70)	68 (62-72)	69 (63-78)	69 (65-74)	73 (64-74)	-
Male, n (%)	34 (68%)	28 (74%)	15 (65%)	12 (63%)	17 (62%)	9 (64%)	-
DM Type 2, n (%)	46 (92%)	34 (89%)	19 (82%)	17 (89%)	24 (88%)	13 (92%)	*p=0.91*
DM Duration (years)	12 (9-22)	13 (11-21)	19 (11-31)	16 (10-27)	16 (12-26)	20 (16-34)	-
Weight (kg)	94 ±1 9 (49 - 136)	92 ± 20 (51 - 131)	87 ± 21 (54 - 134)	87 ± 16 (61 - 116)	91 (78-98)	90 ± 19 (52 - 117)	*p= 0.52*
Height (m)	1.68 ± .09 (1.42-1.87)	1.69 ± .09 (1.42-1.85)	1.67 ± .09 (1.42-1.83)	1.68 ± 0.7 (1.55-1.82)	1.67 ± 0.9 (1.46-1.85)	1.71 (1.58-1.76)	*p=0.97*
BMI (kg/m^2)	33 ± 6 (17 - 44)	32 ± 6 (20 - 43)	31 (25-36)	30 (26-34)	31 ± 6 (21 - 42)	32 ± 7 (20-42)	*p= 0.67*
CKD Stage 3-5, n (%)	27 (54%)	34 (89%)	19 (82%)	17 (89%)	17 (62%)	8 (57%)	*p=0.11*
Vitamin D supplementation, n (%)	37 (74%)	32 (84%)	19 (82%)	12 (63%)	24 (88%)	11 (78%)	*p=0.42*
Vitamin D supplementation (IU)	1400 (1000-2000)	1000 (1000-2000)	1000 (1000-2000)	2000 (1000-2000)	1500 (1000-2000)	2000 (1000-2000)	*p=0.91*

* Data expressed as mean ± standard deviation(min-max) or median ± interquartile range. N= number, DM= Diabetes Mellitus, kg= kilogram, m= meters, CKD= chronic kidney disease, IU= international units. Results from a repeated measures analysis of variance. There was missing data for some individual subjects during the 5-year period which resulted in no significant differences over the five-year study period. Results from a repeated measures analysis of variance or chi-square analysis (year, dmtype, vitD supplementation and CKD stage) between years. A p value ≤ 0.05 was considered significant.

Table 4.2 Laboratory values per year

Variable	Baseline (n=50)	Year 1 (n=38)	Year 2 (n=23)	Year 3 (n=19)	Year 4 (n=27)	Year 5 (n=14)	Reference Range	p value
HbA1c (%)	7.2 (6.7-8.2)	7.3 (6.4-7.9)	7.6 (6.9-8.4)	7.3 (7.0-8.7)	7.1 (6.7-7.9)	7.1 (5.8-7.7)	4.3 - 6.1	*p=0.40*
Random Blood Glucose (mmol/L)	7.4 ± 2.5 (1.7 - 14.4)	5.9 (5.2-9.0)	8.0 (5.0-10.1)	10.0 (7.2-15.5)	8.2 (6.9-11.1)	8.4 (6.9-10.5)	3.3 - 11	***p= ≤0.05***
Creatinine (umol/L)	106 (80-197)	116 (80-231)	181 (113-269)	160 (98-135)	121 (81-210)	150 (71-229)	50 - 105	*p=0.17*
Urea (mmol/L)	7.5 (5.6-15.2)	9.1 (5.4-18.1)	13.1 (7.2-18.8)	13.0 (6.2-19)	8.3 (5.9-19.6)	8.9 (8.2-21)	2.5 - 8.0	*p=0.49*
eGFR (ml/min/1.72m^2)	50 ± 24 (15 - 101)	49 (24-69)	25 (18-54)	30 (17-57)	47 (22-83)	46 (20-75	>59.0	*p=-0.51*
Albumin (g/L)	42 (40-44)	41 ± 3 (32-49)	41 ± 3 (35 - 47)	41 ± 3 (35 - 45)	41 ± 3 (36 - 45)	41 (39-44)	35 - 50	*p=0.76*
Parathyroid Hormone (pmol/L)	4.9 (2.5-8.6)	4.5 (3.4-7.6)	8.4 (3.6-13.2)	6.1 (4.1-15.5)	4.9 (2.8-7.1)	8.9 (3.8-33.3)	1.4 - 6.8	***p= ≤0.05***
Alkaline Phosphatase (U/L)	78 ± 25 (12 -154)	74 (58-85)	83 ± 25 (37 -136)	83 ± 26 (41 - 137)	80 (56-106)	82 (69-104)	30 - 130	*p=0.38*
Cholesterol (mmol/L)	.	3.7 ± 1.1 (2.1-6.0)	3.5 (2.8-4.5)	3.8 ± 0.9 (2.3 - 6.0)	3.3 (2.9-4.2)	2.9 (2.7-3.0)	<6.20	*p=0.48*
Triglyceride (mmol/L)	.	1.7 (1.1-2.3)	1.7 (1.5-3.0)	1.7 (1.0-3.5)	2.3 (1.2-3.0)	1.9 (1.0-3.3)	<1.70	*p=0.87*
HDL (mmol/L)	.	1.07 (0.99-1.23)	1.1 ± 0.2 (0.6 -1.7)	0.97 (0.79-1.15)	0.97 (0.82-1.29)	0.99 (0.78-1.13)	>0.90	*p=0.97*
LDL (mmol/L)	.	1.4 (1.1-2.2)	1.2 (0.8-2.1)	1.4 (1.2-2.0)	1.4 (0.9-1.6)	1.0 (0.7-1.4)	<3.4	*p=0.33*
CRP	.	1.2 (0.6-2.2)	2.1 (0.9-4.9)	2.1 (1.2-5.0)	2.3 (1.0-6.3)	4.5 (1.1-12.3)	< 8.0	*p=0.82*
25(OH)D_3 (nmol/l)	86 ± 28 (21 -169)	94 ± 26 (41-159)	101 ± 40 (42 -194)	91 ± 28 (44 - 138)	100 (74-128)	86 (64-115)	>50	*p=0.48*
1,25 $(OH)_2$ D_3 (pmol/L)	84 ± 33 (23 -159)	81 (61-112)	88 (71-104)	60 (55-96)	89 (63-101)	78 (46-98)	43-168	*p=0.50*

* Data expressed as mean ± standard deviation (min-max) or median ± interquartile range. eGFR= estimated glomerular filtration rate, HDL= High Density Lipoprotein, LDL= Low Density Lipoprotein. Results from a repeated measures analysis of variance. Results from a repeated measures analysis of variance between years. A p value ≤ 0.05 was considered significant.

4.3.2 Longitudinal Body Composition

The data for total and segmental body composition for males and females is presented in **Table 4.3** and **Table 4.4** respectively. Trends in body composition as well as box and whisker plots for the distribution of body composition for males are presented in **Figure 4.3**, **Figure A.5**, **Figure A.6** and **Figure A.7** respectively. Trends in body composition as well as box and whisker plots for the distribution of body composition for females are presented in **Figure 4.4**, **Figure A.8**, **Figure A.9** and **Figure A.10** respectively. There was no effect of time on body composition (total and segmental) ($p>0.001$). The percent of change in body composition per year is presented in **Figure 4.5**. There was no effect of time on percent of change of total body composition ($p>0.05$), apart from percent of lean mass ($p=0.03$).

VitD levels >75 nmol/l were associated with increased percent of fat mass (38% vs 33%) ($p=0.003$), increased total kg of fat (34.3 kg vs 26.6 kg), increased FMI (12.2 vs 9.2 kg/m^2) ($p<0.0001$), lower percent of fat free mass (62% vs 68%) ($p=0.002$) and increased ratio of fat mass/lean mass (0.6 vs 0.5) ($p=0.001$) compared with levels <75 nmol/l. Participants with VitD levels >75 nmol/l had a higher percent of fat and lower percent of lean mass in all the body segments (arms, legs, trunk, android and gynoid) ($p\leq0.05$).

Table 4.3 Body composition for Males per year

Variable	Baseline (n= 29)	Year 1 (n=28)	Year 2 (n=23)	Year 3 (n=19)	Year 4 (n=27)	Year 5 (n=14)	p-value
ASMI (kg/m^2)	8.7 (8.1-9.0)	8.3 ± 1.0	8.2 (7.5-8.8)	8.1 ± 1.1	8.1 (7.2-8.6)	7.0 (6.6-8.3)	*p=0.15*
FMI (kg/m^2)	10.7 ± 3.6	10.4 ± 3.3	11.9 (6.5-14.7)	9.3 (7.0-13.4)	9.9 (7.0-12.1)	8.0 (5.1-13.3)	*p=0.92*
Weight (kg)	97.7 ± 18.9	95 ± 19	92.1 ± 21	90.8 ± 17.1	87.1 ± 17.4	84.5 ± 18.3	*p=0.42*
Percent of Fat							
Arms (%)	29 ± 9	29 ± 8	29 ± 9	30 ± 8	28 ± 7	30 (16-36)	*p=0.99*
Legs (%)	27 ± 6	27 ± 6	28 ± 8	27 ± 7	28 ± 7	26 (21 - 33)	*p=0.99*

Trunk (%)	40 (36-44)	41 (37-45)	43 (33-46)	39 (35-43)	39 ± 6	35 (29-47)	*p=0.92*
Android (%)	45 ± 7	45 (41-49)	46 (39-54)	44 ± 6	43 ± 6	43 (33-48)	*p=0.91*
Gynoid (%)	33 ± 5	32 (28-36)	35 (26-38)	33 (28-38)	33 ± 6	31 (30-39)	*p=0.98*
Total (%)	34 ± 6	34 ± 6	36 (28-42)	32 (29-40)	33 ± 6	31 (26-45)	*p=0.99*
Fat Mass							
Arms (g)	2498 ± 912	2427 ± 846	2445 ± 963	2511 (1837-3332)	2338 ±757	2144 ± 1117	*p=0.94*
Legs (g)	7167 (5248-9830)	6354 (4627-9600)	6328 (4189-10418)	6329 (5019-9171)	6252 (5319-8654)	5856 (4152-8344)	*p=0.99*
Trunk (g)	21159 ± 7156	20864 ± 7019	22758 (13229-28557)	19277 (14119-27052)	19526 (12965-24372)	15187 (9611-27430)	*p=0.79*
Android (g)	4214 ± 1571	4170 ± 1503	4352 ± 1844	3724 (2798-5336)	3802 (2395-5077)	2952 (2134-5328)	*p=0.71*
Gynoid (g)	4268 (3405-5551)	4231 (3212-5255)	2386 (2805-5776)	3966 (3207-5433)	3863 (3220-5269)	4714 (3196-7231)	*p=0.96*
Total (g)	31962 ± 10406	31453 ± 10373	31938 ± 12317	27881 (21521-41226)	29870 (20440-36752)	24139 (14450-41239)	*p=0.88*
Percent Lean Body Mass							
Arms (%)	70 ± 9	71 ± 8	70 ± 9	70 ± 8	72 ± 7	71 ± 11	*p=0.99*
Legs (%)	73 (67-76)	73 (67-77)	69 (66-81)	71 (67-79)	71 ± 7	73 (66-78)	*p=0.99*
Trunk (%)	59 (55-63)	58 (54-63)	56 (53-66)	60 (56-64)	61 ± 6	64 (52-70)	*p=0.92*
Android (%)	55 ± 7	54 (50-58)	53 (45-60)	55 ± 6	56 ± 6	56 (51-66)	*p=0.91*
Gynoid (%)	66 ± 5	67 ± 6	65 (61-73)	66 (62-71)	65 (61-71)	68 (60-69)	*p=0.98*
Total (%)	65 ± 6	65 (59-69)	63 (57-71)	67 (59-70)	66 ± 6	66 ± 10	*p=0.99*
Lean Body Mass							
Arms (g)	5976 ± 1173	5910 ± 1049	5790 ± 1060	5951 ± 928	5934 (4872-6909)	5325 (5157-5472)	*p=0.63*
Legs (g)	19321 ± 3449	19042 (16913-20741)	18127 ± 3589	18219 ± 3027	18585 (16099-19720)	16529 ± 2398	*p=0.35*
Trunk (g)	30407 ± 5575	29697 (26379-32639)	28823 ± 5689	28490 ± 4146	28978 (25938-31430)	27299 ± 5509	*p=0.66*
Android (g)	5010 ± 1111	4985	4770 ± 1094	4765 ± 915	4731 ± 1070	4229 ± 940	*p=0.61*

