THE EFFECTIVENESS OF A COMPREHENSIVE NUTRITION AND EXERCISE PROGRAM ON THE RISK FOR CARDIOVASCULAR DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

by

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ABSTRACT
Chronic kidney disease (CKD) affects a significant proportion of the population, and its incidence and prevalence is increasing. Cardiovascular disease (CVD) is the leading cause of death in this population. Nutrition and exercise each play an important role in decreasing the cardiovascular risk factors that are commonly seen in patients with CKD. However, there is limited information available regarding the combined effects of both nutrition and exercise for improvement in cardiovascular risk factors and health status of individuals with pre-dialysis CKD. The primary purpose of this research was to determine whether a comprehensive nutrition and exercise program reduces the risk for CVD in persons with CKD, compared to a control CKD population not enrolled in the program. We recruited 36 pre-dialysis CKD patients, 21 of whom were randomized to the intervention program, and 15 of whom were randomized to the control group. Participants of the exercise group attended a 5-week "cooking with kidney disease" course and a 1-week shopping tour with a Registered Dietitian. The participants then engaged in a 12-week supervised exercise training program. The control group received usual care for CKD. Patients were assessed at baseline, post-nutrition, and post-exercise. During these days measurements of anthropometric and musculoskeletal fitness, resting measures of cardiovascular health, and results of a sub-maximal aerobic test were collected. No significant improvements were seen in BMI, waist circumference, sum of 5 skinfolds, or musculoskeletal fitness measures (grip strength or flexibility). Participants in the experimental group showed significant improvements in VO_2max post-intervention when compared to baseline (12.7 ± 1.4 vs. 11.9 ± 1.6 ml/kg/min respectively; $p<.05$), but no improvements were seen in the controls. There were significant decreases in systolic blood pressure post-nutrition intervention when compared to baseline (123.7 ± 17.3 vs. 134.4 ± 19.1mmHg respectively, $p<.05$), but values showed a non-significant increase again post-exercise intervention (133.1 ± 17.4mmHg). There was a significant interaction effect ($p=.01$) between groups for small artery compliance post-intervention compared to baseline, with the experimental group improving when compared to baseline (4.6 ± 2.4 vs. 3.5 ± 1.6mL/mmHg, respectively) and the control group showing a decline (3.1 ± 1.2 vs. 4.3 ± 2.4mL/mmHg, respectively). Large artery compliance showed a non-significant interaction effect ($p=.08$) with small increases in the experimental group when compared to baseline (13.1 ± 3.9 vs. 11.4 ± 2.5mL/mmHg, respectively) and small decreases in the control group when compared to baseline (10.4 ± 2.8 vs. 11.1 ± 3.2, respectively). No significant differences were seen in either time-domain or frequency-domain measures of HRV. A comprehensive nutrition and exercise intervention appears to improve vascular health and aerobic fitness, with trends in improvement for BMI, muscular strength, and flexibility.

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DEDICATION

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1. Introduction

Over the last two decades, the incidence and prevalence of chronic kidney disease (CKD) has increased (Schaubel et al., 1999). The leading cause of death in patients who have chronic kidney disease is cardiovascular disease (Hostetter, 2004; McClellan et al., 2004; Sarnak et al., 2003; Schaubel et al., 1999; Wali & Henrich, 2005). Chronic kidney disease patients are at a higher risk for cardiovascular events owing to a number of risk factors for cardiovascular disease (CVD) including abnormal lipid lipoprotein profiles (hyperlipidemia), hypertension, type 2 diabetes, atherosclerosis, and physical inactivity (Boyce et al., 1997; Konstantinidou et al., 2002). However, even in the absence of these more traditional cardiovascular risk factors, mild renal insufficiency alone puts these patients at a higher risk for developing cardiovascular disease (Rahman et al., 2006). This highlights the importance of improving cardiovascular health in patients with chronic kidney disease.

Habitual physical activity is a well known to be an effective primary and secondary preventative strategy for multiple chronic diseases (Warburton et al., 2006a; Warburton et al., 2006c). For instance, routinely engaging in physical activity decreases markedly the occurrence of cardiovascular-related mortality and events (Oguma & Shinoda-Tagawa, 2004; Schiffrin et al., 2007; Warburton et al., 2006d). Moreover, routine physical activity leads to marked reductions in risk factors CVD (Warburton et al., 2006e). This includes changes in traditional risk factors (lipid lipoprotein profiles (Warburton et al., 2006;O'Connor, 1995), blood pressure (Blair et al., 1984; Paffenbarger et al., 1983)), and emerging risk factors (such as heart rate variability (Greiser et al., 2005; Gulli et al., 2003; Okazaki et al., 2005), and arterial compliance (Schiffrin, 2004).

A healthy balanced diet is clearly an important prevention and treatment strategy for chronic kidney disease. Patients with chronic kidney disease (pre-dialysis) are generally recommended to closely monitor and restrict daily dietary sodium and protein intake. The effective reduction of both sodium and protein has been shown to decrease blood pressure, and improve the responsiveness to anti-hypertensive medications in patients with chronic kidney disease(Cupisti et al., 2007). In addition to the improvement in blood pressure control, a restricted protein diet results in a reduction of proteinuria (Walsner et al., 1996). This reduction in proteinuria on its own is beneficial to the cardiovascular health of chronic kidney disease patient because there is a dose-response relationship between proteinuria (specifically albuminuria) and cardiovascular events (Hillege, 2002; Ibsen, 2005).

Nutrition and exercise each play an important role in decreasing the cardiovascular risk factors that are commonly seen in patients with chronic kidney disease. The combination of both diet and exercise has been shown to improve lipid profiles (Schlierf et al., 1995; Welty et al., 2002) in patients with cardiovascular disease. However, there is limited information available regarding the combined effects of both nutrition and exercise for improvement in other cardiovascular risk factors. Moreover, no investigation has examined the health benefits of a comprehensive nutrition and exercise program in patients with chronic kidney disease. Accordingly, additional research is required to determine the effect of a comprehensive nutrition and exercise program on the risk for CVD in individuals with chronic kidney disease. Therefore the proposed research program will directly address the deficits in the literature, and evaluate the effectiveness of a comprehensive nutrition and exercise program on the health status of persons with established chronic kidney disease.

1.1 Chronic Kidney Disease and Cardiovascular Risk Factors

1.1.1 Background

Chronic kidney disease is defined as either kidney damage or decreased kidney function for at least 3 months. Kidney damage can be measured by blood and/or urine markers such as proteinuria- the principal marker of kidney damage. Kidney function is best measured by glomerular filtration rate (GFR). Varying levels of GFR represent varying levels of kidney function, placing CKD into 5 stages. There is an inverse relationship between GFR and stage of CKD, such that decreasing GFR reflects progressively worsening kidney function. Stage 5 is associated with renal failure and a GFR of less than 15 mL/min/1.73m^3 of body surface area, or dialysis (Levey et al., 2003). All stages of CKD prior to Stage 5 are considered to be pre-dialyis. Stage 1 is defined as a normal GFR (≥ 90 mL/min/1.73m^3) and kidney damage (measured by blood and/or urine markers such as proteinuria). At a GFR of ≤ 60 mL/min/1.73m^3 (Stage 3), at least half the function of a normal adult kidney is lost and complications associated with chronic kidney disease increases (Levey et al., 2003).

Along with mild renal insufficiency (Wali & Henrich, 2005), cardiovascular risk factors such as abnormal lipid lipoprotein profiles (dyslipidemia), hypertension, type 2 diabetes, atherosclerosis, and physical inactivity (Hostetter, 2004; McClellan et al., 2004), are highly prevalent in the CKD population. Physical inactivity alone is an independent risk factor for CVD (Barengo et al., 2004). Engaging in physical activity can decrease the risk of dyslipidemia, high blood pressure, type 2 diabetes, and atherosclerosis, greatly decreasing the risk for cardiovascular disease (Warburton et al., 2006c). There is a positive relationship between volume of physical activity and health status, where the individuals who are most physically active have the lowest risk

(Warburton et al., 2006c). Therefore, it is important to increase physical activity in the CKD population, so to decrease the cardiovascular risk factors that are so prevalent in this population.

1.1.2 Dyslipidemia

The occurrence of dyslipidemia in the CKD population is characterized by decreased high-density lipoprotein (HDL) levels and increased triglycerides (TG) (Basile, 2007;International Society of Nephrology, 1990; Fuh et al. 1990) The decrease in HDL levels seen in the CKD population occurs as a result of impaired renal function itself (Miida et al., 2003), along with the insulin resistance prevalent in CKD patients – as insulin sensitivity decreases with a decrease in GFR (Kobayashi et al., 2005). Previous research has indicated that the decrease in HDL levels seen in CKD patients is associated with an increased fractional catabolic rate and decreased levels of apo A I (Fuh et al., 1990) – the principal apolipoprotein that defines HDL as it promotes cholesterol efflux from the tissues to the liver for excretion (Kaysen, 2006). Moreover, kidney function decline appears to be accompanied by a decline in synthetic rate of apo A I. Maturation of the cholesterol ester-poor HDL-3 to cholesterol ester-rich HDL-2 is also impaired in CKD. This is critical, as HDL can only serve its cardioprotective role of reverse cholesterol transport when it is fully matured to HDL-2 (Vaziri, 2006). Therefore, decreased HDL levels are inversely correlated with cardiovascular risk (Castelli et al., 1977; Castelli et al., 1986).

Increased TGs are also an independent risk factor for cardiovascular disease (McBride, 2008), and may increase as GFR function decreases (Samuelsson et al., 1997). Clearance of triglyceride-rich lipoproteins appears to be altered in individuals with CKD, due to reduced lipolysis and altered enzymatic activity that typically regulate

triglyceride levels (International Society of Nephrology, 1990; Vaziri, 2006). As a result, increased TGs are seen in individuals with CKD. Strategies aimed at controlling the decreased HDL levels and increased TG levels in the CKD population may in turn lower the heightened cardiovascular risk seen in these individuals.

1.1.3 Hypertension

Hypertension is a common cardiovascular risk factor in the CKD population, which gets progressively worse with declining kidney function (Agarwal et al., 2005; Basile, 2007). There is a close relationship between kidney function and hypertension, as a major function of the kidneys is to control body fluids and blood pressure (Ruilope et al., 1994). A decline in kidney function can lead to hypertension, while hypertension can also lead to kidney dysfunction (Martinez-Maldonado, 2001; Ruilope & Rodicio, 2001).

Clinical studies have shown a common trigger for hypertension is an increase in intrarenal vascular resistance (Ruilope et al., 1994). Intrarenal vascular resistance in turn triggers a number of pathophysiological changes that lead to hypertension, but this is not yet fully understood. Some of the major changes that are thought to occur, however, include a decrease in renal blood flow and in renal vasoconstriction. A decrease in renal blood flow is inversely correlated with an increase in mean blood pressure, and therefore, may lead to the development of hypertension (Ruilope et al., 1994). Renal vasoconstriction is seen in hypertensive patients, which has been shown to be a result of abnormal renal responses to angiotensin II (Shobck et al., 1983; Williams et al., 1991) or an increased sympathetic activity (Fujita et al., 1990).

Hypertension is thought to lead to renal failure in one of two ways. The first is that hypertension damages preglomerular arteries and arterioles with progressive

luminal narrowing followed by a fall in glomerular blood flow, in turn leading to glomerular ischaemia which causes the damage. An alternative theory is that the elevated pressure to glomeruli causes glomerular hyperfusion and hypertension, which leads to glomerular structural injury and can end in loss of renal function (Ruilope & Rodicio, 2001). Although systolic blood pressures correlated more strongly with cardiovascular outcomes than diastolic blood pressures (Agarwal, 2003; Stamler et al., 1993), studies have shown that improvement in diastolic blood pressure control to 90 mm Hg or lower is associated with a slower rate of decline in renal function (Brazy et al., 1989; Mancini et al., 2003; Walker et al., 1992). Therefore, not only will improvement in blood pressure control help lower the risk of cardiovascular disease directly, but it will also help slow down the progression of renal dysfunction – which is independently associated with an increased risk of CVD.

Whether or not decreased renal function is caused by hypertension or leads to hypertension; the high prevalence of hypertension in the CKD population is present and problematic. Hypertension is a strong predictor of cardiovascular disease (O'Donnell et al., 1997; Stamler et al., 1993; Whelton, 1994), therefore it is important for individuals with CKD to take measures that will help control their blood pressure.

1.1.4 Diabetes

Diabetes (both type 1 and type 2) is the leading cause of end-stage kidney disease in adults (Perneger et al., 1994). When diabetes is the underlying cause of kidney dysfunction, as indicated by proteinuria, it is referred to as diabetic nephropathy (Cooper, 1998). Uncontrolled diabetes can lead to chronic kidney disease as high amounts of glucose induce tissue damage, including the microvasculature in the glomerulus. The primary function of the glomerulus is to filter blood. Therefore, when

protein appears in the urine as a result of diabetic nephropathy, the associated decrease in GFR can only be expected (Cooper, 1998). If diabetic nephropahy is left untreated, it will lead to end-stage renal disease and dialysis or transplant would be necessary.

Hypertension is also seen at the onset of microalbuminuria – one of the first phases of development of diabetic nephropathy. Microalbuminuria is associated with CVD. Suggested explanations for this association include the presence of hypertension, dyslipidemia, and insulin resistance (Yip & Mattock, 1993). Studies have shown that there is up to a threefold increase in risk for CVD event in diabetic individuals (Kannel et al., 1979).

1.1.5 Atherosclerosis

Previous research has shown the presence of advanced atherosclerosis in individuals with CKD compared to healthy controls. Moreover, thickening of the arterial wall increased directly as kidney function decreased (Ekart, 2008; Shoji et al., 2002). Although decreased kidney function itself is directly associated with an increased thickness of arterial walls, independent of other factors, metabolic abnormalities secondary to kidney function may also contribute to advanced atherosclerosis (Jungers et al., 1997; Shoji et al., 2002). Such abnormalities include dyslipidemia, hypertension (Shoji et al., 2002), and insulin resistance (DeFronzo et al., 1981; Razani et al., 2008). Therefore, managing these metabolic abnormalities, along with an effort of minimizing further decreases in kidney function, would help decrease the risk of atherosclerosis and CVD in the CKD population.

1.1.6 Physical Inactivity

The CKD population is generally inactive, thus contributing to the pool of risk factors that increase the occurrence of CVD (Boyce et al., 1997; Johansen, 2005). Inactivity in this population is partly due to the lack of energy and heightened sense of fatigue (Klang et al., 1996). Maximal aerobic power (VO_2max) and muscle strength decrease significantly as kidney failure progresses (Kettner-Melsheimer et al., 1987). Individuals with predialysis CKD already have lower VO_2max than that of nonuremic individuals (Boyce et al., 1997). Participating in regular physical activity has shown to improve aerobic capacity as well as increase strength, and decrease cardiovascular risk factors (i.e. dyslipidemia, hypertension, blood sugar control) (Boyce et al., 1997).

There is limited research examining the health benefits of exercise in pre-dialysis CKD patients. Of the few studies available, one in particular (Boyce et al., 1997) found positive results after investigating the effects of 4 months of supervised exercise classes, which took place three times a week for 1-hour sessions of aerobic training(Boyce et al., 1997). At the end of this program, participants showed significant reductions in systolic and diastolic blood pressures and significant (15%) improvements in VO_2max (Boyce et al., 1997). There were no improvements in GFR, nor significant changes in serum lipid profiles (Boyce et al., 1997). Another study also looked at the effects of a 3 month aerobic exercise program in predialysis patients (Clyne et al., 1991). Results from this study showed improved exercise capacity in participants compared to controls due to improved muscular function (Clyne et al., 1991).

A larger number of similar studies have been performed in CKD patients on dialysis, and have shown similar results. In general, these studies involving aerobic training have shown improvements in VO_2max (Ross et al., 1989; Shalom et al., 1984;

Zabetakis et al., 1982), blood pressure control, and Quality of Life (Painter P, 2000; Suh et al., 2002). There have been mixed results with respect to blood lipids – some have shown a decrease in triglycerides(Goldberg et al., 1983; Goldberg et al., 1980; Suh et al., 2002), or an increase in high-density lipoprotein(Goldberg et al., 1983; Goldberg et al., 1980), and some show no effect on blood lipids (Ross et al., 1989; Shalom et al., 1984).

