2013-07-18

Randomized Controlled Trial of a Behavioral Weight Loss Intervention for Primary Prevention of Renal Decline in Type 2 Diabetics

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RANDOMIZED CONTROLLED TRIAL OF A BEHAVIORAL WEIGHT LOSS INTERVENTION FOR PRIMARY PREVENTION OF RENAL DECLINE IN TYPE 2 DIABETICS

By

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A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

August 2013

UNIVERSITY OF MIAMI

A dissertation submitted in partial fulfillment of
the requirements for the degree of
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Randomized Controlled Trial of a Behavioral Weight Loss Intervention for Primary Prevention of Renal Decline in Type 2 Diabetics (August 2013)

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professor Maria Llabre.
No. of pages in text. (66)

Reduced glomerular filtration rate and increased albuminuria often develop in Type 2 Diabetes Mellitus (T2DM) and are predictive of chronic kidney and cardiovascular disease. Risk for renal disease in T2DM has been associated with cardiometabolic risk factors including, hypertension, dyslipidemia, and hyperglycemia. Weight loss is associated with improved outcomes in T2DM patients with existing renal disease and may also reduce risk in patients without renal disease via reduction of cardiometabolic risk factors. The aims of this study were (1) to examine the effects of a behavioral weight loss intervention on renal outcomes in T2DM patients without evidence of renal disease, and (2) to determine if change in renal outcomes is related to key demographic and cardiometabolic risk factors. A sample of 111 T2DM patients (mean age = 54.81 years, 28.8% male) was recruited from community health clinics and by 'word-of-mouth' and randomized to receive a 17-session lifestyle intervention or usual care (control). Eligible participants were overweight or obese, reported significant symptoms of depression, and had no evidence of existing renal or cardiovascular disease at screening. Demographic, psychosocial, anthropometric, blood and urine measures were collected at baseline and repeated at 6-months and 12-months post randomization. Primary outcomes included

weight, depressive symptoms, glycosylated hemoglobin (HbA1c), creatinine-based estimated glomerular filtration rate ($eGFR_{CR}$), cystatin c and creatinine-based $eGFR_{CY-CR}$, (estimated using Chronic Kidney Disease Epidemiology Collaboration formulas), and urinary albumin to creatinine ratio (UACR). Relative to usual care, the intervention resulted in significant increases in $eGFR_{CY-CR}$ (B= .331, SE = .142, $p < .05$), as well as significant decreases in weight (B = -.320, SE = .125, $p < .01$), depressed affect (B = -.993, SE = .228, $p < .001$), and HbA1c (B = -.068, SE = .030, $p < .05$). There was no effect of intervention on $eGFR_{CR}$ (B = -.146, SE = .119, $p = .219$) or UACR (B = .228, SE = .336, $p = .497$). The model estimated normative change in $eGFR_{CY-CR}$ was significant (B = .468, SE = .200, $p < .05$) and non-linear, indicating a change in direction of the slope after 6 months and an overall decline. Normative change in $eGFR_{CR}$ was not significant, (B= -.146, SE = .119, $p > .05$). Independent predictors of rate of change in $eGFR_{CR}$ were UACR, systolic blood pressure, high density lipoprotein cholesterol (HDL-C) and eGFR at baseline. The intervention effect on eGFR was related to UACR and HDL-C, HbA1C and triglycerides at baseline. UACR increased among all participants (B= .460, SE = .163, $p < .05$), and was related to UACR at baseline. Additional cardiometabolic risk factors were not related to change in UACR. Behavioral weight loss strategies may be implemented to preserve renal function among T2DM patients and prevent or delay the onset of renal disease in this population. Such strategies may be particularly effective for patients with dyslipidemia and hyperglycemia, and less effective for patients with elevated albumin excretion. Future studies should identify potential mediators of beneficial effects.

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Chapter 1: Introduction

Study Rationale

Weight (Bayliss, Weinrauch, & D'Elia, 2012; Kim et al., 2011; Ravid, Brosh, Ravid-Safran, Levy, & Rachmani, 1998), blood pressure (Ravid et al., 1998; Retnakaran, Cull, Thorne, Adler, & Holman, 2006; Yokoyama et al., 2011; Zoppini et al., 2009), glycemic control (Ravid et al., 1998; Retnakaran et al., 2006; Yokoyama et al., 2011), and lipids (Ravid et al., 1998; Retnakaran et al., 2006; Yokoyama et al., 2011) have been shown to influence changes in renal function in individuals with T2DM, and tight control of glucose and blood pressure is recommended to reduce the risk of renal decline in this population (Bakris, 2011; "Standards of medical care in diabetes--2013," 2013). Studies have shown that pharmacological management of glucose (Hsieh et al., 2011), lipids (Athyros, Mitsiou, Tziomalos, Karagiannis, & Mikhailidis, 2010) and blood pressure (Hsieh et al., 2011; Ravid et al., 1993) may reduce the risk of renal disease; weight loss interventions have also shown beneficial effects on kidney function in obese individuals with renal disease and diabetes (Afshinnia, Wilt, Duval, Esmaeili, & Ibrahim, 2010; Navaneethan et al., 2009). No study to date, however, has examined whether a behavioral weight loss intervention can influence the rate of change in kidney function among T2DM subjects without renal disease. Therefore, whether a behavioral weight loss intervention can be implemented as a primary prevention strategy for renal disease in diabetes is unknown. In this randomized controlled trial, we examined effects of an intervention targeting diet, physical activity and stress management on weight, glycemic control, depressive symptoms, and renal outcomes in a sample of overweight/obese adults with T2DM and predominantly unimpaired renal function. We also examined the relationships between baseline risk indicators and change in renal function outcomes

(eGFR and UACR). Primary aims of the present study were to determine intervention effects on weight, glycemic control, depressed affect, and renal function; and how traditional cardiometabolic risk factors (glycemic control, lipids, blood pressure) relate to baseline, change, and intervention effects on renal function. We hypothesized that the intervention would result in decreased weight, depressive symptoms and albumin excretion, and increased glycemic control and eGFR relative to usual care. It was also hypothesized that individuals with greater cardiovascular risk (i.e. higher blood pressure, worse glycemic control, more obesity, and poorer lipid profiles) would have worse renal function at baseline and exhibit steeper declines in eGFR and greater increases in UACR over time.

Excess body weight (Czernichow et al., 2011), poor glycemic control (Andersson et al., 2012), and depression (Black, Markides, & Ray, 2003; W. J. Katon et al., 2005) are independently associated with increased risk of poorer outcomes in T2DM, including diabetic nephropathy (DN), or progressive kidney disease caused by diabetes (de Groot, Anderson, Freedland, Clouse, & Lustman, 2001; Maric-Bilkan, 2013; Ravid et al., 1998). Lifestyle interventions targeting diet and physical activity have successfully resulted in weight loss, and improved glycemic control in T2DM populations (Espeland et al., 2013; Norris et al., 2004; Wing, 2010). Likewise, psychosocial interventions can alleviate depressive symptoms among T2DM patients (Bond, Burr, Wolf, & Feldt, 2010; Penckofer et al., 2012; van der Feltz-Cornelis et al., 2010; Zagarins, Allen, Garb, & Welch, 2012), which may also result in improved outcomes (Wayne J. Katon et al., 2010; Lamers, Jonkers, Bosma, Knottnerus, & van Eijk, 2011; van der Feltz-Cornelis et al., 2010). Although symptoms of depression interfere with diabetes management, including

achievement of diet and physical activity goals (Gonzalez et al., 2007), few studies have examined the effects of multi-component interventions that simultaneously target physical activity, diet, and depressive symptoms in adults with T2DM. Further, certain subgroups, such as ethnic minorities or individuals with low socioeconomic status (SES), are more likely to be overweight or obese, have poor glycemic control, or experience depressive symptoms (Dagogo-Jack, 2003; Golden et al., 2012), and are thus at increased risk of developing DN as a consequence (Collins et al., 2005; Krop et al., 1999; Young et al., 2005). Individuals belonging to these subgroups may face culturally specific barriers to self-management (Larkey, Hecht, Miller, & Alatorre, 2001) that are not addressed in interventions that have been implemented in predominately Caucasian, or higher SES populations. We therefore, tested the effects of this multi-component behavioral intervention on outcomes in a community-dwelling sample composed primarily of ethnic minorities of low SES who are particularly vulnerable to the development of DN.

Impact of Diabetic Nephropathy in Type 2 Diabetes

About 20-40% (Zoppini et al., 2012) of individuals with Type 2 Diabetes (T2DM) will develop diabetic nephropathy. Consequently, diabetes is currently the leading cause of end stage renal disease (ESRD). Diabetic patients with comorbid nephropathy are at greater risk for cardiovascular and all-cause mortality, as well as adverse renal outcomes (Bakris, 2011). Additionally, management of diabetic nephropathy is estimated to cost upwards of $15 billion annually (Gordois, Scuffham, Shearer, & Oglesby, 2004). Screening for kidney dysfunction and management of risk in diabetic patients is recommended to prevent or delay the onset of diabetic nephropathy. Clinical indicators of diabetic nephropathy include renal injury, evidenced by elevated albumin excretion and a

decrease in glomerular filtration rate (GFR) that signals a decline in renal function. Although albuminuria (defined as >30 g albumin excretion per day or urinary albumin to creatinine ratio [UACR] > 30 g/mg) and GFR decline may be affected by separate pathological processes, both GFR and urinary albumin excretion constitute independent risk factors for renal failure, as well as cardiovascular disease and all-cause mortality in patients with T2DM (Cirillo, 2010). In the present study, predictors of change in albumin excretion and GFR in a sample of T2DM patients with no evidence of renal disease at baseline were examined.

Risk for Albuminuria in T2DM

Evidence from cross-sectional studies indicates that among patients with T2DM, albuminuria is associated with retinopathy, neuropathy, hypertension, dyslipidemia, and obesity (Yokoyama et al., 2011). Patients with T2DM and albuminuria also tend to have higher levels of HbA1c, systolic blood pressure and triglycerides, and lower HDL-C and estimated GFR (eGFR) than patients with normal albumin excretion (Yokoyama et al., 2011). Longitudinal studies have also shown that in normoalbuminuric subjects, the onset of microalbuminuria is independently related to retinopathy (Retnakaran et al., 2006; Yokoyama et al., 2011), neuropathy (Yokoyama et al., 2011), smoking (Retnakaran et al., 2006), and male sex (Retnakaran et al., 2006), as well as higher albumin excretion (Retnakaran et al., 2006; Yokoyama et al., 2011), systolic BP (Ravid et al., 1998; Retnakaran et al., 2006), HbA1c (Ravid et al., 1998; Retnakaran et al., 2006; Yokoyama et al., 2011), LDL-C (Ravid et al., 1998; Retnakaran et al., 2006), and triglycerides (Ravid et al., 1998; Retnakaran et al., 2006; Yokoyama et al., 2011), and lower GFR

(Retnakaran et al., 2006), and HDL-C at baseline (Ravid et al., 1998; Yokoyama et al., 2011).

Risk for GFR Decline in T2DM

Patients with impaired eGFR have been shown to have higher levels of triglycerides, LDL-C and inflammatory biomarkers and lower HDL-C compared to T2DM patients with normal GFR in cross-sectional analyses (Lin, Hu, Rimm, Rifai, & Curhan, 2006). Among T2DM patients with normal renal functioning, women (Yokoyama et al., 2011), smokers (Zoppini et al., 2012), older patients (Zoppini et al., 2012), patients with longer duration (Zoppini et al., 2012), albuminuria (Zoppini et al., 2012), retinopathy (Zoppini et al., 2012), neuropathy (Yokoyama et al., 2011), hypertension (Yokoyama et al., 2011; Zoppini et al., 2012), higher HbA1c (Yokoyama et al., 2011), higher systolic BP (Yokoyama et al., 2011), and higher GFR (Yokoyama et al., 2011), and patients on insulin therapy (Zoppini et al., 2012) tend to exhibit rapid decline in GFR. The rate of decline in eGFR is related to subject age (Zoppini et al., 2012), total cholesterol (Ravid et al., 1998), blood pressure (Ravid et al., 1998; Yokoyama et al., 2011), HbA1c (Ravid et al., 1998; Yokoyama et al., 2011), LDL-C (Ravid et al., 1998), HDL-C (inversely) (Ravid et al., 1998), triglycerides (Ravid et al., 1998), albumin excretion (Yokoyama et al., 2011; Zoppini et al., 2012), GFR (Ravid et al., 1998; Yokoyama et al., 2011), obesity (Ravid et al., 1998), female sex (Ravid et al., 1998), retinopathy (Yokoyama et al., 2011), hypertension (Zoppini et al., 2012), insulin treatment (Zoppini et al., 2012), and smoking status at baseline (Ravid et al., 1998). Likewise, onset of renal impairment in subjects with preserved renal function is related to female sex (Retnakaran et al., 2006), retinopathy (Zoppini et al., 2009) and neuropathy

(Retnakaran et al., 2006), as well as longer diabetes duration (Zoppini et al., 2009), increased age (Retnakaran et al., 2006; Zoppini et al., 2009), obesity (Retnakaran et al., 2006; Zoppini et al., 2009), systolic BP (Ravid et al., 1998; Retnakaran et al., 2006; Zoppini et al., 2009), HbA1c (Ravid et al., 1998; Zoppini et al., 2009), cholesterol (Ravid et al., 1998), triglycerides (Zoppini et al., 2009), and albumin excretion (Retnakaran et al., 2006; Zoppini et al., 2009), and decreased insulin sensitivity (Retnakaran et al., 2006), HDL-C (Zoppini et al., 2009), and eGFR at baseline (Retnakaran et al., 2006; Zoppini et al., 2009).