		(4132-5712)					
Gynoid (g)	8809 ± 1516	8717 ± 1587	8413 ± 1705	8372 (7772-9214)	8374 (7621-8894)	7859 ± 1574	*p=0.54*
Total (g)	59457 ± 9352	58817 ± 10103	56403 ± 9799	56412 ± 7467	58740 (51198-61333)	52503 ± 9862	*p=0.47*
Total Mass							
Arms (g)	8215 (7926-8842)	8432 (7755-8841)	8388 (7740-9084)	8707 (8008-9142)	8229 (7955-9618)	8145 (5527-8342)	*p=0.44*
Legs (g)	26805 ± 5458	26443 ± 5698	24903 (20992-32434)	25549 ± 5656	24930 ± 4534	24093 (20932-27209)	*p=0.67*
Trunk (g)	49469 (43334-61478)	50920 ± 11766	50006 ± 13065	48729 ± 9780	47081 ± 10087	45089 ± 11083	*p=0.68*
Android (g)	9225 ± 2383	8928 (7118-11373)	9366 (6651-11408)	8590 (7223-10964)	8489 ± 2130	7589 ± 2265	*p=0.62*
Gynoid (g)	13315 ± 2584	13100 ± 2736	12632 (10415-15419)	12804 ± 2791	12638 (10488-14087)	11473 (10221-14612)	*p=0.83*
Total (g)	91420 ± 17217	90270 ± 17798	88341 ± 20236	87347 ± 15775	87698 (76271-98202)	78060 (74214-90239)	*p=0.62*

Data expressed as mean ± standard deviation or median ± interquartile range. ASMI= Appendicular Skeletal Muscle Mass Index, FMI= Fat Mass Index, Kg= kilogram, m= meter, g= gram. Appendicular Skeletal mas was calculated using the formula: (lean mass from arms (kg) + lean mass from legs (kg)) / height $(m)^2$. Fat Mass Index was calculated using the formula: Total fat mass (kg) /height $(m)^2$. Results from a repeated measures analysis of variance between years. A p value ≤ 0.001 was considered significant.

Table 4.4 Segmental body composition for Females per year

Variable	Baseline (n=16)	Year 1 (n=10)	Year 2 (n=8)	Year 3 (n=7)	Year 4 (n=10)	Year 5 (n=5)	p-value
ASMI (kg/m^2)	7.1 ± 0.8	7.5 (7.0-7.9)	6.9 ± 0.6	7.2 (6.5-7.2)	7.1 (6.7-7.9)	7.0 (6.5-7.5)	*p=0.90*
FMI (kg/m^2)	12.2 ± 4.7	13.3 ± 3.7	11.4 (7.9-14.5)	15.0 (9.3-16.6)	14.1 ± 4.6	16.2 (12.7-17.7)	*p=0.65*
Weight (kg)	83.6 ± 20.9	82.4 ± 15.0	75.4 ± 15.4	78.8 ± 12.7	84 ± 19.5	92.3 ± 18.4	*p=0.64*
Percent of Fat							
Arms (%)	41 (35-46)	43 ± 8	34 (33-48)	48 (37-50)	45 ± 8	50 (40-56)	*p=0.29*

Legs (%)	38 ± 13	40 ±11	28 (20-45)	47 (27-53)	46 (31-53)	51 (37-54)	*p=0.65*
Trunk (%)	44 (40-45)	45 (43-50)	44 (36-47)	48 (41-50)	45 (38-51)	46 (42-50)	*p=0.77*
Android (%)	48 (45-53)	50 (48-54)	46 (40-53)	50 (47-56)	48 ± 8	52 (48-55)	*p=0.79*
Gynoid (%)	43 ± 10	44 ± 9	35 (29-47)	49 (36-55)	48 (37-55)	53 (40-54)	*p=0.66*
Total (%)	42 (34-43)	42 (39-49)	36 (31-46)	48 (35-49)	43 (39-50)	49 (39-51)	*p=0.56*
Fat Mass							
Arms (g)	3508 ± 1693	3524 ± 945	2786 ± 1304	3541 ± 998	4001 (2504-4643)	3722 ±1260	*p=0.83*
Legs (g)	10048 ± 5343	10782 (6920-12247)	6203 (3269-11095)	11397 (5375-15269)	11573 ± 5652	14018 (10410-19518)	*p=0.51*
Trunk (g)	18771 ± 8090	21479 (15795-23243)	16194 ± 7197	20324 (13639-24266)	20002 ± 7778	22182 ± 6358	*p=0.78*
Android (g)	3720 ± 1784	4547 (2885-5096)	3446 ± 1656	3919 ± 1216	4050 ± 1729	4597 ± 1529	*p=0.87*
Gynoid (g)	6030 (3406-8078)	5850 (4680-6244)	4137 (2550-5681)	5896 (3672-7724)	6030 ± 2422	7517 (5262-8479)	*p=0.62*
Total (g)	33165± 14290	35415 (33547-39667)	29332 (19157-37725)	37604 (25691-43287)	36080 ± 13280	42536 (36766-44262)	*p=0.68*
Percent Lean Body Mass							
Arms (%)	58 (53-64)	56 ± 8	63 (51-65)	52 (49-62)	52 (48-62)	49 (44-59)	*p=0.38*
Legs (%)	61 ± 13.2	59 ± 11	71 (54-79)	52 (46-72)	53 (46-68)	48 (45-63)	*p=0.65*
Trunk (%)	55 (52-59)	54 (49-56)	55 (52-63)	51 (49-58)	55 ± 7	53 (49-57)	*p=0.78*
Android (%)	51 (46-55)	49 (46-51)	53 (46-59)	49 (44-52)	51 ± 8	47 (44-51)	*p=0.79*
Gynoid (%)	56 (49-65)	55 ± 9	66 (52-70)	50 (44-63)	51 (44-62)	46 (46-59)	*p=0.57*
Total (%)	57 (57-65)	57 (50-60)	62 (54-69)	51 (50-64)	56 ± 8	50 (48-60)	*p=0.63*
Lean Body Mass							
Arms (g)	4710 ± 841	4359 (3992-5135)	4132 (3724-4654)	4259 ± 632	3823 (3713-4535)	3807 (3720-4055)	*p=0.23*
Legs (g)	14274 ± 2415	14040 (12605-15294)	13079 (12057-15196)	13047 (12553-14408)	13848 (12474-16008)	16018 (13297-16401)	*p=0.81*
Trunk (g)	23878 ± 5320	23969 ± 5276	23015 (22537-23299)	22435 (19793-25752)	22821 (20184-29022)	24655 (21990-30819)	*p=0.90*

Android (g)	3852 ± 977	4002 ± 939	3564 ± 722	3772 (3340-4376)	4066 ± 1153	4014 (3363-5279)	*p=0.79*
Gynoid (g)	6370 (5513-7661)	6614 ± 1166	6226 (5474-6836)	6406 (5913-6485)	6648 ± 1195	6419 (6402-7714)	*p=0.90*
Total (g)	45957 ± 8398	45379 ± 8554	43224 (42184-45999)	44084 (39378-45836)	44722 ± 7809	4437 (42875-54185)	*p=0.91*
Total Mass							
Arms (g)	8219 ± 2331	7971 (7540-8339)	6514 (5553-8677)	7863 (6536-9113)	7917 (5904-9073)	7588 ± 1279	*p=0.71*
Legs (g)	24323 ± 6356	23938 ± 4828	21341 ± 5457	23333 ± 4732	25529 ± 6734	27937 (27315-35536)	*p=0.51*
Trunk (g)	42650 ± 12564	43720 ± 9566	38575 (29601-46164)	41827 ± 8715	43909 ± 11964	44631 (41201-53574)	*p=0.81*
Android (g)	7572 ± 2670	8060 ± 2119	6813 ± 2162	11809 (10078-14209)	8116 ± 2657	8222 (6920-10330)	*p=0.74*
Gynoid (g)	12067 ± 3082	12089 ± 2092	10790 ± 2620	11911 ± 2021	12678 ± 3120	13821 ± 3447	*p=0.60*
Total (g)	79122± 20192	79941 (64177-88956)	70175 (57629-86967)	76982 (64891-87372)	80802 ± 18507	87810 ± 17528	*p=0.64*

Data expressed as mean ± standard deviation or median ± interquartile range. ASMI= Appendicular Skeletal Muscle Mass Index, FMI= Fat Mass Index, Kg= kilogram, m= meter, g= gram. Appendicular Skeletal mas was calculated using the formula: (lean mass from arms (kg) + lean mass from legs (kg)) / height $(m)^2$. Fat Mass Index was calculated using the formula: Total fat mass (kg) /height $(m)^2$. Results from a repeated measures analysis of variance between years. A p value ≤ 0.001 was considered significant.

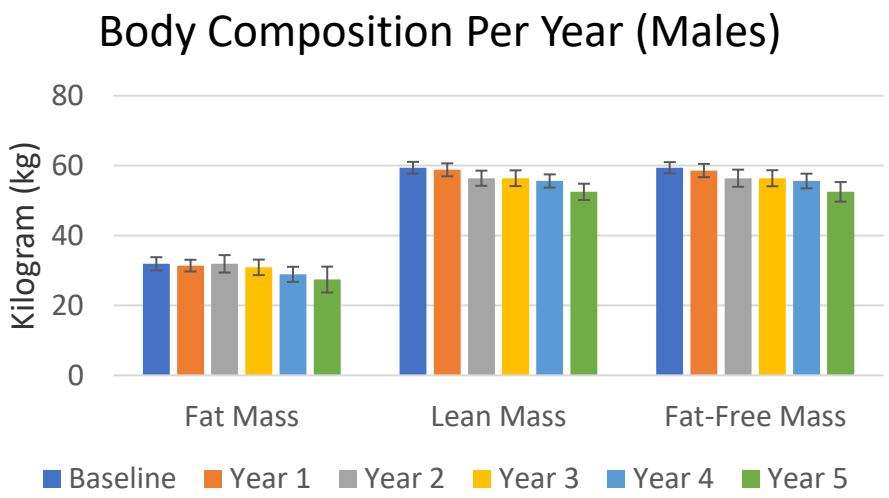


Figure 4.3 Body composition per year for males. Results from a repeated analysis of variance with time. A p value ≤0.05 was considered significant.

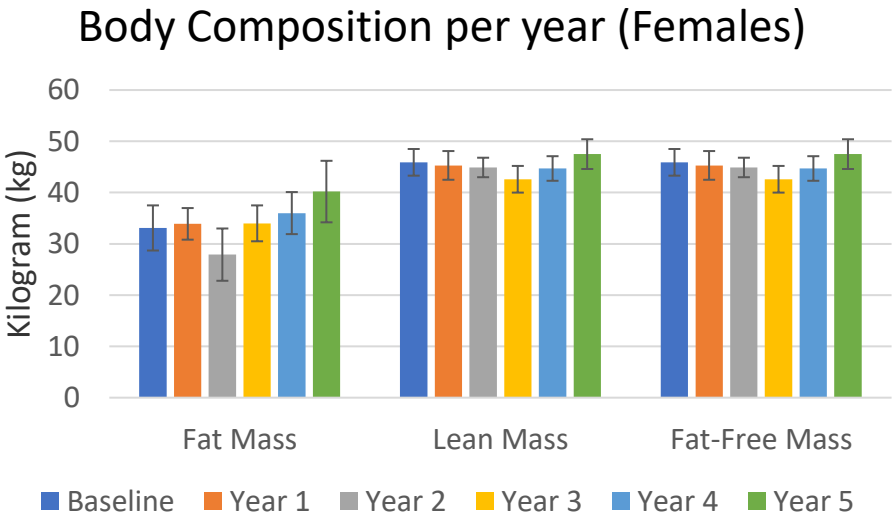


Figure 4.4 Body composition per year for females. Results from a repeated measures analysis of variance with time. A p value ≤0.05 was considered significant.