Studies examining the effects of resistance training, either alone or combined with aerobic training, in dialysis patients have shown significant improvements in strength(Castaneda et al., 2001; Headley et al., 2002; Kouidi et al., 1998; Mercer, 2002), as well as decreased muscle atrophy (Castaneda et al., 2001; Headley et al., 2002), and improved gait speed (Headley et al., 2002; Mercer, 2002). One study examined the effects of a 12-week combined aerobic and resistance training program on pre-dialysis CKD patients compared to healthy subjects engaging in the same program and controls not participating in the program (Heiwe et al., 2001). Significant improvements were seen in muscular strength, dynamic endurance, walking capacity, and functional mobility in both CKD patients and healthy subjects (Heiwe et al., 2001). Although pre-dialysis CKD patients started out with lower muscle function and mobility compared to healthy subjects, they were able to improve after the program to the same extent as healthy subjects (Heiwe et al., 2001). Therefore, it is quite evident that eliminating physical inactivity in the pre-dialysis CKD population has the potential to improve health-related physical fitness (Warburton et al., 2006b).

Engaging in regular physical activity will most likely aid in decreasing the CVD risk factors commonly present in the CKD population. Previous research in pre-dialysis CKD patients has shown significant decreases in both systolic and diastolic blood pressures after 4 months of exercise training (Boyce et al., 1997), and these significant reductions were also seen in CKD patients after only 2 months of exercise training

(Painter et al., 1986). With respect to dyslipidemia commonly seen in this population - although there were no significant improvements in blood lipids seen in pre-dialysis patients after an exercise intervention, one study observed reductions in total cholesterol and triglycerides (Boyce et al., 1997) after 4 months of exercise training. Significant improvements in blood lipids (decreased triglycerides, increased HDL cholesterol) in the CKD population have been seen in studies with exercise interventions of longer duration (12 months)(Goldberg et al., 1986; Harter et al., 1985).

Diabetes has also been shown to be a predictor of cardiovascular mortality in the CKD population(Shlipak et al., 2005). Engaging in physical activity helps prevent type II diabetes in a healthy population as well as increases insulin sensitivity (Helmrich et al., 1991; Holloszy et al., 1986; Warburton et al., 2006a). Therefore, it can be assumed that CKD patients have the potential of reaping similar benefits by engaging in regular physical activity.

As mentioned above, atherosclerosis (thickening of the arterial wall) is inversely correlated with kidney function (Ekart, 2008; Shoji et al., 2002). Research has shown that atherosclerosis is more prevalent in inactive individuals and less prevalent in regular exercisers (Lakka et al., 2001). Metabolic abnormalities secondary to kidney function, such as dyslipidemia, hypertension (Shoji et al., 2002), and insulin resistance (Razani et al., 2008), also contribute to atherosclerosis in the CKD population. As engagement in regular physical activity helps decrease these CVD risk factors, as well as lowering the occurrence of atherosclerosis in the healthy population, CKD patients would also most likely benefit from physical activity.

1.1.7 Kidney Function

Studies have shown an inverse relationship between kidney function and cardiovascular events such that a decrease in kidney function (e.g., GFR) is associated with an increased risk of cardiovascular events and death independent of other cardiovascular risk factors (including hypertension, diabetes, dyslipidemia, and prior CVD) (Basile, 2007; Go et al., 2004; Henry et al., 2002; Herwig-Ulf Meier-Kriesche, 2004; Muntner et al., 2002; Weiner et al., 2004). There are many factors that may interplay with GFR levels to increase the risk of cardiovascular events, but the specific pathophysiology behind it remains unknown (Go et al., 2004).

1.2 Impact of Exercise on CV Risk Profile in the CKD Population

1.2.1 Musculoskeletal Fitness

The musculoskeletal system consists of four components: muscular strength, muscular endurance, muscular power, and flexibility (Warburton et al., 2001b) Improvements in musculoskeletal fitness is positively associated with health-related quality of life and independence (Warburton et al., 2001a). Enhanced musculoskeletal fitness also indirectly decreases the risk for CVD as improvements in musculoskeletal fitness have been shown to decrease certain cardiovascular risk factors (Goldberg et al., 1984; Miller et al., 1984; Pollock & Vincent, 1996; Smutok et al., 1993). For example, resistance training may improve body composition, help treat/control hypertension, decrease abdominal obesity, and help control glucose metabolism especially in those with abnormal glucose metabolism (Warburton et al., 2001a).

1.2.1.2 Muscular Strength

Muscular strength is defined as the maximum tension or force a muscle can exert in a single contraction (Canadian Society for Exercise Physiology, 2003). It is likely that muscular weakness is an important limitation to physical function in individuals with CKD (Johansen, 2005). This in turn will only further lead to inactivity and an increased risk of CVD. It also can lead to decreased functional status and therefore a decreased sense of independence, especially in the elderly (Warburton et al., 2001a). The decline in muscle strength present in the pre-dialysis CKD population, when compared to individuals without CKD, is a result of muscle fibre atrophy as there appears to be a maintenance of muscle cross-sectional area (Leikis et al., 2006; Sakkas et al., 2003). The likely factors that may be associated with fibre atrophy in the CKD population, aside from sarcopenia – the natural process of losing muscle strength with age, include metabolic acidosis (Mitch & Goldberg, 1996), peripheral neuropathy (Sakkas et al., 2003), and malnutrition from a decreased protein/caloric intake (Fahal et al., 1997). Although not as significant as the latter, disuse atrophy in locomotor muscles also contributes to fibre atrophy in CKD patients, due to the high prevalence of physical inactivity seen in this population (Kouidi et al., 1998).

1.2.1.2.1 Uremic Myopathy

Muscular function declines with worsening kidney function and increasing age (Brodin et al, 2001; Heiwe et al., 2001). Past research has shown that exercise capacity declines and muscle weakness increases in parallel to a worsening renal function(Clyne, 1994). Muscular atrophy seen in the CKD population is often described as a

consequence of uremic myopathy (Kouidi et al., 1998), which refers to the functional and structural muscle abnormalities in this population as a consequence of the uremic state itself (Campistol, 2002). Clinical symptoms of uremic myopathy include weakness, exercise limitation, limited endurance, and rapid-onset tiredness(Clyne, 1996).

The pathogenesis of uremic myopathy is not yet completely understood, but evidence to date shows it involves a multitude of contributing factors. Included among these factors are malnutrition and protein deficiency (Kopple, 1978), muscle fiber atrophy(Leikis et al., 2006; Sakkas et al., 2003), the accumulation of uremic toxins in muscles including secondary hyperparathyroidism (Smogorzewski et al., 1988; Thompson et al., 1993), carnitine deficiency (Ahmad et al., 1990), and suboptimal muscle oxygen utilization (Campistol, 2002).

1.2.1.2.2 Grip Strength

A simple, non-invasive method of measuring strength is with the handgrip dynamometer. An individual contracts muscles in the forearm against a stiff spring, and the dynamometer displays a score of strength in kilograms. Grip strength is an accurate measure to determine an individual's overall muscular strength (Canadian Society for Exercise Physiology, 2003). Previous research has shown grip strength with a hand dynamometer to not only be a valid test of strength, but also of health-related physical fitness (Marino et al., 1982; Mathiowetz et al., 1984; Warburton et al., 2006a; Warburton et al., 2006b). Grip strength is related to premature morbidity and mortality; with a decrease in strength correlating to an increase in morbidity and mortality (Fujita et al., 1995; Metter et al., 2002; Rantanen et al., 1998; Warburton et al., 2006a). Past research has also shown that individuals with a lower grip strength have a higher incidence of

chronic diseases, including diabetes and coronary heart disease (Warburton et al., 2006a), which are both highly prevalent in the CKD population.

1.2.1.3 Flexibility

Flexibility makes up another component of musculoskeletal fitness, in addition to muscular strength and endurance (Rantanen, 1998; Kell et al., 1998). It is defined as the range of motion about a joint (American College of Sports Medicine, 1991). Previous research has shown that flexibility decreases with age (Chapman et al., 1972), however an increased rate of decline in flexibility is seen in inactive individuals (Kell et al., 1998). This occurs as inactivity causes degeneration of collagen fibres, cross-linkage formed between adjacent collagen fibrils, joint surface deterioration, decreased viscosity of synovial fluid, and decreased muscle mass (Brooks et al., 1996; Goldspink & Harridge, 2007). Therefore, engaging in physical activity will help prevent a decrease in flexibility, which will improve quality of life as flexibility relates to independent living and an improved ability to perform ADLs (Warburton et al., 2001a).

The sit and reach test is a valid method to measure flexibility (Jackson & Baker, 1986; Jones et al., 1998). It measures hamstring flexibility, which is included in a high number of current fitness tests as decreased hamstring flexibility is associated with lower back pain, postural deviations, gait limitations, increased risk of falling, and an increased risk of musculoskeletal injuries (American College of Sports Medicine, 1995; Grabiner et al., 1993; Jones et al., 1998).

1.2.1.4 Effects of Exercise

Aerobic exercise training helps improve physical functioning and performance, while resistance training appears to improve muscular strength and endurance (Kell et

al., 1998), physical functioning (Johansen, 2005), and aerobic capacity owing to improved muscular strength (Hickson et al., 1980). Previous research has shown exercise training programs to be effective in decreasing muscle fibre atrophy in the CKD population, and therefore, increasing muscular strength (Clyne et al., 1991; Kouidi et al., 1998). Resistance training has been shown to improve functional status and maintain independence by decreasing the loss of muscle strength that comes with aging (American College of Sports Medicine, 1998a). This in turn may improve bone health, decrease number of falls and fractures due to an increased bone mineral density, and improve an individual's ability to engage in ADLs - preventing disability (Warburton et al., 2001b). Also related to functional status, previous research has shown the increase in muscular strength that results from resistance training improves gait speed and mobility (Buchner, 1997; Hunter et al., 2004; Judge et al., 1993b), which are directly related to independent living (Buchner, 1997).

Flexibility also relates to independent living and an improved ability to perform ADLs (Warburton et al., 2001a). Although there is an age-related decline in flexibility, a lot of it can be attributed to inactivity (Warburton et al., 2001a) – which is frequently seen in the CKD population. Individuals participating in resistance training and flexibility exercises a minimum of 2 times a week will most likely experience an improved quality of life as it will help maintain functional status (Warburton et al., 2006e), and the same is likely true for the inactive CKD population.

Aerobic exercise has shown to improve muscle oxygen utilization in healthy individuals (Ingjer, 1979). Therefore, one might assume that the same benefits will be seen in the CKD population as they have suboptimal muscle oxygen utilization during exercise (Campistol, 2002). As muscular strength, endurance, and flexibility are included in the components of musculoskeletal fitness (Kell et al., 1998), an increase in these components will improve musculoskeletal fitness. The benefits associated with an

enhanced musculoskeletal fitness include decreased cardiovascular risk factors, especially positive changes in body composition, decreased basal insulin levels, lower insulin response post-glucose ingestion, and improvements in lipid profiles (Goldberg et al., 1984; Miller et al., 1984; Pollock & Vincent, 1996; Smutok et al., 1993). .Benefits also include an improved quality of life and independence (Buchner, 1997; Hunter et al., 2004; Judge et al., 1993a; Warburton et al., 2001a; Warburton et al., 2006e)

1.2.1.5 Body Mass Index

Body Mass Index (BMI) is a measure of body weight that takes into account height (weight in kg / height in meters^2) (Calle et al., 1999). A healthy weight category for BMI is 18.5 – 24.9, overweight individuals are classified by a BMI of 25 – 29.9, and obese individuals are classified by a BMI of 30 or more (Gilmore, 1999) . However, Asian populations should be considered high-risk with a BMI of 24 or more (Wildman et al., 2004), as these populations tend to have a higher percentage of body fat than Caucasian populations for a given BMI (Chang et al., 2003; Hayano et al., 1999). Previous research has shown there to be a correlation between an increased BMI, a decreased GFR (Hsu et al., 2006; Kawamoto et al., 2008). Obesity itself is an independent risk factor for CKD (Kramer, 2006). Overweight and obese individuals (BMI > 25) are more likely to develop end-stage kidney disease compared to those with a normal BMI, independent of diabetes, lipids, smoking status, and hypertension (Fox et al., 2004; Hsu et al., 2006; Kawamoto et al., 2008).

Obesity, and an increased BMI is associated with a higher risk for development of cardiovascular risk factors (Dalton et al., 2003) and subsequent cardiovascular disease (Field et al., 2001; Hubert et al., 1983). Past research has shown previously sedentary overweight and obese individuals who participate in exercise programs to decrease BMI

in men, and prevent weight gain (measured by weight in kg and BMI) in women compared to their non-exercise controls who gained weight (Donnelly et al., 2003). Similarly, significant weight loss was seen in moderately obese women after participation in an 18-month exercise intervention (Donnelly et al., 2000). Kidney function decreases as BMI increases (Chagnac et al., 2003), therefore it is important for individuals with pre-dialysis CKD to engage in physical activity in order to prevent a worsening of kidney function and further increases in CVD risk. Although these benefits are seen with a decreased BMI, it is also important to look at other measures of body composition as improvements in body composition may occur without any change seen in BMI (Frankenfield et al., 2001).

1.2.1.6 Waist Circumference

Waist circumference (WC) is another measure used to assess health risk, but is positively correlated with abdominal fat content which is an independent predictor of heath risk factors (American Dietetic Association, 1998). The risk of developing health problems is increased with a waist circumference > 102 cm in men and > 88 cm in women of Caucasian origin (Health Canada, 2003; Okosun et al., 2000). However, because differences in body composition are seen among different ethnic groups, cut-off points for WC must also be different (Misra et al., 2005). Evidence has shown Asian populations to have a higher percentage of body fat than Caucasian populations for a given waist circumference (Deurenberg et al., 1998), cut-offs in identification of high-risk Asian patients should be lower. Wildman et al. showed a waist circumference of 80 cm in both men and women are more appropriate to identify Chinese patients with higher CVD risk factor (Wildman et al., 2004). Research has shown that lower cut-off points than what is currently accepted for WC values are also more appropriate for populations

from Poland (Lopatynski et al., 2003), Brazil (Velasquez-Melendez et al., 2002), West Indies (Sargeant et al., 2002), Mexico (Berber et al., 2001), and Iran (Mirmiran et al., 2004). There are also different race-ethnicity-specific WC cutoffs for non-hispanic blacks, Mexican-Americans, non-hispanic whites, African-Americans, and European-Americans (Zhu et al., 2005). Individuals with larger waist circumferences are at a higher risk for CVD as a higher WC is correlated with higher cardiovascular risk factors (Han et al., 1995). Furthermore, within each BMI category (healthy weight, overweight, and obese) individuals with high WC values are at an increased health risk than those with normal WC values (Janssen et al., 2002). This measurement of WC within BMI categories has been shown to better predict health and cardiovascular risk (American Dietetic Association, ; Ardern et al., 2003; Janssen et al., 2004). An increase in physical activity, or participation in exercise programs, will help individuals prevent weight gain or help lose weight as shown by a decrease in WC (American Dietetic Association 1998; Sternfeld et al., 2004).

1.2.1.7 Aerobic Capacity

Individuals with end-stage kidney disease have markedly decreased VO_2max values compared to healthy sedentary controls (Barnea et al., 1980; Kettner-Melsheimer et al., 1987; Latos et al., 1987; Painter et al., 1986). In this population, VO_2max improves by an average of 15% with aerobic exercise training for 8 weeks to 6 months (Johansen, 2005). Although there is not much research about the effects of physical activity and VO_2max in pre-dialysis CKD patients, the research that is present shows similar benefits as that seen in end-stage kidney disease patients where there is an improvement in VO_2max values (Boyce et al., 1997; Clyne et al., 1991). In these studies with pre-dialysis

CKD patients, subjects trained 3 times a week for either 3 or 4 months at a moderate intensity.

It is important to consider aerobic capacity in CKD patients and their ability to improve it. A physically inactive lifestyle in this population has been correlated with increased cardiovascular risk factors, as this type of lifestyle can exacerbate metabolic and cardiovascular abnormalities (Goldberg et al., 1986). Therefore, understanding that pre-dialysis CKD patients can improve their aerobic capacity, gives hope that physical activity can be used in this population to help decrease the presence of cardiovascular risk factors.

1.2.1.8 Arterial Compliance

Arterial compliance is defined as a change in volume for a given change in pressure (McVeigh et al., 2002). The walls of all arteries in the body are distensible - they expand and contract as blood pressure waves from the heart pass through the lumen of arteries (Cohn, 2001). The pressure wave generated from the transmitted flow of blood from the heart during systole is reflected and returned to the heart on arrival at branch points or sites of impedance mismatch (Soungas & Asmar, 2007). In healthy individuals with elastic vessels, this reflected pressure wave is returned to the heart during diastole, where it either merges with the pulse that generated it or is seen soon after it (Soungas & Asmar, 2007). However, in individuals with less compliant (more stiff) arteries the reflected wave arrives back earlier causing augmentation of systolic pressure and a consequent decrease in diastolic pressure (Mackenzie et al., 2002). Thus being said, it is the velocity at which the pressure wave travels through the arteries that is influenced by the stiffness of the arterial walls – the stiffer the walls, the higher the velocity (Mackenzie et al., 2002), and higher risk for cardiovascular-related morbidity and

mortality. Reduced arterial compliance, is directly associated with CVD and cardiovascular-related events (Grey et al., 2003; Mancini et al., 2004).