Potential Mechanisms linking Risk Factors to Nephropathy Onset

Glycemic control. The mechanisms linking these demographic and biological factors to renal disease risk have not been completely elucidated. However, available literature shows that the actions of glucose and hypertension on the renal cell contribute to several processes involved in the pathogenesis of diabetic nephropathy. Glucose promotes accumulation of the extracellular matrix, and enhances membrane permeability (Schena & Gesualdo, 2005). Such structural changes are mediated by advanced glycosylation end products (AGEs) and changes in cytokines and growth factor production and secretion initiated by stimulation of the glucose receptor (Schena & Gesualdo, 2005). In hyperglycemic environments, glucose receptors are upregulated, enhancing the effects of glucose on renal cells (Schena & Gesualdo, 2005).

Blood pressure. Similar to glucose, hypertension in the glomerulus induces mechanical stretch which enhances extracellular matrix accumulation (Hostetter, Rennke, & Brenner, 1982). This mechanical stretch is also related to loss of podocytes, another structural change associated with diabetic nephropathy (Durvasula et al., 2004). There is

strong evidence of an interaction between hyperglycemia and hypertension in the development and progression of renal disease. First, autoregulation of blood pressure in renal cells is disrupted in hyperglycemic environments (Gnudi et al., 2003; Hostetter et al., 1982). Increased intraglomerular pressure, in turn, enhances glucose transport and signaling in the kidney (Gnudi et al., 2003). Studies have also shown that inhibition of one signaling pathway can prevent the negative consequences associated with the other (Thomas et al., 2005).

Blood cholesterol. The role of dyslipidemia in renal disease risk is less well understood. Dysipidemia can contribute to inflammatory, oxidative and endothelial stress and may contribute to risk of atherosclerosis and renal disease via common pathways (Dalrymple & Kaysen, 2008; Ruan, Varghese, & Moorhead, 2009). These pathways involve oxidation of LDL-C molecules, formation of reactive oxygen species and cytokine release, and attraction of macrophages that ultimately leads to the production of foam cells (Dalrymple & Kaysen, 2008). Research also indicates that hyperglycemia may negatively influence lipid regulation in patients with kidney dysfunction, such that AGEs modify LDL-C particles and impair cholesterol clearance processes (Bucala et al., 1994), suggesting an interaction between dyslipidemia and hyperglycemia in the development of nephropathy.

ADA Recommended Treatment Targets for T2DM

As a secondary prevention strategy, the American Diabetic Association (ADA) set a number of treatment targets for management of T2DM to reduce the risk of adverse events and vascular complications like diabetic nephropathy. These treatment targets include an HbA1c below 7%, blood pressure less than 130/80 mmHg, and LDL less than

100 mg/L. Blood pressure and glucose control optimization is recommended to reduce the risk or slow the progression of nephropathy specifically ("Standards of medical care in diabetes--2013," 2013). The ADA has also recommended annual screening for albuminuria and annual measures of serum creatinine for all T2DM patients. Patients with elevated albumin excretion may be treated with ACE inhibitors or ARBs. Lastly, reduction of protein intake is recommended for patients with elevated albumin excretion or GFR decline ("Standards of medical care in diabetes--2013," 2013).

Treatment targets and renal disease risk. A number of studies have tested whether achievement of ADA recommended treatment targets for HbA1c, blood pressure and cholesterol prevents the loss of renal function in T2DM populations. One study showed that patients who achieve the ADA recommended goal of <130/80 mm Hg were less likely to develop microalbuminuria and have annual decline in GFR similar to age-matched controls, while patients with blood pressure ranging from 130/80 to 140/90 showed a steeper GFR decline and 30% developed microalbuminuria (Ravid et al., 1993). There is also evidence to suggest that lipid-lowering drugs also reduce renal disease risk in T2DM patients. Research has shown that use of statins is associated with reduced risk of developing renal dysfunction in diabetic patients without existing renal disease (Athyros et al., 2010). However, most studies have examined the effectiveness of achieving these targets in populations with existing renal disease.

Treatment targets and renal disease progression. In a sample of Chinese patients with T2DM and microalbuminuria, remission to normoalbuminuria over a 4.5 year period was observed in 35.8% of patients and was associated with achievement of HbA1c and SBP goals (Hsieh et al., 2011). In a similar study, effects of 12 months of

intensified treatment with tight glucose regulation and blood pressure treatment on markers of renal function in T2DM patients with hypertension and overt nephropathy were examined. A significant reduction was observed in albumin excretion with no changes in eGFR (Kanaoka et al., 2011). Results of another study showed that achievement of treatment targets for systolic and diastolic blood pressure, total and low-density cholesterol and albuminuria were inversely related to incidence of renal disease in high risk vascular patients. A subsample analysis of T2DM patients revealed that HbA1c levels were more closely related to risk for renal disease than in patients without diabetes (Selvarajah, van der Graaf, Visseren, & Bots, 2011). Overall, the literature suggests that among patients with diabetes and renal disease, management of hyperglycemia, dyslipidemia, and albuminuria can result in improvements in albuminuria; however, there is little evidence for an effect on GFR or clinical outcomes, including incident kidney failure (Slinin et al., 2012). Taken together, these studies provide evidence that early management of blood glucose, blood pressure, and lipids, may reduce incidence of CKD in T2DM patients without renal disease.

Effects of Weight Loss Interventions on Renal Function

In many instances treatment targets may be difficult to achieve or maintain using medication alone (Bryant, Greenfield, Chisholm, & Campbell, 2006). As dyslipidemia, hyperglycemia, and hypertension are all associated with obesity, weight loss via dietary changes and/or physical activity has also been recommended by the ADA to improve lipid profiles, blood pressure management and glycemic control in T2DM populations (Zoppini et al., 2012). Obesity is associated with type 2 diabetes and risk of renal disease as well as increased risk of renal disease within diabetic populations (Eknoyan, 2007).

Weight loss is recommended for overweight or obese persons with diabetes irrespective of renal function and has been shown to have beneficial effects on lipid profiles, inflammation and blood pressure (Klein et al., 2004). Obese patients with kidney disease have benefitted significantly from weight loss interventions (Afshinnia et al., 2010; Navaneethan et al., 2009). However, to our knowledge no study has examined whether a weight loss intervention can reduce the risk of developing renal disease in T2DM patients when compared to treatment as usual.

A review of studies examining the effect of weight loss on kidney function in obese patients with existing CKD indicated a significant reduction in proteinuria following non-surgical interventions (Navaneethan et al., 2009). Four weeks of formula diet intervention for patients with overt diabetic nephropathy resulted in decreases in urinary protein excretion and serum creatinine. These changes were accompanied by significant decreases in blood pressure, HbA1c, total cholesterol and triglycerides. Results showed changes in serum creatinine and urinary protein were related to weight loss but not to changes in other biophysiological measures (Saiki et al., 2005). Authors reported improvements in GFR and creatinine clearance and decreases in albuminuria among obese patients with diabetes and nephropathy in response to a hypocaloric diet. This intervention also resulted in weight loss and changes in blood pressure, triglycerides, and cholesterol profile (Solerte, Fioravanti, Schifino, & Ferrari, 1989). In another study, weight loss following a hypocaloric diet was significantly related to declines in blood pressure for obese individuals with diabetes. Diabetic subjects also showed a decrease in albumin and total protein excretion that was not correlated with metabolic control, blood pressure or weight loss (Vasquez et al., 1984).

Another dietary weight loss intervention resulted in significant reduction in proteinuria in overweight patients with chronic proteinuria, and a subgroup of patients with T2DM. T2DM patients also showed a decrease in BMI and increase in HDL without significant changes in glycosylated hemoglobin, total cholesterol or LDL-C (Morales, Valero, Leon, Hernandez, & Praga, 2003). A 12 week pilot study revealed that a low calorie, vegetarian diet effectively reduced fasting glucose and body weight in patients with non-insulin dependent diabetes, but did not reduce risk of microalbuminuria (Nicholson et al., 1999). Bariatric surgery resulted in decreased albumin to creatinine ratio among obese adults and that patients with diabetes achieved greater benefits. These changes were shown to be related to changes in HbA1c (Agrawal et al., 2008). A lifestyle intervention, consisting of caloric restriction and physical activity, combined with Metformin treatment was associated with declines in urinary albumin excretion, but only in patients with slightly elevated albumin excretion (between 10 and 29 mg/dL). Declines in urinary albumin were related to decreases in blood pressure (Cubeddu, Alfieri, & Hoffmann, 2008). Another study found that six months of aerobic exercise was related to decreased prevalence of microalbuminuria in T2DM (Lazarevic et al., 2007).

The Present Study

These studies show that weight loss can improve renal function in T2DM patients with kidney disease, and that this effect may be at least partially influenced by change in cardiovascular risk indicators, particularly HbA1c, and blood pressure. There is evidence that albumin excretion at baseline is predictive of changes in albuminuria and glomerular filtration rate in response to intervention (Cubeddu et al., 2008; Vasquez et al., 1984). However, the relationship between other baseline factors and intervention effects of renal

outcomes is not known. Knowledge of such relationships would help identify individuals who would benefit the most from such interventions. It is also not known whether weight loss may prevent or delay the onset of diabetic nephropathy in individuals who have T2DM without existing disease. Development of effective prevention strategies is imperative considering the increasing prevalence of T2DM and the burden of comorbid kidney disease in this population. We examined changes in eGFR and UACR, as well as weight, HbA1c, and depressive symptoms in response to a multi-component behavioral intervention in adults with T2DM. We also examined change in eGFR and UACR in relation to demographic (age, sex, diabetes duration, medication use, and smoking) and cardiometabolic factors (Hba1c, blood pressure, and lipids) known to influence renal disease risk in this population.

Chapter 2: Methods

Participants

All participants were enrolled in a randomized controlled trial designed to evaluate the effectiveness of a structured lifestyle intervention entitled: Community Approach to Lifestyle Modification for Diabetes (CALM-D). Goals of the intervention were to reduce weight, increase physical activity, and improve stress management in overweight or obese (BMI values ≥ 27 kg/m2) T2DM patients endorsing significant depressive symptoms (Beck Depression Inventory II [BDI-II] total score ≥ 11) in order to improve HbA1c and renal function. Participants with evidence of CVD or renal disease (dialysis, urine dipstick protein +4, serum creatinine men: ≥ 1.5 mg/dl; women: ≥ 1.4 mg/dl), were excluded from this study, as well as participants with physical or mental limitations preventing them from meeting study demands. Other exclusionary criteria included: blood pressure ≥ 160/100 mmHg, fasting triglycerides ≥ 600 mg/dl, and HbA1c ≥ 11%.

Procedures

Participants were recruited at local community health clinics or referred by word-of-mouth. Eligibility for study participation was ascertained by a physician. The study protocol, including the screening and full study informed consent forms, was approved by the University of Miami Human Subjects Research Office, Institutional Review Board, Medical Sciences Committee A. During screening, patients were administered screening informed consent, medical eligibility form, and BDI-II. Demographic, medical history, anthropometry, blood pressure, psychosocial, urine and blood measures were taken at baseline. Full-study informed consent was administered to eligible participants.

Participants were then randomized to either 12 months of lifestyle intervention (CALM-D) or a usual care control condition (see Figure 1) using a block randomization schedule with blocks of 4 to 10 participants. Assessments were repeated at 6- and 12-months post-randomization. We used "intent-to-treat" analysis; therefore, data from all eligible participants for whom baseline blood or urine measures were available were included in these analyses.

Participants randomized to treatment received a 17 session, structured lifestyle intervention. Each participant received a weight goal (7% weight loss) and physical activity goal (150 minutes aerobic activity/week) at the beginning of the intervention. Intervention participants were given a scale to monitor weight, as well as materials to monitor and record daily food intake. Participants also wore an activity monitor to assess physical activity. Sessions were approximately 1.5 to 2 hours in duration and covered a range of topics related to diet, physical activity and psychosocial well-being. Session objectives included identifying and eating less fat, being active as a way of life, managing negative thoughts and emotions, problem solving, medication adherence, assertiveness, and staying motivated. The first half of the intervention consisted of 4 weekly and 4 bi-weekly sessions. During these sessions, participants learned strategies to achieve physical activity and dietary goals. The second half of the intervention consisted of 9 monthly sessions, focused on problem solving and maintenance of behaviors. At the conclusion of each session, participants completed a mastery form to assess their comprehension of the material and homework assignments to incorporate material into their daily lives.

Participants assigned to usual care received a short educational booklet that covered topics related to diabetes management, but were not instructed to make any

changes to diet, physical activity patterns or stress management practices. All participants received compensation for completing assessments at baseline ($225) and 6 and 12-months ($100 each); intervention participants were also compensated ($10) for attendance at individual sessions.

Measures

Medical Family History questionnaire. The Medical Family History questionnaire was administered during the baseline visit to assess diabetes duration, smoking status and medication usage. Diabetes duration was calculated by subtracting participant age of diagnosis from current age. Diabetes duration was entered as 0 for participants who were previously undiagnosed. Participants also self-reported smoking history. Smoking status was dummy-coded with 0 representing never smokers and 1 representing current or former smokers. Usage of antihypertensive, antihyperlipidemic and antihyperglycemic medications were also self-reported and dummy-coded based on participant exposure. These were later collapsed into a single medication usage variable that was the sum of the three.