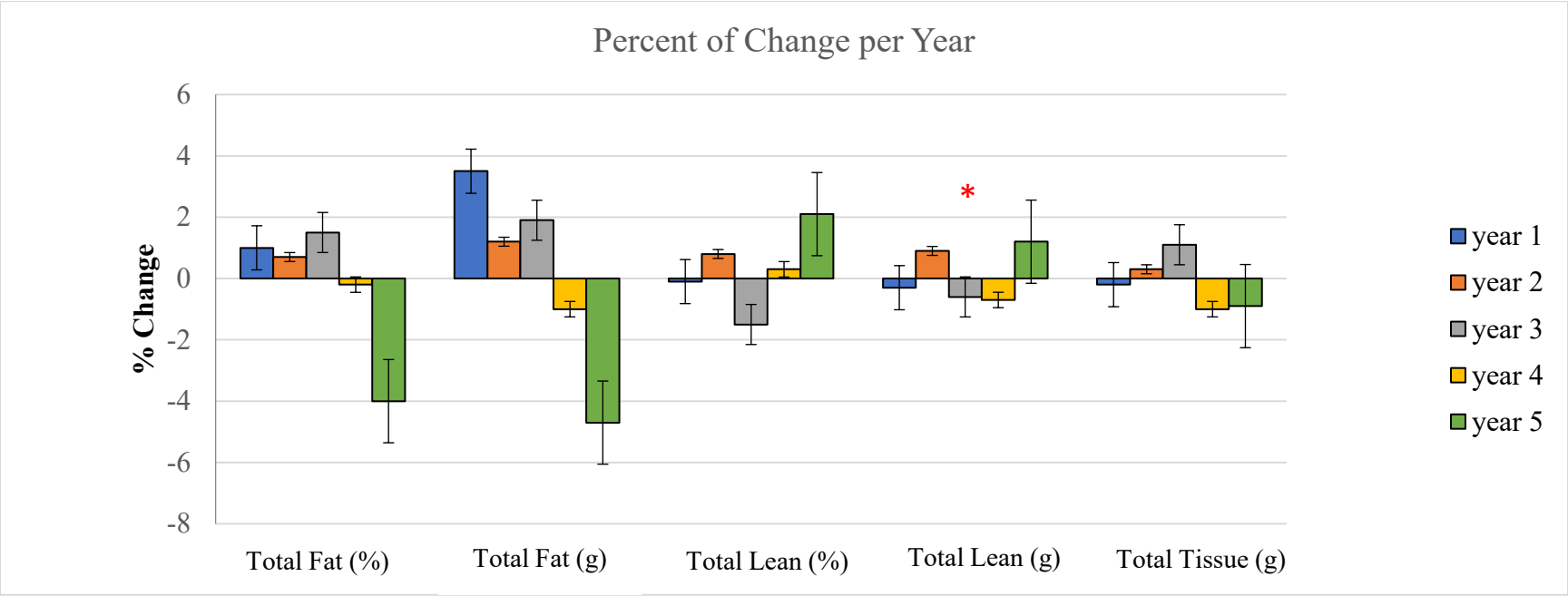


Figure 4.5 Yearly percent change in body composition (year 1-5). Data are represented as means ± standard error. There was a statistical difference in the percent change of lean body mass between years ($p<0.05$). Percent of change was calculated for total percent of fat, total grams of fat, total percent of lean mass, total grams of lean mass and total grams of tissue per individual. Percent of change was calculated using the formula ((value year y- value year x) * 100) / value year x. Results from a repeated measures analysis of variance between years. Values with an asterisk are significantly different at $p\leq0.05$.

4.3.3 Longitudinal trends in HRQoL, cognition and depression

Data for HRQoL is presented in **Figure 4.6**. There was no effect of time on any domain of HRQoL (SF-36 scores) ($p>0.05$). VitD >75 nmol/l was associated with higher scores in the Vitality domain (56 ± 18 vs 48 ± 20) ($p=0.02$) and the Mental Component Summary (MCS) (55 ± 9 vs 51 ± 10) ($p=0.01$) of the SF-36. Participants scored more than 5 points below the Canadian normative data for age and gender in the physical functioning, role physical, bodily pain, general health and vitality domains (11). A 5-point difference is considered

clinically significant. Participants from RIC had lowers scores in the General Health Perception (43 vs 60) (p=0.01) and Social Functioning (77 vs 90) (p=0.02) domains of the SF-36 compared to participants from DNPC. However, no other differences were noted between clinics between clinics in other HRQOL domains (p>0.05).

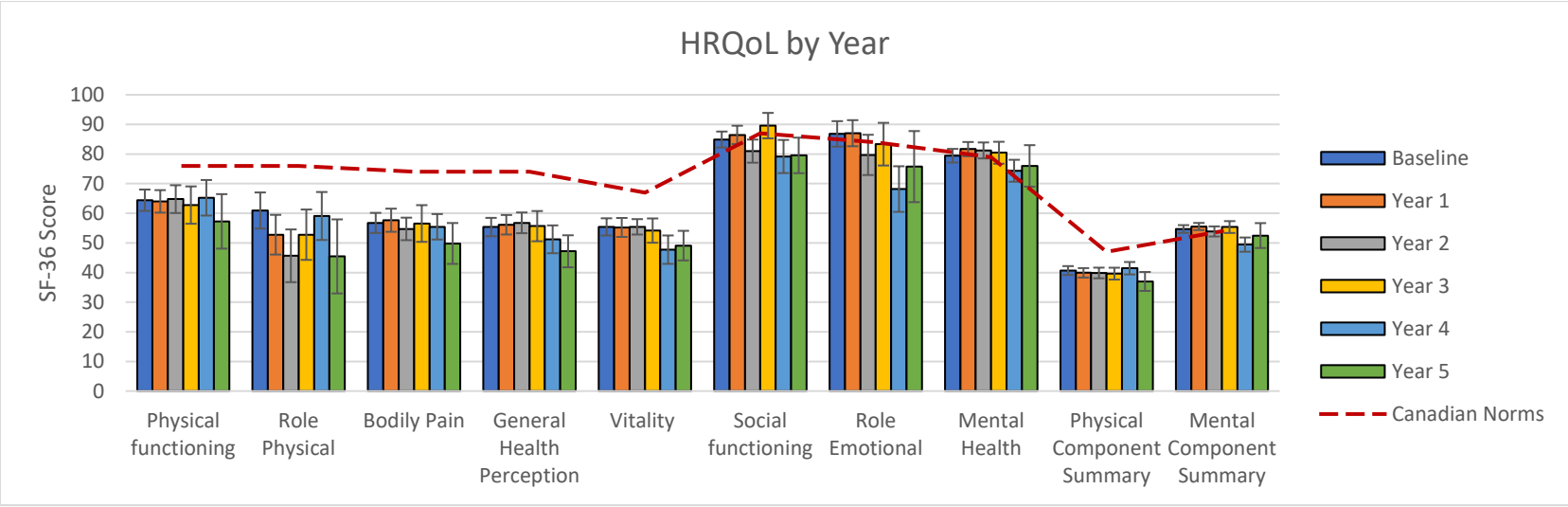


Figure 4.6 HRQoL per year (SF-36 Scores). HRQoL data for all the domains and component summaries of the SF-36 per year (year 1-5). Domains include Physical functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, Role Emotional, and Mental Health. Component summaries included Physical Component Summary and Mental Component summary. Columns for each individual year are represented in different colors. An orange dashed line represents the average Canadian normative values for age and gender. There was no effect of time on any of the domains of the SF-36. Physical functioning, Role Physical, Bodily Pain, General Health and Vitality scores were at least 5 points lower than Canadian normative values. Results from a repeated measures analysis of variance between years and t-test between normative values and participant scores. Values reflect mean ± standard error. A p value ≤0.05 was considered significant.

Data for MMSE is presented in **Figure 4.7**. Box and whisker plots for MMSE scores per year are shown in **Figure A.11**. All participants scored >24 points on the MMSE, meaning that all participants had cognitive scores within the reference range for age and gender (175). There was no effect of time on MMSE scores ($p>0.05$). Participants with vitD levels >75 nmol/l had higher MMSE scores than those with levels <75 nmol/l (28 ± 1 vs 27 ± 1 respectively) ($p=0.03$). Participants from DNPC had higher MMSE scores compared to participants from RIC (28 ± 1 vs 27 ± 1 respectively) ($p=0.04$). While the MMSE scores were statistically significant (between sufficient and insufficient vitD levels as well as between clinics), the difference in one point in MSSE is not clinically relevant as both scores are indicative of 'normal' cognitive status (175).

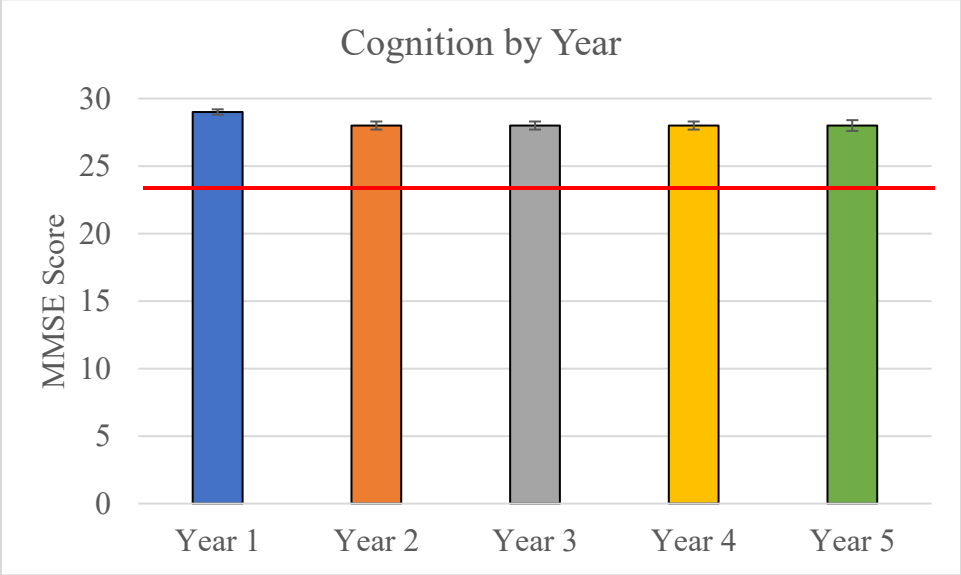


Figure 4.7 Cognition per Year (MMSE Scores). Yearly data for Mini Mental State Examination (MMSE) scores (year 1-5). Values reflect mean ± standard error. Red line represents a score of 24. Scores above 24 points reflect normal cognition. The mean values for each year were above 24 points. Results from a repeated measures analysis of variance between years. There was no difference in MMSE scores between years.

Data for MDI presented in **Figure 4.8** and **Figure 4.9**. Box and whisker plots for MDI scores per year are presented in **Figure A.12**. There was no effect of time on MDI scores, nor in the prevalence of depression. Participants with levels >75 nmol/l had lower MDI scores than

participants with levels <75 nmol/l (8 ± 8 vs 12 ± 9 respectively) (p=0.04). Female participants had higher MDI scores than male participants (11.3 ± 8.8 vs 7.8 ± 7.2) (p=0.04). MDI scores were negatively associated with age (p=0.01). Participants from RIC had higher MDI scores than participants from DNPC (8 ± 7 vs 11 ± 10) (p=0.05).