There are different methods of measuring arterial compliance, but one that proves to be valid and easy to conduct is the pulse wave velocity (PWV) technique. Pulse wave velocity measures the speed of travel of the pulse wave along an arterial segment of known length ($PWV = D/\Delta T$). Two pulse wave forms are recorded at known distances (D) apart in order to measure the time delay between these recorded waves by applanation tonometry. Transit time (ΔT) is calculated using the first wave at the proximal site and second wave at the distal end. Continuous pulse wave signals are measured with pressure tonometers placed on the maximal arterial pulse (Soungas & Asmar, 2007). This technique slightly flattens the arterial wall. By normalizing circumferential stresses in this way, the electrical resistance of a small piezoelectric crystal in the tip of the tonometer varies directly with intra-arterial pressure (Hayward et al., 2002). This allows for an accurate recording of the pressure waveform. Increased PWV reflects a more elastic vasculature.

Another technique of measuring arterial compliance that proves to be valid is referred to as pulse contour analysis. This analysis is performed on a 30 sec collection of radial artery blood pressure waveforms (Diagnostics, 2001). These waveforms are collected using a sensor placed over the radial artery (Cohn, 2001) at the point of greatest pulsation (Diagnostics, 2001). The sensor contains a piezoelectric element along with internal circuitry that strengthens the waveform signal (Diagnostics, 2001), which is then displayed on a computer screen. Results from a computer assessment of the diastolic decay of collected arterial waveforms are based on a modified Windkessel model (electrical analog model) representing the vasculature of a capacitive compliance element (large artery elasticity index), an oscillatory compliance element (small artery elasticity index), an inductance and a resistance (systemic vascular resistance) (Cohn,

2001; Diagnostics, 2001). The arterial waveforms are calibrated with a cuff on the opposite arm that senses the oscillations created by blood as it starts flowing back into the arm (Cohn et al., 1995). The sensor adjusts itself with repeated calibrations until an optimal, stable waveform is achieved (Cohn et al., 1995). This waveform is then stored into a computer system for compliance analysis (Cohn et al., 1995). The computer system uses the modified Windkessel model to analyze and display results (Diagnostics, 2001).

Chronic kidney disease patients have reduced arterial compliance (Covic et al., 2005; Toussaint & Kerr, 2007; Wang et al., 2007). An association is seen between a decreasing GFR and decreasing arterial compliance (Lacy et al., 2006), and patients with end-stage renal disease (ESRD) have higher PWV values than age-matched healthy individuals (Safar et al., 2002). This indicates that a decrease in kidney function further reduces arterial compliance. A reduced arterial compliance has been associated with increased cardiovascular risk factors in the CKD population (Covic et al., 2005; Wang et al., 2007). Therefore interventions to try and improve arterial compliance may help prevent cardiovascular-related mortality in this population.

Aerobic exercise programs have improved arterial compliance in previously sedentary healthy individuals (Cameron & Dart, 1994; Tanaka et al., 2000). There are a few different explanations about the physiological mechanics behind how exercise improves arterial compliance. One suggestion is that regular physical exercise increases nitric oxide formation resulting in vasodilatation and a reduction in peripheral vascular tone (Hornig et al., 1996). Also, studies have shown a reduction in sympathetic activity with a shift towards enhanced vagal activity after training in patients with congestive heart failure (Coats et al., 1992; Middlekauff et al., 1998). Other possible causes of the improvement in arterial compliance seen after exercise include decreased wall thickness or intrinsic changes in wall composition and smooth muscle activation, as well as an

altered loading of collagen and elastin (Parnell et al., 2002). There is no present research studying the effects of exercise on arterial compliance in pre-dialysis CKD patients, and given results seen in previous literature on the beneficial effects of exercise on cardiovascular health, it is highly likely that similar beneficial results will be seen in the CKD population.

1.2.1.9 Decreased Blood Pressure

A previous study examined the effects of 4 months of aerobic training, 3 times per week, at a moderate intensity (starting at 50 – 60% heart rate reserve, gradually increasing to 70%) in pre-dialysis CKD patients on blood pressure (Boyce et al., 1997). There was a significant reduction in both systolic and diastolic blood pressure after exercise training, when compared to baseline, with greater changes seen in systolic blood pressure (mean decrease of 20 mmHg) than diastolic (mean decrease of 11 mmHg). After 2 months of detraining, these patients had significantly higher blood pressures than what was seen after exercise training (Boyce et al., 1997), showing the exercise training itself is what decreased blood pressure. Another study showed haemodialysis patients that participated in a similar exercise program for 3 months had a reduction in antihypertensive medication, when compared to a control group who did not engage in exercise (Miller et al., 2002).

The proposed mechanisms for the blood pressure lowering effects of exercise in individuals with hypertension (but not necessarily with CKD) include neurohumoral, vascular, and structural adaptations (Pescatello et al.). Possible explanations for the antihypertensive effects of exercise include decreases in catecholamines and total peripheral resistance, improved insulin sensitivity, and alterations in vasodilators and vasoconstrictors (Pescatello et al.). Although no conclusions can be made about the

specific mechanisms behind the benefits exercise has on blood pressure, it is well known that it does help lower blood pressure in a hypertensive CKD population.

1.2.1.10 Heart Rate Measurements

1.2.1.10.1 Resting Heart Rate

The risk of mortality and cardiovascular deaths increases progressively in relation to increases in resting heart rate (Dyer et al., 1980; Gillum et al., 1991; Greenland et al., 1999; Kannel et al., 1987). There have been no previous studies that looked at resting heart rate in the pre-dialysis CKD population, and none have been done on the effects of exercise on resting heart rate. However, because the risk of cardiovascular deaths increases as heart rate increases, it is important to look at the effects of an intervention on resting heart rate.

1.2.1.10.2 Heart Rate Variability

Heart rate variability (HRV) is a non-invasive method of measuring autonomic activity in the heart (Ranpuria et al., 2008). It demonstrates the amount of change between RR intervals (or heart rate) from one cardiac cycle to the next (Ranpuria et al., 2008). Heart rate is recorded with an electrocardiogram, and the variability between RR intervals upon analysis serves as markers of autonomic regulation of the heart (Bernardi et al., 1996). There are various ways of quantifying HRV, but two of the most common include time-domain and frequency-domain measures (Ranpuria et al., 2008).

Time-domain analysis measures normal RR intervals, and from this various measurements can be extrapolated. These measurements include the standard

deviation of all normal RR intervals (SDNN), the root-mean square of the difference of successive RR intervals (rMSSD), and the number of times per hour that two consecutive RR intervals differ by more than 50 ms over 24 hours (pNN50) (Ranpuria et al., 2008). A high HRV, denoted by a high SDNN and its variables, is seen in normal individuals without CVD (Ranpuria et al., 2008).

Frequency-domain analysis separates heart rate into constituent frequency component. Fast Fourier transformation accomplishes this by breaking down the heart rate signal into a set of sine and cosine waves (Ranpuria et al., 2008). High frequency (HF) interval variability, 0.15-0.40 Hz, relates to parasympathetic influence, while low frequency (LF), 0.04-0.15, relates to both sympathetic and parasympathetic influence (Bernardi et al., 1996). The LF:HF ratio represents a measure of parasympathetic-sympathetic balance, and therefore of autonomic status (Bernardi et al., 1996). Previous research has shown that shifts in HRV away from parasympathetic influence and predominance towards sympathetic predominance is correlated with an increased risk for CVD (Ditor et al., 2005), as HRV measures activity at rest. However, there is a decreased risk for CVD when shifts towards parasympathetic predominance are seen – noted by decreases in LF:HF ratio and decreases in LF (Ditor et al., 2005).

Low HRV has been linked with an increased occurrence of cardiovascular morality and risk factors (Bruyne et al., 1999; Liao et al., 1997). There is not much research that has studied the HRV in the pre-dialysis CKD population, however a previous study shows predialysis CKD individuals to have a decreased HRV compared to individuals with normal kidney function (Furuland et al., 2008).

Low physical activity, as seen in the CKD population is a strong predictor of worsened HRV. However, engaging in regular physical activity improves HRV (Earnest et al., 2008; Felber Dietrich et al., 2008; Kiilavouri et al., 1995). Although no previous research shows the effect of physical activity on heart rate variability in pre-dialysis CKD

patients, one could assume it would improve HRV as engagement in regular physical activity has shown a beneficial effect on HRV in end stage CKD patients (Deligiannis et al., 1999).

1.3 Impact of Nutrition on CV Risk Factors in the CKD Population

1.3.1 The CKD Diet

Individuals with CKD benefit from a modified diet low in protein, sodium, potassium and phosphate. In CKD patients, protein-rich foods can lead to metabolic acidosis and accumulation of uremic toxins (Mitch et al., 2004). Waste products of protein accumulate in the body proportionately to the degree of renal insufficiency (Mandayam et al., 2006). Protein intake will determine the level of urea production and the production of other nitrogenous waste products – which can be measured by serum urea nitrogen (Maroni et al., 1985). As uremic symptoms are correlated with the level of serum urea nitrogen, this would explain the reduction of uremic symptoms in predialysis patients consuming low protein diets (no more than 0.8 g of protein/kg per day plus 1 g of protein per gram of proteinuria) (Gin et al., 1994; Walser et al., 1999). In turn, protein restriction delays the need for dialysis (Walser et al., 1999). The forestalling of dialysis may also occur due to the possibility that a low protein diet slows the progression of GFR decline, however studies are still inconclusive (Fouque et al., 1992; Levey et al., 1996).

Not only will the accumulation of waste nitrogen be reduced with a low-protein diet, but it will also reduce phosphates, acid, and salt. Therefore, low-protein diets will help reduce the likelihood of the pre-dialysis CKD patient to develop hypertension, hyperphosphatemia, and metabolic acidosis (Aparicio et al., 2000; Mitch et al., 2004).

Registered Dietitians in nephrology can effectively review diet options to individuals with CKD, as dietary recommendations will vary based on individual preferences, kidney function, and various other health parameters. They are able to provide necessary guidance and support to these individuals, and are the nutrition information resource for practitioners treating pre-dialysis CKD patients (Stall, 2008).

2 Objectives

The primary purpose of this research program was to determine whether a comprehensive nutrition (counseling and cooking classes) and exercise program would reduce the risk for cardiovascular disease in persons with chronic kidney disease, compared to a control chronic kidney disease population not enrolled in the comprehensive program.

3 Hypotheses

3.1 Effect of Nutrition and Exercise Intervention on Cardiovascular Disease Risk

It is anticipated that a novel nutrition and exercise intervention will significantly reduce the risk for cardiovascular disease of patients with chronic kidney disease.

3.2 Effects of Intervention compared to Usual Care

We anticipated that the patients participating in the comprehensive nutrition and exercise program will exhibit reduced cardiovascular risk over the course of the intervention (in comparison to usual care).

4 Research Methods

4.1 Participants

We recruited 36 patients with chronic kidney disease - 21 were used as participants for the study, and 15 were used as controls. There was a lower number of participants in the control group due to a higher number of drop-outs, likely due to the fact that there was less motivation to participate in this group. The criteria for inclusion in the study included: (1) an estimated GFR of 20 – 50 mL/min for ≥ 3 months; (2) proteinuria ≥ 1 gram/day; (3) adult (≥ 19 years of age); and (4) physician approval to exercise. Participants also included individuals with co-morbidities such as hypertension, type 2 diabetes, and established cardiovascular disease. This was to maximize the ecological validity of the proposal and the potential transferability of the findings of the study to the treatment of patients with chronic kidney disease (who often exhibit multiple chronic conditions).

4.1.1 Recruitment

Chronic kidney disease subjects were recruited through an established collaboration with a nephrologist and Richmond Family Practice Physicians. We contacted the physicians directly, and distributed recruitment posters to nephrology clinics in hospitals within the Vancouver area.

If interested, physicians selected eligible patients and referred them to come to the Garratt Wellness Centre in Richmond for an information session about the CKD diet and benefits of exercise, as well as information on our program. Patients were handed out consent forms if interested, and were cleared by their doctor prior to starting the

program.

4.1.2 Sample Size

Using a moderate to large effect size, preliminary calculations revealed we would need to recruit 102 subjects total (51 participants, and 51 controls) in order to obtain a power of 90% for this study. A hypothesized difference in proportion of 0.3 (α = 0.5, power of 90%) was estimated in improvement levels of primary outcome variables. Sample size was chosen in consultation with a statistician from the Vancouver Coastal Health Research Institute. However, only 45 participants were recruited who met inclusion criteria and who were willing to participate in our program. Of these 45, 36 completed the entire length of our program. Dropouts were mostly due to illness, and one death (unrelated to the program and due to previously undiagnosed cancer).

4.1.3 Experimental Group

The patients in the experimental group received individual nutrition counseling in English, Cantonese, or Mandarin (to accommodate the three major languages spoken in the Richmond region). These patients attended a 5-week “cooking with kidney disease” course (1 x 2-hour sessions per week) and one week (1 x 1-hour) shopping tour in one of the above languages. Cooking classes included a renal cookbook with recipes, and education sessions with a Registered Dietitian and cook educator in one of the above languages. Each week focused on a different nutrition topic (self-management, sodium, protein, potassium, phosphate, label reading/eating out) where the Registered Dietitian first educated participants on the weekly topic, and the cook then guided the class in cooking the recipes relevant to the topic that week.

Dietary guidelines were individualized to participants by a RD, who set individual guidelines based on lab values and degree of kidney dysfunction. The majority of participants, however, were on a 2 g sodium restriction, and a conservative amount of protein (around 0.8 g protein/kg/day). If the participants had excessive losses of protein with proteinuria, they were recommended to increase their intake according to losses (i.e. proteinuria of 6 g, then replace another 6 g of protein in their diet). Phosphate and potassium were restricted on an individual basis according to specific lab values of the individuals.

At the end of the nutrition component, the patients engaged in a 12-week supervised exercise training program at the Garratt Wellness Centre in Richmond. The Garratt Wellness Centre offers specialized programs, education and resources to help Richmond residents manage their chronic conditions and improve the quality of their lives. The centre has a fully equipped kitchen and gym. All training sessions were created and supervised by a nurse and a CSEP-Certified Exercise Physiologist. At the beginning and end of each class, each participant took their blood pressure with an automated blood pressure cuff (BP TRU, BPM-100). At the beginning of each class they also put on a heart rate monitor (Polar, FS1;US model # 190027166). Each participant was given an exercise log on the first exercise class which included their individualized target heart rate ranges for the warm-up, cardio, and cool-down portions of the aerobic component of the class. They recorded their blood pressures, heart rates, and RPE for each stage of aerobic exercise into this log every class.

The training consisted of 60 min aerobic and resistance exercise sessions conducted 3 days per week for 12 weeks. The aerobic training portion consisted of continuous 30 min of exercise on the cardiovascular equipment of their choice (treadmill, cross-trainer, stationary bike, recombinant bike, rowing machine) in the gym of the wellness centre. For this portion, participants engaged in a 10 min warm-up at a very

light intensity (< 20% of individualized heart rate reserve or < 2 RPE), followed by 20 min of cardiovascular exercise at a moderate intensity (40-59% of heart rate reserve or 4 – 6 RPE) broken into two 10 min stations (i.e. 10 min on a treadmill, 10 min on a bike). The aerobic portion ended in a 5 min cool-down at a very light intensity with all resistance removed. Participants were progressed gradually during the program as most were unaccustomed to exercise upon commencement. Participants started with the full warm-up and ended with the full cool-down, but only engaged in 10 min cardio for the first week, and 15 min cardio for the next few sessions until they reached the full 20 min of cardio exercise. This was not only to prevent injury and risk of cardiovascular events in an inexperienced population, but also to increase compliance (Johansen, 2005).

After the aerobic portion, a CSEP-Certified Exercise Physiologist led the class through the resistance training portion. This portion followed standardized guidelines for rehabilitation settings consisting of 1 set of 8 – 10 exercises (with large muscle groups - Hamstrings, Gluteus muscles, Gastrocnemius/Soleus, Pectoralis Major, Latissimus Dorsi/Rhomboids/Erector Spinae, Biceps, Triceps) performed at a moderate intensity (approximately 10 – 15 repetitions), but was progressed gradually as tolerated to avoid injury. The exercises were performed with resistance bands.