Beck Depression Inventory. Depressive symptomatology was assessed using the Beck Depression Inventory II (BDI-II) total score. The BDI-II is a screening tool for depressive symptoms which instructs patients to endorse the degree to which they have experienced various symptoms of depression over the past 2 weeks using a multiple choice scale. Possible total scores on the BDI-II range from 0 – 63, with scores < 14 indicating minimal depressive symptoms, scores 14-19 indicating mild depressive symptoms, scores of 20 – 28 indicating moderate symptoms, and scores of 29-63 indicating severe depressive symptomatology. The BDI-II has demonstrated internal

reliability, convergent and discriminate validity in older community-based samples (Segal, Coolidge, Cahill, & O'Riley, 2008). Evidence also indicates comparable reliability and validity between English and Spanish language versions (Wiebe & Penley, 2005).

Body mass index. The standard formula was used to calculate BMI (kg/m^2) based on height and weight measurements. Participants were weighed using a Tanita Body Composition Analyzer (TBF-300A). Height was assessed using a stadiometer.

Blood pressure. Three blood pressure measurements were taken at two minute intervals from the participant's right arm using an automatic sphygmomanometer (the OMRON HEM-907 XL) with the patient seated, following a period of quiet rest. The average of the three measures was used for the present study.

Laboratory measures

Urinary albumin to creatinine ratio (UACR). Urinary albumin and urinary creatinine excretion were assessed using a sample from the first urination of the day. Urinary albumin to creatinine ratio (UACR) was calculated by dividing milligrams of albumin excretion by grams of creatinine excretion. Participants with undetectable albumin concentrations (< .3 mg) were assigned a value of .01 for the purpose of statistical analysis.

Blood measures. Blood was drawn following a 12 hour fast during baseline and follow-up visits by an experienced phlebotomist. Serum creatinine, serum cystatin C, C-reactive protein, interleukin-6, fibrinogen, LDL-C, HDL-C, hbA1c, and triglycerides were assessed using blood samples.

Estimated glomerular filtration Rate (eGFR). GFR is the gold standard indicator of global renal functioning. Methods of objectively quantifying GFR are costly, time consuming, and labor intensive. The estimation of GFR based on endogenous biomarkers of filtration is common practice in research (Cirillo, 2010). Serum creatinine is currently the most commonly used biomarker in the estimation of GFR (Cirillo, 2010; Dharnidharka, Kwon, & Stevens, 2002). However, research has shown that serum creatinine concentrations are influenced by factors other than renal function, such as body mass and composition, age, dietary intake and tubular secretion (Cirillo, 2010). Also, GFR estimates based on serum creatinine tend to underestimate GFR in populations with normal or near normal functioning (A. D. Rule et al., 2004). Cystatin C has been proposed as a biomarker that may improve or replace creatinine based estimates. Cystatin C is produced at a stable rate and freely filtered in the glomerulus. Unlike serum creatinine, cystatin C is thought not to be affected by age, body mass, or sex (Simonsen, Grubb, & Thysell, 1985). However, other factors like diabetes and inflammation have been shown to associate with cystatin C concentrations (Stevens et al., 2009).

Cystatin C may also be more suitable for evaluating renal function in obese subjects (Marwyne et al., 2011), as well as detecting early decline in renal function in subjects with normal or elevated GFR (Perkins et al., 2005), and subjects with T2DM (Yang, Peng, Lin, Wang, & Huang, 2007). Interestingly, a separate study reported cardiovascular risk factors may associate with cystatin C via non-GFR pathways, and examination of these relationships between risk and eGFR may be improved by the use of creatinine based equations (Andrew D. Rule, Bailey, Lieske, Peyser, & Turner, 2013). Based on the reported limitations and differences in estimation methods, we used two

separate estimates of GFR to evaluate renal function. Glomerular filtration rate was estimated based on serum creatinine(Inker, Shaffi, & Levey, 2012) and cystatin C & creatinine concentrations using the CKD-EPI equations (See Table 1) (Inker, Schmid, et al., 2012). Correlations among the two GFR estimates at all three time points ranged from .622 - .819, $p < .0001$. It should be noted that as a result of study inclusion criteria and GFR estimation methods, the minimum estimated GFR for eligible participants varied as a function of age and gender.

Statistical Analyses

Intervention and control participants were compared on baseline characteristics to determine whether randomization was successful. Differences in continuous variables were evaluated using t-tests. For non-normal variables, t-tests were conducted on log-transformed values. Chi square tests of independence were used to evaluate differences in categorical variables. An alpha level of .05 was used for all significance tests.

Analysis of normative change and intervention effects. An extension of latent growth modeling was used to evaluate intervention effects on outcome variables (Muthén & Curran, 1997). Traditional latent growth models use longitudinal data to capture two unobserved variables involved in change processes, an intercept (initial level) and a slope (magnitude and direction of change). A useful application of this technique in the evaluation of intervention effects, involves the partitioning of change into normative and treatment associated change. The normative slope captures normal change in the outcome variable as a function of time expected to occur in all participants. The treatment effect corresponds to additional change in the outcome variable after accounting for normative change that is observed only in the treatment participants.

Normative change. Normative change in each outcome was specified to occur in a linear fashion over the entire 12-month period for each outcome. However, normative change in $eGFR_{CY\text{-}CR}$ was not linear as the slope changed after the first 6 months. Therefore, for this variable, change during months 6-12 was estimated freely. Intercept estimates, as well as the mean and variance estimates for the normative slope were held equal across treatment and control groups. In all models, residual variances for each measure were estimated as equal across time points to ease model estimation. The beta for normative change estimates can be interpreted as monthly change in the outcome variable. Positive estimates indicate a monthly increase while negative estimates indicate a decrease.

Intervention effects. The additive effects of treatment were expected to occur over the first 6 months of the intervention, and be maintained during months 6 – 12 for the following outcome variables: weight, depression, HbA1c, and UACR. However, intervention effects on eGFR were expected to occur more slowly and were specified to occur over the year. Mean, variance, and covariances of the additive slope were set at 0 for the control group and estimated only for the treatment group. The significance of the mean estimate of the additive slope was evaluated to determine if the intervention had a meaningful effect on change in each variable. Intervention effects are reported as betas and can be interpreted as monthly change in the outcome variable after accounting for any normative change that may occur. Depending on the direction of normative change, positive estimates may indicate a greater increase or smaller decrease per month in the outcome, while negative estimates indicate a greater decrease, or smaller increase.

Predictors of continuous change in renal outcomes. To determine how baseline demographic and cardiometabolic risk factors related to renal outcomes and change in renal outcomes, predictors were added to renal outcome models. First, demographic covariates (including: age, sex, diabetes duration, smoking, and medication use) were added to each model to predict initial values, as well as normative and treatment associated change. Next, the effect of cardiometabolic risk factors (blood pressure, glycemic control, lipids) on intercept, normative change, and treatment associated change in each renal outcome was tested in a univariate model adjusted for the effects of demographic covariates. Finally, a multivariate model for each renal outcome was specified to examine all relationships simultaneously (See Figure 2).

Predictors of albuminuria and rapid eGFR decline. Predictors of change in renal function were also examined categorically using clinical endpoints. Differences in baseline risk factors among individuals who exhibited rapid decline in eGFR and those who did not were examined. A rapid decliner was defined as an individual whose eGFR decreased by 4% of initial eGFR or more over the year, as described in previous studies(Zoppini et al., 2012). We also compared participants who progressed to microalbuminuria during the course of the study to those who did not. Between group comparisons included the following continuous variables: age, diabetes duration, initial eGFR (cystatin and creatinine estimates) initial UACR, BMI, waist circumference, systolic BP, diastolic BP, HDL-C, LDL-C, triglycerides, HbA1c, fasting glucose, HOMA-ir, insulin sensitivity index, CRP, IL-6, BDI total score. Proportions of the following categorical variables were also compared: medication use (glycemic, hypertensive, and lipid lowering), albuminuria, eGFR $\leq$ 90 ml/min, hypertensive, gender,

smoking status, randomization group, and albuminuria progression. Differences were evaluated using t-tests and chi-square tests of independence for continuous and categorical variables respectively. Subjects who had existing albuminuria (n = 9) at baseline assessment were not included in the comparative analysis, or in the analysis of change in UACR.

Chapter 3: Results

Descriptive data

Table 2 displays sample characteristics at baseline. The sample consisted of mostly middle aged (mean age = 54.81 ± 7.36 years), minority (85% Hispanic; 11% Black), women (71.2%), who were overweight or obese (mean BMI = 32.59 ±4.66 kg/m^2), and relatively poor (mean household income = $14,382 ± $10,832) with depressive symptoms (mean BDI = 20.22 ± 7.13). Fifty-six percent of the total sample was prescribed antihypertensive medications, 84% antihyperglycemic medications and 42% antihyperlipidemic medications at study onset. Mean $eGFR_{CR}$ and $eGFR_{CY\text{-}CR}$ estimates indicated renal function in the unimpaired range on average. One (1%) participant began the study with $eGFR_{CR}$ below 60 ml/min, while 6 participants (7%) had $eGFR_{CY\text{-}CR}$ estimates below 60 ml/min. Mean UACR for the total sample was 12 mg/g, with 9 participants entering the study with an UACR greater than 30 mg/g. Fifty-seven participants were randomized to usual care, while 54 were randomized to treatment condition. Participants assigned to intervention and control groups differed as a function of ethnicity, with participants identifying as Caucasian being overrepresented in the control group (9%), compared to the intervention group (0%). There were no other significant differences at baseline between intervention and control participants.

Intervention effects

Figures 3 – 8 display means and standard error bars for intervention and control participants at baseline, 6-months, and 12-months for the following variables: weight, HbA1c, BDI total score, UACR, $eGFR_{CR}$, and $eGFR_{CY\text{-}CR}$. Table 3 displays intervention effects on each outcome with associated p-values.

Weight. Initial weight (M = 85.31 kg, SE = 1.35, p < .001) did not differ as a function of randomization ($p > .05$), and mean normative weight change over the 12 month period was not significant (B = - .033, SE = .039, $p > .05$) for the cohort. The mean of the treatment effect on weight was significant (B = -.320, SE = .125, $p < .01$), indicating an average of .32 kg of weight loss per month over the first 6 months of intervention that was maintained through the 12 month assessment. There was significant variability in initial weight (B = 197.716, SE = 27.042, $p < .001$), normative weight change (B = .048, SE = .020, $p < .05$), and treatment associated weight change (B = .625, SE = .253, $p < .05$). These results indicate significant variability in initial weight, and weight change, and intervention effects on weight respectively. This model demonstrated reasonable fit of the data, X^2 (8) = 15.10, $p = .057$, RMSEA = .127, 90% C.I (.000, .224)

HbA1c. Initial Hba1C (M = 7.73, SE = .13, $p <.001$) did not differ between intervention and control participants ($p > .05$). The normative slope indicated a trend toward an overall normative increase in HbA1c scores (B = .018, SE = .011, $p < .10$), corresponding to an increase of .018% per month among all participants. The mean of the treatment effect however, was significant (B = -.068, SE = .030, p < .05), indicating participants in the treatment group showed a monthly decline in HbA1c of .068%, after accounting for the expected increase of .018%. There was significant variability in HbA1c at baseline (B = 1.287, SE = .242, $p < .001$), but not in normative change (B < .001, SE = .002, $p > .05$) or treatment associated change (B = .019, SE = .019, $p > .05$). These results indicate that although initial glycemic control tended to vary, participants changed in a similar fashion. This model fit the data well, X^2 (8) = 14.52, $p = .069$, RMSEA = .122, 90% C.I (.000, .220).

BDI II total score. Mean BDI scores at baseline (M = 19.75, SE = .65) did not differ according to treatment group ($p > .05$). Participants in both groups exhibited a significant decline in BDI scores (B = -.357, SE = .111, $p = .001$) of .36 units per month. Participants in the treatment group demonstrated a significant additional decline (B = -.993, SE = .228, $p < .001$) of about .99 units per month. Variance in both initial status (B = 19.160, SE = 7/914, $p < .05$) and normative change (B = .359, SE = .171, $p < .05$) were significant, indicating significant heterogeneity among participants in baseline BDI and change in BDI as a function of time. The variance of the treatment effect on BDI was not significant (B = .262, SE = 1.022, $p > .05$) indicating similar intervention associated changes in BDI across all participants. This model also demonstrated reasonable fit of the data, X^2 (8) = 13.91, $p = .084$, RMSEA = .115, 90% C.I (.000, .214).

UACR. Mean albumin excretion at baseline (M = 5.76, SE= .70) did not vary by treatment group ($p > .05$), and did not have significant variability (B = 6.65, SE = 9.13, p = .466), suggesting homogeneity in initial albumin excretion. The mean of the normative change was significant (B = .460, SE = .163. p = .005) and had significant variability (B = .971, SE = .349, $p = .005$) suggesting an overall positive, but variable, trajectory of change at a rate of about .460 mg/g/month. The mean of the treatment effect on UACR was not significant (B = .228, SE = .336, $p = .497$). The variance estimate of the treatment effect was constrained equal to the variance of the normative change. Initial UACR was related to normative change in UACR (B = 3.313, SE = 1.293, $p = .010$) and treatment associated change (B =11.421, SE = 2.369, $p < .001$), indicating individuals with higher albumin excretion at baseline tended to increase at a faster rate in both groups. Treatment associated change and normative change were not associated (B = -

.105, SE = .770, p = .891). This model did not have good fit the data, (X^2 (9) = 15.15, p = .087, RMSEA = .117, 90% C.I (.000, .217), and therefore results should be interpreted with caution.