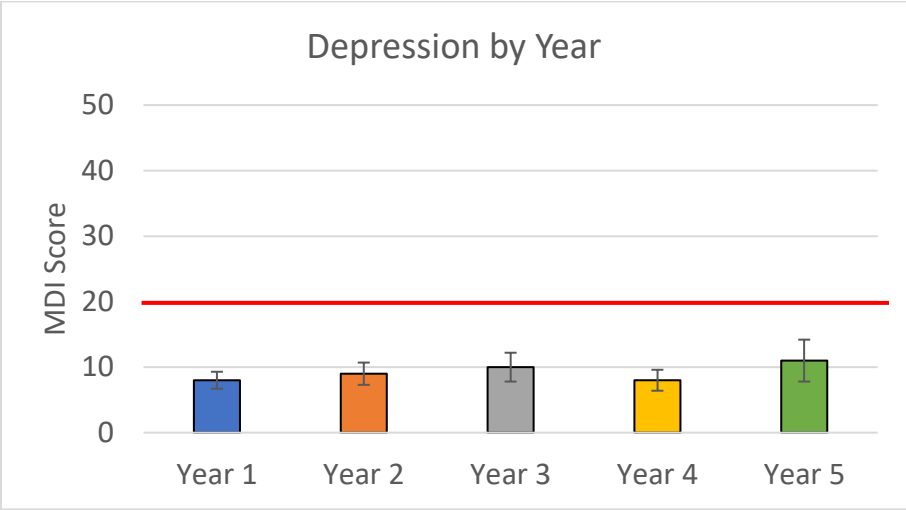


Figure 4.8 Depression per year (MDI scores). Yearly data for year 1-5. Values reflect mean ± standard error. Red line represents a score of 20. **Scores above 20 points reflect depression.** Results from a repeated measures analysis of variance between years. There was no difference in MDI scores between years. A p value ≤ 0.05 was considered significant.

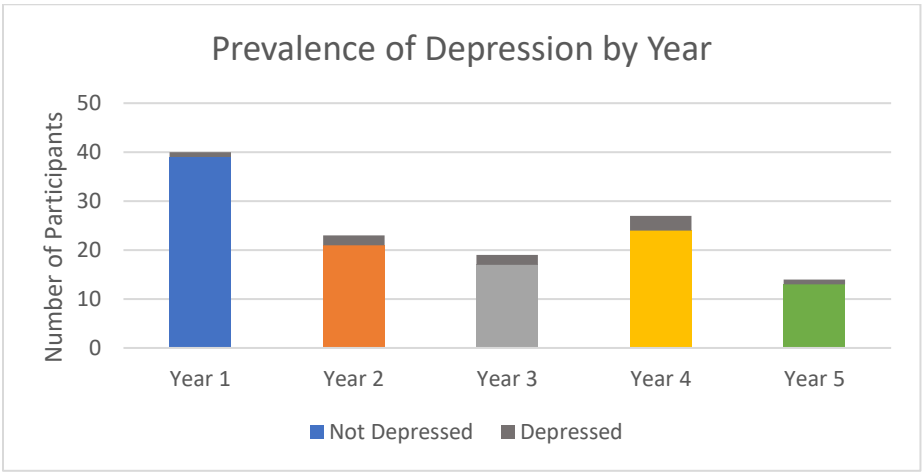


Figure 4.9 Prevalence of depression by year. **A score >20 in the MDI was considered to indicate the presence of depression.** The column represents the total number of participants in each year. The grey cap on each column represents the number of participants with depression on each year. The prevalence of depression per year was of (1/38) in year 1, (2/23) in year 2, (2/19) in year 3, (3/27) in year 4 and (1/14) in year 5. There was no difference in prevalence of depression between years (chi-square analysis) (p=0.89).

4.4 DISCUSSION

The objective of this study was to analyze the effect of time and vitD status on body composition, HRQOL, mental health and cognitive status over five years in a cohort of adults with CKD and DM. To our knowledge, there are no longitudinal studies that have examined the effects of vitD, DM and CKD in HRQoL over a period of five years. In this cohort, there was no significant effect over time on body composition (total or segmental, lean mass or fat mass), HRQoL, cognition or mental health. This is an important finding, as elderly participants, especially those with conditions like DM and CKD are reported to have declines in these parameters as they age (9, 183). The typical decline of lean mass per year after age 60 in both males and females ranges between 1.5-3% per year (147), but fat mass may remain stable or increase (183). Interestingly, the participants in this cohort overall experienced stable lean body mass with only 0.25% reductions in lean body mass and a 1.8% increase in fat mass that did not reach significance. Several reasons may potentially explain the stability in these participants. These include a) participants were closely managed by health care providers with a mean number of 10 ± 8 outpatient visits to health care providers (Alberta Health Services) over the study duration; b) dietary intake was stable with no major changes in energy and protein intake over the study duration (data not shown); c) patients reported stable, but reduced, health status as noted by the stability in the number of co-morbid conditions. In addition, while physical domains of the HRQOL were 10 points lower in this population compared to Canadian norms (11), they were also very stable with no significant declines over the five years. Although HRQOL has been found to be significantly reduced in patients with more advanced CKD (109), consistent with our findings, Meuleman et al conducted a longitudinal study in pre-dialysis patients (CKD stages 4-5) with an average age of 64 years old, and found no changes in HRQoL over a period of 18 months (103).

VitD concentrations remained stable throughout the study likely secondary to the high adherence to prescribed vitD therapy. VitD levels >75 nmol/l were associated with higher adiposity, increase in some HRQoL domains (vitality and MCS), higher cognition scores and lower depression scores. Though cognition and depressions scores were statistically significant between vitD status > and < 75 nmol/l, the difference was not clinically significant. This may indicate the need for sufficient vitD status in order to achieve a stable healthy aging with a stable HRQoL. The cohort in this study were well supplemented, on average consuming >1000 IU/day. This reflects the active recommendation for vitD supplementation in the clinics from which these patients were recruited.

Studies examining the association between mental health, depression and vitD deficiency are highly prevalent within the literature (9, 15, 115, 130-132, 184, 185). However, some investigators see relationships; while others have failed to demonstrate a relationship between vitD and these variables (7, 123, 124, 126). The relationship between vitD status and HRQoL in the literature is not consistent; this inconsistency is contributed to by differences in study design (length of study, vitD supplementation, types of supplements use and the rates of supplementation) (122, 123, 125-127, 186). Studies indicate that vitD deficiency is associated with reduced HRQOL in some clinical populations over the shorter term, but others have failed to demonstrate these relationships (126). In our cohort, vitD sufficiency was associated with an increase of more than 5 points in the vitality domain of the SF-36, which is considered clinically relevant. In 2014, Williams et al conducted a study to longitudinally (4 years) assess the relationship between vitD status and the incidence of depression in healthy elderly participants (70-79 years old) (131). They found that participants with lower vitD levels had a higher risk of developing depression over a period of 4 years (HR (95% CI): 1.65 (1.23-2.22). Yalamanchili et al conducted a study comparing the effect of a one-year treatment with different vitD doses on the risk of depression (184). They

found no significant effect on depression in dose ranges (400-4800 IU/day) (184). These observations could be due to sample size, or the small number of depressed individuals in the study (184). Slinin et all conducted a study in 2010 to longitudinally (4 years) analyze the relationship between VitD status and cognition in heathy elderly men (>65 years old) using the modified MMSE (8). They found increased odds and trends towards reduced cognitive scores with lower vitD status (odds ratio (OR) 1.84), but it did not reach significance (8). Our study confirms these findings, as vitamin D in sufficiency was only associated with very small differences in cognitive scores and only modest differences in depression prevalence and HRQOL. Hence, while optimizing vitD status is important in this group to prevent deficiency, it is unclear the extent to which this may impact overall HRQOL, depression and cognition over the long term. Other factors, such as glycemic control, inflammation and CKD disease progression, may be more important determinants.

Participants recruited from RIC had, in average, lower MMSE scores, higher MDI scores and lower scores in the General health perception and social functioning scores of the SF-36 compared to participants recruited from DNPC. Participants from RIC also had a higher number of inpatient and emergency health events. This could be related to their more advanced renal disease (evidenced by their lower eGFR and higher number of health events), as well as with their lower vitD status and supplementation prevalence compared to DNPC participants. Though both RIC and DNPC work with patients with renal disease, there are differences in clinical practice models between groups. DNPC, as its name suggests, has a multidisciplinary approach based on nurses and registered dietitians with the purpose of achieving glucose control and preventing complications like diabetic nephropathy (182). On the other hand, participants in RIC tend to have a more advanced CKD not necessarily related to DM, thereby the treatment goals (such as preserving kidney function) and the approaches to achieving them may be different from DNPC.

In this cohort, participants from RIC had a trend towards lower vitD status and had lower $1,25(OH)_2D_3$ levels compared to participants from DNPC. This could be contributed to by their lower eGFR, but it is likely related to the lower prevalence of vitD supplementation in participants from RIC. VitD supplementation is known to prevent some co-morbid conditions (e.g. fractures, depression) in this patient group, making a treatment model that highlights vitD supplementation crucial for these patients in order to prevent or slow down the appearance of these conditions. Further work is needed to explore the interrelationships between vitD status and cognition.

This study had some limitations, mainly that not all participants attended every follow up visit. Data from participants who attended every visit and for those who did not is shown in Appendix 4.4. Participants from the Follow up study who completed all measures up to date had lower eGFR (42 vs 51) ($p=0.03$) and were older (69 vs 65) ($p=0.001$) than those who did not. Though some participants differed between years, average scores for individual variables (anthropometric, clinical, laboratory, HRQoL, Mental Health, cognition) remained stable for the duration of the study. Another limitation is the possible selection bias caused by the longitudinal follow-up of only 50 of the 120 participants of the original RCT. However, it does not appear to be a major factor in this analysis as there seemed to be no differences between anthropometric, clinical, demographic or laboratory factors between the participants that participated in the follow up study ($n=50$) and those who did not ($n=70$) ($p>0.05$). Importantly, there is no evidence that there were any differences between overall health status as no differences were observed between the total number of co-morbid conditions or differences in the incidence of deaths or total number of outpatient events between RCT participants who enrolled in the follow up and those who did not. While our sample size was small, a post hoc analysis showed enough power for primary variables ($\beta>0.8$). In addition, while not all participants came to each annual follow-up visit, we did not see any major effects of the 'individual subject' on these factors. An important element of

this study was its length (5 years), as well as the use of repeated measures in important factors for healthy aging. The use of repeated measures in this population is important to see the longitudinal trajectories in a cohort of pre-dialysis participants that were well supplemented on an ongoing basis with vitD.

In summary, time had no effect in body composition, HRQoL, cognition or mental health in a cohort of participants with DM and CKD with stable vitD status. Participants in this cohort were well supplemented with vitD and had a low incidence of vitD insufficiency (<75nmol/l). VitD levels >75 nmol/l were associated with higher adiposity and higher scores in the vitality domain and the MCS of the SF-36. Future studies examining the impact of vitD supplementation on functional measures of muscle strength and functionality and an examination of the potential underlying mechanisms contributing to alterations in body composition and mental health are warranted.

Chapter 5: Conclusions and General Discussion

This thesis studied the interrelationships between vitamin D status, body composition, HRQoL, mental health, and health care utilization in an ambulatory population of adults with DM and CKD. Chapter 3 focused on the body compositional, HRQOL, mental health and cognitive differences between frail and non-frail adults in adults with DM and CKD (stages 1-5) and their interrelationships with vitamin D status using a cross-sectional study design. In this study we showed that frailty in adults with DM and CDK was associated with reduced lean body mass, reduced HRQOL (physical domains), increased depression and vitD inadequacy (chapter 3). Health utilization (inpatient and emergency events) was elevated in this cohort, especially in those with frailty and advanced CKD. The amount of health utilization (inpatient, emergency and total events) found in frail participants was higher than those without frailty and the provincial averages (chapter 4) (181). In the second study, we examined the longitudinal interrelationships between body composition, HRQOL, depression, cognitive status and overall vitD status over five years (Chapter 4) in the same population. Results from this study indicated that adults with CKD and DM with vitD sufficiency experience remarkably stable body composition, reduced, but stable HRQOL and mental health (depression/cognitive status) over the long term. This study is currently ongoing but preliminary results are presented over 5 years.