4.1.4 Control Group

The patients in the control group received standard care for chronic kidney disease including regular visits to their physician and a dietitian if necessary.

4.2 Procedure

All patients participated in baseline, 6 month, and 12 month testing sessions. The 6 month time point was post-nutrition classes, and 12 month time point marked the end of the exercise classes, and therefore, the end of the comprehensive program.

Both groups of CKD patients, subjects and controls, went through the same testing procedures following the same time lines throughout the study (at baseline, 6 month, and 12 month). During the first testing session, patients were given consent from their doctors to participate in exercise, provided written informed consent, and completed a Par-Q. During each testing session, the patients filled out a Healthy Physical Activity Participation Questionnaire. Each of the 3 testing sessions was broken down into 3 parts: (1) anthropometric and musculoskeletal fitness measures (weight, height, waist circumference, grip strength, flexibility, skinfold measurements); (2) resting measures of cardiovascular health (blood pressure, arterial compliance, and heart rate variability); and (3) 6-minute submaximal walk test.

4.2.1 Testing Part 1

4.2.1.1 Body Mass, Standing Height, and Waist Circumference

Body mass (kg) was measured with an electronic scale (Zenith, Guangdong, China), and recorded at the beginning of each of the 3 testing sessions. Patients were instructed to remove their shoes, and step onto the scale. Their weight was recorded to the nearest 0.1 kg (Canadian Society for Exercise Physiology, 2003). Height (m) was recorded using a stadiometer (Seca, Model 214, Ontario, CA). Patients were told to stand without footwear with their back straight against the measuring stick of the

stadiometer, and heels against the base. They were instructed to take a deep breath in, at which point their height was recorded to the nearest 0.5 cm (Canadian Society for Exercise Physiology, 2003). Waist circumference (cm) was measured using a small anthropometric measuring tape, placed horizontally midway between the iliac crest and bottom of the rib cage. Participants were asked to take a normal inhalation and the measurement was recorded at the end of normal expiration to the nearest 0.5 cm (Canadian Society for Exercise Physiology, 2003). The measurement was read on the right side of the individual.

These measurements were recorded at the beginning of each testing session, followed by measurements of grip strength (hand dynamometer (kg)), flexibility (sit-and-reach (cm)), and skinfold measurements at 5 sites (triceps, biceps, subscapular, iliac crest, medial calf (mm)).

4.2.1.2 Grip Strength

Patients were told to stand with their feet shoulder width apart, and to squeeze the hand dynamometer as hard as they could. They did this with each hand, and the experimenter recorded the force (kg) they achieved. They were asked to repeat the test in order to achieve accuracy of results.

4.2.1.3 Flexibility

Patients were asked to stretch their hamstrings for 20 – 30 seconds for each leg, demonstrated by a CSEP-CEP, in order to prepare them for the sit-and-reach flexibility test. After removing their shoes, patients were instructed to keep their feet flat against the sit-and-reach box. They were told to keep their knees unbent, take a breath in, and

with one hand over the other exhale as their fingertips push the sliding marker as far as they can along the measuring stick on the sit-and-reach box. This distance was recorded in centimeters.

4.2.1.4 Skinfold Measurements

A CSEP-CEP took skinfold measurements at 5 sites (triceps, biceps, subscapular, iliac crest, medial calf) using a HarpendenTM skinfold caliper, according to Canadian Physical Activity, Fitness and Lifestyle Appraisal (CPAFLA) guidelines on positioning of the caliper at each site (Canadian Society for Exercise Physiology, 2003). All measurements were first land marked according to CPAFLA guidelines and measurements were made on the right side of the body to the nearest 0.2 mm. Two full sets of measurements were taken, in the order listed above. If there was difference greater than 0.4 mm between the two measurements, a third was taken. The closest two measurements were averaged (Canadian Society for Exercise Physiology, 2003). The sum of five skinfolds (SO5S) was determined by adding the mean values for each skinfold in mm.

4.2.2 Testing Part 2

This portion of testing was taken in a dark, quiet room in order to obtain resting measures of blood pressure, arterial compliance, and heart rate variability. Patients started lying supine, and a 3-lead ECG was placed on them as well as an automated blood pressure cuff. Arterial compliance was measured at rest. The patient then underwent 5-10 min of supine rest, and beat-by-beat arterial blood pressure (finger photoplethysmography) and heart rate (via a 3 electrode, single lead system) was

recorded. The patient then stood up quickly and remained standing for the next 5 mins, and standing measures of beat-by-beat blood pressure and heart rate were recorded. Upon standing, if the subject felt dizzy, nauseated, light-headed, or faint, they were told to stay sitting until these symptoms subsided. All pre-syncopal symptoms were recorded.

4.2.2.1 Blood Pressure

Blood pressure was measured beat-by-beat via finger phytoplethysmography (Finapres; Ohmeda) during both 5 min supine rest and 5 min standing rest. The cuff was placed on the middle or index finger of the subject's right hand. Readings obtained from the Finapres were verified and corrected using automated blood pressure measurements which were taken simultaneously on the right arm during the same 10 mins. The following formula was used to calculate mean arterial pressure (MAP): [(SBP-DBP)/3] + DBP. A data acquisition system (Powerlab 16/30, ADInstruments, Colorado Springs, CO) was used to record beat-by-beat blood pressure.

4.2.2.2 Arterial Compliance

We used the HDI/Pulse Wave CR-3000 Cardiovascular Profiler to non-invasively assess small and large arterial compliance. This profiler uses applanation tonometry to measure radial pulse waves of the right arm of supine subjects. The waveform was calibrated with an automated blood pressure cuff on the left arm (HDI/Pulse Wave CR-3000 CV Profiler, HDI Hypertention Diagnostics). This measure was taken in all patients on all three testing days.

4.2.2.3 Heart Rate

Participants were instrumented with a 3-electrode ECG in order to measure continuously heart rate during all supine and standing resting measures. A data acquisition system (Powerlab 16/30, ADInstruments, Colorado Springs, CO) and laptop computer were used for HR and ECG recordings.

4.2.2.4 Heart Rate Variability

Sections of heart rate ECG data were visually examined and analyzed following its collection. Heart rate variability was analyzed by looking at R-R intervals, using Chart V5.5.6 (ADInstruments). Both time-domain (SDNN, NN50, RMSSD) and frequency-domain (LF, HF, LF/HF ratio) measures were examined in order to measure autonomic activity in the heart.

4.2.3 Testing Part 3

The last part of testing involved the 6–minute walk test (Brooks et al., 2003), where patients followed the protocol outlined by the American Thoracic Society. This submaximal test was the most suitable for the CKD population participating in this study as there are so many co-morbidities present in this population, most of which are cardiovascular related. The 6-minute walk test is strongly indicated for interventions in patients with moderate to severe heart or lung disease (Brooks et al., 2003), therefore it suit this CKD population well.

The walk test was performed in the hallway of the Garratt Wellness Centre in Richmond, which allowed the walking course to be 20 m in length. A cone was placed at

either end of the 20 m course, with a foot distance for the patient to have been able to turn around the cone without making the course longer, skewing results. Patients were at rest for a minimum of 10 min before commencement of the test. During this point, the patient stood and rated their baseline dyspnea and overall fatigue using a 10-point Borg scale. They also put on a heart rate monitor (Polar, FS1; Polar Electro, Oy, Finland), and their baseline heart rate was recorded. Throughout the test, the patient called out the heart rate that displayed on their heart rate monitors at every minute. The patient was instructed to cover as much distance as possible during the 6 min walk, and the test was stopped if the patient experienced tightness and/or pain in the chest, dizziness, lightheadedness and/or nausea, or extreme shortness of breath, or any form of bone or muscular pain that is too uncomfortable to continue. This did not have to happen. Once they completed the test, they were seated right away, and a CSEP-CEP measured and recorded their blood pressure manually. They were also asked to again state their baseline dyspnea and overall fatigue based on the 10 point RPE Borg Scale.

Absolute contraindications for the 6 minute walk test include unstable angina and myocardial infarction, both during the previous month. Relative contraindications include a resting heart rate of more than 120, a SBP of more than 180 mmHg, and a diastolic blood pressure of more than 100 mmHg. However, all patients were cleared by the referring physician before participating.

5 Statistical Analysis

The primary outcome variables were compared between groups (control and experimental) across the intervention using a 2 x 3 repeated measures mixed model analysis of variance (Group (2 levels) x Time (3 levels)). The data analysis program Statistica 6.0 (Stats Soft, Tulsa, OK), was used to carry out the ANOVA. Tukey post hoc comparisons were also conducted using Statistica when significant differences were observed. Results were considered significant at an alpha of $p \leq 0.05$. Data are presented as mean $\pm$ SD.

6 Results

6.1 Body Composition

6.1.1 Body Mass Index

No significant differences were found in BMI between testing days of participants in the experimental or control group, nor was there a significant interaction found between the two groups. However, there were small non-significant trends in improvement from testing day 1 to testing day 3 in experimental group participants but no significant changes seen in BMI between testing days among control group participants (see figure 1).

6.1.2 Waist Circumference

No significant interaction was found between groups when looking at waist circumference, indicating that neither the experimental or control group was affected by the intervention for this measure. Trends in improvement were seen between testing days in participants in both the experimental and control group, but none were significant (see figure 2).

6.1.3 Skinfold Measurements

Although there was no significant interaction effect between groups or significant differences within groups, sum of 5 skinfolds showed trends in improvement in the experimental group, and slight increases in the control group (see figure 3).

6.2 Musculoskeletal Fitness

6.2.1 Grip Strength

There were no significant differences seen in total grip strength within or between groups (see figure 4).

6.2.2 Flexibility

Although no significant differences were seen in sit-and-reach values to measure flexibility, either between or within groups, there were non-significant increases in flexibility in the experimental group from testing day 1 to testing day 3, and non-significant decreases in flexibility in the control group along the same timeline (see figure 5).

6.3 Aerobic Capacity

Although there was no significant interaction between groups, participants in the experimental group had significantly higher VO_2max results post exercise intervention, in comparison to post-nutrition as well as baseline (day 1: 15.9 ± 1.6, day 2: 15.9 ± 1.7, day 3: 16.7 ± 1.4; $p < .05$). There were no significant improvements seen in the control group (see figure 6).

6.4 Blood Pressure

6.4.1 Resting Blood Pressure

There were no significant differences between groups or within the control group from day 1 to day 3 (see figure 7). However, there was a significant decrease in systolic blood pressure after the nutrition intervention compared to baseline,(day 1: 134.4 ± 19.1, day 2: 123.7 ± 17.3; $p < .05$) but values increased again after the exercise intervention, although this change increase was not significant (day 3: 133.1 ± 17.4).

There were no significant differences in diastolic blood pressure, either within or between groups, but trends were similar to that seen with systolic blood pressure. There was a decrease in values in the experimental group post-nutrition intervention, followed by an increase post-exercise intervention. Resting diastolic blood pressure showed a slight, non-significant, decline in the control group between testing days (see figure 8).

With respect to mean arterial blood pressure (MAP) values, there was no significant interaction between groups or within the control group from day 1 to day 3 (day 1: 97.4 c 7.4, day 2: 97.0 ± 10.0, day 3: 97.0 ± 11.7). Participants in the experimental group had significantly higher MAP after the nutritional intervention compared to baseline, but there were no significant differences seen post-exercise intervention (see figure 9).

6.5 Arterial Compliance

Although there was no significant interaction between groups for large artery compliance, there were non-significant trends in improvement seen in the experimental group, and a non-significant decline seen between testing days in the control group (see

figure 10). The interaction between groups was close to being statistically significant, at $p = .08$.

There was a significant interaction effect for small artery compliance ($p = .001$), indicating that the groups were affected differentially by the intervention. The experimental group showed an improvement over time (day 1: 3.5 ± 1.6, day 2: 4.3 ± 1.6, day 3: 4.6 ± 2.4), whereas, the control group showed a decline (day 1: 4.3 ± 2.4, day 2: 3.4 ± 1.6, day 3: 3.1 ± 1.2), see figure 11.

6.6 Heart Rate

6.6.1 Resting Heart Rate

There were no significant differences found between groups or within either the experimental group or control for resting heart rate (see figure 12).

6.6.2 Heart Rate Response

There was a significant interaction effect for heart rate response during the 6-minute walk program. The experimental group showed a significant improvement over the course of the intervention (day 1: 106 $\pm$ 32.0, day 2: 107 $\pm$ 24.7, day 3: 100 $\pm$ 35.5 bpm), while the control group showed a significant decline over the same time line (day 1: 94 $\pm$ 32.0, day 2: 103 $\pm$ 24.7, day 3: 104 $\pm$ 35.5 bpm) (see figure 13).

6.6.3 Heart Rate Variability

Analysis of Time-domain measures showed no significant differences between groups or within. Specifically, there were no significant improvements seen in RMSSD values for both the experimental group or control group (see figure 14). No significant improvements were seen for NN50 values either in the experimental group or in the control (see figure 15). SDNN values were consistent with other time-domain variables as no significant differences were seen in either the experimental group or among controls (see figure 16).

Frequency-domain measurements were similar as there were no significant improvements seen between groups, or within groups between testing days. There were trends in improvement of LF values in the experimental group, but no improvement in the control group (see figure 17). There were no improvements in HF values for the experimental group or control (see figure 18). LF:HF ratio also showed no improvement in either group (see figure 19).

7 Discussion

The present study demonstrated significant improvements in vascular health measures as well as aerobic fitness for individuals in the experimental group after participating in a comprehensive nutrition and exercise program. Trends in improvement at the end of the program when compared to baseline were also seen in this group for BMI and flexibility. Although these latter changes were not statistically significant, they hold clinical significance suggesting the success of this type of intervention to improve specific musculoskeletal measures. Taken together with the improvements seen in cardiovascular health measures, specifically in arterial compliance and aerobic fitness measures (predicted VO2max), this research study indicates that a comprehensive nutrition and exercise intervention can help decrease cardiovascular risk in pre-dialysis CKD patients.

Individuals with CKD have reduced arterial compliance (Covic et al., 2005; Toussaint & Kerr, 2007; Wang et al., 2007), and consequently are at increased risk for cardiovascular risk factors (Covic et al., 2005; Wang et al., 2007). Although previous research has shown aerobic exercise programs to improve total systemic and large artery compliance in previously sedentary healthy individuals (Cameron & Dart, 1994; Tanaka et al., 2000), there has been no past research investigating the effects of exercise on arterial compliance in pre-dialysis CKD individuals. Our study has demonstrated significant improvements in small artery compliance in the experimental group after completing the intervention, compared to a decline that was seen in the control group along the same timeline. This significant interaction effect illustrates that a combined nutrition and exercise intervention can improve vascular health and help decrease cardiovascular risk in individuals with pre-dialysis CKD. This is important as individuals with CKD have worsened arterial compliance when compared to a healthy

population (Covic et al., 2005; Toussaint & Kerr, 2007; Wang et al., 2007), putting them at a higher risk for CVD (Grey et al., 2003; Mancini et al., 2004). Baseline small artery arterial compliance values in our population were extremely low when compared to an asymptomatic population (3.5 $\pm$ 1.6 vs. 6.5 $\pm$ 2.2 mL/mmHgx100), respectively), and even lower than values seen in patients with cardiomyopathy (3.8 $\pm$ 1.8 mL/mmHgx100) (Zhou et al., 2008). Because there is an association between improved arterial compliance and a decreased risk for CVD (Grey, 2003; Mancini, 2004), our research demonstrates the ability to decrease this risk by significantly improving arterial compliance after participating in a combined nutrition and exercise program for only 18 weeks.

