CLINICAL SIGNIFICANCE OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

by

KATHRYN MARIE DANIEL

Presented to the Faculty of the Graduate School of

The University of Texas at Arlington in Partial Fulfillment

of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

THE UNIVERSITY OF TEXAS AT ARLINGTON

May 2008

ACKNOWLEDGEMENTS

This study would not have been accomplished without the vision, dedication and mentoring of faculty and peers who shared their passion with me thus enabling this writer to finish the task. Specifically, the members of my dissertation committee Drs. Carolyn Cason, Barbara Raudonis and Belinda Vicioso, as well as Dr. Pat Gleason-Wynne, are to be commended for their guidance and patience. No part of this accomplishment would have ever been possible without the continuous support of parents, grandmother, siblings, and friends, too numerous to mention individually as well as the grace of God, too abundant to be shared in human expression. It takes a village……..

April 17, 2008

ABSTRACT

CLINICAL SIGNIFICANCE OF CHRONIC KIDNEY DISEASE IN THE ELDERLY

Kathryn Marie Daniel, PhD.

The University of Texas at Arlington, 2008

Supervising Professor: Carolyn L. Cason, PhD.

Background: Chronic kidney disease (CKD) is a common chronic disease which can be very costly to treat if it progresses to end stage renal disease. Screening for chronic renal insufficiency (CRI) is widely available, yet little is known about which screening estimation formula is most appropriate in elderly patients.

Review of literature: The two most common formulas for estimation of glomerular filtration rate (GFR) are the Cockcroft/Gault (CG) and the Modified Diet in Renal Disease (MDRD). Both are based on demographic variables such as age, and gender as well as creatinine. The CG formula also includes patient weight; the MDRD

formula includes race: black: yes or no. Both formulas were developed in middle aged (not elderly) cohorts who were primarily men and Caucasian.

Methods & design: This is a secondary data analysis of an existing database collected from retrospective chart review of a convenience sample. GFR was calculated by both MDRD and CG. Characteristics of patients with and without CRI were compared. Characteristics of patients who experienced a rapid decline in GFR over the two year study period by the two formulas were also described.

Results: 311 patients were included in the analysis. Patients identified with renal insufficiency were 22% of the total sample regardless of the formula used for estimation. The sample consisted of 75% women who were 65% African American with a mean age of 72 (SD 7). At least 63% of the sample was overweight or obese. The CG formula tended to identify patients with less comorbidity than the MDRD where the patients seemed to be more advanced in the course of their disability. Both formulas were associated with congestive heart failure, beta blocker use, avoidance of metformin, as well as higher creatinine, and BUN levels and lower hemoglobin levels. Latino ethnic identity had a protective effect. When the CG formula was calculated with ideal body weight, the resulting eGFR correlated best with MDRD.

Summary: Older patients should be screened for renal insufficiency. The Cockcroft/Gault formula using ideal body weight may provide the most conservative and useful estimation of GFR in elderly patients.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

CHAPTER 1

BACKGROUND AND SIGNIFICANCE OF GLOMERULAR FILTRATION MEASUREMENT IN ELDERLY SUBJECTS

Introduction

The prevalence of renal disease is increasing worldwide and especially in developing countries. Worldwide estimates are that chronic kidney disease affects over 50 million people including 1 million currently receiving renal replacement therapy such as peritoneal dialysis, hemodialysis or renal transplant (Dirks et al., 2005). In the United States (US) the prevalence of renal disease is disproportionately high in African American and Hispanic population groups (Chiapella & Feldman, 1995).

Diabetes is the most common comorbid primary condition which precedes end stage renal disease (ESRD). Projections of diabetes prevalence in the US suggest an increase of 165% by 2050 with the greatest increase in incidence among African Americans and persons older than age 75 (Boyle et al., 2001). Countries around the world are struggling to find cost effective interventions to slow the progression of chronic kidney disease (CKD) and reduce the incidence of end stage renal disease requiring dialysis and/or renal transplant therapy. Renal replacement therapy and dialysis are federally guaranteed entitlement benefits in the US as well as many other developed countries. Current estimates are that approximately 11% of the US

population is affected by CKD (US Renal Data System, 2007). Of those with CKD, 1% progress to kidney failure which is treated only by dialysis or transplant. In 2003, 453,000 Americans required dialysis or transplantation. This is projected to increase to 651,000 by 2010. Expenditures related to renal replacement therapy account for 16.5% of Medicare spending. This is twice the amount spent just 10 years ago. Total expenditures for care of Medicare patients with CKD amount to almost 24% of Medicare costs (US Renal Data System, 2004).

Problem

Patients experience no symptoms of kidney disease until the damage is already quite advanced. Outpatient measurement of renal function is often not practical and can be difficult for patients and providers. Providers must often rely upon indirect screening measures to estimate renal function for decision making, because lengthy, burdensome, testing procedures are not practical for screening. Yet knowledge of renal function is integral to providers' ability to safely care for patients. Choices about medication therapy and diagnostic interventions depend on the ability of the body to metabolize and clear drugs prescribed or used in diagnostic procedures.

As persons mature into their senior years of life, body composition and function changes. Medication doses that were once appropriate may no longer be appropriate because of disproportionate adipose to lean body mass relationships. In addition, drug trials have historically excluded elderly subjects and/or those with multiple co-morbidities, so recommended drug doses based on younger adults may be inappropriate

for older adults. Elderly patients are rarely part of the drug trial sample used for decision making about safety or dose efficacy (Bugeja, Kumar, & Banerjee, 1997).

Estimation equations are a quick and simple way for clinicians to determine an individual patient's level of kidney function or glomerular filtration rate (GFR). The GFR determined by estimating equations helps to define where a patient falls within the stages of chronic kidney disease (CKD). An estimation of GFR is helpful in safely prescribing medications cleared or metabolized by the kidney. An estimated GFR is essential before diagnostic tests utilizing potentially nephrotoxic contrast medium can be ordered. The data to support appropriate estimation formula selection for different populations are lacking. Formula development has occurred in predominantly Caucasian non elderly samples yet, minority elderly subjects are at the highest risk of CKD and its associated complications.

This study explored the differences in GFR estimation when these formulas were applied to data on elderly subjects available in an existing database. This study describes the characteristics of elderly subjects that are associated with rapid declines in renal function. With increasing age, a slow, gradual decline of 1-2 cc/year loss in GFR is predictable, but rapid decline is not and carries with it greater risk of such negative outcomes as end stage renal disease (ESRD) and cardiovascular disease (CVD) events. Brugts and associates, for example, found that a 10 ml decrease in GFR was associated with a 32% increased risk of myocardial infarction (MI) (Brugts, Knetsch, Mattace-Raso, Hofman, & Witteman, 2005).

Framework

The framework used for this study is presented in Figure 1. It depicts the concepts that contribute to the etiology of renal disease. In this model, CKD and CVD are parallel contributors leading to the same end condition: system failure. Age, gender, ethnicity and family history are non-modifiable risk factors. Individuals are born with these variables and they cannot be changed. Obesity, hypertension, diabetic control, nutritional status, and lifestyle are modifiable risk factors. These characteristics are acquired and may sometimes be the result of or affected by lifestyle choices.

When the cumulative effect of increased risk is realized, the processes of CVD and CKD are initiated. They almost never occur in isolation, but rather occur concurrently. The presence of albumin in the urine is often discovered at the same time as hypertension is diagnosed. Hypertension is often associated with left ventricular hypertrophy (LVH). As GFR declines, CVD events such as peripheral vascular events, cerebral vascular events and myocardial infarction increase in incidence. With heart failure as the end stage of scarred heart muscle, kidney failure often occurs, so that CKD and CVD reach the end point of system failure. By understanding the factors that accompany or precede the development of CKD at the levels of increased risk, initiation, and progression, interventions can be designed and tested with the purpose of preventing or arresting the downward spiral of kidney and cardiovascular decline.

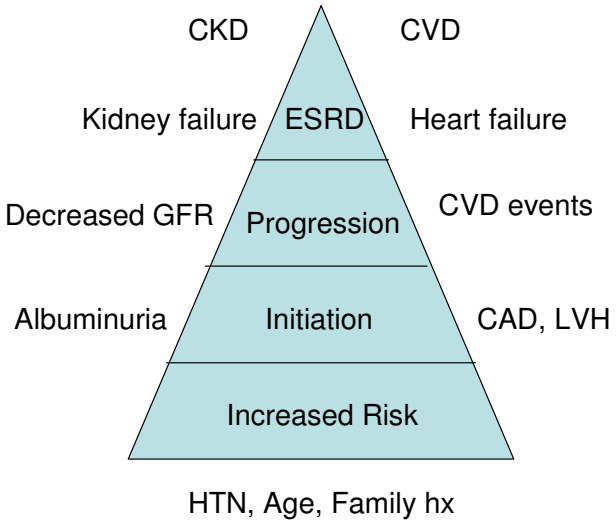

Figure 1. CKD Model (National Kidney Foundation, 2007)

Risk factors contributing to the etiology of CKD

Risk factors known to contribute to the development of CKD are hypertension, advanced age, family history, diabetes, gender, obesity, and ethnicity. Some are modifiable and some are not.

Modifiable risk factors

Hypertension is a known contributor to the development of CKD. Hypertension is defined and classified by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) as pre-hypertension, stage 1 hypertension or stage 2 hypertension (Chobanian et al., 2003). Pre-hypertension is defined as systolic blood pressure between 120-139mm Hg or diastolic blood pressure between 80-89 mm Hg measured while seated on at least two separate office visits. Stage 1 hypertension is defined as systolic blood pressure between

140-159 mm Hg or diastolic blood pressure between 90-99 mm Hg measured while seated on at least two separate office visits. Stage 2 hypertension is defined as systolic blood pressure greater than or equal to 160mm Hg or diastolic blood pressure greater than or equal to100 mm Hg measured while seated on at least two separate office visits.