$eGFR_{CR}$. The estimated mean intercept (M = 102.23, SE = 1.37, p < .001) corresponding to the average $eGFR_{CR}$ at baseline, had significant variability (B = 165.620, SE = 28.081, p < .001), and did not differ between intervention and control participants (p > .05). The mean of the normative change was not significant, (B = -.146, SE = .119, p = .219). The mean of the treatment effect was also not significant, (B = .197, SE = .168, p = .240). The variance estimates of normative change and treatment effect were estimated as equal, and also were not significant (B = .068, SE = .172, p = .691). Initial $eGFR_{CR}$ was not related to normative change in $eGFR_{CR}$ (B = .748, SE = 1.928, p = .698) or the treatment effect on $eGFR_{CR}$ (B = -3.096, SE = 2.38, p = .193). Normative change and treatment associated change were not associated (B = .003, SE = .169, p = .988). These results indicate that the mean $eGFR_{CR}$ did not change significantly over the course of the year in intervention or control participants, and that rates of change did not vary according to initial $eGFR_{CR}$. This model fit the data well, (X^2 (9) = 8.33, p = .502, RMSEA < .001, 90% C.I (.000, .145)).

$eGFR_{CY\text{-}CR}$. The estimated mean intercept (B = 87.10, SE = 1.87, p < .001) had significant variability (B = 277.756, SE = 46.691, p < .001), and did not differ between intervention and control participants (p > .05). The mean of the model estimated normative change during the first 6 months was significant, (B = .468, SE = .200, p = .019), and was followed by a more rapid decrease. The variance estimate of the normative change was constrained equal to the variance of the treatment effect (B = .128,

SE = .193, p = .508). The mean of the treatment effect on $eGFR_{CY-CR}$ was also significant, (B = .331, SE = .142, p = .020), indicating an increase in $eGFR_{CY-CR}$ among treatment participants at a rate of .331 ml/month after accounting for normative change. Initial eGFR was negatively related to normative change in $eGFR_{CY-CR}$, (B =-7.051, SE = 2.968, p = .018), indicating participants with higher eGFR at baseline tended to decline at a more rapid rate. The relationship between initial $eGFR_{CY-CR}$ and treatment associated change in $eGFR_{CY-CR}$ was not significant, (B = -3.382, SE = 2.433, p = .164). This model also fit the data, (X^2 (8) = 10.42, p = .237, RMSEA = .083, 90% C.I (.000, .208)).

Predictors of renal outcomes

Continuous change.

$eGFR_{CR}$. In univariate analyses, age and triglycerides were negatively related to initial $eGFR_{CR}$, while female sex and HDL-C were positively related to $eGFR_{CR}$. Men, older individuals, and those with higher triglycerides and lower HDL-C at baseline had a lower $eGFR_{CR}$ at baseline. Current or previous smoking and albumin excretion were negatively related to normative rate of change, and HDL-C was positively related to normative change. Smokers, and those with greater albumin excretion declined faster, while those with greater HDL-C declined more slowly. Systolic BP and HDL-C were negatively related to the treatment effect on $eGFR_{CR}$, indicating those with higher BP and higher HDL-C benefited less from treatment. Triglycerides were positively associated with the treatment effect on $eGFR_{CR}$, indicating a greater treatment associated benefit for those with greater triglycerides at baseline.

In the final model, adjusted for all demographic covariates and all biological risk factors, only age and triglycerides were related to initial $eGFR_{CR}$. These results indicate

that older participants and participants with higher triglycerides had lower initial eGFR values. HDL-C and systolic BP were positively related to normative change (associated with an increase), while albumin excretion at baseline remained negatively associated with normative change (associated with a decrease). Therefore, although there was no meaningful normative change overall in $eGFR_{CR}$, participants with lower systolic blood pressure, higher albumin excretion, and lower HDL-C at baseline tended to decline at a faster rate. HDL-C and UACR were also negatively related to treatment associated $eGFR_{CR}$ change, indicating participants in the treatment group with lower HDL-C and lower albumin excretion at baseline had greater treatment associated increases in $eGFR_{CR}$ values (See Table 4).

$eGFR_{CY-CR}$. Initial $eGFR_{CY-CR}$ was also negatively related to age and triglycerides at baseline. None of the predictor variables was associated with normative change in $eGFR_{CY-CR}$. Male sex, higher HbA1c, and higher triglycerides, at baseline were associated with greater treatment associated increases in $eGFR_{CY-CR}$ in univariate models. In the multivariate model, age and triglycerides remained negatively related to initial $eGFR_{CY-CR}$. Multivariate predictors of the treatment effect on $eGFR_{CY-CR}$ included age, medications, smoking, diabetes duration, UACR, HbA1c, and triglycerides. Additionally initial $eGFR_{CY-CR}$ was negatively related to treatment associated change, ($B = -4.745$, $SE = 2.259$, $p = .036$). Older individuals, previous or current smokers, and participants with higher HbA1c and higher triglycerides at baseline had greater increases associated with treatment. Female sex, use of more medications, and lower UACR and eGFR at baseline were associated with less pronounced treatment associated increases (See Table 5).

UACR. None of the included predictor variables was related to initial UACR or normative change in UACR. In univariate analysis, LDL-C was positively associated with treatment associated change in UACR, suggesting a steeper increase in UACR among treatment participants with higher baseline LDL-C. In the multivariate analysis, none of the predictors was related to UACR intercept or change in UACR (normative or treatment associated). Initial UACR remained positively related to normative change in UACR (B = 2.624, SE = 1.052, p = .013) and treatment associated change in UACR (B= 11.022, SE = 2.422, p < .001). Normative change and treatment effects in UACR were not related (B = -.693, SE = .421, p = .100). Overall, these results indicate an increase in albumin excretion among all normoalbuminuric subjects over the course of the year among average participants who were not on medications. This increase was greater for participants with greater albumin excretion at baseline. After accounting for effects of baseline UACR, no other predictor was related to change in albumin excretion (See Table 6).

Clinical endpoints.

Albuminuria onset. Twenty-nine (26%) participants were missing urinary data at either baseline or 12-months. Of the remaining 82 subjects, 66 (80.5%) remained in the normoalbuminuric stage through the course of the intervention. Six participants (8%) had microalbuminuria at baseline, 3 (4%) remained in the microalbuminuric stage or progressed to macroalbuminuria while 3 (4%) showed remission, achieving normoalbuminuria by 12 months. Ten participants (12%) who began normoalbuminuric stage progressed to microalbuminuria by 12 months.

We compared those who progressed to microalbuminuria to those who did not on key variables of interest (see Table 7). Compared to non-progressors (n = 66), progressors (n = 10) had a lower initial eGFR, were more likely to have an eGFR below 90 ml/min and higher initial UACR values. Progressors also had decreased levels of HDL-C, and increased IL-6 compared to non-progressors and were more likely to be former or current smokers. There was no difference in medication use between progressors and non-progressors.

Rapid decline.

$eGFR_{CR}$. Twenty-eight participants were missing serum creatinine data at either baseline or 12-months. Twenty-two (27%) of the remaining 83 showed a decline in eGFR ≥4% of their initial eGFR and were considered rapid decliners, 61 (73%) showed an increase in eGFR or a decline of < 4% relative to their initial eGFR and were considered non-decliners. Decliners and non-decliners were compared on variables of interest (see Table 8). Compared to non-decliners, rapid decliners had higher initial eGFR estimates (creatinine based), and exhibited greater declines in eGFR. Rapid decliners were also less likely to be on glycemic medications at study onset, $p = .015$.

$eGFR_{CY\text{-}CR}$. Sixty-three (57%) participants had cystatin-c data available at baseline and 12-months. Among these, 18 (29%) were rapid-decliners and 45 (71%) were considered non-decliners. Decliners had higher baseline $eGFR_{CY\text{-}CR}$ values (creatinine and cystatin based), were less likely to have impaired kidney function at baseline, and had more negative change in $eGFR_{CY\text{-}CR}$ values (creatinine and cystatin based). Decliners also had lower triglyceride values and were less likely to be hypertensive at baseline. There was no difference in medication use between these two groups (See Table 9).

Chapter 4: Discussion

The major finding of the present randomized control trial was that a behavioral weight loss intervention program improved kidney function relative to usual care in a cohort of adults with T2DM and no evident renal disease. These findings suggest a potential role for behavioral interventions in the primary prevention of CKD in this at risk sample. Intervention participants also showed significant decreases in weight, depressed affect, and HbA1c relative to participants assigned to usual care. It should be noted that 86% of participants assigned to the intervention condition were prescribed antihyperglycemic medications at study onset so that the effect on HbA1c reflects an improvement in glycemic control beyond what could be expected using pharmacotherapy alone. These results are particularly important because the present sample was composed of overweight/obese individuals who reported clinically significant levels of depressive symptoms at baseline. Improvements in weight and glycemic control are often difficult to achieve in patients with depressed affect (Gonzalez et al., 2007). Likewise, hyperglycemia (Lustman & Clouse, 2007) and obesity (Milaneschi et al., 2012; Zhao et al., 2011) may increase risk of depression in T2DM. These results support the use of interventions that target depressive symptoms as well as diet and physical activity in the management of T2DM risk.

Intervention Effects on Renal Outcomes

eGFR decline. We found evidence of a beneficial effect of intervention on renal function in individuals with T2DM and without existing renal disease, suggesting there may be a role for behavioral interventions in the prevention or delay of diabetic nephropathy. Further, results indicate that the observed effect is moderated by traditional

risk indicators at baseline, including HbA1c, LDL-C, and triglycerides, as well as systolic BP and HDL-C. Previous research has demonstrated that behavioral interventions may benefit individuals with existing nephropathy. Two of the reviewed studies reported improvements in eGFR in T2DM patients with nephropathy following a weight loss intervention (Saiki et al., 2005; Solerte et al., 1989). One study reported this improvement was related to weight loss (Saiki et al., 2005), and another did not examine this association although the intervention resulted in changes in weight, blood pressure triglycerides and cholesterol (Solerte et al., 1989). Both of these studies used creatinine based estimates of renal function. The present study adds to this literature in a number of ways. First, we examined these relationships in a healthier population, in terms of kidney function, using two different methods of GFR estimation. We were also able to identify potential moderators of this treatment effect, although the study was not sufficiently powered to examine mediation effects. However, our results indicate that participants with the greatest cardiometabolic risk, that is lower HDL-C, greater triglycerides, LDL-C and HbA1c, may also benefit the most from participation in a behavioral weight loss intervention.

Albumin Excretion. We did not observe any intervention effects on rate of change in albumin excretion in this population. We also did not find any baseline factors that moderated the effect of treatment on albumin excretion. Previous studies examining effects of weight loss on albumin excretion in T2DM have shown promising results (Cubeddu et al., 2008; Lazarevic et al., 2007; Morales et al., 2003; Nicholson et al., 1999; Saiki et al., 2005; Solerte et al., 1989; Vasquez et al., 1984). Decreases in albumin or protein excretion as a function of weight loss have been linked to changes in weight

(Saiki et al., 2005), HbA1c (Agrawal et al., 2008), and blood pressure (Cubeddu et al., 2008) as well as elevated albumin excretion at baseline. Interestingly, another study reported decreases in albumin excretion that were independent of changes in metabolic control, weight, and blood pressure (Vasquez et al., 1984). Other intervention studies reporting changes in albumin excretion and risk indicators did not examine whether a decrease in risk factors mediated decreases in albumin excretion. Previous studies have also reported changes in albumin excretion are related to baseline albumin excretion (Cubeddu et al., 2008; Vasquez et al., 1984) and glomerular filtration rate (Cubeddu et al., 2008). Several of these studies examined remission of existing albuminuria and thus say little concerning the prevention of albuminuria in this population. Studies examining effects of weight loss on albumin excretion in mixed samples, or samples without existing albuminuria did not have adequate control groups (Agrawal et al., 2008; Cubeddu et al., 2008; Lazarevic et al., 2007; Nicholson et al., 1999), were retrospective (Agrawal et al., 2008), or focused on effects of a surgical intervention (Agrawal et al., 2008). This is the first analysis testing the effects of a randomized behavioral intervention on change in albumin excretion in a sample of normoalbuminuric subjects.

Differences in intervention approaches may also explain differential findings between studies. Most of the studies reviewed here utilized rigorous, supervised interventions, requiring a great degree of experimental control. Intervention modalities included hypocaloric diets (Morales et al., 2003; Saiki et al., 2005; Solerte et al., 1989; Vasquez et al., 1984), low-protein diets (Nicholson et al., 1999), supervised exercise training (Lazarevic et al., 2007), and additional medication (Cubeddu et al., 2008). In contrast, the present intervention was much less controlled. The dietary component of the

intervention focused on reduction of fat intake and total caloric intake, but not protein intake. Further, participants planned their own meals and monitored their own food intake. The physical activity component of the intervention consisted mainly of brisk walking. Participants were encouraged to try other forms of physical activity and to incorporate more active lifestyle choices. However, participants engaged in and monitored exercise on their own. We did not make any changes to participant medication, while the majority had been prescribed antihyperglycemic medications at study onset; about half were prescribed antihypertensive or antihyperlipidemic medication. We used an intent-to-treat analysis, utilizing all data from randomized participants regardless of whether they received the intervention or achieved intervention goals.

Predictors of Initial Status and Normative Change in Renal Outcomes

eGFR. Initial eGFR was lower for older participants and those with more triglycerides and less HDL-C. An age related decline in eGFR has been well documented in the literature (Anderson & Brenner, 1986). Although older participants had lower initial eGFR, they did not have a greater rate of decline. It should be noted that the age range of this sample is restricted. It is possible that an effect of age on normative rate of eGFR change would be observed in a sample including younger participants. We observed an overall decline in cystatin-based eGFR of .633 ml/min/1.73m^2 over the year. The creatinine-based estimate of normative decline was 1.75 ml/min/1.73m^2. The estimated rates of eGFR decline in our subjects are similar to estimates previously published based on objectively measured GFR (-1.68 ml/min/year) in a T2DM sample (Silveiro, Friedman, de Azevedo, Canani, & Gross, 1996), and estimates based on

creatinine clearance in healthy populations in the same age range (from -1.64 to -0.73 ml/min/year) (Rowe, Andres, Tobin, Norris, & Shock, 1976).