Research is limited observing the relation of diet and arterial compliance. There have been a number of studies investigating the association between dietary fat and vascular health, some looking at the relationship between low-fat ($\leq$ 30% of energy intake) versus a high-fat diet ($\geq$ 30% of energy intake), or the differences between saturated and unsaturated fat on vascular health. The studies looking at the difference between a high-fat vs. low-fat diet either showed a decrease in arterial compliance 6 hours after consuming a high-fat diet (Nestel et al., 2001), or an improvement in pulse wave velocity with both isocaloric energy-restricted diets (either low-carbohydrate, high saturated fat or high-carbohydrate, low saturated fat for 8 weeks) (Keogh et al., 2008). Although the nutrition intervention of our study did not focus on the amount or type of fat consumed, we did focus on limiting the amount of protein. This includes protein from animal source which is generally high in saturated fats. Therefore, the participants would have become more aware of their protein intake, and would then also be aware of decreasing saturated fat intake. More closely related to our study, however, previous literature has illustrated an association between low-sodium diets (an 8 week period) and improvements in large artery compliance in hypertensive individuals (Gates et al.,

2004). The results we found are similar to previous studies looking at fat intake and sodium intake, as we found a significant improvement in small artery compliance, and close to significant improvements in large artery artery compliance after the nutrition-intervention. Although this improvement was not statistically significant, it holds clinical significance because individual improvements are still beneficial even though the group did not reach significance. We may have found significant results between baseline and post-nutrition intervention if our study design was longer (perhaps 8 weeks instead of 6), if we had a larger sample size, or if adherence to following the dietary recommendations that were taught to the participants in their cooking classes was controlled for and/or more strict. However, we did not take note of adherence to dietary recommendations.

We found significant changes in small artery compliance post-intervention and there was a trend for large artery compliance to be improved following the intervention. Perhaps if the study were of longer duration, significance in improvements of large artery compliance would have also been obtained. However, changes in small artery compliance may hold more significance as previous research has showed a correlation between small artery compliance using pulse-contour analysis to a cardiovascular event, but non between large artery compliance and a cardiovascular event (Grey et al., 2000). Although large artery and small artery compliance are correlated, they measure different aspects of the pulse pressure waveform. Large artery compliance is primarily derived from the exponential decay of the diastolic waveform, while small artery compliance is derived from the oscillations that occur in the arterial system, creating a decaying sinusoidal wave superimposed on the exponential decay (Cohn & Finkelstein, 1992). Large artery compliance has been shown to be more sensitive to aging, while small artery compliance appears to be more closely related to vascular disease associated with hypertension, diabetes, and atherosclerosis (Glasser et al., 1997). This may explain why we found significant improvements in small artery compliance, but none in large

artery compliance. Although we did not see significant improvements, there was still a 15% change from baseline to the end of the intervention in the experimental group, while the control group showed a 10% decline over the same timeline. Again, our results showed extremely low baseline values for large artery compliance when compared to an asymptomatic population(11.1 $\pm$ 2.6 vs. 13.7 $\pm$ 3.7 mL/mmHgx100, respectively) (Zhou et al., 2008). Therefore, regardless of the fact that our results were not significant for large artery compliance, the 15% change in improvement in the experimental group gives hope to the pre-dialysis population that if they were to engage in these types of interventions they will increase their dangerously low values, and prevent further decline that would put them at an even greater risk for CVD.

Chronic kidney disease individuals who develop end-stage kidney disease have much lower VO_2max values when compared to healthy physically inactive controls (Barnea et al., 1980; Kettner-Melsheimer A, 1987; Latos et al., 1987). If these individuals could improve their aerobic capacity before reaching end-stage kidney disease, this would most likely decrease their cardiovascular disease risk as improved VO_2max values are associated with a decreased cardiovascular risk profile (Tell & Vellar, 1988). Our study showed significant improvement in predicted VO_2max values of the experimental group post-exercise intervention when compared to baseline and post-nutrition intervention. These results were not seen in the control group, demonstrating that 3 months of exercise classes 3 times a week incorporating both aerobic and resistance training was responsible for this improvement in aerobic fitness. Our findings were similar to previous literature showing improvement in aerobic capacity of pre-dialysis CKD individuals after training aerobically 3 times a week for 3 or 4 months (Boyce et al., 1997; Clyne et al., 1991). However, ours was the first study to examine the effects of combining both aerobic and resistance training on aerobic capacity in the pre-dialysis CKD population.

Muscular weakness is commonly seen in the CKD population as a result of a combination of factors, including sarcopenia, metabolic acidosis (Mitch & Goldberg, 1996), peripheral neropathy (Sakkas et al., 2003), uremic myopathy (Kouidi et al., 1998), malnutrition from a decreased protein/caloric intake (Fahal et al., 1997), and disuse atrophy due to the high prevalence of physical inactivity seen in this population (Kouidi et al., 1998). A previous study examined the physical work capacity in CKD, and found pre-dialysis CKD patients to have a 31% reduction in muscle strength in men and 47% reduction in women (Kettner-Melsheimer et al., 1987). This reduction in muscle strength only increases as the disease progresses and individuals require hemodialysis (Kettner-Melsheimer et al., 1987). It is important to try to improve muscular strength in the pre-dialysis CKD population in order to prevent a further decrease in muscle strength, and a worsened functional status which may lead to a decreased sense of independence (Warburton et al., 2001a) and limited physical function (Johansen, 2005). Past literature has shown a 6-month exercise program to be effective in improving muscular strength in the CKD population (Kouidi et al., 1998). Although this exercise program was similar to our design in that it consisted of aerobic training, resistance training, and stretching, the individuals in the study done by Kouidi et al. (1998) were on hemodialysis. Muscular strength of the lower limbs was measured using a dynamometer (Kouidi et al., 1998).The predialysis CKD patients failed to show improvements in musclular strength, more specifically grip strength measured by a hand dynamometer. It is likely that these results would have been different if our participants engaged in the exercise program for a longer duration. Another study done by Boyce et al. (Boyce et al., 1997) looked at thigh muscular strength assessing a knee extension/flexion movement after 4 months of an exercise program consisting solely of aerobic training on a stationary bike combined with walking. Exercise training resulted in a significant increase in knee flexion torque, but none in knee extension torque (Boyce et al., 1997). This study did not include

resistance training as our study did. Perhaps if we measured muscle strength of the lower limbs, significant improvements in muscular strength may have been observed.

Flexibility is another musculoskeletal measure important for independent living and ADLs (Warburton et al., 2001a). Flexibility has been shown to decrease with age (Chapman et al., 1972), but a decline in flexibility is accelerated in inactive individuals (Kell et al., 2001). The CKD population is generally inactive (Boyce et al., 1997; Johansen, 2005), and therefore are likely to have decreased flexibility (Johansen, 2005). In order to reverse this, we examined the effect of an exercise intervention consisting of aerobic training, resistance training, and flexibility exercises on sit-and-reach scores – a measure of flexibility. Although non-significant, there were improvements in flexibility measures in the experimental group after the intervention, compared to a slight decline in flexibility measures in the control group. This not only provides evidence that physical inactivity can accelerate a decline in flexibility, but also that engaging in resistance training and flexibility exercises 3 times a week improves flexibility. These individuals will most likely experience an improved health status as an improved flexibility has been shown to help maintain functional status (Warburton et al., 2006a). This research is the first of its kind to demonstrate improvements in flexibility in a pre-dialysis CKD population after participating in an exercise intervention. Perhaps if the exercise program was of longer duration, significant results would have been achieved, but we must not overlook the importance of an improvement in flexibility measures for individuals as it will still most likely impact their QOL.

There were no improvements found for BMI measurements in our study. Past literature has shown improvements in BMI in previously sedentary healthy men, and the prevention of weight-gain in previously sedentary healthy women who participated in a moderate-intensity exercise program for 16 months compared to non-exercise controls (Donnelly et al., 2003). Another study showed significant weight loss in previously

sedentary healthy women after participation in an 18-month exercise intervention (Donnelly et al., 2000). It is likely that our study participants would have also experienced a decline in BMI values if the duration of the exercise program was longer than 12 months, as seen in these similar studies. We didn't put any focus on caloric restriction during the nutrition component of our comprehensive intervention. Also, caloric intake was not monitored throughout the study. There may have been an increase in caloric intake associated with the increase in physical activity, which may have prevented decreases in BMI.

Both waist circumference measurements and sum of 5 skinfolds showed trends in improvement for both the experimental and control group. This is possibly reflective of an intervention effect, where individuals may have been more aware of what they were eating and their activity levels upon exposure to this study, that even individuals who were not participating in the intervention lost some weight because of this increased awareness.

Previous literature has shown significant reductions in both systolic and diastolic blood pressure after 4 months of exercise training, 3 times per week, at a moderate intensity (gradually increasing to 70 % of heart rate reserve) in pre-dialysis CKD patients (Boyce et al., 1997). The individuals in this study started at an intensity of 50 – 60% of their heart rate reserves, and gradually increased to 70% of heart rate reserve for 60 min. of aerobic exercise (Boyce et al., 1997). Our study did not show significant reductions in blood pressure post-exercise intervention when compared to baseline. However, the duration of our exercise program was shorter (3 months compared to 4 months) and individuals only trained aerobically for 30 min as there was a resistance and flexibility component as well. Also, individuals were training at a lower intensity (40 – 59% of heart rate reserve) than the study done by Boyce et al. Perhaps if the duration of the exercise program was longer, and individuals trained at a higher

percentage of heart rate reserve, significant changes in blood pressure would have been observed.

The individuals participating in our study did show significant reductions in blood pressure after the nutrition-intervention compared to baseline, but blood pressure increased again post-exercise intervention, although non-significant. The decrease in blood pressure values post-nutrition intervention is likely associated with a decrease in sodium intake as this was a major part of the dietary guidelines and cooking component in our study. Previous literature has shown a low sodium diet to decrease blood pressure after a 30-day period (Sacks et al., 2001), so it is not surprising that after 6 weeks of nutrition/cooking classes the participants in our study had a significant decrease in resting blood pressure. It would have been interesting, however, to have recorded sodium intake in participants throughout the intervention.

A possible explanation for the increase back to baseline values may be that participants either stopped following dietary recommendations for sodium restriction, or that they decreased blood pressure medications during the exercise program. A previous study examined the effects of a 6-month aerobic exercise intervention amongst hemodialysis patients (Miller et al., 2002). There were no significant changes in blood pressure post-intervention compared to baseline, however 54% of participants in the exercise group had a reduction in antihypertensive medication compared to only 12.5% of participants in the control group (Miller et al., 2002). For future studies, it is recommended that any changes in blood pressure medications be evaluated in order to better monitor improvements in blood pressure control.

We found no significant changes in resting heart rate post-intervention when compared to baseline or when compared to controls. However, most of the participants were taking beta-blockers at baseline and throughout the intervention, which would have lowered heart rate (Task Force Members et al., 2004). If medications were decreased

throughout the program, there could have been improvements in heart rate that were not seen as medications did not stay the same throughout the intervention period. Although research is limited in examining the effects of an exercise intervention on heart rate in hypertensive individuals on beta-blockers, there is one study in particular that looks at the effects of exercise on exercise tolerance and exercise-conditioning response, but not heart rate specifically (Ades et al., 1988). This study examined the differences between a non-selective beta-block (propranalol), a selective beta-blocker (metropolol), and a control (no medications) in hypertensive patients during a 10-week aerobic exercise intervention. Results showed individuals on non-selective beta-blocker medications to have limited aerobic conditioning as they were unable to reach the same aerobic capacity as individuals on selective beta-blockers and controls. Also, when individuals on non-selective beta-blockers discontinued these medications during the exercise program, their blood pressures returned to their original hypertensive levels. Compared to when individuals on selective beta-blockers discontinued use they remained normotensive and were able to stay of blood pressure medications as long as they continued in the exercise program (Ades et al., 1988). This is important to note as it would be interesting to look at the types of blood pressure medications the participants in our intervention were on, and to look at the effects it had on aerobic capacity, blood pressure, and heart rate.

Although no significant differences were seen in resting heart rate, we did see a significant interaction effect for heart rate response when looking at every minute of the 6-minute walk test. This may be of importance as it may indicate that the pre-dialysis population can improve their exercise tolerance after engaging in only 3 months of an exercise intervention.

Previous research has shown improvements in HRV after a 6-month exercise program in patients with end stage CKD (Deligiannis et al., 1999); however to date there

has not yet been any literature examining the effects of an exercise program on HRV in pre-dialysis CKD patients. Decreased HRV has been associated with an increased CVD risk, putting pre-dialysis CKD individuals at a higher risk for CVD as this population tends to have a lower HRV when compared to healthy controls (Furuland et al., 2008). Our study showed no significant improvements in heart rate variability measures. Perhaps the duration of the study was not long enough to see significant changes. Also, there was a high amount of variability in our measurements. This may be due to the fact that data collection was done in a wellness centre, and although we did our best efforts to keep the room the patient was in as quiet as possible, there was sometimes background noise. This may have increased sympathetic stimulation in the individual at rest during the data collection process of HRV, which would in turn alter heart rate variability measures (i.e. greater sympathetic stimulation would increase LF and alter LF:HF values) (Ditor et al., 2005).

8 Limitations and Future Considerations

The duration of the exercise component of this intervention was only 3 months long. Although significant results were seen in vascular health and aerobic fitness, there were non-significant trends in improvement in grip strength, flexibility, BMI, HRV, and large artery compliance that may have been significant if the duration of the exercise program was lengthened. Previous literature showed significant improvements in grip strength after either 4 or 6 months of exercise training (Boyce et al., 1997; Kouidi et al., 1998). Past studies also show significant improvements in HRV after participation in a 6-month exercise program among patients with end-stage CKD (Deligiannis et al., 1999). Along with this, decreases in BMI were only seen in exercise interventions of 16 or 18 months (Donnelly et al., 2003; Donnelly et al., 2000). Therefore, it is likely that participants in our study would have seen similar changes in musculoskeletal fitness and HRV if the exercise program was 6-months in duration. Significant improvements in BMI, waist circumference, and sum of 5 skinfold measures may similarily have been seen if the program lasted at least 1-year. Perhaps a larger sample size also would have allowed significant improvements to be seen in these measures.

Significant improvements in resting blood pressure were only seen post-nutrition intervention, but then blood pressure values increased again post-exercise intervention. Blood pressure medications were not monitored throughout our study, but future studies should be done to record any changes in blood pressure medications after a comprehensive nutrition and exercise intervention. It is likely that some participants either decreased or were taken off their blood pressure medications, causing an increase in mean resting blood pressure values. It would be important to note for resting heart rate as well, as beta-blockers can mask a change in this measure (Task Force

Members et al., 2004) However, it is extremely beneficial if these individuals were able to decrease their blood pressure medications throughout the duration of the intervention.

Also related to blood pressure, past literature that showed significant improvements in resting blood pressures of pre-dialysis CKD individuals occurred after exercising for 4 months at a higher intensity than our intervention (70% heart rate reserve vs. 40-59% in our study) (Boyce et al., 1997). Additionaly, the individuals in the study by Boyce et al. engaged solely in aerobic exercise for 60 min. This could have also posed a limitation on our study as we incorporated resistance exercises as well as flexibility exercises during the 60 min. duration classes. Resistance training programs do result in slight decreases resting blood pressure (Kelley & Kelley, 2000), however not to the same extent as aerobic exercise programs (Whelton et al., 2002). Therefore, future studies should explore the effects of combination exercise programs (aerobic, resistance, and flexibility training) of a longer duration and higher intensity on blood pressure while monitoring changes in blood pressure medications.

The strength of this study could have been increased if dietary intakes were recorded. The use of 24-hour recalls would have been beneficial, although would have greatly increased the amount of time for data collection and analysis. Another option could have been to use self-reported 24-hour recalls, although they would not have been as reliable. A record of this information would have allowed more accurate analysis of results post-intervention. For example, no significant improvements were seen in BMI, waist circumference, or sum of 5 skinfolds. There is potential that energy-intake outweight energy-expenditure, but without a record of dietary intakes we cannot come to this conclusion. Also, there was a significant reduction in blood pressure post-nutrition intervention which likely resulted from a decrease in sodium intake. It would have been interesting to see if the individuals then increased their sodium intake back to baseline

levels, which could have partly explained the increase in blood pressure post-exercise intervention.

Table 1: Participant Characteristics

Group	N	Age, yr	M:F ratio	Asian:Caucasian Ratio	Average GFR	% with Diabetes	Height, cm	Weight, kg
Experimental	21	63.4 ± 12.1	3:2	11:10	37.2 ± 3.2	48	166.0 ± 9.8	75.9 ± 21.7
Control	15	63.4 ± 11.8	2:3	2:13	38.4 ± 3.0	44	164.6 ± 8.7	82.8 ± 19.6

Figure 1: Body mass index (BMI) following a comprehensive nutrition and exercise program.