The mechanism of action by which hypertension is related to kidney disease is thought to be damage to the tubules that occurs over years of elevated blood pressures. Most hypertension is diagnosed as "essential hypertension" which implies that there is no known root etiology, yet treatment can be very effective in lowering the risks associated with hypertension. There is evidence that strict control of hypertension decreases risk of rapid development of CKD (Lindeman, Tobin, & Shock, 1984b).

Diabetes affects nearly 21 million people in the US. Most diabetes in the US is considered to be type II which develops as a result of either a lack of insulin production or poor insulin utilization. Within the industrialized world, diabetes appears to increase in prevalence in direct relationship as developing countries abandon traditional lifestyles to adopt western lifestyles in diet and activity. There is no evidence that strict control of diabetes decreases risk of rapid development of CKD as well as risk of ESRD. This may be because adult onset diabetes often is subclinical and undiagnosed for several years before the patient develops symptoms. By the time the disease is discovered, microvascular changes have often already occurred in target organs.

Obesity is defined as body mass index (BMI) greater than 30 (Centers for Disease Control, 2007). Obesity is epidemic in the US and growing around the world. As developing countries adopt western diet and lifestyles, obesity seems to be a direct

result. There appears to be a direct correlation of obesity with diabetes, type II. Some experts have even gone so far as to label the common occurrence of obesity and diabetes as “diabesity” (From the NIH: Successful diet and exercise therapy is conducted in Vermont for "diabesity".1980). Obesity is a primary risk factor for both heart disease and diabetes which are both risk factors for renal disease.

Non modifiable risk factors

Glomerular function has been shown to decline in older Americans, aged 60 or more, at approximately 1cc/year for each year of life. Rapid decline has been defined as decline that exceeds 8-10cc/year. However, all individuals do not decline in renal function with age.

Individuals with a family history of renal disease have a higher risk of also developing renal disease. Approximately 23% of ESRD patients report a family history of renal disease (Freedman et al., 2005). Much of the etiology for genetically transmitted renal disease is glomerulonephritis syndromes.

Women are at higher risk of developing CKD than are men, although disease progression is slower (Guan, 2006). Although this is not fully understood, it is believed to be related to smaller muscle mass as well as fewer net glomeruli and smaller body habitus overall.

The first longitudinal study to look at glomerular filtration rate over time in older individuals was published from the Baltimore Longitudinal Study on Aging (Rowe, Andres, Tobin, Norris, & Shock, 1976). This study showed that normal subjects followed longitudinally also had a decline in GFR with age. More robust descriptive

observational data is reported from the same study, but looking at longer periods of time by Robert Lindeman from data collected between 1958 and 1981 (Lindeman, Tobin, & Shock, 1985). These data were derived from 446 men who were included in the study who had at least five creatinine clearance determinations during the study period. The study sample was primarily well educated, middle class Caucasian men who volunteered to participate. When subjects with possible renal or urinary tract diseases or on antihypertensive or diuretic medication therapy were removed from the study sample, 254 subjects remained who were considered to have "normal" renal function. The mean decrease in creatinine clearance was 0.75 ml/min/year. One third of the subjects had no absolute decrease in function and there was a small group of subjects who showed a statistically significant increase in creatinine clearance with age.

Poverty and Race

Socioeconomic status has been identified as a predictor of end stage renal disease (Cass, Cunningham, Wang, & Hoy, 2001). Many other factors connected to poverty are also predictive of poor outcomes, such as access to care, health literacy, and lack of resources for medication therapy as well as a higher incidence of obesity, less regular physical activity and poorer quality diet (Zunker and Rutt, 2007). In a large population based retrospective study conducted in Sweden that included all the residents of Sweden, low socioeconomic status was associated with increased risk of chronic renal failure (Fored et al., 2003). The authors concluded that lower socioeconomic status appears to be an independent risk factor for chronic renal failure in Sweden.

The concept of race has different definitions on every continent. There is little international agreement on these definitions as there are few genetic markers. Race is a continuous variable that is self-identified into nominal categories. In the United States, population research usually conforms to the standard definitions established by the US Census Bureau. This assumes homogeneity within each group which is a limitation.

It is almost impossible to separate true genetic influences from the learned behaviors of culture that is learned in families. In the US, research has identified that persons of African ancestry (African Americans) have a higher than usual risk of hypertension, diabetes and renal disease (Coresh, Astor, Greene, Eknoyan, & Levey, 2003). This same generalization can also be applied to Native American populations (Narva, 2002), Hispanic American populations (Chiapella & Feldman, 1995) and other recent immigrants to the United States. First generation immigrants seem to have the least negative health impact upon moving to the US, but the longer immigrants live in the US and the more "westernized" their diet becomes, the more they are afflicted with chronic health issues such as obesity, diabetes, renal disease and heart disease (Morales, Lara, Kington, Valdez, and Escarce, 2002).

These generalizations cannot be extrapolated to persons of African ancestry in other countries (Seedat, 1996). Seedat found striking differences in prevalence and complications of hypertension among different racial groups in South Africa. In Brazil, racial definitions are so blurred and mixed that differentiation into homogeneous ethnic categories is almost impossible, yet there does seem to be some evidence for worse prognosis in persons of African or Asian descent (Oliveira, Romão, & Zatz, 2005).

In the US, CKD has been observed to occur much more frequently in persons of African American descent (Ferdinand & Saunders, 2006). However, as other ethnic minorities continue to assimilate into the American population, the incidence of CKD is rising among them as well (Peralta et al., 2006). It is possible that this association of ethnic minorities with CKD may be more a reflection of access to resources and lifestyle choices associated with poverty and acquisition of western dietary and lifestyle habits than actual genetic traits. The same trends are found around the world in indigenous groups. For example Pima Indians, Native Americans, aboriginals in Australia and Pacific Islands as well as First Nations people in Canada also exhibit an increased incidence of CKD as they assimilate into western culture and lifestyle. Peralta and colleagues (Peralta, Ziv et al., 2006) found that kidney disease in elderly African American subjects seems to be more related to environmental and social factors than genetic factors.

Purpose

Knowledge about an individual's renal function is an important piece of information for clinicians who medically manage elderly patients. Current formulas for estimation of glomerular filtration rates were developed based on a younger and or mostly Caucasian sample, yet individuals who are most at risk for the development of kidney disease are older and predominantly minority. The two most often used are the Cockcroft/Gault (Cockcroft and Gault, 1976) and the MDRD (Levey, 1999).

This study provides information for clinicians about characteristics of individuals at highest risk of developing CKD and comparing them to those who do not.

By learning more about the characteristics of such individuals, clinicians can better understand which patients are at risk for CKD and therefore more likely to benefit from renoprotective interventions.

This study explored the usefulness of GFR estimation formulas by describing differences in characteristics of patients who were identified with chronic renal insufficiency (GFR < 60) by these formulas. This study also described characteristics of patients that were associated with rapid declines in renal function estimated by these formulas. The questions guiding this study were:

Questions

1. What are the characteristics of the patients identified by the Cockcroft/Gault (CG) formula with and without chronic renal insufficiency (CRI)?
2. What are the characteristics of patients identified by the modified diet in renal disease formula (MDRD) with and without CRI?
3. What are the differences and commonalities of patients identified with CRI by CG and MDRD?
4. What are the characteristics of patients who experience rapid declines in GFR when GFR is determined by CG and MDRD formulas?

Summary

The prevalence of renal disease is increasing in the US and around the world. Expenditures by Medicare for care of patients with CKD amount to almost 24% of Medicare. The risk factors for renal disease are age, gender, ethnicity, family history,

obesity, hypertension, diabetes, nutritional status and lifestyle. Chronic renal insufficiency is a common and under diagnosed problem in the elderly; there are few if any symptoms until the deterioration in kidney function is advanced. If unrecognized, patients with renal insufficiency are at increased risk of exposure to potentially nephrotoxic therapies and interventions.

Clinicians must use estimation formulas based on widely available common laboratory tests to screen patients for renal insufficiency. The formulas that have been developed through regression equations and are in wide use were not developed or standardized in an elderly population.

CHAPTER 2

REVIEW OF LITERATURE

Introduction

This chapter reviews the pathophysiology of the kidney as well as naturally occurring substances such as creatinine and cystatin C that are used to evaluate kidney function. The most commonly used formulas for estimating glomerular filtration rate and the existing research on their accuracy and reliability when used in elderly populations are included.

The Kidney

The primary function of the kidney is the maintenance of internal homeostasis of fluids, excretion of metabolic wastes, conservation of nutrients and regulation of acid-base balance (McCance & Huether, 2006). The functional unit of the kidney is the nephron. Within each nephron, the process of glomerular filtration occurs. Through the different membranes of the glomerulus, proximal tubule, Loop of Henle, and distal tubule, via both active and passive transport, wastes are excreted and nutrients conserved, and electrolyte balance is maintained. When damage occurs within the nephron, wastes are no longer cleared from the body, fluid is retained, and nutrients are no longer conserved. The kidney functions as a filter for wastes from the body. When the kidney fails to clear the wastes from the body, they accumulate. The health of the

kidney directly impacts an individual's overall health. The ability of the kidney to filter waste products directly impacts any medications prescribed or diagnostic procedure.

The kidney is also the site where an important hormone, erythropoietin is produced. Erythropoietin stimulates the bone marrow to generate new blood cells. When erythropoietin production declines, red blood cell production also declines, eventually leading to anemia. Cognition clouds as a result of increasing anemia, medications may become less effective as protein and albumin in the serum drop and overall mortality is increased. By compromising already failing kidneys with nephrotoxic agents, the rate of decline of renal function is exacerbated. The kidney serves as the primary site of solute filtration and fluid excretion. Renal function is an integral part of most of the body's physiologic function.