Participants with lower systolic BP, lower HDL-C, and greater albumin excretion tended to decline at a faster rate. Rapid decline was most likely to occur in subjects with elevated eGFR at baseline, subjects on fewer medications, subjects without hypertension, and subjects with lower triglycerides. Albuminuria (Retnakaran et al., 2006; Zoppini et al., 2012; Zoppini et al., 2009) and elevated eGFR (Yokoyama et al., 2011) are known risk factors for renal disease. Likewise, studies have provided evidence that antihypertensive, antihyperlipidemic and antihyperglycemic medications may delay the onset or slow the progression of renal disease (Bakris, 2011; Wolf & Ritz, 2003). Previous literature has also shown high triglycerides (Lin et al., 2006; Ravid et al., 1998; Zoppini et al., 2009) and high blood pressure (Retnakaran et al., 2006; Yokoyama et al., 2011; Zoppini et al., 2012; Zoppini et al., 2009) constitute additional risk factors for renal decline in this population; while HDL-C may have a renoprotective effect (Lin et al., 2006; Zoppini et al., 2009). There is evidence that both renal adiposity (Li et al., 2011) and hypertension (Tomaszewski et al., 2007) are important drivers of hyperfiltration often observed in metabolic syndrome. The literature also shows that decreased HDL-C in metabolic syndrome is also related to glomerular hyperfiltration (Tomaszewski et al., 2007). Although these analyses have focused on metabolic syndrome components in predominately healthy populations (Tomaszewski et al., 2007), or in animal models (Li et al., 2011), a number of longitudinal studies in adults with T2DM shave shown that hyperfiltration is associated with a rapid subsequent decline in GFR (Moriya et al., 2012; Ruggenenti et al., 2012; Silveiro et al., 1996). Therefore, factors associated with initial

elevations in GFR may ultimately contribute to GFR decline and later renal impairment. However, other longitudinal studies have shown that lower baseline eGFR is associated with more rapid decline (Retnakaran et al., 2006; Zoppini et al., 2012). Future studies should be conducted to further elucidate the relationship between baseline GFR (in the normal, elevated or impaired range) and subsequent change.

Albumin excretion. Albumin excretion at baseline was not related to any of the predictors examined in the present study. Albumin excretion tended to increase as a function of time. Medication use was not associated with reduced likelihood of progressing to albuminuria. However, higher albumin excretion and IL-6, and lower eGFR and HDL-C at baseline were associated with risk for microalbuminuria. These results suggest a role for medication in treatment of albuminuria, but not prevention. Results also suggest a potential protective role for HDL-C in the development of diabetic nephropathy. Additionally, subclinical variations in albumin excretion were associated with risk of microalbuminuria. Researchers have argued that albumin excretion below the accepted cutoff of 30mg/g is associated with cardiovascular (Cubeddu et al., 2008) and renal risk, and have suggested a new threshold to identify individuals at increased risk (Zamora & Cubeddu, 2009). Results from a five year longitudinal study showed that among subjects with normoalbuminuria, and normal or elevated GFR at baseline, albumin excretion at baseline was the most important predictor of subsequent microalbuminuria (Silveiro et al., 1996). Our results also suggest a role of inflammatory processes in the development of albuminuria. Researchers have reported positive correlations between albumin excretion and inflammation, suggesting a role for inflammatory cytokines in renal injury (Choudhary & Ahlawat, 2008; Pruijm et al., 2012;

Yu, Yang, & Yu, 2010) in T2DM (Choudhary & Ahlawat, 2008), hypertension (Yu et al., 2010), and the general population (Pruijm et al., 2012).

While microalbuminuria is traditionally accepted as the first clinical manifestation of diabetic nephropathy (Bakris, 2011), these results add to previous literature showing a rapid decline in GFR may occur early in subjects who ultimately develop microalbuminuria. A previous longitudinal study in Pima Indians with T2DM indicated that although albuminuria was the stronger predictor of end stage renal disease (ESRD), renal function decline, defined as a decline >3.3% per year, often preceded albuminuria and was also predictive of ESRD (Pavkov et al., 2012). Likewise, the U.K. Prospective Diabetes Study (UKPDS) study showed that over 15 years, ~40% of patients developed albuminuria, and ~30% of T2DM patients developed renal impairment. However, only half of those who ultimately progressed to renal impairment developed albuminuria first (Retnakaran et al., 2006). Overall, the literature indicates albuminuria does not necessarily precede GFR decline, and that those who exhibit a rapid decline in GFR are at least as likely to develop later albuminuria as those who do not (Pavkov et al., 2012; Retnakaran et al., 2006; Yokoyama et al., 2011). Results of this analysis indicate that low GFR is a risk factor for progression to albuminuria, while albumin excretion at baseline was not a risk factor for rapid decline in GFR.

Strengths and Limitations

Objective measurements of GFR are difficult and costly to obtain, and available formulas for estimation have a number of limitations (Cirillo, 2010). Serum creatinine is still the most commonly used marker for estimation of GFR (Perkins et al., 2005). However, cystatin c may be more suitable for evaluating renal function in the normal

range, and detecting early changes in this population (Yang et al., 2007). Differential effects of intervention as a function of GFR estimation method have been reported previously (Juraschek, Appel, Anderson, & Miller, 2013); and researchers have argued that both creatinine (Levey, Perrone, & Madias, 1988) and cystatin c concentrations (Andrew D. Rule et al., 2013; Stevens et al., 2009) are affected by non-renal factors. Indeed, these extraneous relationships may have introduced confounds into the present analysis. However, the use of both methods of estimation provided insight into the impact of measurement on the observed results.

Two other important strengths of this study are the population examined and the intervention employed. We selected a diverse, low-income, community-based sample with limited exclusion criteria and implemented a feasible, low-demand intervention that did not require extensive provider training. Results from epidemiological studies have shown that Black (Young et al., 2005) and Hispanic (Collins et al., 2005) T2DM patients are at increased risk for developing kidney disease in comparison to their white counterparts. Furthermore, socioeconomic status is inversely related to risk of chronic kidney disease (Krop et al., 1999). Potential mechanisms explaining increased risk are access to or utilization of care (Kuo et al., 2003; Larkey et al., 2001) and cultural norms (Larkey et al., 2001).

We used a novel statistical method that allowed us to differentiate normative and treatment associated change processes in renal outcomes. This is important because diabetic nephropathy progresses in stages, and both albumin excretion and GFR are expected to change as a function of time and disease process (Bakris, 2011). The present analysis was limited by the relatively small sample size, missing and/or undetectable

data, short follow-up period, and the availability of only 3 time points of data. We were not able to determine whether change in risk factors was related to change in renal outcomes. Further, we were only able to examine linear change in these outcomes.

This study was also limited because 25% of participants assigned to intervention received 0 treatment sessions and 51% received 6 or fewer sessions. Nevertheless, using an "intent-to-treat" model with an intervention carried out on T2DM participants who were primarily middle-aged, racial/ethnic minority, overweight/obese, and relatively poor with symptoms of moderate to severe depression, the intervention demonstrated significant improvements in terms of weight loss, depressive symptoms, HbA1c and $eGFR_{CY\text{-}CR}$. Finally, it should be noted that the improvements in depression symptoms, HbA1c, and $eGFR_{CY\text{-}CR}$ occurred in the context of a treatment program characterized by modest demands on the participants and relatively small weight loss.

Chapter 5: Conclusions

This study provides evidence that participation in a lifestyle intervention can help prevent decline in renal function in T2DM patients with relatively unimpaired kidney function. Individuals who have greater cardiometabolic risk (i.e. greater albumin excretion and lower HDL-C) according to traditional risk factors also exhibit a steeper decline in renal function. However, these individuals also seemed to experience the greatest treatment associated benefits. It could be that individuals who began the study at higher risk also had the most improvements in these risk factors. However, we were unable to identify potential mediators of this effect. Within this sample, individuals showing most rapid decline in renal function had elevated renal function at baseline. This supports the conclusion that the progression of nephropathy in T2DM patients may have a heterogeneous presentation, as individuals may develop renal impairment with or without showing previous hyperfiltration or microalbuminuria. Future research with larger samples over longer follow-up periods is needed to examine the earliest stages of diabetic nephropathy in T2DM populations, and different trajectories to renal disease outcomes, as well as examine how cardiometabolic risk factors may influence these trajectories.

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Figure 1. Consort diagram of study participants