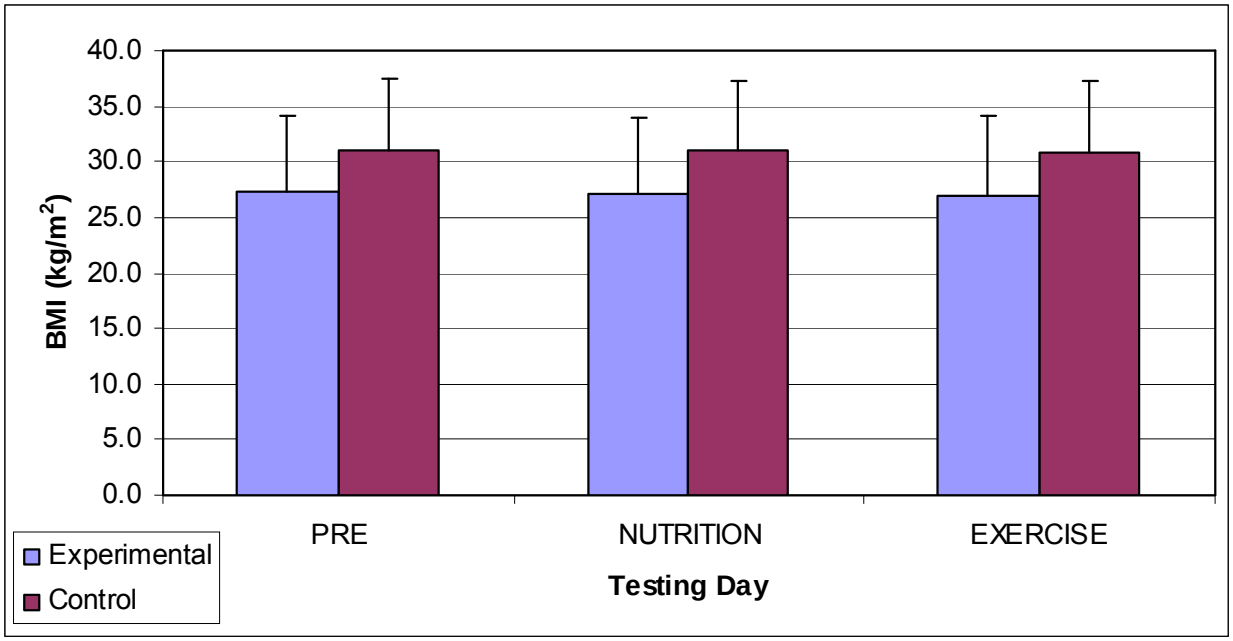


Figure 2: Waist circumference (WC) following a comprehensive nutrition and exercise program.

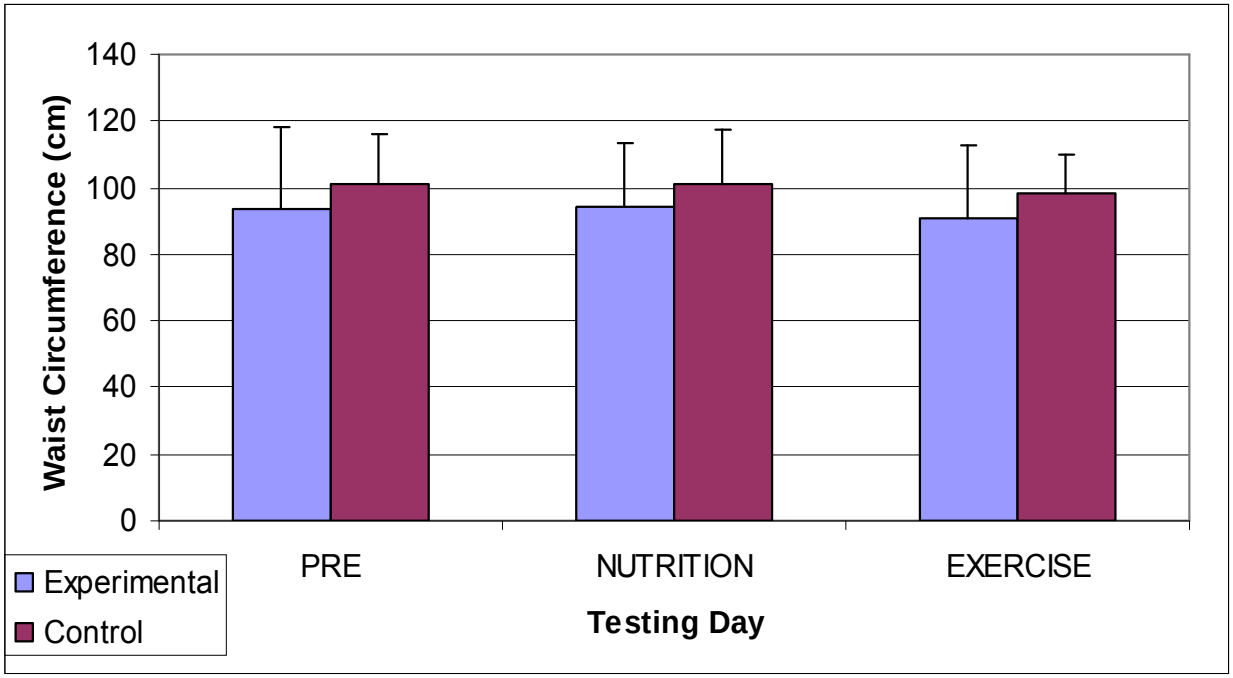


Figure 3: Sum of 5 Skinfolds (SO5S) following a comprehensive nutrition and exercise program.

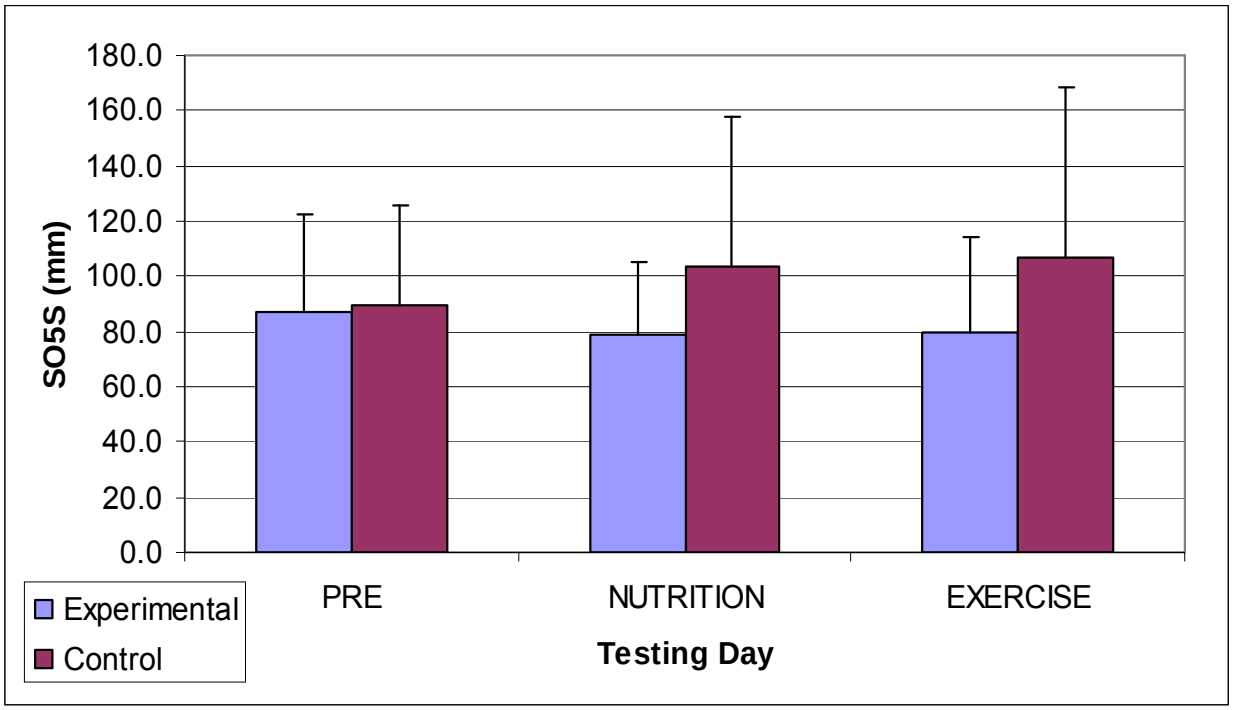


Figure 4: Grip strength following a comprehensive nutrition and exercise program.

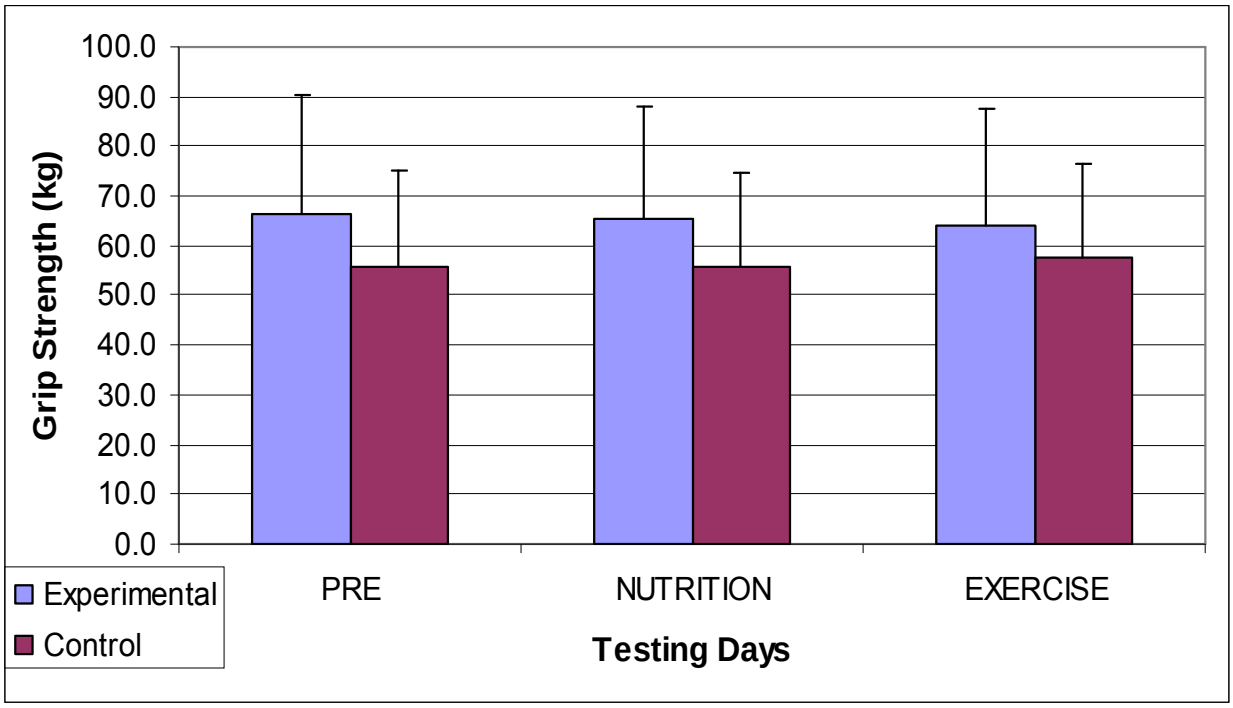


Figure 5: Flexibility following a comprehensive nutrition and exercise program.

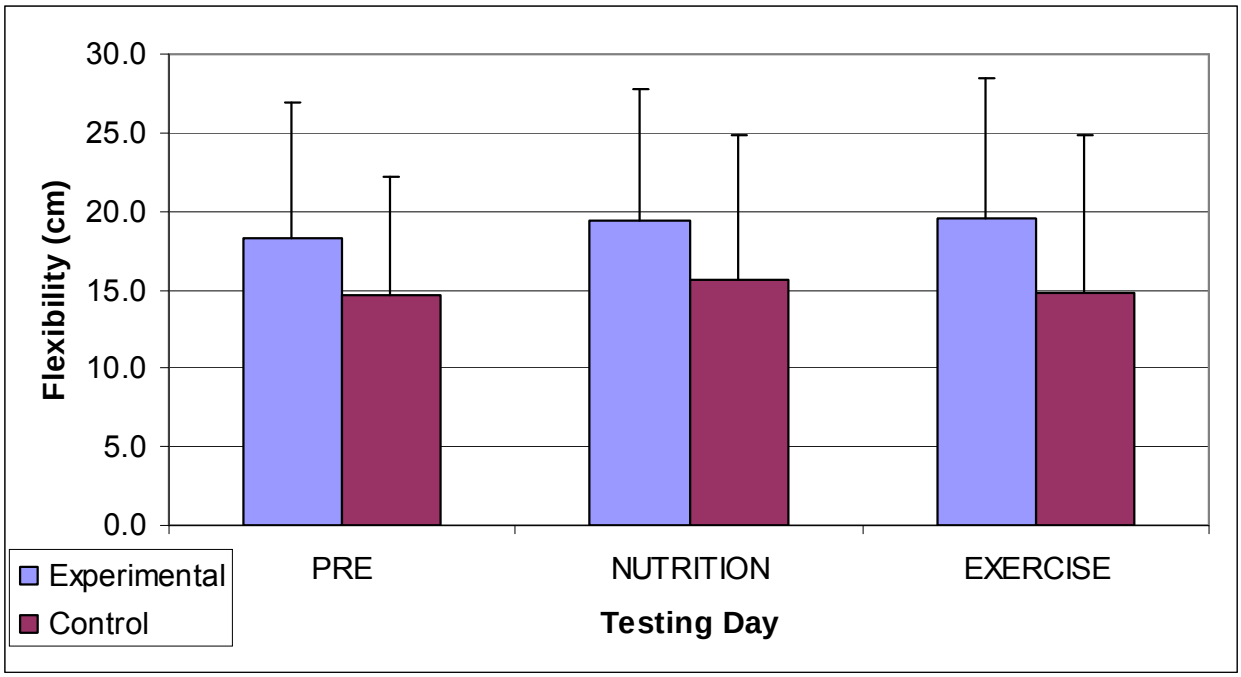
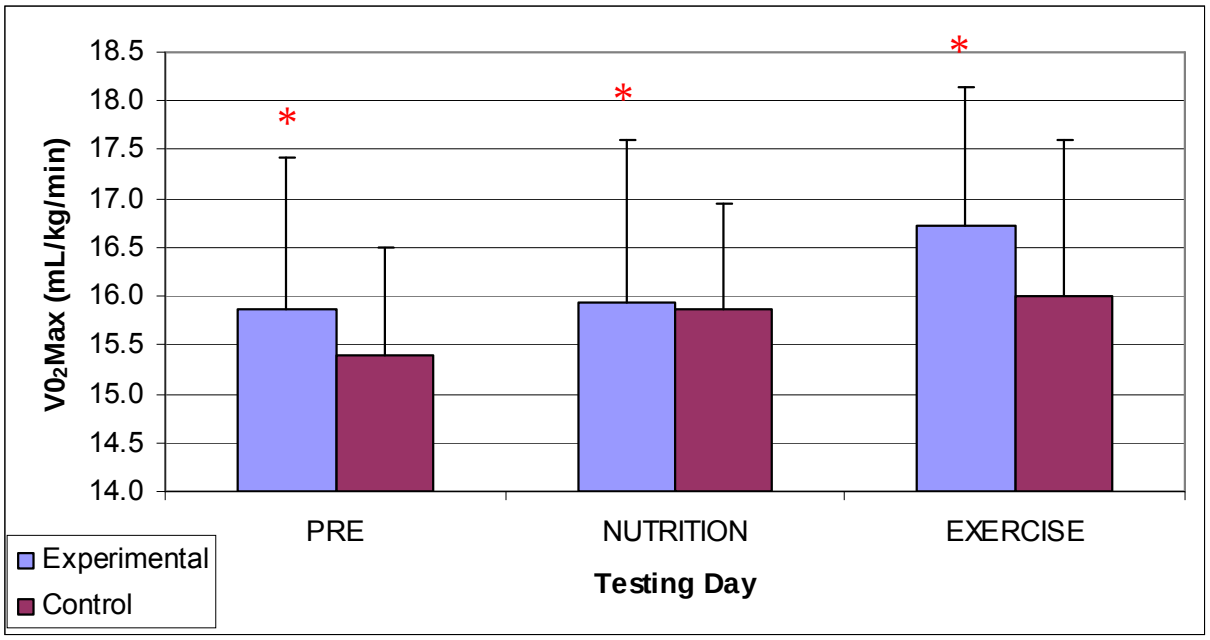
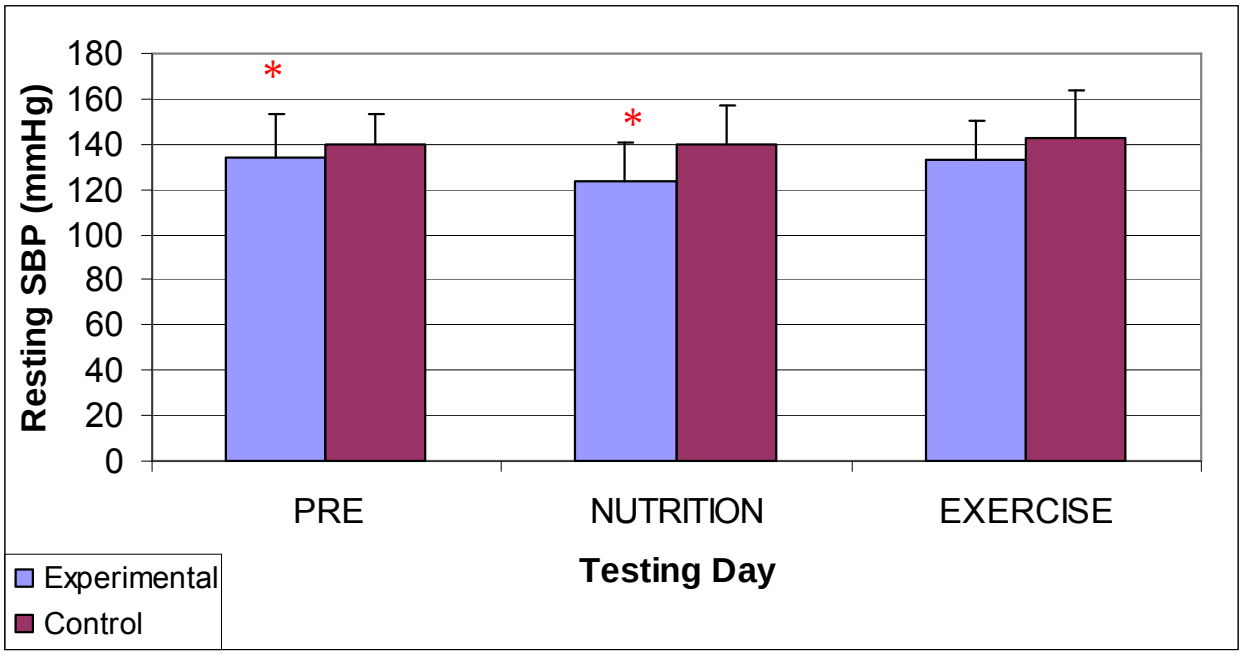


Figure 6: VO^2Max (ml/kg/min) following a comprehensive nutrition and exercise program.