Loss of Kidney Function

Aging is associated with subtle losses of glomeruli due to vascular ischemia and scarring. This leads to an almost inevitable loss of glomerular function measured by decreasing glomerular filtration rate. Multiple studies have shown that most persons experience at least some decline in glomerular filtration rate of approximately 1cc/year after the age of 50 (Lindeman & Goldman, 1986). The "normal" process of aging is accelerated by diseases such as hypertension and diabetes which accelerate the rate of glomerular loss.

With aging, the number of nephrons in the kidney declines, glomerular capillaries atrophy and overall functional kidney mass declines resulting in a kidney with less reserve, more vulnerable to injury from nephrotoxic drugs and diseases. These

changes are thought to be the result of loss of nephrons that occurs as the result of damage caused by years of hypertension or diabetes or obesity. When the membrane or the transport mechanisms break down, all functions of the kidney are affected. Metabolic wastes such as creatinine are not transported adequately across the membrane and levels build up in the serum.

Correlates of Renal Function

The naturally occurring substance which correlates best with kidney function across all ages has historically been creatinine. Creatinine is a byproduct of muscle mass and dietary protein intake. Theoretically a constant amount is produced and a constant amount is filtered out of the serum by the kidney. However as people age, not only muscle mass and dietary protein intake decline, but creatinine clearance also declines. Therefore, it is common for individuals with diminished renal function to have normal serum creatinine values as they age.

Creatinine as an independent indicator of renal function becomes less reliable as age increases due to losses of muscle mass and declining protein intake. Thus, estimating formulas based on biochemistry that declines in specificity with age, becomes less and less accurate as patients age.

Cystatin C is a more recently discovered marker of renal function. Cystatin C and creatinine are both proteins found in serum, but cystatin C is not produced by muscle mass, so some of the problems with low creatinine production in elderly patients with low muscle mass can be avoided. Cystatin-C is a low molecular weight protein

produced at a constant rate by all nucleated cells, and its levels in the blood are not impacted by age, gender, race, or lean muscle mass (Shlipak et al., 2005).

Measurement of Renal Function

According to Levey (1989), the most accurate and predictive tests for detecting renal disease are inulin infusion clearance or I-iothalamate or iohexal injection (Levey, 1989). An inulin infusion test requires the patient to have an established intravenous access, be thoroughly hydrated with at least two liters of fluids before a catheter is inserted and urine measured periodically for volume and inulin clearance as inulin is being infused through the IV. Inulin is not readily available and is insoluble at room temperature. To prepare for the test, inulin must be heated and then cooled overnight followed by a specific equilibration period just prior to administration. I-iothalamate and iohexal are similar in terms of inconvenience. Rather than an intravenous infusion, the patient receives a radioisotope-labeled marker administered as a onetime subcutaneous injection that is excreted by the kidney. Excretion of the isotope in the urine is measured over the subsequent 12 hours (Baracskay et al., 1997). These tests are expensive and time consuming for the patient as well as unavailable outside of a research setting.

Historically, serum and urine creatinine have been the markers of choice for the estimation of renal function (H. Burkhardt, Bojarsky, Gretz, & Gladisch, 2002)(H. Burkhardt, Hahn, Gretz, & Gladisch, 2005)(Couchoud, Pozet, Labeeuw, & Pouteil-Noble, 1999)(Nordén, Björck, Granerus, & Nyberg, 1987). The ease of measurement of

serum creatinine is a practical alternative because its measurement is readily available to clinicians.

The original gold standard for renal function was a 24 hour creatinine clearance. To obtain this test, the subject is required to collect all voided urine for a 24 hour period. At the same time, a random serum creatinine is collected by venipuncture. The 24 hour creatinine clearance is the difference between the serum creatinine level and the amount of creatinine contained in the 24 hour collection of urine. Because the collection of 24 hours of urine is often very challenging for patients, other methods were sought that have a high degree of correlation with 24 hour creatinine clearance.

Estimating equations and their derivation

Estimating equations were first proposed by Cockcroft and Gault in 1976 (Cockcroft & Gault, 1976). The purpose was to develop an easy method to predict renal function from common, easily obtainable serum biochemistry. The best method for measuring renal function at the time was 24 hour creatinine clearance, so the estimating equation measured how closely it could predict the creatinine clearance produced by a 24 hour creatinine clearance. In 1999, Andrew Levey and colleagues followed a similar pathway to produce a simpler estimating formula which involves more easily obtained variables and developed the Modified Diet in Renal Disease (MDRD) estimation formula (Levey & Bosch, 1999). The specifics of each formula's development will be discussed below.

Cockcroft/Gault formula in elderly subjects

The Cockcroft/Gault formula uses the variables of serum creatinine, weight, gender and age to predict creatinine clearance (Cockcroft & Gault, 1976). The authors developed and tested the equation on 236 mostly male (96%) inpatients at the Queen Mary Veteran's Hospital in Montreal, Quebec. All subjects who were participants in the study had at least two measured 24 hour urinary creatinine clearances that were stable over time (defined by the authors as not differing by more than 20% from one measurement to the next). The subjects did not have known renal disease. The authors compared the measured 24 hour creatinine clearance of each subject to the predicted creatinine clearance from four different equations, two equations by Jelliffe (1971 1973), one by Edwards and Whyte (1959) and the last determined from multiple regression of variables based on a separate sample of 249 patients. The resulting equation has since been known as the Cockcroft/Gault equation for estimating creatinine clearance. It had the highest correlation with 24 hour creatinine clearance of any formula to date with a correlation coefficient of 0.83. The authors speculate that the reasons for their improved accuracy over any prior formula are due to the inclusion of age and weight as variables. They suggest that the inclusion of these variables may help to capture the decline in muscle mass that occurs with aging. They also speculate that a correction to ideal body weight (IBW) might be advisable in cases where subjects have marked obesity, have ascites, or have conditions associated with muscle atrophy.

In 1980, Gral and Young published their findings based on 26 nursing home residents. All subjects had "normal" serum creatinine values. They compared measured

24 hour creatinine clearance with estimated creatinine clearance using the original Cockcroft/Gault and a modified Cockcroft/Gault which utilizes lean body weight instead of measured body weight. They found the highest correlation (r =0.85) between endogenous creatinine clearance and the modified Cockcroft/Gault using lean body weight. The original formula using measured weight, had a respectable correlation of r = 0.75. The authors recommend either formula as appropriate for use in clinical practice, although they recognize that producing a lean body weight for a given patient would be difficult without a measured height. Measuring height in non ambulatory and/or osteoporotic nursing home patients is problematic.

Researchers in Sweden compared the Cockcroft/Gault formula using various body weight measures in a large sample of adults over age 18 (Nygaard, Naik, Ruths, & Krüger, 2004a). They compared the result of the equations when total weight, ideal body weight, and adjusted body weight (lowest of total and ideal) were used. They also included estimated glomerular filtration rates using the Sawyer equation which is based on lean body mass. It is important to note these estimates were compared against iohexal clearance and not creatinine clearance. The mean age of the sample was 59 years with a range of 24-85 years old. There were 376 women and 474 men in the sample. They found that regardless of which formula was used, when ideal body weight was used to calculate, the formula best approximated iohexal clearance.

Friedman, Norman and Yoshikawa (1989) evaluated the correlation between estimated and measured 24 hour creatinine clearance in 15 young and 15 elderly subjects. The formulas used for comparison were the Cockcroft/Gault and Lott-Hayden.

They observed a good correlation between both formulas and measured creatinine clearance only in the elderly sample (r = 0.73). As in previous studies by other investigators, all subjects had "normal" serum creatinine. The strength of their research is that their sample consisted of healthy ambulatory elders instead of hospitalized elders or nursing home residents. The mean age of their elderly sample was 79.4 years.

In 1988, researchers from the University of Maryland School of Medicine in Baltimore Maryland, compared estimated creatinine clearance produced by two different equations (Cockcroft/Gault and Jelliffe) with measured creatinine clearance in nursing home residents who had chronic indwelling urinary catheters (Drusano, Muncie, Hoopes, Damron, & Warren, 1988). Their sample consisted of 19 female nursing home residents; all but one was older than 70 years of age. The patients were severely debilitated; 18 of 19 were dependent in all six activities of daily living. Both estimating equations produced poor agreement (only slightly greater than 50%) with measured creatinine clearance, Cockcroft/Gault only very slightly better than the Jelliffe formula. The Jelliffe equation produced results in which 11 of 19 results were more than 20% higher than measured creatinine clearance meaning that the estimation equations underestimated renal insufficiency. The Cockcroft/Gault equation produced results in which 10 of 19 results differed by more than 20% from measured creatinine clearance. Their recommendation was that neither formula was adequate for clinical use in frail elderly subjects and that new equations need to be developed.

Nygaard, Naik, Ruths and Kruger (2004) assessed renal function in a cross-sectional sample of elderly persons in Norway. They specifically studied three

populations of persons aged 70 or more who presented with different functional levels: community dwelling elderly subjects, inpatients on a geriatric ward and nursing home residents. The main outcome measure was estimated glomerular filtration rate by the Cockcroft/Gault formula. When the subjects were compared by functional category, 75% of the community dwelling elderly subjects, 78% of the inpatient elderly subjects, and 91% of the nursing home residents had moderate to severely impaired glomerular filtration rates. Further evaluation revealed that 99% of the subjects aged 85 or greater had renal impairment that required dosing adjustments in medication. They concluded that renal impairment is common in old age and its assessment is especially important among the oldest and frailest in nursing homes.

Quartorolo, Thoelke and Schafers (2007) calculated the estimated glomerular filtration rate by Cockcroft/Gault on elderly hospitalized patients and reported it to the physicians involved with their care. They measured whether or not the physicians had a change in prescribing behavior after being notified of their patient's glomerular filtration rates. Awareness of chronic kidney disease was impacted, evidenced by increased diagnosis of renal disease, but prescribing behavior did not change.