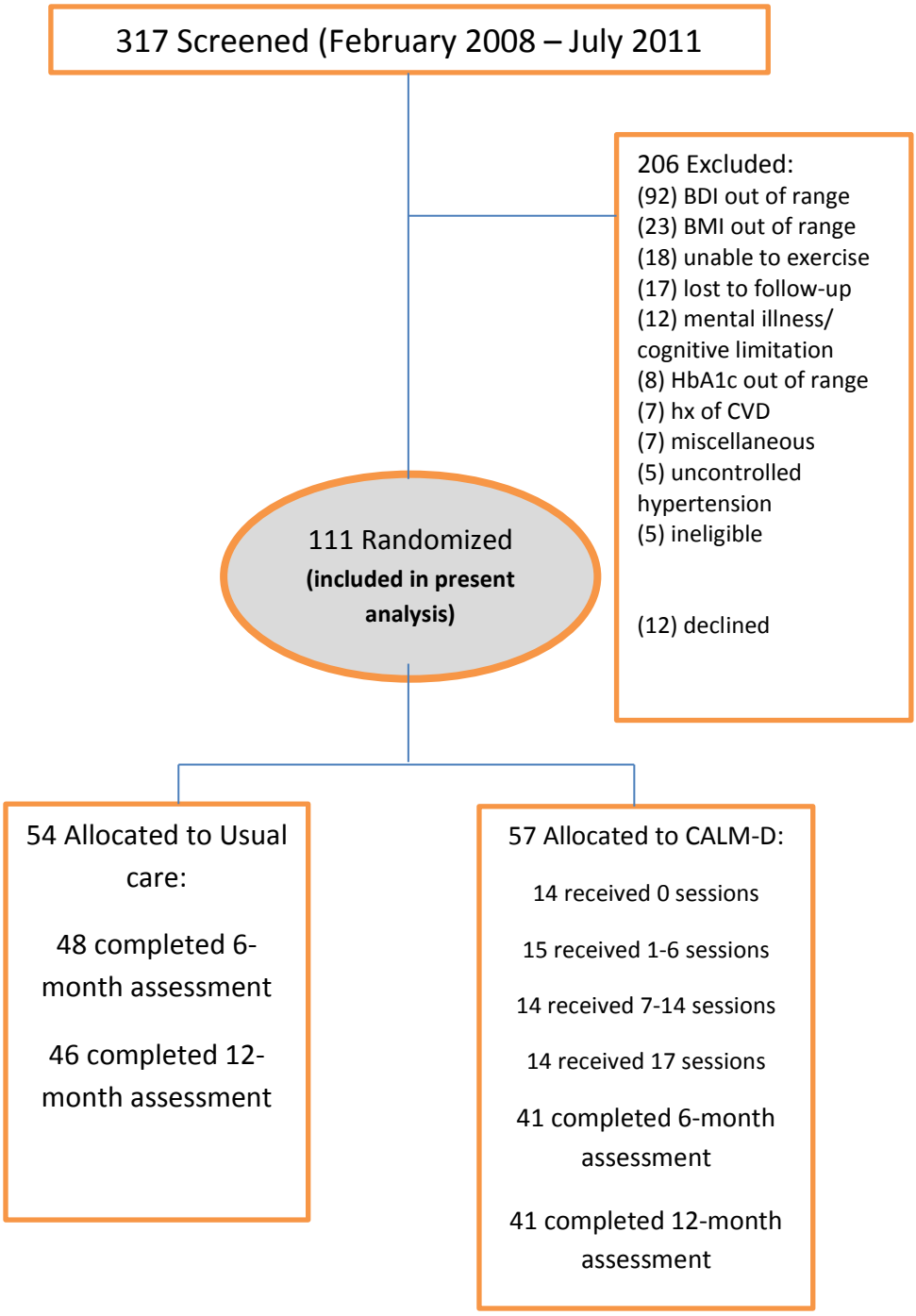

Figure 2. Multivariate model illustration

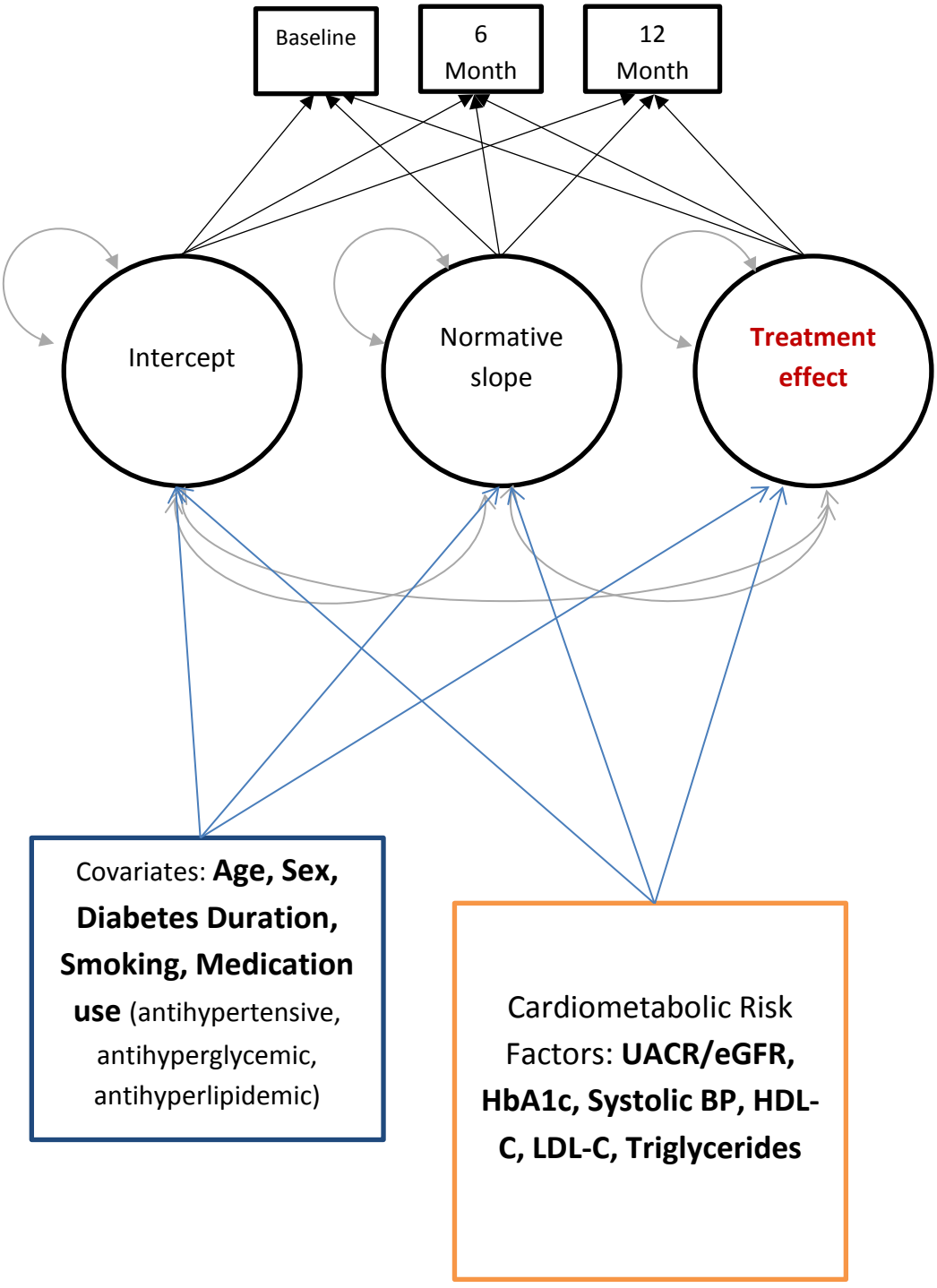

Figure 2 displays the multivariate model specified for renal outcomes (eGFR and UACR). Abbreviations: BP – blood pressure; $eGFR_{CR}$ – creatinine-based estimated glomerular filtration rate; $eGFR_{CR\text{-}CY}$ – cystatin C and creatinine based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; UACR – urinary albumin to creatinine ratio.

Figure 3

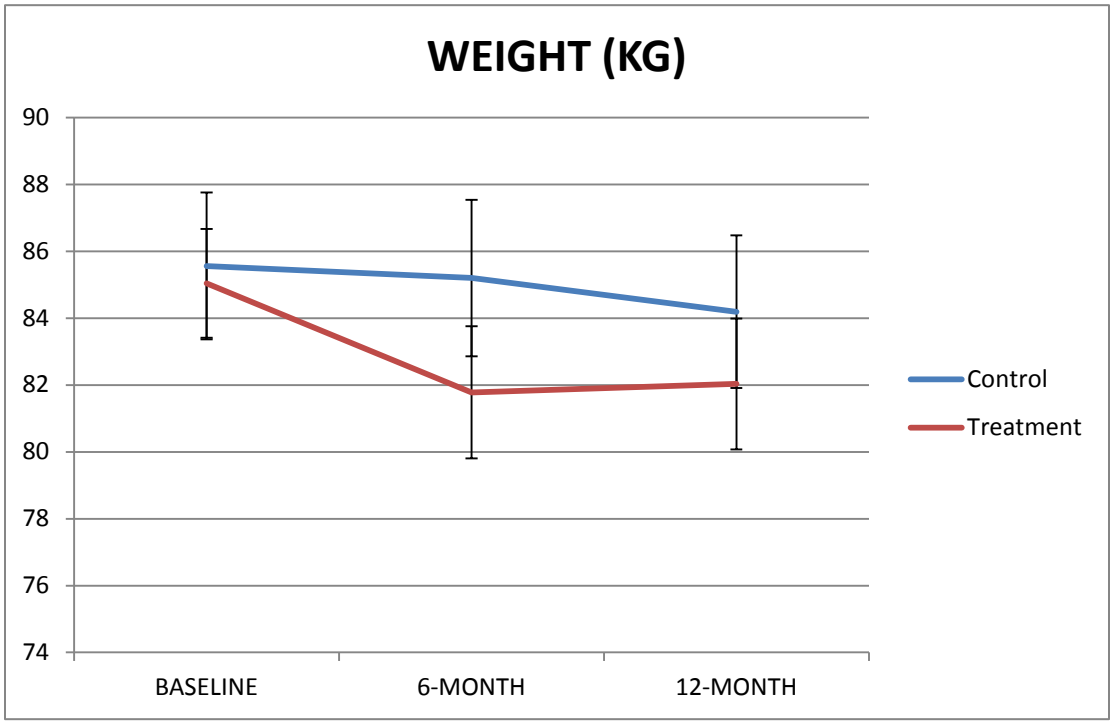

Figure 3 displays mean weight in kilograms at baseline, 6 month, and 12 months for intervention and control participants. Error bars represent standard errors.

Figure 4

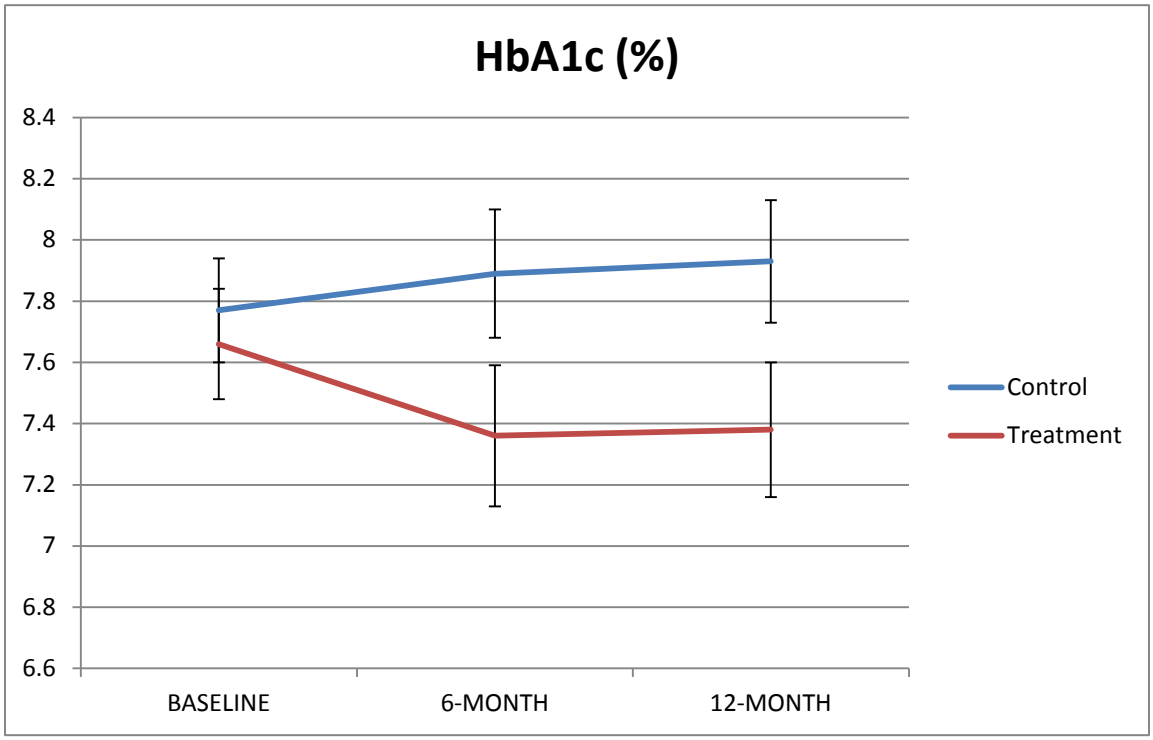

Figure 4 displays mean glycosylated hemoglobin in % at baseline, 6 month, and 12 months for intervention and control participants. Error bars represent standard errors.

Figure 5

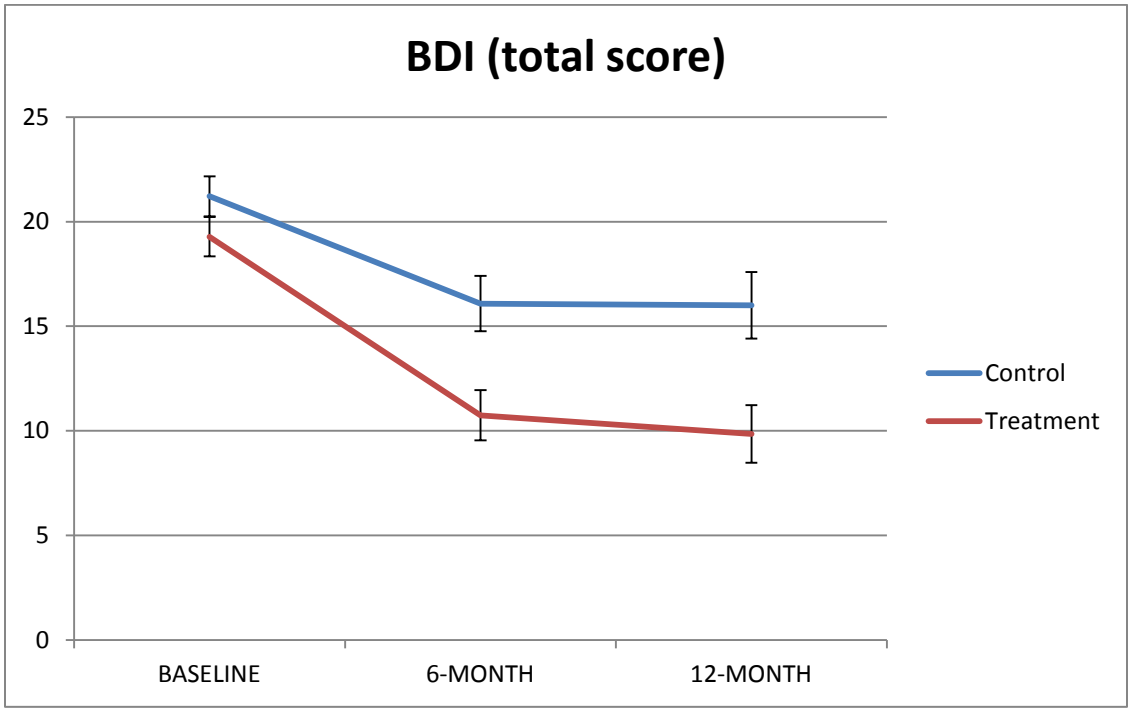

Figure 5 displays mean Beck Depression Inventory total scores at baseline, 6 month, and 12 months for intervention and control participants. Error bars represent standard errors.

Figure 6

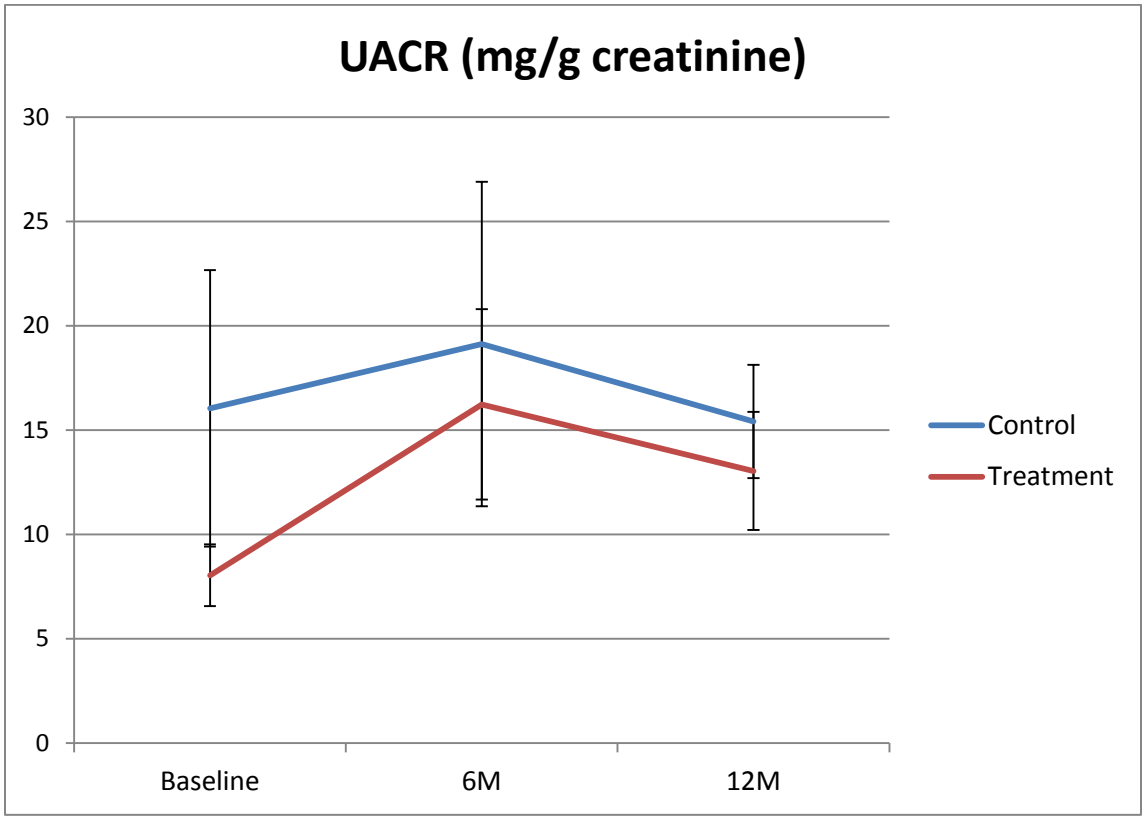

Figure 6 displays mean albumin to creatinine ratios in milligrams of albumin/ gram of creatinine excreted at baseline, 6 month, and 12 months for intervention and control participants. Error bars represent standard errors.