* **p<0.05**

Figure 7: Resting systolic blood pressure (SBP) following a comprehensive nutrition and exercise program.



* **p<0.05**

Figure 8: Resting diastolic blood pressure (DBP) following a comprehensive nutrition and exercise program.

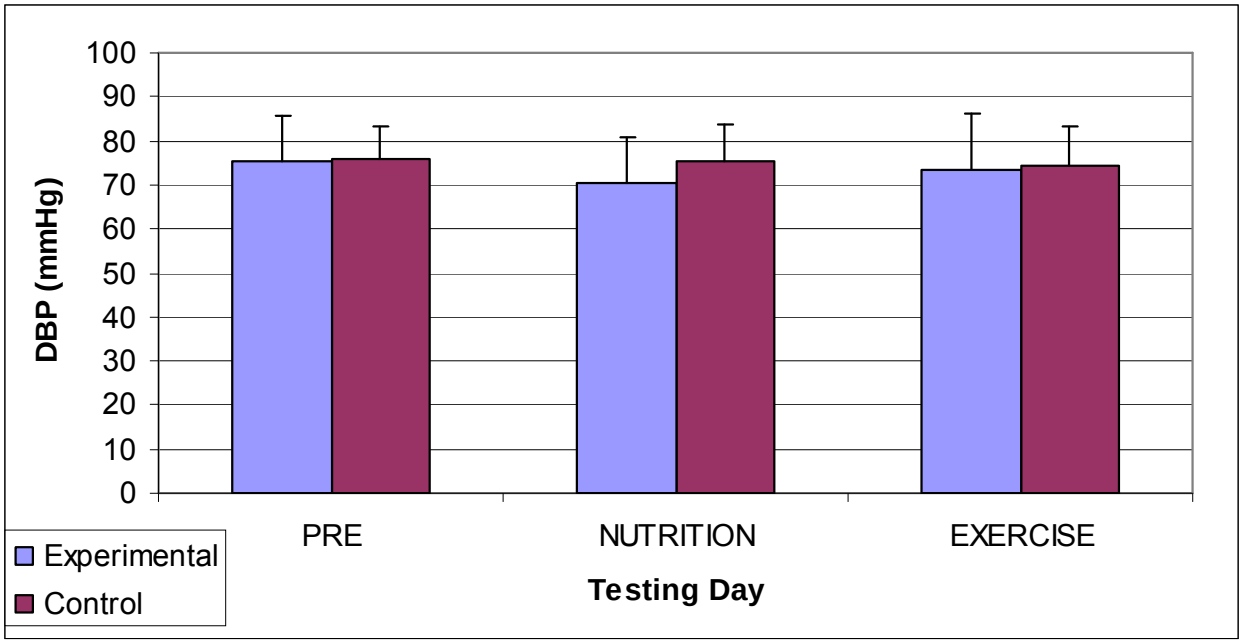


Figure 9: Resting mean arterial pressure (MAP) following a comprehensive nutrition and exercise program.

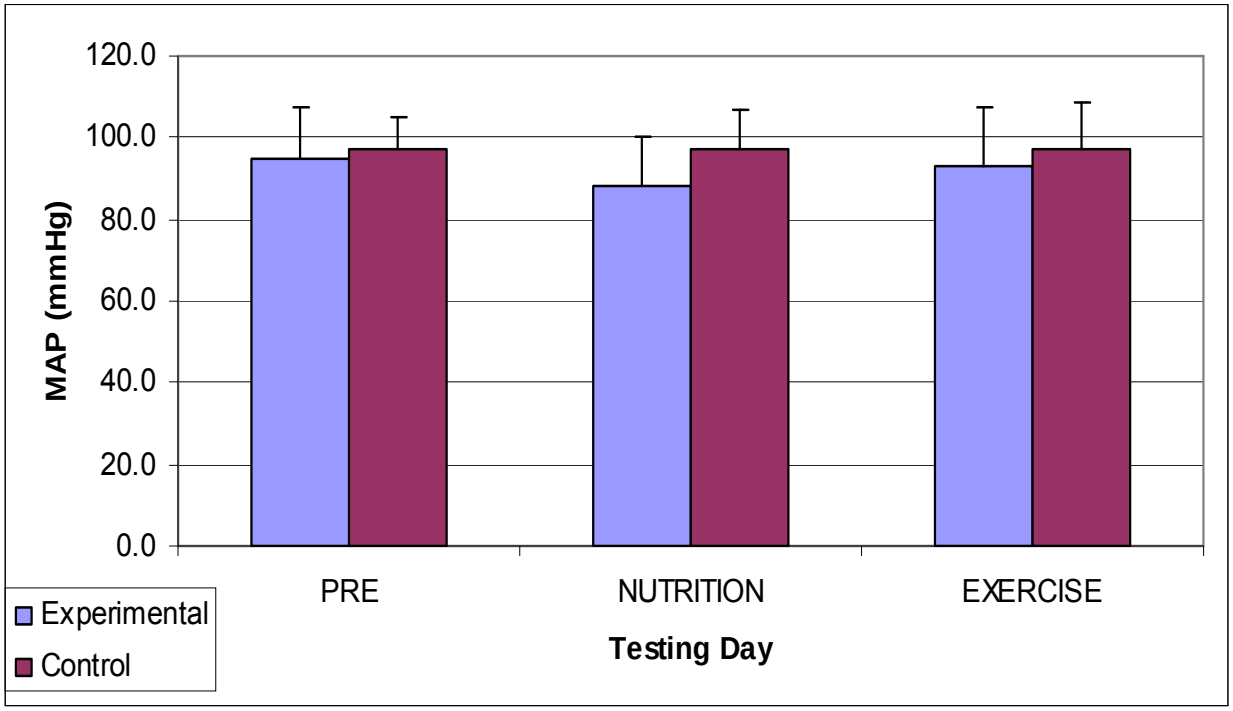


Figure 10: Large artery compliance (LA) following a comprehensive nutrition and exercise program.

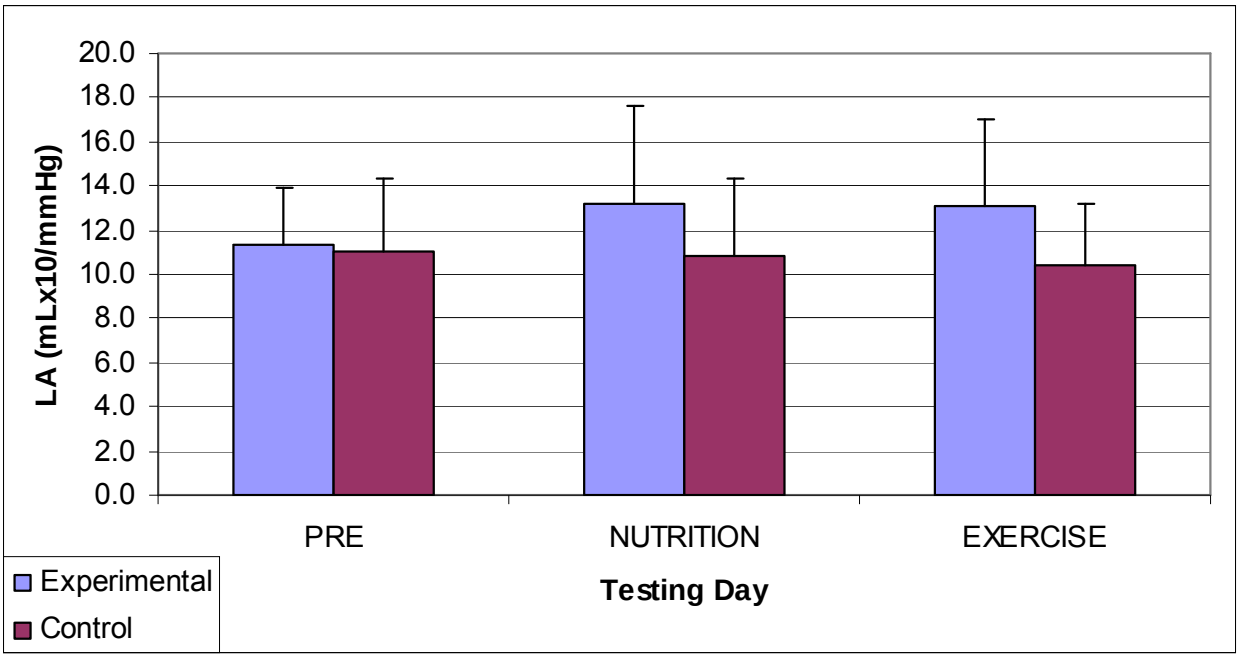
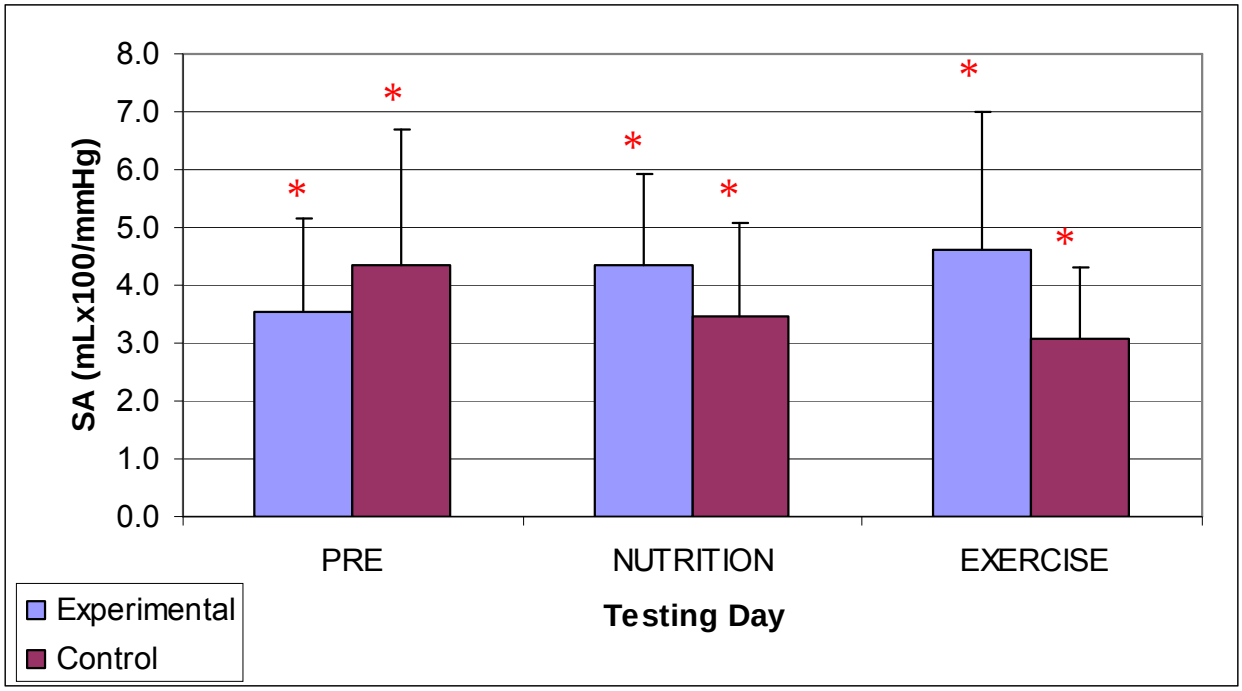


Figure 11: Small artery compliance (SA) following a comprehensive nutrition and exercise program.



* **p<0.05**

Figure 12: Resting heart rate (RHR) following a comprehensive nutrition and exercise program.

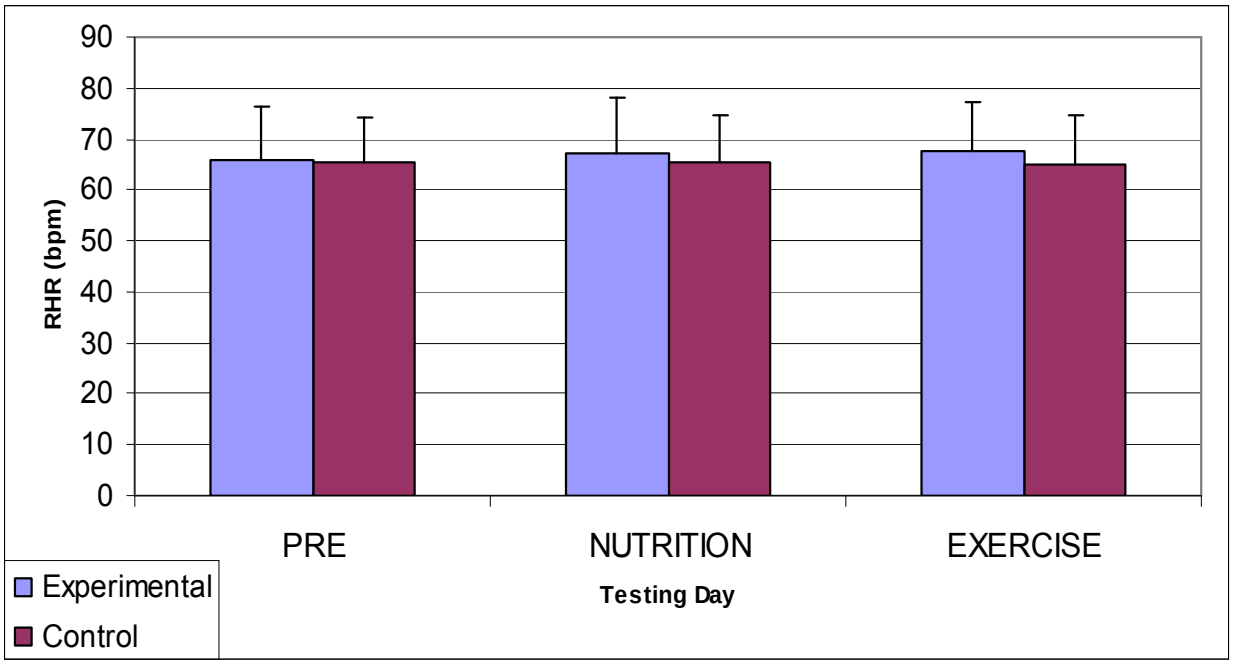


Figure 13: Heart rate (HR) response following a comprehensive nutrition and exercise program

* **p<0.05**

Figure 14: RMSSD following a comprehensive nutrition and exercise program.