One of the most interesting and significant studies to be published strictly on the use of creatinine alone to predict renal function was published in 2007 (Giannelli et al., 2007). This study was a cross-sectional population based study of older Italian subjects. There were 660 participants aged 65 to 92 with normal serum creatinine. When glomerular filtration rates were estimated by both the Cockcroft/Gault formula (using serum creatinine) and by urinary creatinine clearance, prevalence of renal impairment

(defined as GFR < 60) increased dramatically with age. In the oldest cohort of subjects who were greater than 85 years old, 96.8% of the subjects had renal impairment but had normal serum creatinine levels. The study stratified patients according to CKD class and compared the percent of subjects in each class with creatinine levels. The group's conclusion was that when used in isolation, serum creatinine is an unreliable indicator of impaired renal function.

MDRD formula in elderly subjects

The second most popular equation was developed in the 1990s by a large group studying the impact of dietary protein intake on renal disease (Levey & Bosch, 1999). The scientists performed a multiple regression on 1628 subjects who had known renal disease. They compared their estimations to inulin clearance instead of creatinine clearance. The initial equation included gender, race (Black or not Black), age, serum creatinine, serum albumin and serum urea nitrogen. The formula was later abbreviated and albumin and urea nitrogen were dropped. This equation is easier for laboratories to use to produce an estimated GFR (eGFR) because weight is not a variable in this equation; all the other variables besides creatinine are demographic. The weakness of this equation is that the subjects in the sample from which the regression equation was drawn were middle aged (subjects' mean age was 50.6 years) and not elderly subjects. Also all the subjects in the sample had known advanced kidney disease.

Amit Garg and associates published a secondary analysis of 5,248 subjects 60 years of age and older who were participants in the National Health and Nutrition Examination Survey III (NHANES) which is reflective of data gathered from 1988-

1994 (Garg et al., 2001). Their study was intended to answer the question of whether renal insufficiency was associated with malnutrition, independent of relevant demographic, social and medical conditions. Using the MDRD formula, estimated GFR less than 30 was present in 2.3% of men and 2.6% of women. These participants demonstrated low protein and energy intake and higher serum markers of inflammation. Thirty-one percent of individuals with malnutrition had GFR less than 60. GFR less than 30 was independently associated with malnutrition in this study.

Also in 2001 N. J. Van den Noortgate published an observational study of subjects older than 80 years of age who were admitted to an acute care geriatric ward (Van den Noortgate,N J., Janssens, Afschrift, & Lameire, 2001). The sample had 220 subjects and compared estimated GFR by Cockcroft/Gault with MDRD. They found a correlation of $r = .66$ between the estimating formulas, but also noted a high incidence of acute renal failure in this population when hospitalized for an acute illness.

In 2003, E. J. Lamb also published an observational study comparing eGFR estimations using both creatinine based formula of Cockcroft/Gault and MDRD with 51 Chromium ethylenediaminetretraacetic acid (EDTA). This study included 52 patients aged 69-92. These patients had multiple comorbidities excluding renal transplant/dialysis and cognitive impairment (Lamb et al., 2003). They concluded that the MDRD did not improve the estimate of GFR when compared with Cockcroft/Gault formula in older Caucasian subjects with known chronic renal disease. He made this conclusion based on data that showed the smallest standard deviation of difference when the CG formula was used with insignificant differences in regression analyses

between the CG and MDRD formulas. Most impressive was the much lower frequency of misclassification of renal insufficiency when CG was used versus MDRD.

One of the best studies to date done in an elderly population was published in 2004 by Garg and colleages. The study is important because the sample included 9,931 long term care residents who were at least 65 years of age. This study was a cross-sectional analysis of NHANES III data. The researchers compared the estimates of GFR produced by the Cockcroft/Gault and MDRD formulas. They found that the Cockcroft/Gault formula produced a consistently lower estimate than did the MDRD, which was most pronounced in the oldest subjects.

Ingela Fehrman-Ekholm and Lars Skeppholm (2004) compared estimated creatinine clearance using the Cockcroft/Gault, Walser, and Levey (MDRD) formulas with iohexal clearance. They chose to measure the estimating equations against iohexal due to its high correlation with inulin, the gold standard for measurement of renal clearance. Renal function was measured with iohexal clearance in 52 healthy older persons, aged 70-110. At the same time, blood samples were collected for serum creatinine and estimated GFR was calculated using each formula. eGFR correlated with age with an annual decline of 1.05cc/year. Using formulas for estimation of clearance, this study found the best correlation with the MDRD. Cockcroft/Gault underestimated creatinine clearance compared to measured creatinine clearance.

When compared with a previous study published by Drusano in 1988, this study differs in that these were healthy older persons of both gender, predominantly male, and the Drusano subjects were female nursing home residents with indwelling catheters.

The Drusano study compared eGFR to 24 hour creatinine clearance and this study compared eGFR to iohexal. Both studies reported that CG formula produced lower eGFR estimates. The differences in the study sample may account for the differences in findings and conclusions.

In 2005, Brugts, et al. looked at the question of whether or not renal function is an independent predictor of cardiovascular disease in the ambulatory population. The researchers measured whether or not subjects had documented myocardial infarction and whether or not this was correlated with eGFR by Cockcroft/Gault or MDRD estimations of GFR. Their sample included 4,484 subjects in Rotterdam with a mean age of 69.9 years. They concluded that renal function is an independent predictor of the subsequent development of myocardial infarction in elderly subjects, regardless of which formula was used to estimate GFR. They found the CG formula to be more sensitive and that is the formula they used when they reported their findings. They further noted that a 10 ml decrease in GFR was associated with a 32% increased risk of myocardial infarction. This study implies that early identification of subjects with decreased renal function could identify subjects who are at increased risk for coronary heart disease.

Burkhardt and colleages published their work in 2005 about 29 women and 32 men aged 60 and older in an acute care ward in Germany. They measured inulin clearance and creatinine clearance as well as estimated GFR by Cockcroft/Gault and MDRD formulas. They concluded that estimating errors are large when used in an acutely ill subject. All estimating formulas were superior to creatinine alone when

correlated with either creatinine clearance or inulin infusion. In this setting they found the MDRD to be best followed by the Cockcroft/Gault.

Fontsere and colleages studied 87 Caucasian adults with known Chronic Kidney Disease classes four or five indicating an eGFR less than or equal to 30 (Fontseré et al., 2006). All were ambulatory outpatients with no other known comorbidities. The group was split for analysis into two groups; younger than age 65 or 65 and older. The purpose of their study was to compare the accuracy of estimating formulas in older patients. They found that both formulas were more accurate in younger subjects. They concluded that the more important variable than age is nutritional status. They measured nutritional status as a binary variable on either side of the median calculated on the basis of measured creatinine clearance and serum creatinine to produce a variable called creatinine production. Since older patients are more likely to have poor nutritional status, they often have less accurate estimations of GFR, but younger subjects with poor nutritional status will also have equally inaccurate estimations of GFR.

Hemmelgarn and associates (2006) in Alberta, Canada published a descriptive, cross-sectional analysis of estimated GFR measured by MDRD in a database of 10,184 subjects who were 66 years of age. The data were derived from retrospective record review. They concluded that the majority of subjects included in this 2 year study had no or minimal progression of CKD. However, subjects with diabetes had the greatest declines. It is important to note that the population of Alberta, Canada has less than 1% African ancestry, so although this study was a very large sample it was an almost totally Caucasian sample.

In France, Laroche and associates (2006) studied a mixed group of ambulatory and institutionalized elders who were at least 75 years old with a mean age of 87. They measured serum creatinine and estimated GFR by both Cockcroft/Gault and MDRD equations, then correlated the CKD classes identified by each formula. They found a weak concordance between classes of the two formulas. Values estimated by MDRD were consistently higher than those produced by Cockcroft/Gault. They were unable to say which formula was superior except to note that although a lower estimation may represent a false positive finding in some subjects, it may prompt clinicians to safer, more conservative nephro-preserving therapies.

Maaravi and colleages (2006) conducted a longitudinal study of 445 subjects all aged 70 years to study the effect of low estimated GFR on longevity. They measured serum creatinine and estimated GFR by Cockcroft/Gault and MDRD, then looked at all cause mortality. They were able to conclude that moderate renal insufficiency measured by Cockcroft/Gault is a strong and independent predictor of mortality. They further noted that most of the subjects who had moderate renal insufficiency had normal serum creatinine.

O'Hare, et al. (2006) wanted to know whether or not the same levels of eGFR have the same significance in older and younger subjects. Their study looked at prevalence of CKD measured by MDRD by age category and associated risk of death in a veteran sample aged 18 – 100. They found that the overall prevalence of CKD Class 3 (eGFR $\leq$ 60) or more was 20%. They concluded that mortality risk stratification in elderly patients should not be based on the same eGFR cut points as younger groups.

They recommended further work be done to develop finer categorization of risk in elderly subjects in the 30-59 eGFR (CKD class 3) group.

Pedone, Corsonello, and Incalzi (2006) studied 7,747 acute care geriatric ward patients whose mean age was 77.8. They compared estimated GFR by Cockcroft/Gault and by MDRD 1 and MDRD 2. MDRD 1 includes serum albumin and BUN in addition to all other variables. MDRD 2 is abbreviated and only requires demographic variables with serum creatinine. They found mean eGFR by Cockcroft/Gault to be 51.2, by MDRD 1 to be 54.9 and MDRD 2 to be 64.7. They concluded that although the formulas have good agreement, they cannot be used interchangeably in individual patients or populations.

Owens, et al. (2007) studied 456 subjects to determine whether or not CKD class predicted major amputation. The sample was 60% men, 82.5% Caucasian whose mean age was 68 years. Subjects were recruited among patients who were undergoing first time lower extremity bypass surgery. They found that age, CAD, diabetes, hypertension, and critical ischemia were significant predictors of mortality. After adjustment only age remained; subjects with CKD Class 5 were more like to have a major amputation than any other class. They concluded that the higher the CKD class, the greater the risk of poor outcomes.