Both studies consistently showed that vitD levels >75 nmol/l were associated with higher adiposity and decreased lean mass. In the second study (chapter 4), vitD levels >75 nmol/l were associated with higher HRQOL (mental health and vitality domains). Though participants with levels >75 nmol/l had statistically higher cognition scores and lower depression scores, these differences were not clinically significant. These findings suggest that vitD deficiency may indirectly be one of the elements related to the development of frailty in the elderly with CKD and DM but may not be the only nutritional consideration in the etiology of this disorder. However,

vitD deficiency is a prevalent condition in the elderly due to decreased endogenous synthesis, particularly in adults living with DM and CKD living in northern Alberta (1, 4, 39, 49, 150, 167). VitD status was not associated with demographic factors such as age, gender, DM type or DM duration, but participants who took VitD supplements (>1000 IU/d) had higher vitD status (>75 nmol/l) than those who did not.

Participants from this study were mainly recruited from the Diabetic Nephropathy Prevention Clinics (DNPC) and the Renal Insufficiency Clinics (RIC), Northern Alberta Renal Program. These two clinics are both run by interdisciplinary health care teams that focus on optimizing nutritional care within the overall context of chronic disease management. However, there are inherent differences between these two clinics due to the differences in their respective clinical populations that may have contributed to overall study findings. DNPC is a clinic with a multidisciplinary approach (registered dietitians and nurses), that focuses on glycemic control for the prevention of comorbidities such as diabetic nephropathy in adults with DM only (182). RIC focuses on the prevention of further decline in kidney function in patients with CKD of heterogeneous etiology, which may not be solely due to the complication of diabetes. While the number of co-morbid conditions did not differ between clinic populations in our cohort, participants from RIC had more advanced kidney disease and increased number of health events (emergency and inpatient), as well as increased depression and lower cognition scores and lower scores in some domains of HRQoL (Vitality and Mental Component Summary). In addition, VitD status was higher in DNPC patients, which could be explained by the high prevalence and consistency in use of vitD supplementation (>1000 IU/D) prescribed in these clinics. Therefore, this may have impacted study findings by generating a bias towards DNPC having better results related to vitD status (ie, better cognition or lower depression), however it could also be related to the lower eGFR found in RIC participants. VitD $1,25(OH)_2D_3/25(OH)D_3$ ratios were tightly related

to kidney function, with a lower ratio in more advanced CKD indicating that advancing CKD impacts over all vitD status. Participants with a lower eGFR had, on average, lower serum concentrations of $1,25(OH)D_3$. This would also be important element behind the relationships between vitD, clinics and the outcomes found in this study.

These studies had some limitations that may have further impacted overall study findings. These included the lack of functional measures of muscle strength when we assessed frailty. (**chapter 3**). The Edmonton Frail Scale is a self-reported tool and thus subject potentially to individual bias. Hence, it is possible that we under-estimated the prevalence of frailty in our study. However, this tool has been validated for use in the clinical setting and has shown a 75% sensitivity and a specificity of 88% for detecting frailty when compared to other tools such as the Fried's Frailty Phenotype (152, 155, 156). Fried's Frailty Phenotype is considered one of the most accurate diagnostic tools for physical frailty, as in includes functional measures like handgrip strength and walking speed (141). Though self-reported tools are useful in a clinical setting where access to functional tests might not be possible, it would be important to address this point in future studies in order to have a more accurate estimation of frailty prevalence. This would also be helpful to understand the potential underlying issues related to impaired muscle functionality in this patient population and how this may influence overall HRQoL. Another limitation was that not all participants attended every follow up visit and some of them did not finish the study yet leading to smaller sample sizes at years 4-5 of the evaluation (**chapter 4**). Despite this potential limitation, we did not find any significant differences in primary outcomes between those who attended each follow up visit and those that did not over the five-year period. Conferred strengths of this study include the repeated measures of important clinical outcomes over five years in a stable and ambulatory population with a significant co-morbid burden. This study is the first study to longitudinally evaluate body compositional and bone health changes, HRQOL, health care events

and measures of cognition and depression in the context of overall vitamin D status in ambulatory patients with both DM and CKD over 5 years.

5.1 Clinical Relevance and Clinical Implications

This study illustrates that patients with frailty have decreased physical functioning and HRQoL. This is relevant as this translates to increased depression and health utilization, which poses a significant burden both for the individual as well as the health care system. Frailty is a condition that involves both physical and psychosocial elements, meaning that its etiology goes further than just physiological decline (6, 109, 142). Elements like social support, perception of health, cognition and mood are also key to the development of frailty (25, 27, 143). This means that the strategies developed for the prevention/treatment of frailty should focus on physical rehabilitation/strength, prevention of comorbidities and social/psychological support programs that will enable the adults with DM and CKD to remain within the community in relatively stable health for the longer term (25, 159, 187, 188). Most of the participants with frailty in this cohort fell into the category of pre-frail, which is considered a stage of increased vulnerability without the presentation of all the symptoms of frailty (24, 188). The assessment of frailty at this stage is crucial given that the patients have increased vulnerability but could potentially be prevented from further decline into moderate or severe frailty (187, 188). Ideally, diagnostic and rehabilitation strategies should aim to catch patients in the pre-frail phase before the patients suffer the physical and psychological effects of more severe frailty (depression, decreased quality of life, increased morbidity) and when the chances for positive outcomes with rehabilitation is still likely feasible.

Some specific strategies that could be considered for the prevention/treatment of frailty include resistance exercises and nutritional counseling aiming to prevent lean body mass loss as well as nutritional deficiencies such as vitD deficiency (160, 187, 189-194). Previous studies have shown that supplementation with nutrition supplements like leucine and protein along with

resistance exercise can benefit lean mass in elderly populations (187, 190, 194, 195). Hence, it is important to consider the development of lifestyle regimens that can address the risk for frailty in this population. An important element that should be considered when developing these strategies is the restrictions inherent to this population, both physical and physiological and to identify the time span by which these interventions might be helpful. Elderly participants have limitations in movement and strength, which should be taken into consideration when developing exercise strategies (25, 187, 192, 193). Interventions aimed at the pre-frail population may be the most effective, since research suggests that the efficacy of resistance exercise may be limited in those with frailty due to the significant limitations in cognitive and physical function (147, 192, 196, 197). Patients with renal disease, especially in the pre-dialysis stage, can have restrictive diets that could make these strategies challenging especially if they involve higher protein intakes (23, 198-200). For example, recommendations for protein intake typically are significantly lower than 1 g/kg/d for severe end-stage disease (23, 198, 199). However, this strategy may be more appropriate for those with CKD stages 1-4 where dietary protein intake may be less compromised due to better kidney function (23). In our study the majority of participants consumed between 0.8-1.2 g/kg/d, which should be sufficient to ensure sufficient protein synthesis to minimize the risk for skeletal muscle catabolism (201, 202). A study done by Castaneda *et al* in CKD patients showed benefits of resistance exercise even in the presence of protein restriction (0.6 g/kg), meaning that successful strategies could potentially be developed even in the presence of protein restrictions (200, 203). It would be important to analyze the effects of protein quality vs quantity in this population, using protein levels normal in CKD diet (0.6-0.8 g/kg). The successful management, and preferably prevention, of frailty could considerably increase the HRQoL of these patients, as well as significantly decrease the costs for health care systems.

This study also showed that in a cohort of patients with DM and CKD with good vitD supplementation, as well as stable VitD status, body composition (total/segmental), HRQoL, and mental health (depression and cognition) remained stable for a period of 5 years. This is important as patients with chronic conditions like DM and CKD often experience significant reductions in HRQOL and overall health in shorter time spans (7, 102, 104, 109, 110, 117). The fact that these patients show no significant decline over time suggests that these patients are well managed by the health care teams, and that vitD supplementation might be one of the important factors involved in this stability. Models of clinical care that take into consideration elements beyond the main pathology, such as vitD supplementation to prevent comorbidities, are essential in the management of these conditions. Multidisciplinary approaches have proved to be helpful in other populations as well, for example in decreasing hospital admission and mortality rated on heart failure patients and decreasing the risk of diabetic foot ulceration (204-206). It is important to aim for long-term stability, both in health and in HRQoL in this population in order to prevent complications such as depression or frailty.

Though vitD deficiency is highly prevalent in CKD, we have shown that with adequate vitD supplementation (1000-2000 IU/d), these patients can achieve a sufficient vitD status (>75 nmol/l). Maintaining sufficient vitD levels diminishes the risk for adverse health outcomes related with vitD deficiency such as poor bone health, poor muscle health and decreased mental health. The presence of these adverse health outcomes presents a negative risk for public health, as it translates into increased number of comorbidities and health care needs. A sufficient vitD status has been related with some elements of healthy aging, such a decreased depression and normal cognition both in this study and in others (115, 130, 132, 161). These findings illustrate the need for continuous vitD supplementation in this population. All health care professionals working with this population should consider supplementing their patients with vitD in order to decrease the

high incidence of vitD deficiency, as well as to prevent complications related with vitD deficiency. Previous studies done by our group and others suggest that VitD supplementation above the recommended dose of 600 IU/day and closer to 1,000-2,000 IU/d is warranted (7, 35, 61, 126, 207).

5.2 Future Directions

Having a better understanding of the mechanisms of frailty (both physical and psychosocial) and their relationship with nutritional elements such as vitD status as well as other micro and macro nutrients could help in the development of preventive/treatment strategies for this condition. The study of the mechanisms involved in vitD metabolism (activation, transportation and elimination) are highly relevant in a population with CKD, as it would illustrate the exact effects CKD has on these processes and how that affects health outcomes. By better understanding the effects of CKD on vitD, new and more precise vitD supplementation strategies could be developed for this population; particularly those that may benefit from these therapies: the pre-frail patient.

Consideration of other lifestyle interventions such as resistance exercise in the context of vitD adequacy as a treatment for frailty in the adult with CKD and DM would confer increased rigor to these studies. Rehabilitation strategies aimed at early identification of frailty and especially those vulnerable/pre-frail to ensure effective prevention in vulnerable populations are warranted. Examples of relevant future studies include longitudinal studies evaluating the relationship between vitD and frailty, using specialized tools and functional tests such as handgrip strength. Lifestyle intervention strategies, such as a combination of resistance exercise and diet (protein, vitamin D), could be an essential element in the development of programs aiming for the prevention of frailty (159, 187, 192, 208). The use of elastic band exercises have proven to have

beneficial effects in older individuals, and could be an exercise used in participants with limited mobility in the home setting (192). Diet studies analyzing the effect of nutritional elements such as protein (leucine, creatine), energy and micronutrients could shed light in the effects on diet in the development of frailty. This would aid in determining the relationship between vitD status and muscle mass and strength, as well as the relationship with cognition and depression, which are main elements in the characteristics of frailty.

5.3 Final Conclusions

Overall, the participants in this study remained stable, having no significant changes in health outcomes over a period of 5 years. The overall vitD status in this ambulatory population of adults with CKD and DM was high, as well as the number of participants consuming vitD supplements. VitD supplementation was related with sufficient vitD status (>75 nmol/l), highlighting the need for vitD supplementation in this population. Participants from the DNPC clinics had better vitD status and higher incidence of supplementation reflecting on the active encouragement of vitD supplementation found in these programs. Participants from RIC had a more advanced CKD as well as a longer DM duration. This translated into participants from RIC having a higher incidence of depression and lower scores in some HRQoL domains.