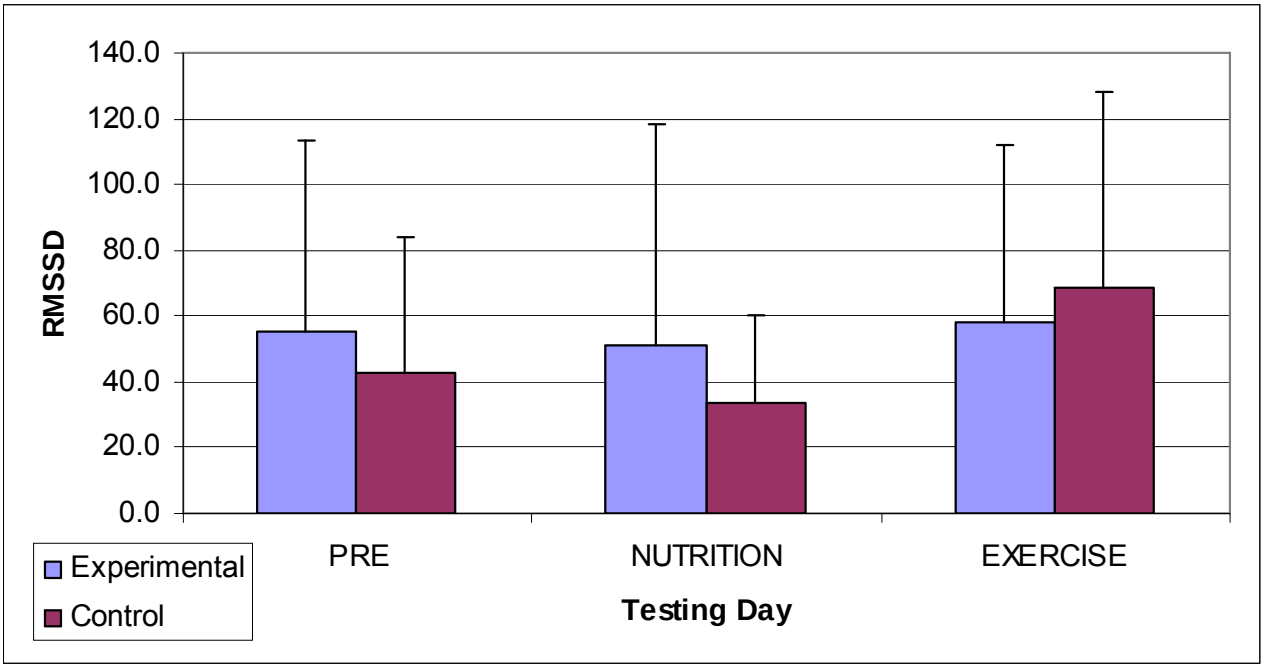


Figure 15: NN50 following a comprehensive nutrition and exercise program.

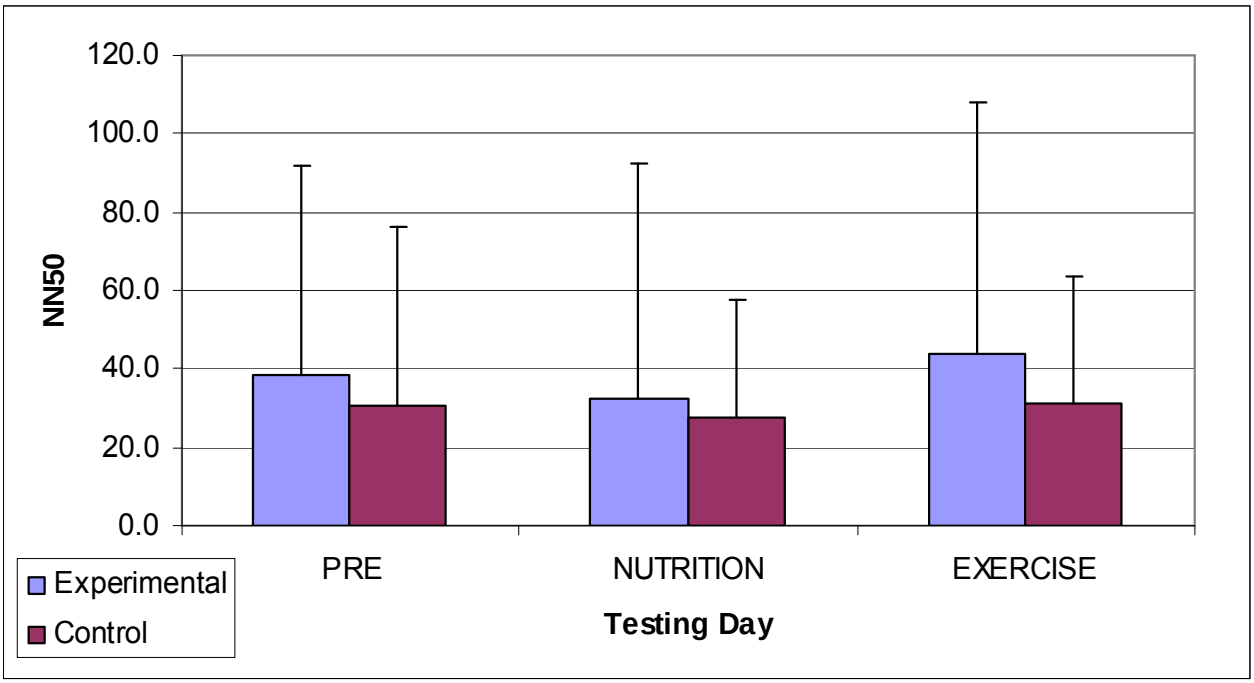


Figure 16: SDNN following a comprehensive nutrition and exercise program.

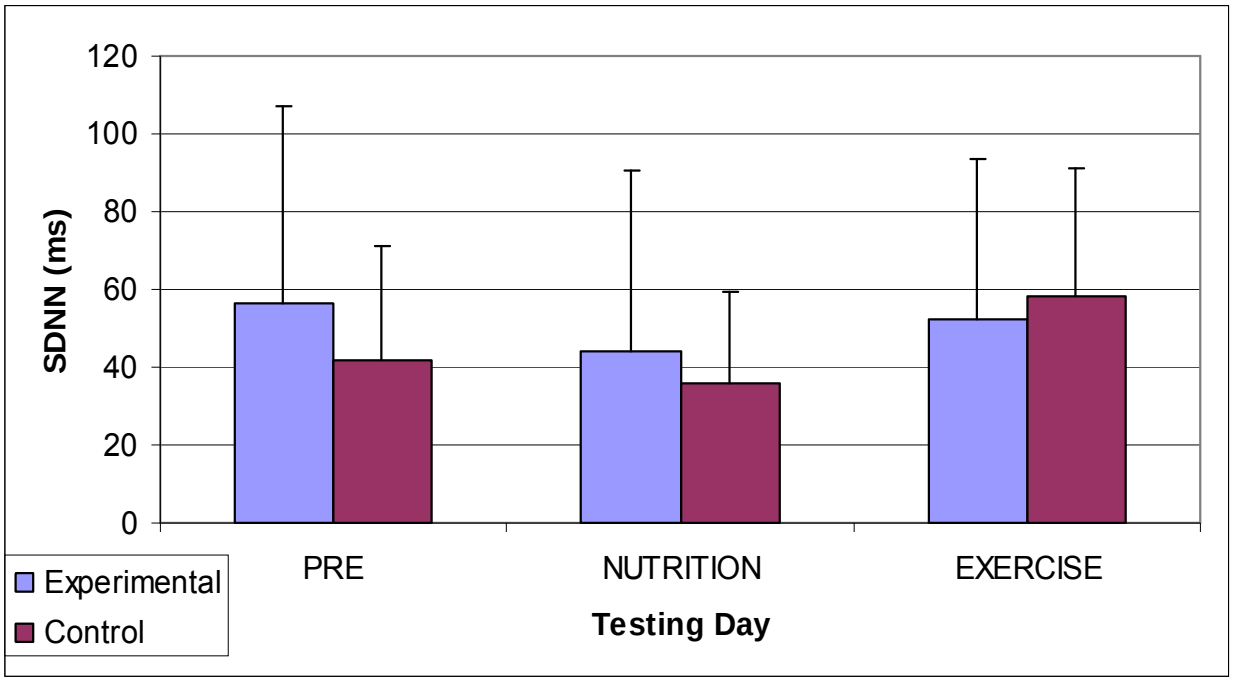


Figure 17: Low-frequency (LF) values following a comprehensive nutrition and exercise program.

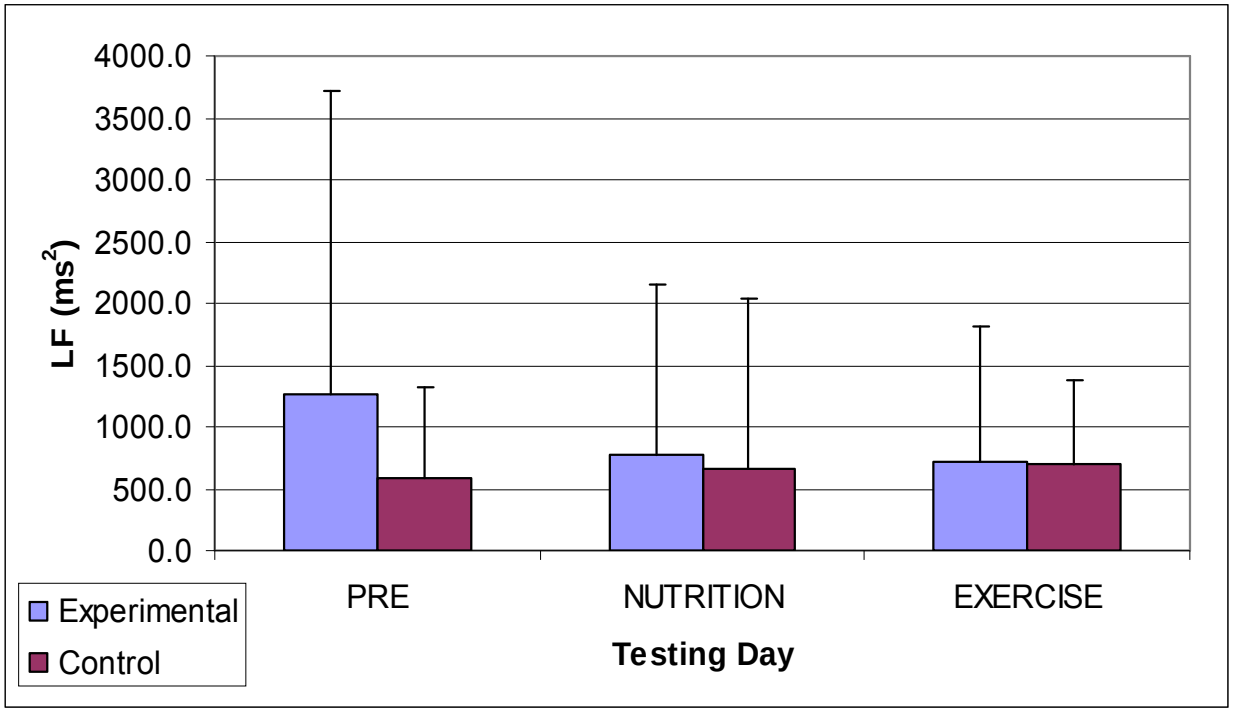


Figure 18: High-frequency (HF) values following a comprehensive nutrition and exercise program.

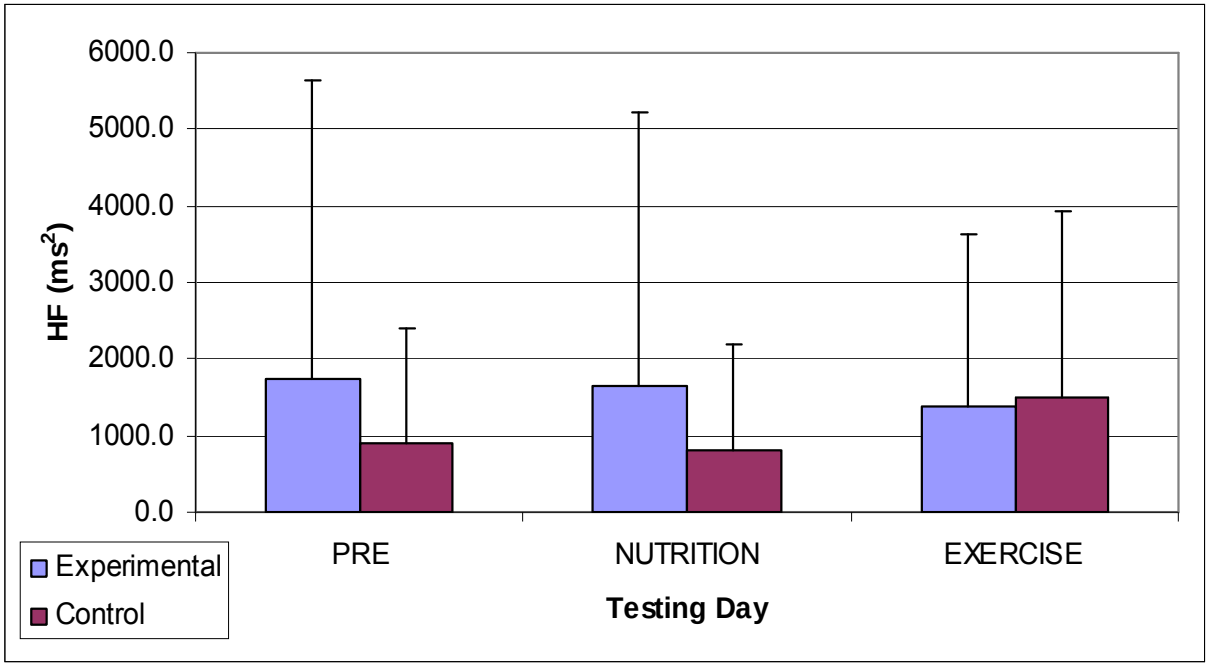
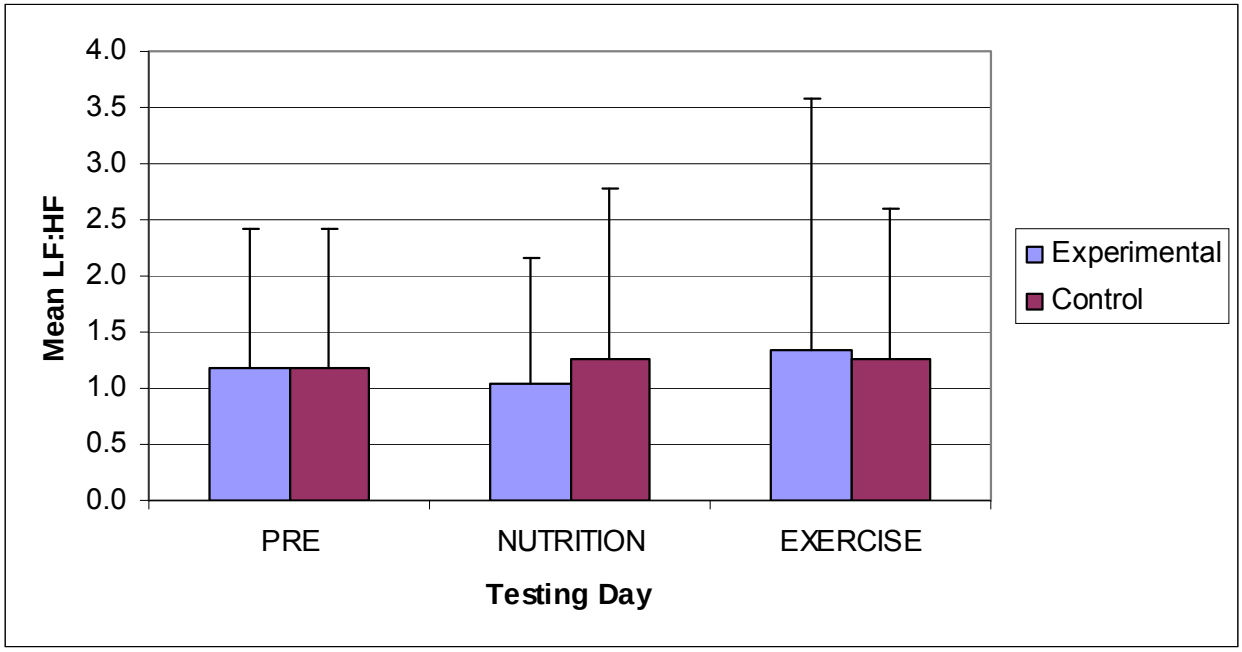


Figure 19: Low-frequency to high-frequency (LF:HF) ratio following a comprehensive nutrition and exercise program.



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