Wyatt and colleagues studied the behavior of providers in the Bronx Veterans Administration who were notified of their patients eGFR by MDRD during a one year period (Wyatt, Konduri, Eng, & Rohatgi, 2007). They found that overall routine CKD reporting modestly improved the recognition of patients with CKD, but did not

significantly impact their clinical care. There were better results in the subgroup of patients with diabetes who were identified with CKD. This group of diabetic patients with CKD did achieve more treatment goals than patients without documented CKD.

Cystatin C in elderly subjects

One year after publishing a study comparing the Cockcroft/Gault and MDRD, Van Den Noortgate published a second study in 2002 which included cystatin C as well as estimated GFR by Cockcroft/Gault and MDRD. The sample in this study included only 48 subjects, with a mean age of 84.4 years who had no evidence of acute illness or malignancy seven days after admission to a geriatric ward. In this study they found that the Cockcroft/Gault formula provided a good estimate of GFR when the GFR was less than 60. However they believe that when eGFR is less than 60 by Cockcroft/Gault, this formula underestimates GFR. They did not find that cystatin C was superior to creatinine in estimating GFR in elderly subjects. The differences in findings between this study and their earlier study may be attributable to the variance in physical state of the patients (acute illness vs. non acute illness).

Burkhardt, Bojarsky, Gretz, and Gladisch (2002) studied 30 subjects who were aged 57-90 years treated in the Geriatric Department for pulmonary or cerebral diseases. They measured Cystatin C, serum creatinine, inulin clearance, and urinary creatinine clearance. From the serum creatinine, they estimated GFR by the Cockcroft/Gault formula. From the cystatin C, they derived an estimation formula by regression analysis and then compared all measures to inulin clearance. They concluded that estimation by Cockcroft/Gault formula and cystatin C based equations are a slight

improvement over urine creatinine clearance, but no formula is sufficiently precise in the elderly.

Also in 2004, Wasen and colleages studied 1,246 community dwelling residents in Finland. Their study design was cross-sectional retrospective review and compared eGFR by Cockcroft/Gault, MDRD and by cystatin C. The estimations by Cockcroft/Gault produced 59% moderate or severe CKD while estimations by MDRD only produced 39% moderate or severe CKD. Estimations based on cystatin C measurement correlated more closely to MDRD than Cockcroft/Gault.

Arimoto and colleagues (2005) in Japan studied the clinical significance of cystatin C levels in subjects with mild to moderate heart failure. Their sample consisted of 140 subjects with heart failure and 64 age matched control subjects without heart failure. Cystatin C was measured on intake into the study and then subjects were followed for a median 480 days with end points of cardiac death or rehospitalization for progressive heart failure. The mean age of the study population was 66 $\pm$ 13 years. They found that a change of 1 SD in cystatin C level was an independent predictor of cardiac events.

MacIsaac and colleages (2006) studied 251 consecutive participants in Heidelberg, Australia to compare the predictive performance of cystatin C based GFR estimation with creatinine based GFR estimation. Their study sample's mean age was 60 $\pm$ 1 (range 22-84) years. They found that all three formulas produced similar precision and accuracy; estimates of GFR based on cystatin C were not superior to creatinine based estimates in this population.

Hermida and Tutor (2006) compared eGFR by creatinine based formulas with eGFR by cystatin C based formula in subjects known to have decreased creatinine production. They found that when creatinine production was above 800 mg in 24 hours, creatinine based formulas were reliable. However when creatinine production was below 800 mg in 24 hours, formulas based on creatinine may produce false negatives in subjects who otherwise would have CKD. This finding is significant because older subjects may produce less creatinine.

Odden and colleagues (2006) studied cystatin C levels and correlated that variable to functional status in older patients. They found cystatin C to more reliably predict poor functional status than creatinine based formulas. Higher cystatin C predicted poorer functional status. Only if eGFR was less than 60 by creatinine based formula was creatinine sensitive in predicting poor functional status.

Rule, Berstralh, Slezak, Bergert, and Larson (2006) compared cystatin C with creatinine for estimation of GFR measured by iothalamate. They first produced a regression analysis in healthy persons without kidney disease to produce an equation for estimation of GFR using cystatin C, and then compared the results of this equation with the MDRD and Cockcroft/Gault creatinine based estimates. The highest correlation was with the cystatin C based equation ($r = .853$), which was only slightly higher than the MDRD ($r = .825$) or the Cockcroft/Gault ($r = .796$). It is very significant to note that their sample was not elderly. The sample's mean age was 51 ± 15 years. They also noted that cystatin C levels are affected by inflammation and immunotherapy which may confound test results in some patients.

A very important study by Shlipak et al. was designed to evaluate cystatin C as a prognostic biomarker for death, cardiovascular disease and incident CKD among elderly persons without chronic kidney disease (Shlipak et al., 2006). This study was a secondary data analysis of 4,663 persons age 65 and older who participated in the Cardiovascular Health Study (CHS) who were not institutionalized and were currently living in the community and expected to continue to do so for the subsequent three years, not receiving any treatment for a cancer diagnosis and able to give consent without proxy. They found that 78% of subjects did not have CKD at baseline and that cystatin C had a higher prognostic value as a biomarker of risk for all cause mortality, death from cardiovascular disease and CKD. Median time until endpoint in this longitudinal study was 9.3 years. Their study concluded that cystatin C is a better prognostic indicator of mortality that either creatinine alone or any version of estimated GFR.

McManus, Shlipak, Ix, Ali, and Wooley (2007) studied the relationship of cystatin C to cardiovascular functional status. Selection criteria did not include a lower age limit, but the subjects were recruited from several sites in the San Francisco Bay area including the Department of Veterans Affairs. The mean age of the 906 participants was 65 $\pm$ 10 for participants with normal exercise capacity and 71 $\pm$ 11 for participants with poor exercise capacity. Although the subject recruitment strategy did not intentionally seek an older sample, the individuals who chose to participate were older. The authors found that cystatin C concentrations were linearly associated with

worse exercise capacity and heart rate recovery. They found that cystatin C concentrations were superior to creatinine based measures.

Menon and associates (2007) conducted a secondary analysis of the original MDRD Study which was a randomized, controlled trial of the effect of protein restriction and blood pressure control on the progression of kidney disease. The sample included 840 non-elderly patients with known kidney disease (predominantly nondiabetic kidney disease) who were Class 3 or 4 CKD. They were able to assay original samples from the study participants to determine cystatin C levels. From this data, the research team concluded that the association of cystatin C with all cause and CVD mortality was as strong as or stronger than iothalamate GFR.

Pucci and associates studied the correlation of cystatin C and creatinine based estimates of GFR with iohexal clearance in 288 diabetic patients (Pucci et al., 2007). There is little information about the age of the subjects. In this sample, cystatin C had a higher correlation (r = .857) with iohexal clearance than either of the creatinine based measures.

Rodondi and associates (2007) specifically studied cardiovascular disease by correlating carotid artery intimal thickness with measures of renal disease in middle-aged adults. They did not find that cystatin C was superior to creatinine based estimates of GFR, but rather that microalbuminuria was a more reliable predictor of carotid artery intimal thickness than any of the serum based markers in this population.

Singh and associates studied the strengths of association of eGFR by creatinine based formulas and cystatin C with inflammatory biomarkers (Singh, Whooley, Ix, Ali,

& Shlipak, 2007). They found a strong and direct association between fibrinogen and C-reactive protein which disappeared after being controlled for creatinine. This further supports the finding that cystatin C is strongly influenced by inflammatory processes, making its use as a marker for CKD less reliable in populations with inflammation.

A very recent study from Sweden compared GFR in a group of 34 ambulatory subjects aged 75-103 calculated from creatinine clearance, iohexal injection, eGFR by Cockcroft/Gault and eGFR by cystatin C (Thylen, Klaren, End, Bergman, & Odar-Cederlof, 2007). Their preliminary findings found that eGFR by Cockcroft/Gault (mean GFR 30) had the highest correlation to iohexal clearance (mean GFR 36) of any method, including cystatin C (mean GFR 42).

There is still great difference of opinion on whether or not cystatin C based estimation of GFR is better or equal to creatinine based formulas. There are definitely populations such as patients without inflammatory conditions where cystatin C is more accurate and reliable, but more research needs to be done.

Clinical significance of GFR measurement in elderly patients

Clinical significance is the usefulness of knowledge in the clinical setting. Although study findings may be statistically significant, these same findings may lack relevance in a given setting. For clinicians to provide the most effective management for their patients, study findings must also be evaluated in light of clinical significance. A measured difference of 0.1mg/dL change in creatinine may not be statistically significant, but it may be clinically significant for an individual patient. Or the opposite scenario could exist; a statistically significant change may be clinically insignificant. It

may represent the beginning of a trend towards improved function after an acute insult or worsening of a chronic condition. Only when information is considered in the context of a given patient's overall health does a small change aquire meaning.

There is evidence that CKD often occurs concurrently with other disease processes. Some of these appear to be the result of the same pathophysiology that contributes to CKD. When CKD occurs in the context of other comorbid diseases and conditions, it is associated with and influences the outcomes of other health conditions. Information about the status of a given patient's kidney function gives providers clues about other risk factors to monitor which are important in managing that patient's health risk. For example, the presence of CKD has been found to be associated with cardiovascular disease and is considered a CVD equivalent when predicting an individual patient's risk. In fact, in patients with CKD or ESRD, CVD is the leading cause of death (Foley et al., 2005). Rahman and associates found that a low GFR independently predicted coronary heart disease (Rahman et al., 2006). Brugts and colleagues found that "renal function is a graded and independent predictor of the development of myocardial infarction in an elderly population" (Brugts et al., 2005).