Most of the participants with frailty in this cohort fell into the pre-frail category. Participants with frailty had a higher number of health events, increased depression and lower HRQoL. While most participants had significantly lower HRQoL than Canadian norms, participants with frailty had significantly lower HRQoL than those without frailty (11). The prevention/treatment of frailty is an important public health concern, as it causes a burden to the patient and the health system; predisposing to the individual to reduced HRQOL beyond that of the original disease. In study 1 (chapter 3) vitD was not related to depression scores, cognition or

HRQoL, while in study 2 (chapter 4), there was an association with these. This inconsistency is likely related to the differences in sample size and differences in study design because longitudinal studies provide valuable information regarding the evolution of changes in health care status. Both repeated measures and a larger sample size likely contributed to the ability to discriminate associations between vitD status and changes in mental health. Both frailty and vitD deficiency remain public health concerns, especially in populations with DM and CKD. A better understanding of the underlying mechanisms for the development of frailty, as well as the role of vitD on them is required.

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APPENDIX 1: Additional Data

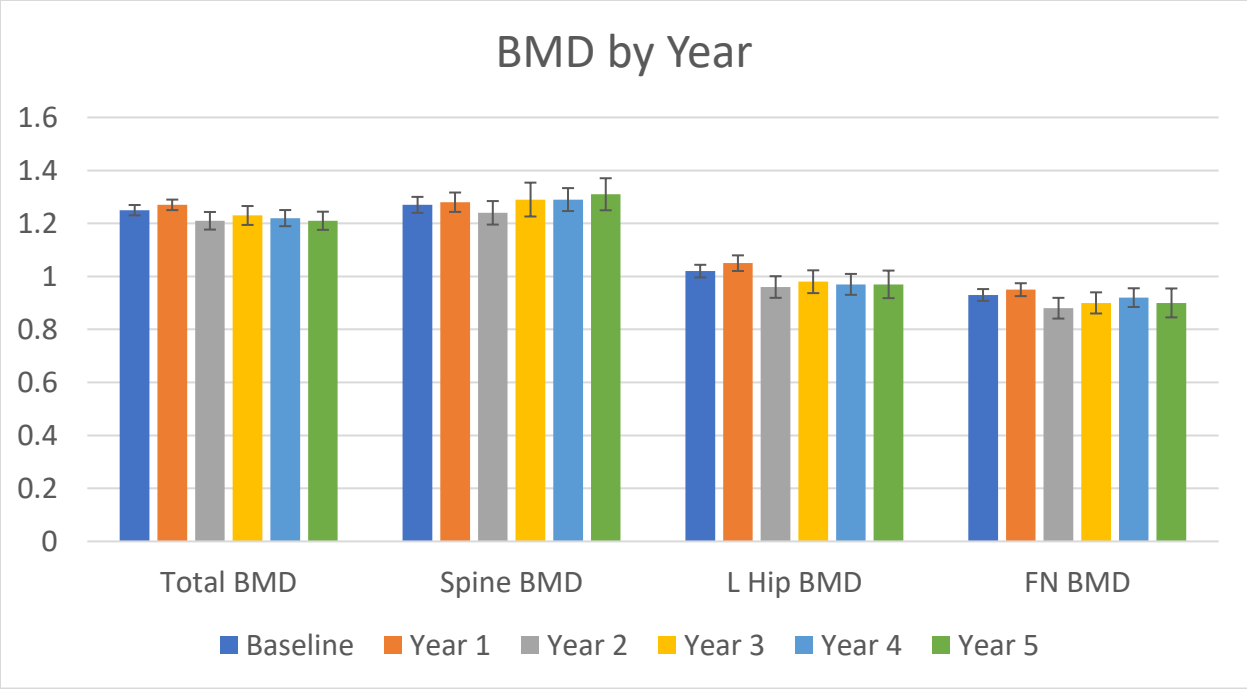
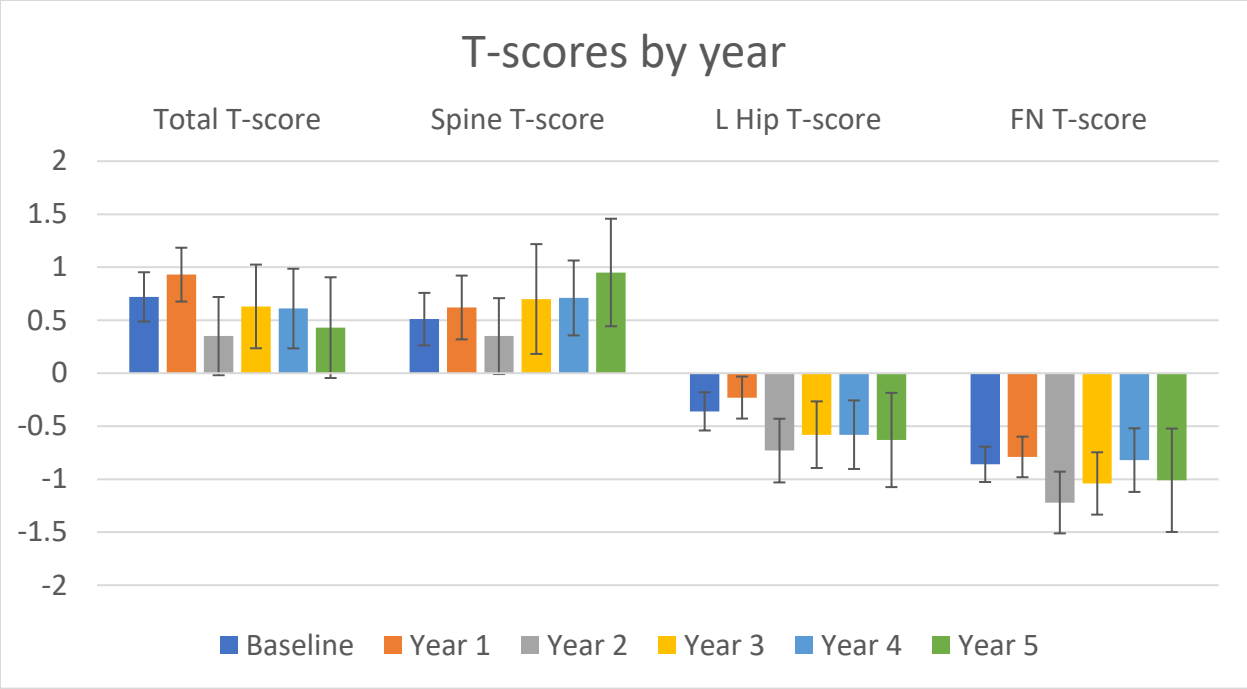


Figure A.1 Changes in Bone Mineral Density per year. Bone Mineral Density was calculated using DXA. Changes in Bone Mineral Density per year are represented in appendix 4.1. Bone Mineral Density is shown in the following segments: Total BMD, Spine BMD (L1-L4), Left Hip BMD, Femoral Neck BMD (left femoral neck). Values represent mean ± standard error. There was no difference in bone mineral density between years.

Figure A.2 T-scores per year



T-scores were calculated using DXA. Changes in T-scores per year are represented in appendix 4.1. T-scores are shown in the following segments: Total T-score, Spine T-score (L1-L4), Left Hip T-score, Femoral Neck T-score (left femoral neck). Values represent mean ± standard error. There was no difference in T-score between years.

Table A.1 Post Hoc calculations

	Vitamin D >75 vs <75 nmol/l	
	p-value	Power (%)
Age	p=0.87	3.4
Male n(%)	p=0.29	97.9
Weight	**p= 0.02**	62.7
Height	p=0.06	49.8
BMI	**p=0.0002**	97.4
DM Type 2 n(%)	p=0.60	99.9
DM Duration (years)	p=0.63	6
CKD Stage 3-5 n(%)	p=0.63	100
Vitamin D Supplementation n(%)	**p<0.0001**	100
Vitamin D Supplementation (IU)	p=0.13	50.1
eGFR (ml/min/1.72m2)	p=0.21	22
HbA1c (%)	p=0.84	5.8
Random Blood Glucose (mmol/L)	p=0.75	4.4
Albumin (g/L)	p=0.36	12.1
PTH (pmol/L)	p=0.08	27.7
Urea (mmol/L)	p=0.87	3.6
Creatinine (umol/L)	p=0.10	32.7
C-Reactive Protein (mg/dL)	p=0.69	6.6
MMSE Score	**p=0.03**	60.6
MDI Score	**p=0.04**	47.8
Physical functioning	p=0.64	6.5
Role Physical	p=0.89	3.4
Bodily Pain	p=0.57	8.7
General Health Perception	p=0.95	2.8
Vitality	**p=0.02**	60.3
Social functioning	p=0.10	34.3
Role Emotional	p=0.19	23.6
Mental Health	p-0.06	44
Physical Component Summary	p=0.36	15
Mental Component Summary	**p=0.01**	69.2
FMI (kg/m2)	**p<0.0001**	99.5
ASMI (kg/m2)	p=0.80	6.9
% Fat Arms	**p<0.0001**	98.3
% Fat Legs	**p=0.007**	75.9
% Fat Trunk	**p=0.0004**	92.6
% Fat Android	**p=0.0002**	95.1
% Fat Gynoid	**p=0.007**	74.2
Total % Fat	**p=0.0002**	93.7

Fat Mass Arms (g)	**p=0.0003**	96.9
Fat Mass Legs (g)	**p=0.008**	78.5
Fat Mass Trunk (g)	**p<0.0001**	98.6
Fat Mass Android (g)	**p<0.0001**	99
Fat Mass Gynoid (g)	**p=0.01**	87.7
Total Fat Mass (g)	**p=0.0001**	98.4
% Lean Arms	**p<0.0001**	98.3
% Lean Legs	**p=0.006**	77.8
% Lean Trunk	**p=0.0004**	92.6
% Lean Android	**p=0.0002**	95.1
% Lean Gynoid	**p=0.008**	73.9
Total % Lean	**p=0.0002**	94.1
Lean Mass Arms (g)	**p=0.001**	79.6
Lean Mass Legs (g)	p=0.90	3.3
Lean Mass Trunk (g)	p=0.09	41.8
Lean Mass Android (g)	**p=0.01**	69.6
Lean Mass Gynoid (g)	p=0.16	28.2
Total Lean Mass (g)	p=0.68	6
Total Mass Arms (g)	p=0.93	3
Total Mass Legs (g)	p=0.06	49.9
Total Mass Trunk (g)	**p=0.0008**	94
Total Mass Android (g)	**p=0.0002**	97.6
Total Mass Gynoid (g)	**p=0.002**	91.7
Total Mass (g)	**p=0.005**	82

Post hoc power calculations for analysis by vitamin D status > and < 75 nmol/l using and alpha of 0.05.