Figure 7

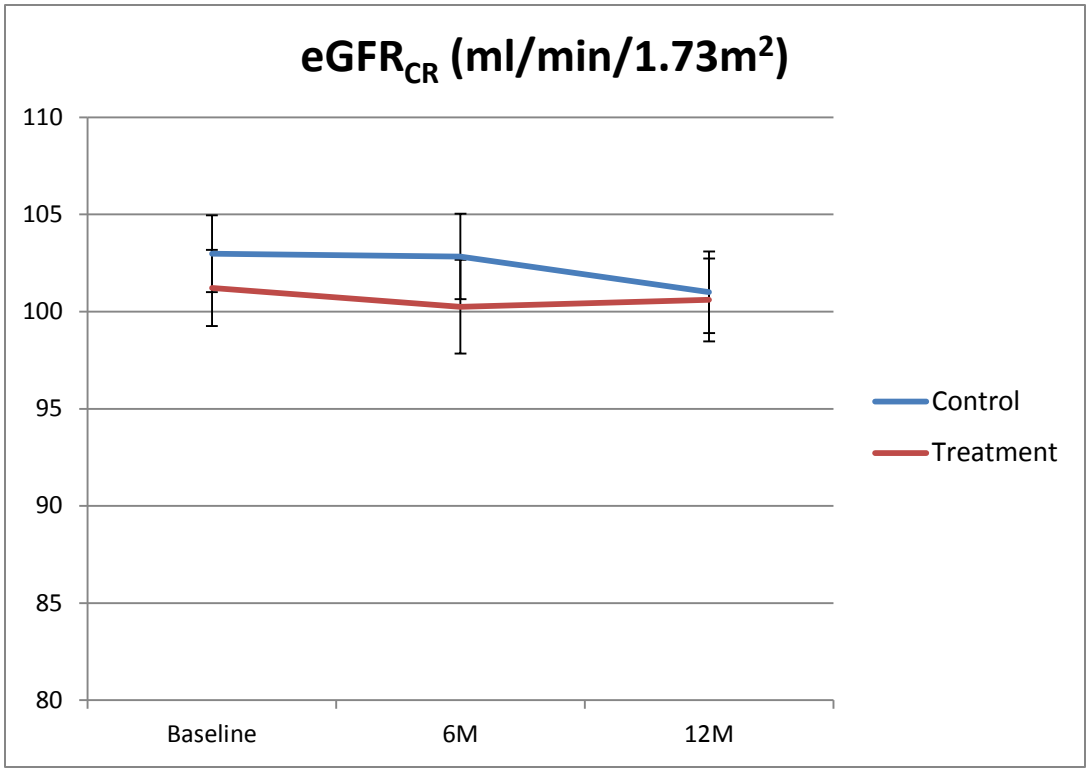

Figure 7 displays mean creatinine based eGFR in milliliters per minute at baseline, 6 month, and 12 months for intervention and control participants. Error bars represent standard errors.

Figure 8

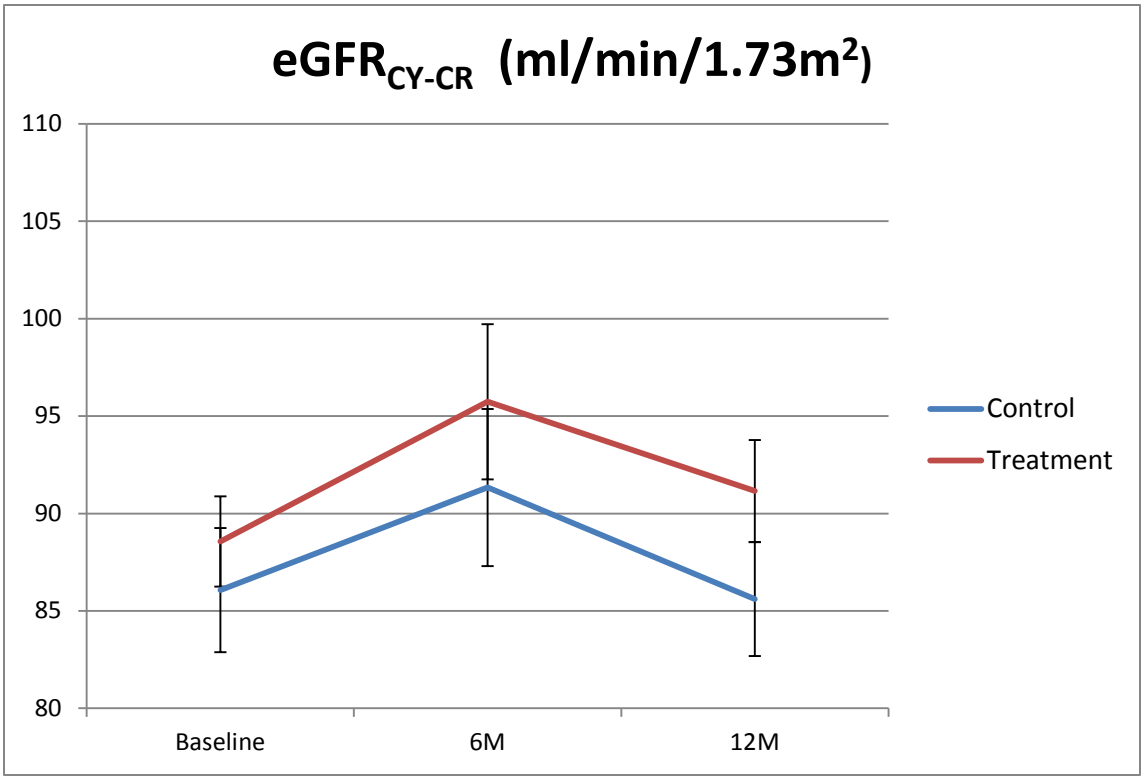

Figure 8 displays mean cystatin and creatinine-based eGFR in milliliters per minute at baseline, 6 month, and 12 months for intervention and control participants. Error bars represent standard errors.

Table 1. Equations used for estimation of glomerular filtration rate (eGFR)

Sex	Scr (mg/dl)	Scys (mg/l)	Equation for eGFR
Creatinine equation ($eGFR_{CR}$)			
Female	≤0.7	-	$144 \times (Scr/.7)^{-0.329} \times 0.993^{age}$ [x 1.159 if black]
	>0.7	-	$144 \times (Scr/.7)^{-1.209} \times 0.993^{age}$ [x 1.159 if black]
Male	≤0.9	-	$141 \times (Scr/.7)^{-0.411} \times 0.993^{age}$ [x 1.159 if black]
	>0.9	-	$141 \times (Scr/.7)^{-1.209} \times 0.993^{age}$ [x 1.159 if black]
Creatinine-cystatin C equation ($eGFR_{CR-CY}$)			
Female	≤0.7	≤0.8	$130 \times (Scr/.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ [x 1.08 if black]
		>0.8	$130 \times (Scr/.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ [x 1.08 if black]
	>0.7	≤0.8	$130 \times (Scr/.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ [x 1.08 if black]
		>0.8	$130 \times (Scr/.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ [x 1.08 if black]
Male	≤0.9	≤0.8	$135 \times (Scr/.7)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ [x 1.08 if black]
		>0.8	$135 \times (Scr/.7)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ [x 1.08 if black]
	>0.9	≤0.8	$135 \times (Scr/.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ [x 1.08 if black]
		>0.8	$135 \times (Scr/.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ [x 1.08 if black]
Abbreviations: Scr, serum creatinine; Scys, Serum Cystatin C			

Table 2. Baseline Sample Characteristics

	Total (N=111) M ± SD / n (%)	Control (n=54) M ± SD / n (%)	Treatment (n=57) M ± SD / n (%)	p-value
Age (yrs)	54.81 ± 7.36	54.78 ± 6.34	54.84 ± 8.27	.964
Male	32 (28.8)	12 (22.2)	20 (35.1)	.135
Ethnicity				.042
Hispanic	94 (84.7)	42 (77.78)	52 (91.2)	
Black	12 (10.8)	7 (13)	5 (8.8)	
White	5 (4.5)	5 (9.1)	0	
Household Income ($)	14382 ± 10832	14096 ± 9730	14674 ± 11956	.798
Years of Education	12.46 ± 3.36	12.27 ± 3.57	12.64 ± 3.16	.571
Weight (kg)	85.30 ± 14.24	85.57 ± 16.20	85.04 ± 12.22	.849
Body Mass Index (kg/m^2)	32.59 ± 4.66	32.85 ± 5.54	32.34 ± 3.65	.572
Diabetes Duration (yrs)	6.89 ± 7.38	7.56 ± 8.43	6.26 ± 6.20	.387
eGFRcr (ml/min/1.73m^2)	102.07 ± 14.23	102.98 ± 14.16	101.21 ± 14.37	.527
eGFRcy (ml/min/1.73m^2)	87.39 ± 17.58	86.07 ± 19.91	88.57 ± 15.35	.522
UACR(mg/g)	12.00 ± 34.22	16.04 ± 47.33	8.04 ± 10.66	.609
Micro/Macroalbuminuria	9 (8.7)	6 (11.8)	3 (5.8)	.281
HbA1c (%)	7.72 ± 1.32	7.77 ± 1.23	7.67 ± 1.40	.678
Systolic BP (mmHg)	128.81 ± 18.48	126.98 ± 16.34	130.57 ± 20.32	.310
Diastolic BP (mmHg)	78.07 ± 10.51	78.78 ± 10.40	77.39 ± 10.66	.492
HDL-C (mg/dL)	43.15 ± 10.99	44.67 ± 9.06	41.71 ± 12.46	.079
LDL- C (mg/dL)	101.87 ± 34.16	97.48 ± 29.39	106.02 ± 37.92	.198
Triglycerides (mg/dL)	163.24 ± 83.55	161.85 ± 85.02	164.56 ± 82.88	.910
Antihypertensive medications	62 (55.9)	30 (55.6)	32 (56.1)	.950
Antihyperglycemic medications	93 (83.8)	44 (81.5)	49 (86)	.522
Antihyperlipidemic medications	47 (42.3)	22 (40.7)	25 (43.9)	.740
Steps Per Day	4040 ± 29.14	3540 ± 2315	4487 ± 3322	.123
BDI Total Score	20.22 ± 7.13	21.21 ± 7.12	19.28 ± 7.08	.155
Smoking status				.138
Never	62 (55.9)	32 (59.3)	30 (52.6)	
Previous	41 (36.9)	16 (29.6)	25 (43.9)	
Current	8 (7.2)	6 (11.1)	2 (3.5)	

Abbreviations: BDI- Beck Depression Inventory; BP – blood pressure; $eGFR_{CR}$ – creatinine-based estimated glomerular filtration rate; $eGFR_{CR\text{-}CY}$ – cystatin C and creatinine based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; UACR – urinary albumin to creatinine ratio.

$\alpha = .05$

Table 3. Intervention Effects on Selected Outcomes

Outcome	Beta	Standard error	p-value
Weight	-.320	.125	.010
HbA1c	-.068	.030	.022
BDI Total Score	-.993	.228	<.001
UACR	.228	.336	.497
$eGFR_{CR}$	.197	.168	.240
$eGFR_{CY-CR}$	.331	.142	.020

Abbreviations: BDI- Beck Depression inventory; $eGFR_{CR}$- creatinine-based estimated glomerular filtration rate; $eGFR_{CY-CR}$- cystatin-c and creatinine-based estimated glomerular filtration rate; UACR- urinary albumin to creatinine ratio.
$\alpha = .05$.