Patients with CKD have increased risk for anemia and complications of anemia due to the lack of erythropoietin production. Controversy over the appropriate pharmacologic management of this related anemia has flooded the literature for several years and is beyond the scope of this study. Data also strongly suggest that when blood pressure is tightly controlled, the incidence of ESRD is decreased and progression of CKD is slowed (Lindeman, Tobin, & Shock, 1984a; Toto et al., 1995). When providers

know of these associations, more aggressive management of hyperlipidemia and blood pressure become standard management. Diabetes alone is the single most common denominator of ESRD. By understanding more about the characteristics of high risk patients with and without CKD, interventions can be developed and tested to prevent CKD or halt the progression of CKD to ESRD.

A 2008 publication by Melloni and colleages underscores the clinical utilization of GFR estimates in elderly patients. This group of scientists compared antithrombotic dose adjustments in 46,942 subjects with non ST segment elevation acute coronary syndrome in the CRUSADE study, which were based on GFR estimates by both formulas. They found a 20% disagreement between the two formulas. They concluded that estimation of GFR by the Cockcroft/Gault formula was preferable because when it was used to calculate dose adjustments of antithrombotic medications; small, female, and elderly patients had a reduced risk of bleeding.

Summary

Renal function declines with age, as much as 1cc/year. It is a challenge for clinicians to estimate renal function when creatinine production from muscle mass and dietary protein intake are declining at the same time creatinine clearance in the kidney is also declining. Fontsere (2006) found that nutritional status was more important than age in predicting renal function.

Patients who have renal insufficiency may have normal serum creatinine values. Serum creatinine is by itself an unreliable indicator of renal function in the elderly (Giannelli, 2007). The original gold standard for information for clinicians to evaluate

renal function was 24 hour creatinine clearance. This test is inconvenient and difficult for patients to collect a 24 hour urine specimen and takes several days to result.

The Cockcroft/Gault formula was developed to correlate with 24 hour creatinine clearance. This equation uses age, gender, serum creatinine, and weight to estimate eGFR. Most of the evidence in support of the Cockcroft/Gault formula used measured body weight. There is some evidence that using ideal body weight improves the estimate of GFR and that these estimates correlate best with iohexal clearance.

The MDRD formula was published in 1999 and was derived from a much larger sample, but also one that had few older subjects. The patients also had known kidney disease. The MDRD formula is simpler for many clinicians and laboratories to use because a weight is not required for the equation. The MDRD uses age, gender, serum creatinine and race (Black yes or no) to estimate GFR.

CG consistently yields a lower estimate of GFR than does the MDRD. MDRD appears to yield a better estimate of eGFR when the patient is acutely ill. Garg (2004) found that CG produced consistently lower estimates of GFR than MDRD especially in the oldest subjects. Fehrman-Ekholm (2004) found MDRD correlated most closely with iohexal clearance and that CG consistently underestimated GFR when compared with measured 24 hour creatinine clearance. Laroche (2005) also found that MDRD estimates were consistently higher than CG estimates.

When outcomes were considered, Brugts (2005) found that renal function is an independent predictor of the subsequent development of myocardial infarction in elderly subjects. Maaravi (2006) found moderate renal insufficiency was a strong and

independent predictor of mortality. Owens (2007) found that when studied in patients undergoing lower extremity bypass surgery, the lower the eGFR (or higher the CKD class), the greater the risk of poor outcomes. Melloni (2008) found that when eGFR was estimated by CG and dosages adjusted accordingly, small, female, and elderly patients' prescribed antithrombotic medication for non ST segment acute coronary syndrome had a reduced risk of bleeding.

All this evidence supports the position that accurate information about patients' renal function is essential for clinicians to provide safe and informed care for their elderly patients. Different formulas may be more or less appropriate in different populations of patients.

CHAPTER 3

METHODS AND PROCEDURES

Introduction

This study explored the differences in GFR estimation when the MDRD and Cockcroft/Gault formulas were applied to data from elderly subjects. This study also described characteristics of elderly subjects that were associated with rapid declines in renal function.

Research Design

This study was a secondary analysis of an available database. Descriptive and correlational statistics were used to address the questions of the study. The database included medical and demographic data from an ambulatory geriatric care clinic associated with a large teaching health care facility. The owner of the database gave permission for these data to be used for the purpose of this study (See Appendix A for letter of permission).

The clinic is located on the grounds of a large county medical center. The entire complex is accessible via public transportation and free parking is available. The majority of the patients are from lower socioeconomic groups and represent many ethnic minorities and first generation immigrants.

The clinic provides primary medical care to geriatric patients defined by the clinic as individuals at least 60 years of age. Patients are seen for their acute and chronic medical complaints. The clinic is open during regular business hours of eight to five, Monday through Friday and patients are seen by appointment only. Patients are seen by and care managed by the same provider on every visit whenever possible. When appropriate, patients are referred for subspecialty care. If an established patient walks in with an acute complaint, the nurses triage the patient to either be worked into the schedule if appropriate and possible or assist the patient in accessing urgent care services through the emergency department.

The clinic is staffed by geriatricians (fellowship trained, board certified physicians in geriatrics), internal medicine residents in training, geriatric fellows in training, nurse practitioners, a social worker, a pharmacist, and a registered dietician. An administrator, nurses, a full time Spanish language translator and front office personnel complete the geriatric focused team who provide the care in this clinic.

The majority of the patients who attend this clinic are eligible for Medicare because they are over 65 years of age. Many are also eligible for Medicaid benefits because of their profound lack of resources. Some patients are over 65, yet are ineligible for any payor source such as Medicare or Medicaid and are full charity patients of the county. The overwhelming majority of the patients are members of one of the many ethnic minorities and/or first generation immigrants. The largest racial group represented in this clinic is African American. The second largest identifiable group is

identified as Latino. Because women outlive men in this age group, the clinic has more female patients than male patients.

The Database

The database was developed to examine the relationship of renal function to dietary protein and multiple other descriptive variables. The subjects were selected for inclusion in the research database because they had been referred to the clinic dietician and had been in the database for at least two years. Study personnel reviewed potential patients found within the dietician's database who had been seen at least two years before the date the data collector was reviewing the dietician's database. When patients met the above criteria, their chart was retrieved and the selected data were collected. All variables with the exception of demographic variables were collected from the date of dietary interview and two years after the dietary interview. Laboratory data for each patient was retrieved from the electronic health record of the hospital healthcare system. Laboratory values were included which met the rule of being within a 6 month window (between 3 months before and after the date of dietary interview) as well as within the same interval window on the two year anniversary of the date of dietary interview. At no time was personally identifying information such as name or birth date or any hospital identification number collected in the database.

Data collectors for this database consisted of two nursing students from a local university, one graduate and one undergraduate. The graduate student was a Gerontologic Nurse Practitioner and the undergraduate nursing student was also

qualified as a licensed medical social worker with many years of experience in geriatric settings.

Data elements within the database

The data elements were divided into tables for illustration of the types of data available within the database. Table 1 lists demographic variables. Since demographic variables are contained within both GFR estimating formulas, an examination of their relationships to renal function is warranted. The second table defines functional variables such as dependence or independence in cooking, shopping or medication administration. These variables may reflect physical frailty as the result of disease or perhaps disease is the result of dependence. The third table lists physiologic variables such as blood pressure, height, and weight. Again, physiologic variables have also been associated with renal function, so an examination of the relationship of these variables to GFR is also warranted. The fourth table lists comorbid diseases, contrast exposure and lifestyle habits such as smoking and dietary protein intake. It is known that renal disease occurs more often when associated with these situations. Dietary protein intake was estimated from dietary recall of patients and only included one day of recall. The fifth table lists medications and the last table lists laboratory variables. The medications included in the database were considered potentially nephrotoxic or were associated with conditions that may be associated with renal disease. The laboratory values collected within the database were also reflective of renal disease and therefore were examined for their association with CKD. Columns four and five in Table 1 list the % of data available within the database (data that were not missing).

***Table 1*. Demographic variables**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
Age	Years of age	Interval	99%	NA
Gender	Identified gender of subjects	Nominal	98%	NA
Outcome data	Status of patient if no data available at 2 years	Nominal	NA	4%
Race	Ethnic identity recorded in the medical chart by health care providers	Nominal	98%	NA

Table 2. **Functional variables**

Variables	**definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
Functional status	Independent in cooking	Nominal	97%	81%
	Independent in shopping	Nominal	93%	79%
	Independent in medications	Nominal	89%	74%
MMSE	MMSE score	Interval	28%	15%
Recreational participation	Recreational participation reported by the patient	Nominal	92%	82%

Table 3. **Physiologic variables**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
Blood pressure	Systolic and diastolic blood pressure measurement	Interval	97%	89%
Height	Height in inches	Interval	98%	NA
Left Ventricular Hypertrophy	Degree of systolic dysfunction found on echocardiogram	Ordinal	54%	NA
Weight	Body weight in pounds	Interval	99%	88%

***Table 4*. Diagnostic and comorbid variables**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
Cognitive status	Presence or absence of a diagnosis of dementia in the chart	Nominal	88%	81%
Comorbid diagnoses	Hypertension	Nominal	97%	87%
	Coronary Artery Disease (CAD)	Nominal	86%	80%
	Congestive Heart Failure (CHF)	Nominal	92%	84%
	Cancer	Nominal	89%	82%
	Gout	Nominal	90%	83%
	Transient Ischemic Attack (TIA) or Cerebrovascular Accident (CVA)	Nominal	88%	82%
	Cirrhosis	Nominal	86%	78%
	History of UTIs	Nominal	91%	84%