Table A.2 Participants that attended all visits vs those who did not

Variable	Attended all visits (n=13)	Did not attend every visit (n=37)	p value
Male n(%)	9 (62%)	24 (64%)	p=0.78
Age (years)	70 ± 7 (52 - 82)	65 ± 9 (37 - 84)	**p=0.001**
Weight (kg)	86 ± 14 (56 - 110)	93 ± 21 (49 - 136)	**p=0.01**
Height (m)	1.68 ± .06 (1.53 - 1.78)	1.67 ±0.1 (1.42-1.87)	p=0.83
BMI (kg/m^2)	30 ± 5 (21 - 39)	33 ± 6 (17 - 44)	**p=0.008**
ASMI (kg/m^2)	7.6 ± 1.1 (5.0 - 9.5)	7.8 ± 1.0 (5.6 - 10.8)	p=0.21
FMI (kg/m^2)	11.1 ± 3.7 (5.8 - 17.5)	11.5 ± 4.1 (3.9-20.1)	p=0.57
DM Type 2 n(%)	2 (15%)	2 (5%)	p=0.09
DM Duration (years)	19 ± 14 (3 - 53)	18 ± 10 (4 - 55)	p=0.54
Vitamin D Supplementation n(%)	9 (69%)	29 (78%)	p=0.11
Vitamin D Supplementation (IU)	1325 ± 704 (100-4000)	1589 ± 669 (400-4000)	**p=0.03**
HbA1c (%)	7.5 ± 1.9 (5.0-19.9)	7.6 ± 1.3 (5.4 - 12.5)	p=0.72
Random Blood Glucose	7.8 ± 3.6 (1.7 - 21.7)	8.7 ± 3.9 (2.2 - 22.1)	p=0.16
Creatinine (umol/l)	174 ± 92 (70 - 536)	158 ± 113(50 - 627)	p=0.37
Urea (mmol/l)	12.2 ± 5.8 (3.4 - 21.9)	11.7 ± 7.7 (2.1 - 29.5)	p=0.68
eGFR (ml/min/1.72m2)	42 ± 25 (9 - 101)	51 ± 28 (6 - 97)	**p=0.03**
Albumin (g/l)	41 ± 2 (36 - 47)	41 ± 3 (32 - 49)	p=0.88
Parathyroid Hormone (pmol/L)	9.3 ± 8.0 (1.4 - 33.4)	8.2 ± 11.0 (1.1 - 93.2)	p=0.51
Alkaline Phosphatase (U/L)	82 ± 21 (45 - 134)	82 ± 43 (12 -370)	p=0.96
Cholesterol (mmol/L)	3.6 ± 1.0 (2.1 - 6.0)	3.6 ± 1.0 (2.1 - 6.6)	p=0.92
Triglyceride (mmol/L)	2.5 ± 1.5 (0.7 - 7.2)	2.1 ± 1.4 (0.4 - 6.7)	p=0.26
HDL (mmol/L)	1.0 ± 0.3 (0.6 - 2.2)	1.1 ± 0.4 (0.6 - 3.1)	p=0.93
LDL (mmol/L)	1.5 ± 0.8 (0.1 - 3.6)	1.5 ± 0.7 (0.07 - 3.8)	p=0.30
CRP (mg/dL)	3.9 ± 5.3 (0.05-29.9)	5.6 ± 13.8 (0.2 - 94.0)	p=0.46
25(OH)D$_3$ (nmol/l)	100 ± 34 (42 - 226)	87 ± 29 (21 - 169)	**p=0.01**
1,25 (OH)$_2$ D$_3$ (pmol/l)	80 ± 30 (13 - 163)	91 ± 58 (10 - 479)	p=0.19
MMSE	28 ± 1 (24-30)	28 ± 2 (24.5 - 30)	p=0.66
MDI Score	8 ± 7 (0 - 34)	10 ± 8 (0 - 40)	p=0.41
Physical functioning	66 ± 23 (15 - 100)	62 ± 26 (5 - 100)	p=0.37
Role Physical	52 ± 41 (0 - 100)	55 ± 41 (0 - 100)	p=0.59
Bodily Pain	60 ± 25 (10 - 100)	53 ± 21 (0 - 100)	p=0.07
General Health Perception	56 ± 18 (17 - 87)	54 ± 22 (10 - 92)	p=0.61
Vitality	53 ± 17 (0 - 85)	54 ± 20 (0 - 95)	p=0.80
Social functioning	84 ± 22 (38 - 100)	84 ± 19 (25 - 100)	p=0.78
Role Emotional	82 ± 29 (0 - 100)	83 ± 33 (0 - 100)	p=0.82
Mental Health	80 ± 17 (28 - 100)	79 ± 14 (44- 100)	p=0.78
Physical Component Summary	40.7 ± 9.1 (22.9-59.7)	39.4 ± 10.0(13.2-57.3)	p=0.43
Mental Component Summary	40.7 ± 9.9 (20.9-71.6)	54.4 ± 8.4(30.6-66.6)	p=0.68

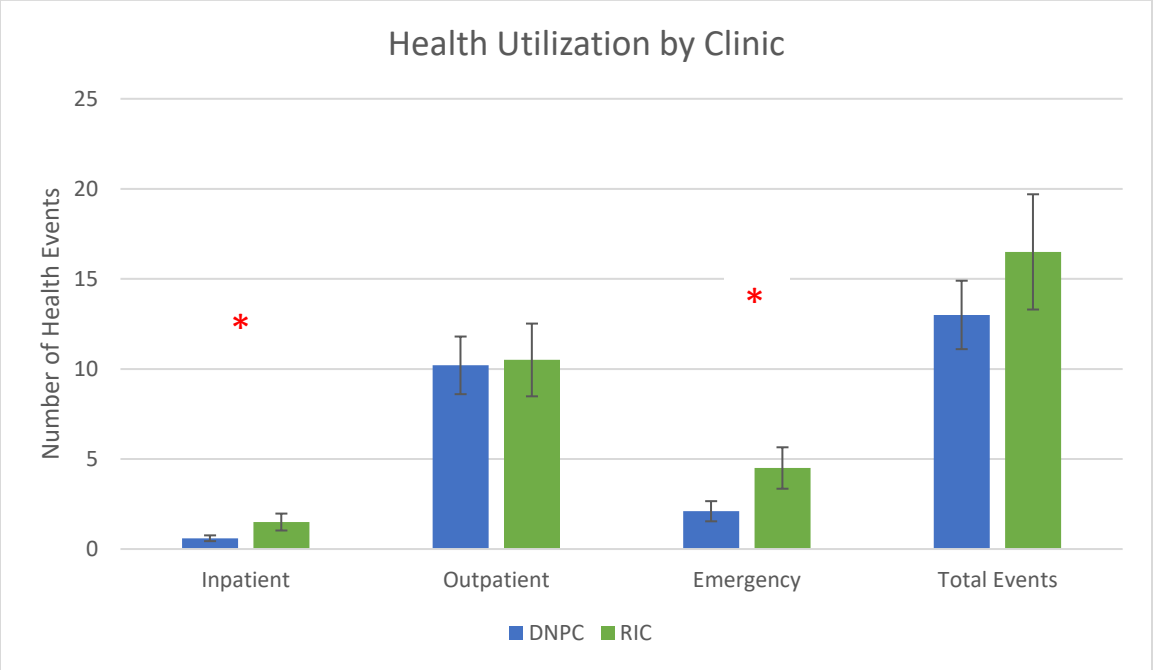
Data expressed as mean ± standard deviation(min-max) or median ± interquartile range. N= number, DM= Diabetes Mellitus, kg= kilogram, m= meters, IU= international units eGFR= estimated glomerular filtration rate, HDL= High Density Lipoprotein, LDL= Low Density Lipoprotein. Results from a t-test variance between groups (attended all visits vs not all visits). *A p value < 0.05 was considered significant.*

Table A.3 Anthropometric, demographic, clinical and laboratory data for DNPC and RIC

Variable	DNPC (n=29)	RIC (n=16)	p value
Male n(%)	19 (65%)	11 (68%)	p=0.82
Age (years)	66 ± 7 (53 - 78)	64 ± 10 (37 - 77)	p=0.55
Weight (kg)	98 ± 17 (63 - 136)	85 ± 22 (49 - 125)	**p=0.03**
Height (m)	1.68 ± .11 (1.42 - 1.87)	1.68 ± .07 (1.54 - 1.84)	p=0.95
BMI (kg/m^2)	34 ± 5 (25 - 44)	30 ± 7 (17 - 40)	**p=0.02**
DM Type 2 n(%)	29 (100%)	12 (75%)	**p=0.004**
DM Duration (years)	14 ± 8 (3 - 32)	22 ± 14	**p=0.02**
Co-morbidities (n)	5 ± 2 (1 – 10)	5 ± 2	
Vitamin D Supplementation n(%)	27 (93%)	7 (43.7%)	**p=0.0002**
Vitamin D Supplementation (IU)	1442 ± 700 (100-2775)	1171 ± 407(800-2000)	p=0.33
HbA1c (%)	7.4 ± 1.2 (5.0 - 10.6)	7.9 ± 1.4 (5.5 - 11.7)	p=0.23
Random Blood Glucose (mmol/l)	7.4 ± 2.2 (4.1 - 12.3)	7.2 ± 3.5 (1.7 - 14.4)	p=0.90
Creatinine (umol/L)	106 ± 54 (50-289)	216 ± 59 (112 - 377)	**p=<0.0001**
Urea (mmol/L)	8 ± 4 (4 - 18)	16 ± 5.9 (6.9 - 25.6)	**p=<0.0001**
eGFR (ml/min/1.72m2)	57 ± 19 (18 - 101)	26 ± 6.9 (15 - 42)	**p=<0.0001**
Albumin (g/L)	42 ± 3 (36 - 46)	41 ± 4 (33 - 46)	p=0.48
Parathyroid Hormone (pmol/L)	4.6 ± 4.5 (1.1 - 21.0)	9.6 ± 4.6 (6.0 - 25.1)	**p=0.001**
Alkaline Phosphatase (U/L)	74 ± 25 (12 - 120)	88 ± 24 (62 - 154)	p=0.08
25(OH)D$_3$ (nmol/l)	91 ± 18 (58 - 133)	76 ± 41 (21 - 169)	p=0.08
1,25 (OH)$_2$ D$_3$ (pmol/L)	96 ± 32 (36 - 159)	60 ± 24 (23 - 113)	**p=0.0003**
MMSE[a]	28 ± 1 (25 - 30)	27 ± 1 (24 - 30)	**p=0.04**
MDI Score[a]	8 ± 7 (0 -34)	11 ± 10 (2 - 40)	**p=0.05**
Physical functioning	68 ± 26 (5 - 100)	57 ± 24 (5 - 95)	p=0.20
Role Physical	65 ± 43 (0 - 100)	55 ± 41 (0 - 100)	p=0.47
Bodily Pain	59 ± 26 (10 - 100)	50 ± 21 (12 - 100)	p=0.27
General Health Perception	60 ± 18 (25 - 87)	43 ± 22 (13 - 82)	**p=0.01**
Vitality	57 ± 21 (0 - 95)	51 ± 20 (5 - 80)	p=0.31
Social functioning	90 ± 17 (38 - 100)	77 ± 21 (38 - 100)	**p=0.02**
Role Emotional	92 ± 23 (0 - 100)	80 ± 35 (0 - 100)	p=0.18
Mental Health	82 ± 15 (44 - 100)	76 ± 19 (28 - 100)	p=0.22
Physical Component Summary	42.8 ± 10.6 (17.2-57.2)	37.3 ± 10.0 (20.2-51.0)	p=0.18
Mental Component Summary	56.3 ± 8.6 (30.6 - 71.6)	52.5 ± 10.7 (20.9-64.8)	p=0.20

Data expressed as mean ± standard deviation(min-max) or median ± interquartile range. Data shown represents values from baseline. [a]= values calculated cross-sectionally from all visits. N= number, DM= Diabetes Mellitus, kg= kilogram, m= meters, IU= international units eGFR= estimated glomerular filtration rate. Results t-test between groups (DNPC vs RIC). *A p value < 0.05 was considered significant.*

Figure A.3 Health utilization by clinic



Data from the average number of health events (inpatient, outpatient, emergency and total events) from baseline up to 2017 by clinic. Data is represented as mean ± standard error. RIC= Renal insufficiency clinic, DNPC=Diabetic Nephropathy Prevention Clinic. Results from a t-test between groups (DNPC vs RIC). *Values with an asterisk are significantly different at p≤0.05.*

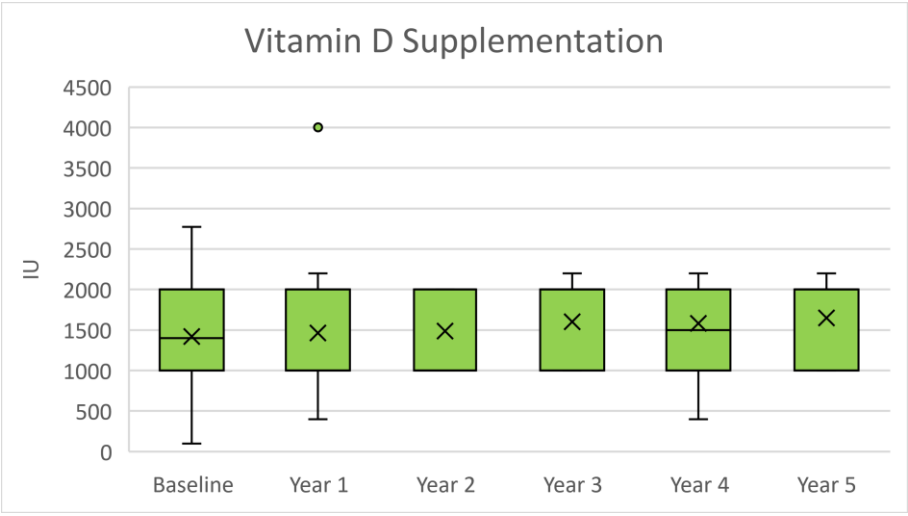


Figure A.4 Vitamin D supplementation doses per year. Supplementation doses for those participants taking vitamin D supplements per year.