Table 4. Predictors of change in UACR

	Intercept			Normative Change			Treatment Effect		
Predictor	Beta	SE	p	Beta	SE	p	Beta	SE	p
Univariate models									
Age	-.041	.097	.673	-.007	.024	.770	-.015	.047	.741
Sex	-1.400	1.508	-.353	.518	.362	.153	-.897	.706	.204
Medications	-.309	.719	.667	-.262	.179	.143	.021	.377	.956
Smoking	.368	1.456	.800	.468	.344	.173	.063	.698	.928
Diabetes Duration	.855	.822	.298	.230	.194	.235	.212	.389	.586
GFRcr	-.068	.054	.209	-.011	.012	.319	-.027	.027	.320
Systolic BP	0.016	0.041	.694	-0.006	0.01	.556	0.018	0.019	.355
HbA1c	0.674	0.531	.204	-0.152	0.152	.317	0.287	0.277	.300
HDL-C	-1.808	2.858	.527	-0.911	0.574	.113	.422	1.259	.737
LDL-C	-0.009	0.021	.669	-0.005	0.005	.248	.020	.010	.048
Triglycerides	1.806	1.395	.196	.011	0.295	.970	0.801	0.673	.234
Multivariate model									
Age	-.033	.100	.739	-.003	.022	.871	-.026	.049	.591
Sex	-1.645	1.372	.231	.552	.296	.063	-.576	.678	.396
Medications	.226	.646	.726	-.047	.149	.753	-.376	.362	.299
Smoking	-1.266	1.283	.324	.257	.277	.354	.169	.623	.786
Diabetes Duration	-.502	.805	.533	-.041	.187	.828	.393	.416	.345
GFRcr	-.062	.050	.213	-.013	.011	.217	-.012	.027	.644
Systolic BP	.032	.038	.392	.001	.008	.928	.010	.018	.575
HbA1c	.891	.539	.098	-.176	.123	.153	.459	.288	.111
HDL-C	-1.099	2.711	.685	-.889	.546	.104	.757	1.339	.572
LDL-C	-.023	.020	.245	-.005	.005	.237	.016	.010	.109
Triglycerides	-.139	1.437	.923	-.468	.302	.122	.946	.720	.189

Abbreviations: BP – blood pressure; $eGFR_{CR}$ – creatinine-based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; UACR – urinary albumin to creatinine ratio.
$\alpha = .05$

Table 5. Predictors of change in $eGFR_{CR}$

	Intercept			Normative Change			Treatment Effect		
Predictor	Beta	SE	p	Beta	SE	p	Beta	SE	p
Univariate models									
Age	-.897	.173	<.001	-.002	.019	.917	.008	.023	.743
Sex	5.421	2.712	.046	-.263	.288	.362	-.199	.364	.585
Medications	.359	1.266	.777	-.019	.123	.874	.188	.168	.264
Smoking	-1.683	2.626	.522	-.540	.262	.039	.301	.342	.378
Diabetes Duration	.471	1.470	.749	-.133	.141	.346	.025	.184	.892
UACR	.028	.038	.460	-.011	0.004	.006	-0.010	0.012	.401
Systolic BP	0.079	0.071	.263	0.011	0.007	.095	-0.023	0.009	.008
HbA1c	1.008	1.032	.328	-0.088	0.116	.449	.248	.150	.098
HDL-C	12.194	5.237	.020	1.301	0.495	.009	-2.829	.596	<.001
LDL-C	0.012	0.039	.753	-0.002	0.004	.599	0.004	0.005	.468
Triglycerides	-6.466	2.613	.013	-0.010	0.250	.969	0.696	0.328	.034
Multivariate model									
Age	-.960	.183	<.001	-.009	.017	.610	.032	.021	.113
Sex	3.453	2.865	.228	-.285	.273	.297	.016	.320	.961
Medications	.697	1.338	.602	.031	.122	.799	.198	.162	.221.
Smoking	-1.708	2.701	.527	-.481	.250	.054	.326	.303	.282
Diabetes Duration	-.312	1.640	.849	-.223	.149	.134	.066	.184	.721
UACR	.033	.040	.413	-0.012	0.004	.004	-.026	.010	.010
Systolic BP	.071	.077	.353	0.015	0.007	.041	-0.015	0.009	.081
HbA1c	1.141	1.067	.285	.048	.115	.678	.092	.138	.504
HDL-C	9.249	5.678	.103	1.022	0.472	.030	-2.572	.592	<0.001
LDL-C	.015	.041	.716	-.004	.004	.237	.005	.004	.214
Triglycerides	-6.050	2.980	.042	.071	.253	.779	.236	.323	.466

Abbreviations: BP – blood pressure; $eGFR_{CR}$ – creatinine-based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; UACR – urinary albumin to creatinine ratio.
$\alpha = .05$

Table 6. Predictors of change in GFR_{CY-CR}

	Intercept			Normative Change			Treatment Effect		
Predictor	Beta	SE	p	Beta	SE	p	Beta	SE	P
Univariate models									
Age	-1.080	.240	<.001	.045	.031	.147	.017	.017	.337
Sex	3.690	3.608	.306	-.057	.512	.911	-.649	.273	.017
Medications	.876	1.734	.614	-.017	.219	.939	-.011	.133	.933
Smoking	-2.962	3.588	.409	.576	.415	.165	.411	.278	.140
Diabetes Duration	2.563	1.930	.184	-.390	.226	.085	-.146	.145	.314
UACR	0.024	0.134	0.857	-.005	.020	.788	0.005	0.018	0.769
Systolic BP	0.010	0.099	0.922	.022	.016	.161	-0.012	0.009	0.197
HbA1c	.900	1.510	.551	.121	.237	.610	.407	0.095	<.001
HDL-C	11.886	8.370	0.156	.355	1.115	.750	-0.774	0.643	0.229
LDL-C	0.016	0.053	0.767	.004	.008	.646	<.001	0.004	0.979
Triglycerides	-8.574	3.346	0.010	-.145	.433	.737	0.621	0.223	0.005
Multivariate model									
Age	-1.022	.243	<.001	.011	.018	.546	.040	.015	.010
Sex	.553	3.634	.879	.206	.244	.399	-.424	.262	.105
Medications	1.775	1.742	.308	-.004	.102	.966	-.247	.122	.043
Smoking	-2.674	3.544	.451	.530	.402	.187	.955	.260	<.001
Diabetes Duration	1.254	2.141	.558	.017	.122	.892	-.523	.149	<.001
UACR	.089	.128	.487	.001	.008	.865	-.025	.012	.041
Systolic BP	.038	.098	.697	-.008	.007	.250	-.004	.008	.612
HbA1c	.251	1.543	.871	.050	.109	.646	.525	0.107	<0.001
HDL-C	6.694	8.209	.415	-.229	.454	.613	.349	.641	.586
LDL-C	.052	.053	.328	.007	.006	.203	-.002	.004	.614
Triglycerides	-9.786	3.689	.008	-.266	.252	.291	.834	.262	.001

Abbreviations: BP – blood pressure; $eGFR_{CR-CY}$ – cystatin C and creatinine based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; UACR – urinary albumin to creatinine ratio.
$\alpha = .05$

Table 7. Characteristics of Albuminuria Progressors and Non-Progressors

	Non-Progressors (N = 66)		Progressors (N = 10)		
	Mean	**Std Error**	**Mean**	**Std Error**	**p-value**
Age	55.56	0.94	54.50	2.45	.683
Age at Diagnosis	48.30	1.25	47.60	2.95	.837
Diabetes Duration	7.26	0.91	6.90	2.01	.807
initial $eGFR_{CR}$	101.95	1.64	91.68	6.30	.038
initial $eGFR_{CY-CR}$	87.68	2.47	70.73	4.30	.013
initial UACR	4.82	0.70	12.09	2.51	<.001
change in $eGFR_{CR}$	0.47	1.17	-0.37	4.67	.864
change in $eGFR_{CY-CR}$	1.40	1.26	9.77	5.20	.029
change in UACR	2.07	0.81	32.10	3.32	<.001
BMI	31.94	0.48	32.07	0.63	.872
Waist Circumference	104.32	1.29	109.64	4.24	.166
SBP	128.50	2.19	122.70	5.68	.341
DBP	76.79	1.14	77.10	3.08	.922
HDL-C	45.41	1.48	37.40	3.63	.019
LDL-C	100.33	3.82	89.08	14.48	.321
Triglycerides	158.92	9.97	202.20	40.80	.250
HbA1c	7.56	0.15	7.58	0.50	.965
Fasting Glucose	122.04	4.64	118.22	6.88	.746
CRP	4.17	0.42	6.69	2.40	.389
IL-6	1.84	0.12	2.95	0.66	.022
BDI II total score	19.81	0.88	20.50	1.34	.768
	n	**%**	**n**	**%**	**p-value**
$eGFR_{CR} < 90$	10	15.2	4	40.0	.059
$eGFR_{CY-CR} < 90$	35	64.8	8	100.0	.044
Hypertensive	45	68.2	6	60.0	.607
Male	20	30.3	3	30.0	.985
Smokers	24	36.4	8	80.0	.009
Intervention	32	48.5	6	60.0	.497
Decliners ($eGFR_{CR}$)	15	23.1	3	30.0	.632
Decliners ($eGFR_{CY-CR}$)	16	32.0	1	12.5	.261

Abbreviations: BDI- Beck Depression Inventory; BMI- body mass index; CRP- C reactive protein; DBP- diastolic blood pressure; $eGFR_{CR}$ – creatinine-based estimated glomerular filtration rate; $eGFR_{CR-CY}$ – cystatin C and creatinine based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; IL-6 – interleukin 6; LDL-C – low density lipoprotein cholesterol; SBP- systolic blood pressure; UACR – urinary albumin to creatinine ratio.
$\alpha = .05$

Table 8. Characteristics of Rapid Decliners and Non-Decliners ($eGFR_{CR}$)

	Non-Decliners (N = 61)		Rapid Decliners (N = 22)		
	Mean	**Std Error**	**Mean**	**Std Error**	**p-value**
Age	55.11	0.95	55.45	1.67	.856
Age at Diagnosis	48.64	1.07	47.36	2.70	.664
Diabetes Duration	6.48	0.75	8.09	2.07	.462
initial $eGFR_{CR}$	98.30	1.83	106.37	2.79	.023
initial $eGFR_{CY-CR}$	84.11	2.53	87.46	4.75	.516
initial UACR	7.61	1.38	13.72	4.39	.240
change in $eGFR_{CR}$	4.54	0.90	-12.26	1.55	<.001
change in $eGFR_{CY-CR}$	4.82	1.40	-4.36	1.74	<.001
change in UACR	5.46	1.65	1.81	4.10	.416
BMI	31.96	0.47	33.72	1.49	.270
Waist Circumference	104.73	1.43	108.08	2.35	.235
SBP	127.08	2.29	128.82	4.50	.712
DBP	77.26	1.27	74.86	2.04	.329
HDL-C	43.74	1.26	45.00	3.51	.902
LDL-C	99.58	4.43	104.02	6.97	.602
Triglycerides	173.57	11.73	158.05	16.20	.395
A1C	7.59	0.17	7.68	0.29	.799
Fasting Glucose	120.66	4.52	126.27	8.14	.540
CRP	4.46	0.53	5.86	1.26	.598
IL-6	1.99	0.16	2.25	0.29	.438
BDI II total score	19.76	0.86	20.91	1.56	.504
	n	**%**	**n**	**%**	**p-value**
$eGFR_{CR} < 90$	14	23.0	2	9.1	.158
$eGFR_{CY-CR} < 90$	36	73.5	10	58.8	.258
Micro/macro albuminuria	3	5.0	3	14.3	.162
Hypertensive	41	67.2	14	63.6	.761
Male	17	27.9	6	27.3	.957
Smokers	23	38.3	11	50.0	.342
Intervention	32	52.5	8	36.4	.195
Progressors	7	12.3	3	16.7	.633

Abbreviations: BDI- Beck Depression Inventory; BMI- body mass index; CRP- C reactive protein; DBP- diastolic blood pressure; $eGFR_{CR}$ – creatinine-based estimated glomerular filtration rate; $eGFR_{CR-CY}$ – cystatin C and creatinine based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; IL-6 – interleukin 6; LDL-C – low density lipoprotein cholesterol; SBP- systolic blood pressure; UACR – urinary albumin to creatinine ratio.
$\alpha = .05$

Table 9. Characteristics of Rapid Decliners and Non-Decliners ($eGFR_{CY-CR}$)

	Non-Decliners (N = 45)		Rapid Decliners (N = 18)		
	Mean	Std Error	Mean	Std Error	p-value
Age	54.87	1.17	53.83	1.69	.631
Age at Diagnosis	48.18	1.18	45.28	3.11	.393
Diabetes Duration	6.69	1.07	8.56	2.14	.760
initial $eGFR_{CR}$	99.81	2.17	107.58	2.63	.046
initial $eGFR_{CY-CR}$	82.86	2.67	91.61	4.24	.085
initial UACR	9.47	2.22	8.19	2.47	.556
change in $eGFR_{CR}$	2.75	1.27	-6.33	1.92	<.001
change in $eGFR_{CY-CR}$	6.78	1.20	-8.24	0.87	<.001
change in UACR	6.22	2.18	0.24	2.55	.119
BMI	31.71	0.50	32.14	0.93	.666
Waist Circumference	103.64	1.33	104.97	2.72	.625
SBP	131.40	2.78	123.67	3.78	.128
DBP	78.93	1.36	75.72	2.44	.229
HDL-C	44.49	1.44	43.50	2.02	.784
LDL-C	101.19	5.24	105.16	8.02	.685
Triglycerides	190.04	14.94	128.61	14.72	.005
HbA1c	7.41	0.18	7.63	0.29	.536
Fasting Glucose	118.44	4.75	118.67	9.65	.981
CRP	4.72	0.68	5.23	1.12	.938
IL-6	1.89	0.16	1.75	0.19	.925
BDI II total score	19.54	1.07	21.78	1.51	.254
	n	%	n	%	p-value
Micro/macro albuminuria	3	6.8	1	5.6	.854
$eGFR_{CR} < 90$	11	24.4	1	5.6	.084
$eGFR_{CY-CR} < 90$	34	75.6	9	50.0	.049
Hypertensive	34	75.6	9	50.0	.049
Male	13	28.9	4	22.2	.590
Smokers	21	46.7	7	38.9	.574
Intervention	24	53.3	6	33.3	.151
Progressors	7	17.1	1	5.9	.261

Abbreviations: BDI- Beck Depression Inventory; BMI- body mass index; CRP- C reactive protein; DBP- diastolic blood pressure; $eGFR_{CR}$ – creatinine-based estimated glomerular filtration rate; $eGFR_{CR-CY}$ – cystatin C and creatinine based estimated glomerular filtration rate; HbA1c- glycosylated hemoglobin; HDL-C – high density lipoprotein cholesterol; IL-6 – interleukin 6; LDL-C – low density lipoprotein cholesterol; SBP- systolic blood pressure; UACR – urinary albumin to creatinine ratio.
$\alpha = .05$