Table 4. **- continued**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
	Peripheral Vascular Disease (PVD)	Nominal	89%	81%
	Diabetes	Nominal	92%	86%
	Nephrolithiasis	Nominal	86%	78%
	Hepatitis C	Nominal	88%	83%
	Atrial fibrillation	Nominal	89%	79%
	Benign Prostatic Hypertrophy (BPH)	Nominal	87%	77%
	Chronic Kidney Disease (CKD)	Nominal	89%	79%
	medication non adherence	Nominal	83%	79%
Contrast exposure	Computed Tomography (CT) of the abdomen	Nominal	11%	7%
	CT of the chest	Nominal	4%	6%
	CT of the pelvis	Nominal	8%	8%

Table 4. **- continued**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
	CT of the head	Nominal	3%	3%
	Magnetic Resonance Imaging	Nominal	9%	8%
	Magnetic resonance angiography	Nominal	0.3%	3%
	Intravenous Pylogram (IVP)	Nominal	2%	0.3%
	Coronary angiogram	Nominal	1%	0
Dietary protein content	Calculated protein intake based on dietary recall of patient	Interval	68%	NA
Smoking status	History of smoking	Nominal	81%	76%
	Current smoker	Nominal	87%	71%
	Pack years of smoking	Interval	12%	10%
Urinary Tract Infections (UTI)	Number of UTIs treated during 2 year study period	Interval	NA	2%

***Table 5*. Medication variables**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
Anti-hypertensive drug classes	Beta blockers	Nominal	90%	81%
	Angiotensin converting enzyme inhibitors (ACEI)	Nominal	92%	86%
	Angiotensin Receptor Blockers (ARB)	Nominal	87%	83%
	Calcium Channel blockers (CCB)	Nominal	89%	84%
	Alpha blockers	Nominal	91%	84%
diuretic class	Loop diuretic	Nominal	89%	84%
	Thiazide diuretic	Nominal	89%	81%
diabetic drug classes	Sulfonylureas	Nominal	91%	82%

Table 5 **- continued**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
	thiazolidinediones	Nominal	89%	79%
	Insulin	Nominal	91%	80%
	Metformin	Nominal	91%	82%
Hormone replacement	thyroid replacement hormone	Nominal	92%	85%
NSAID	COX1	Nominal	93%	84%
	COX2	Nominal	88%	80%
Drugs that interfere with coagulation	ASA	Nominal	93%	83%
	Warfarin	Nominal	90%	84%
	Clopidogrel	Nominal	89%	81%
SSRI	Any SSRI	Nominal	95%	87%
Statin	Any statin	Nominal	92%	84%

Table 5. **- continued**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
iron supplement	Any iron supplement	Nominal	88%	81%

***Table 6*. Laboratory variables**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
Chemistry	Sodium	Interval	96%	90%
	Potassium	Interval	96%	91%
	Glucose	Interval	82%	70%
	Chloride	Interval	95%	88%
	Bicarbonate	Interval	93%	85%
	Base Urea Nitrogen (BUN)	Interval	97%	91%
	Creatinine	Interval	97%	91%
	Uric acid	Interval	3%	4%

Table 6. **- continued**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
	Calcium	Interval	54%	40%
	Phosphorus	Interval	42%	35%
	Albumin	Interval	45%	31%
	Protein	Interval	34%	25%
lipid profiles	Total cholesterol	Interval	82%	70%
	Low Density Lipoprotein	Interval	77%	69%
	High Density Lipoprotein	Interval	82%	71%
	Triglycerides	Interval	82%	71%
Hematology	Hemoglobin	Interval	78%	70%
	White Blood Cells (WBC)	Interval	83%	69%

Table 6. – **continued**

Variables	**Definition**	**Type of data**	**% of complete data at time 1**	**% of complete data at time 2**
	Eosinophil Sedimentation Rate (ESR)	Interval	7%	5%
Endocrinology	Thyroid stimulating hormone	Interval	78%	57%
	Glycosolated hemoglobin	Interval	56%	49%
	C Reactive Protein (CRP)	Interval	1%	3%
Urinalysis	Presence of protein in random urine sample	Ordinal	41%	35%
	Presence of > 5 WBC in random urinalysis	Nominal	6%	5%
	Urine microalbumin	Interval	3%	1%

Procedure to prepare the data for analysis

The procedure used for this study was a secondary analysis of the database obtained from the geriatric ambulatory clinic. The database was de-identified data and subjects could not be identified. The owner of the database gave permission for this analysis; see letter of permission in Appendix A. The database was received in SPSS format.

Not all variables included in the original database were included in this analysis. If the % of missing data exceeded 30% of the total database, that variable was not included in the analysis (D. Cipher, personal communication, February 15, 2008). Because most of the variables are nominal, statistical strategies to deal with missing data were not appropriate, subjects with missing data were not included in the final analysis. Dietary protein intake was not included in the analysis because of the method of data collection (dietary recall) which has been known to produce poor quality of data. Glycosolated hemoglobin was included in the analysis even though only 56% of the patients had such a laboratory test. This number however represented over 90% of the diabetic patients within the database. Generally only a diagnosis of diabetes or glucose intolerance would justify a clinician ordering the exam. Left ventricular hypertrophy was also included in the analysis even though data were only available on 56% of the database. Again, echocardiography is only utilized as a diagnostic tool when clinicians suspect cardiac pump pathology.

The analysis began with a careful examination of each variable included in the database for range and frequencies. The calculated variables were produced from syntax

files (see appendix C and D). After the GFR estimates were calculated by each formula (MDRD and CG), the subjects were assigned to the appropriate CKD class according to their calculated GFR. CKD class membership was used to divide the sample into those with and without CRI (above or below GFR of 60). The bivariate variable thus created (with or without CRI) determined group membership for the analysis that answered the first three study questions. A final interval variable was calculated by subtracting the calculated GFR by each formula at time 2 from the calculated GFR at time 1 by each formula. Patients who experienced 20cc or greater decline in eGFR were classified as having rapid decline according to each formula. This variable was the dependent variable for question four of this study.

Statistical procedures to answer the study questions

In order to answer the study questions, once the subjects were assigned to CKD classes, comparisons were made of those subjects with CRI and those without CRI. How similar or different were the subjects identified with CRI by the different formulas? The data were received as an SPSS file and were analyzed using SPSS. Each question dealt with differences between patients with and without renal insufficiency. Chi squares were done to evaluate nominal and ordinal variables and analysis of variance was used to evaluate interval variables that met the threshold of no more than 30% missing data. To answer the final question, the dependent variable was rapid decline of GFR by more than 20cc over the two year study period. The statistical test that was utilized was chi square for nominal and ordinal variables and ANOVA for

interval variables to discover whether any of the variables were correlated with the rapid decline. For all statistical analysis the alpha was set at 0.05.

Limitations

This analysis was limited to the available data within the database. Due to the nature of this database (retrospective record review), it was expected that there would be missing data.

Summary

The purpose of this study was to describe variables that were associated with chronic renal insufficiency in elderly subjects. It also described variables that were associated with rapid declines in renal function in elderly patients. By conducting this analysis in a population that was most like those at highest risk of suffering from chronic kidney disease, knowledge was built that helps to identify risk factors for chronic kidney disease. When variables that contribute to the development of CKD are known, clinicians can make more informed decisions that contribute to better care of patients with chronic renal insufficiency.

CHAPTER FOUR

RESULTS

Sample Demographics

The study sample consisted of 311 subjects. The mean age of all subjects was 73 (SD 8). The subjects' ages ranged from 56-94 years. The distribution of subjects' age was slightly skewed toward younger aged persons (see figure 2). The sample was mostly female (73%), (see figure 3). Fifty-eight % of the sample were identified as African American, 23% Latino, 11% Caucasian, non-Latino, 2.3% Indian/Pakistani, 1.6% Asian/Pacific Islander, 0.3% Native American and 1.9% "other" or unidentified (see Figure 4).

Functional status of the sample as a whole was 34% dependence in cooking, 40% dependence in shopping, and 14% dependence in medications. Recreational participation reported by patients consisted of 3% who reported going to a senior center, 23% who reported walking, 57% who reported no activity, and 9% who reported various other types of activity.

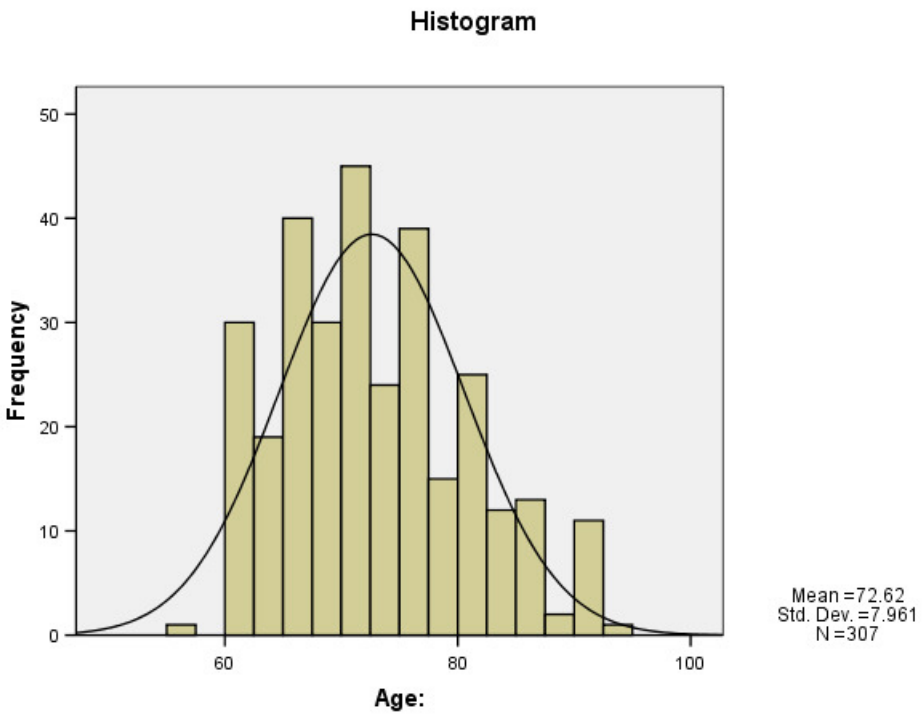

Figure 2. Age distribution of subjects within the database.