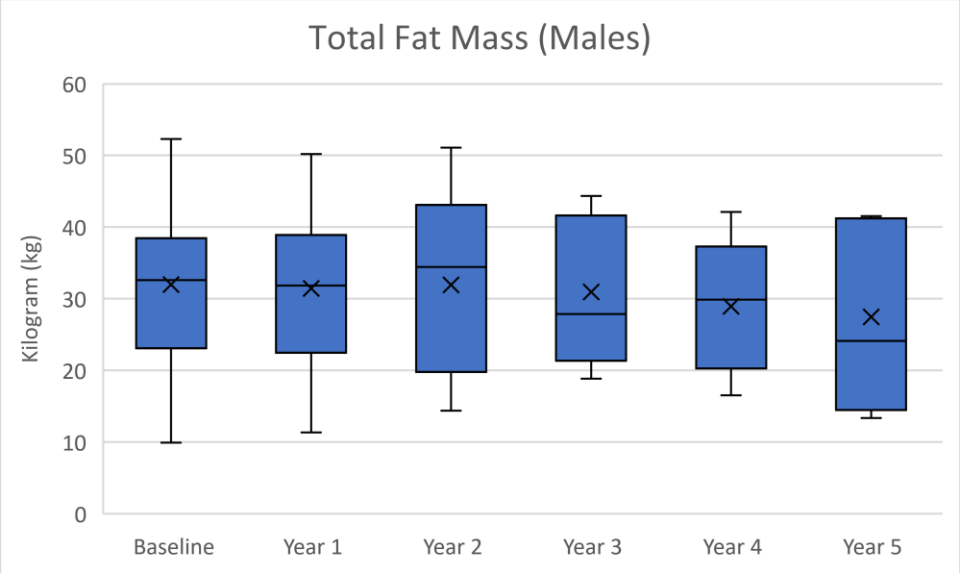


Figure A.5 Total Fat Mass per year for males.

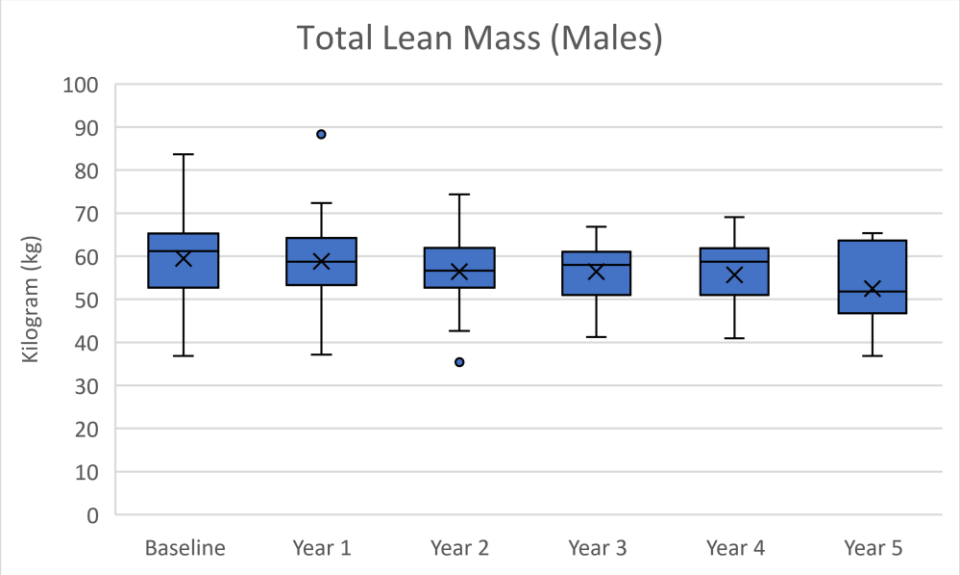


Figure A.6 Total Lean mass per year for males.

Figure A.7 Fat-free mass per year for males.

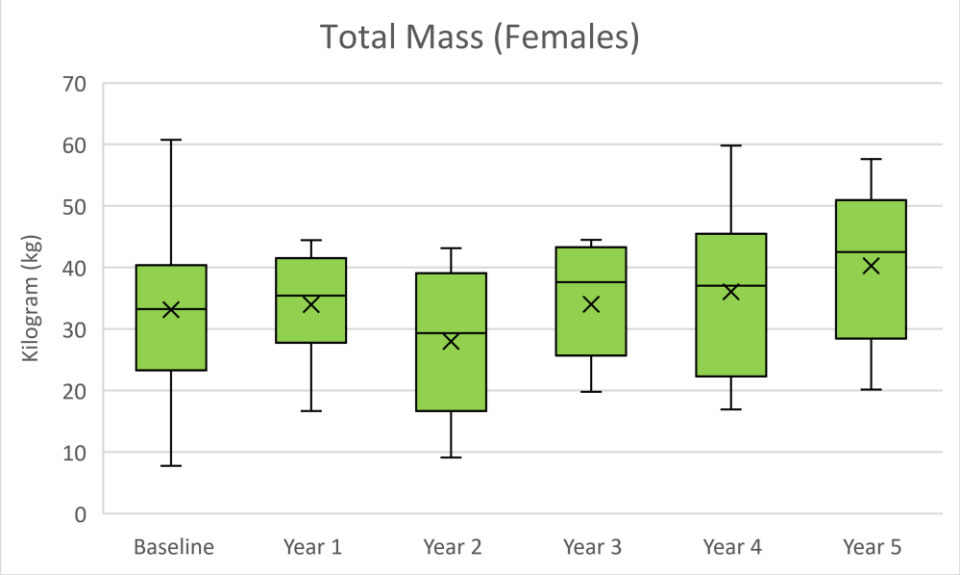


Figure A.8 Total fat mass per year for females.

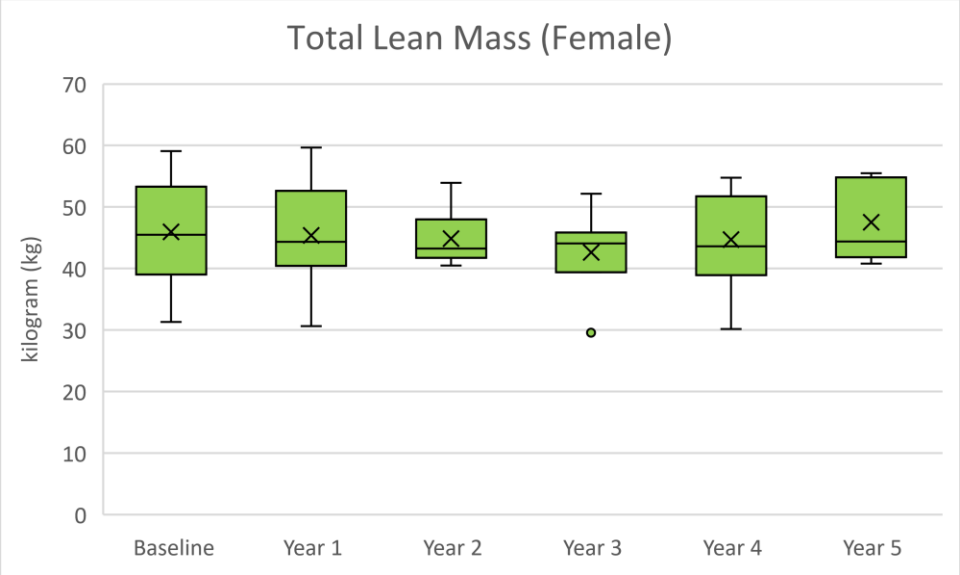


Figure A.9 Total lean mass per year for females.

Figure A.10 Fat-free mass per year for females.

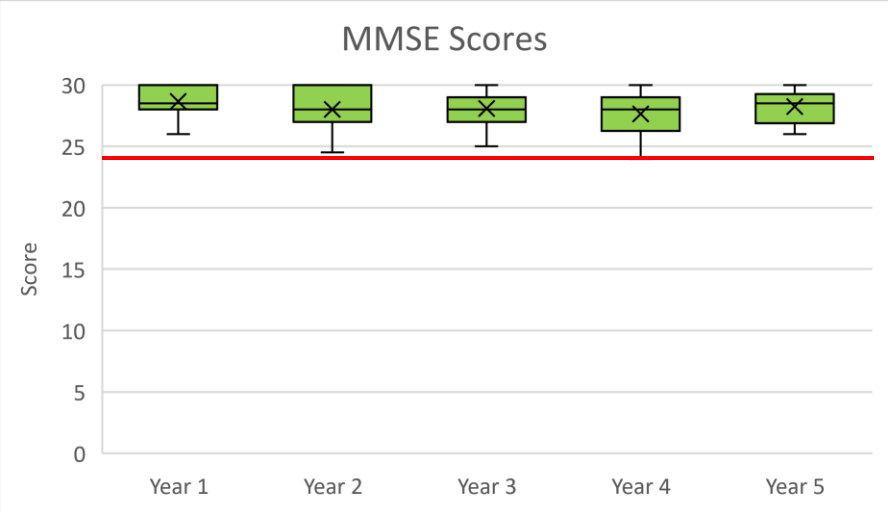


Figure A.11 MMSE scores per year. A participant with a score <24 is considered as cognitively altered.

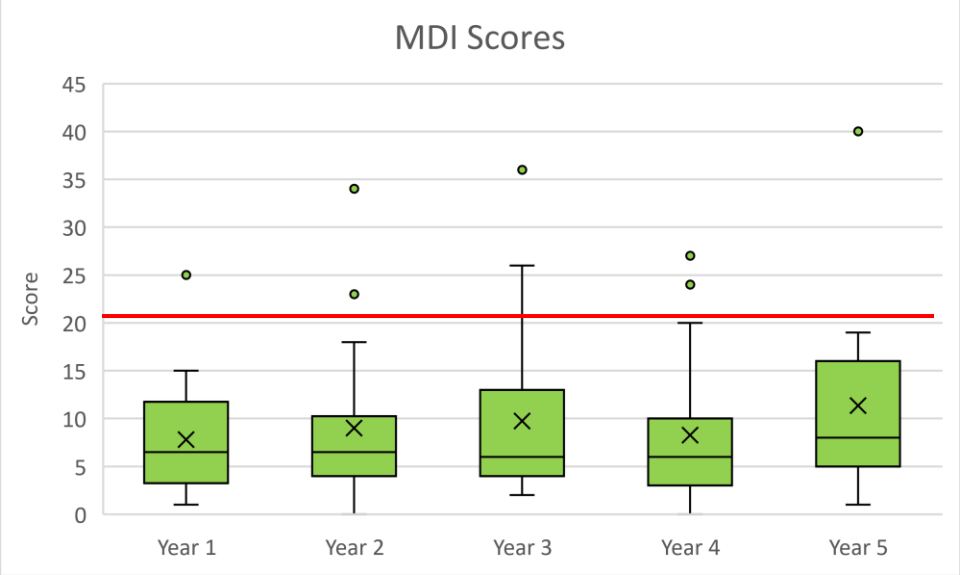


Figure A.12 MDI scores per year. Scores above 20 points reflect depression.