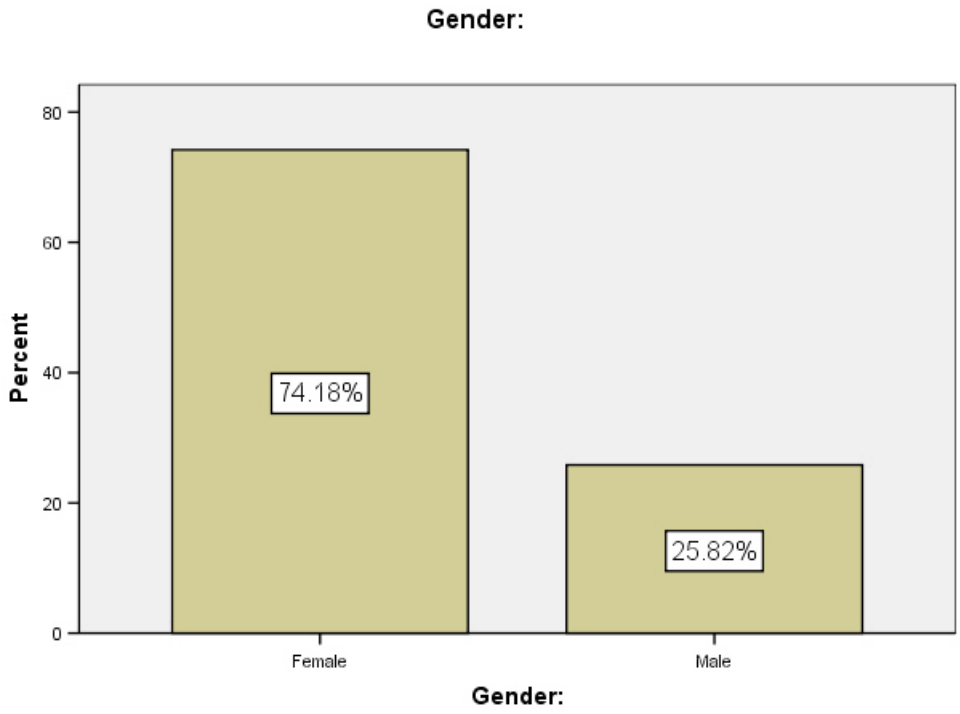

Figure 3. Gender distribution of subjects within the database.

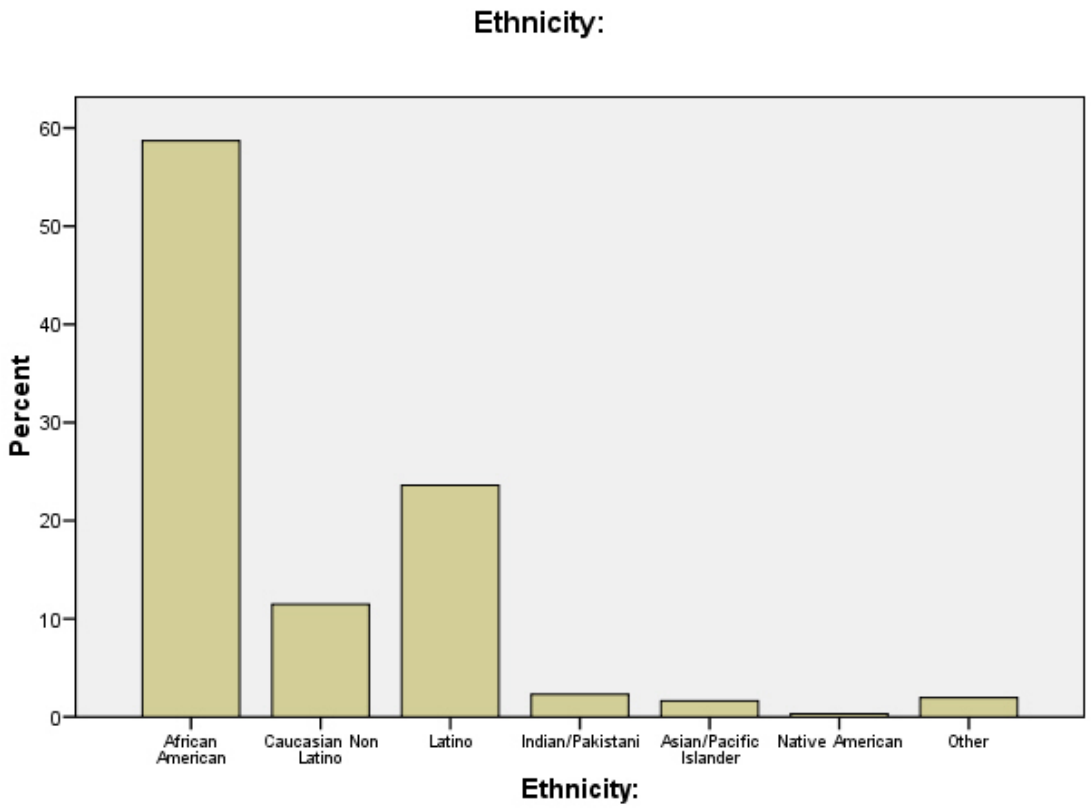

Figure 4. Racial/ethnic distribution of subjects within the database

Characteristics of Patients Identified with and without CRI estimated by Cockcroft/Gault

Of the sample who had data sufficient to calculate eGFR by CG (n = 297), 229 patients (77%) did not have renal insufficiency and 68 patients (23%) did have renal insufficiency (see Table 7). When examined with independent sample t-tests, patients who had renal insufficiency were significantly older (t = -8.073, df = 295, p = .013). The mean age of patients with renal insufficiency was 79 (SD 9) compared with a mean age of 71 (SD 7) in patients without renal insufficiency (see Figure 5).

Table 7. **Demographic variables of patients with CRI estimated by CG**

	women	**Men**	**Total**
With CRI n = 68	45 (66%)	23 (34%)	68 (23%)
Without CRI n = 229	178 (78%)	51 (22%)	229 (77%)
Total	223 (75%)	74 (25%)	297 (100%)

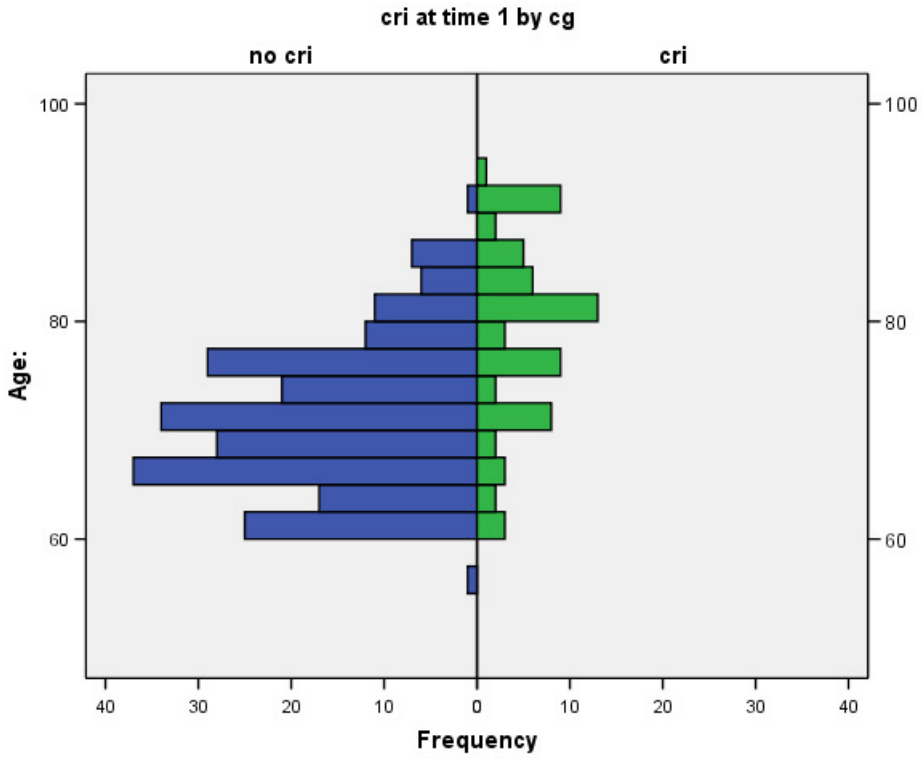

Figure 5. Age distribution of renal status estimated by CG

In regard to gender, the difference between men and women in the sample was statistically significance at (X^2 = 3.741, df = 1, p = .05). Although overall men were 25% of the sample, the percent of men who had renal insufficiency estimated by CG was 34%. Women were

75% of the overall sample, and 66% of women had renal insufficiency. This association was weak at r =.11. The odds ratio was 1.74 for women over men to have renal insufficiency. The confidence interval was .988 to 3.221 for women and .98 to 1.368 for men. Proportionally, men were more likely to be identified as having CRI when GFR was estimated by CG than were women.

Table 8 shows that over half of the sample were African American. Another 24% were Latino. Each racial/ethnic category was analyzed by chi square against all other racial categories combined. When African American patients were compared against all other racial/ethnic groups, renal insufficiency occurred significantly more often than in any other group (see Table 9), but the association was weak at r = .13. The odds ratio for African Americans was 1.895 times that of all other ethnic groups combined of having renal insufficiency. The confidence interval was 1.065 to 3.373 for African Americans who have renal insufficiency. Proportionally, African American patients were more likely to be identified as having CRI when GFR is estimated by CG than are persons from any other racial group.

Table 8. **Percentages of ethnic/racial characteristics associated with CRI when estimated by CG**

Race	**With CRI n (%)**	**Without CRI n (%)**	**Total n (%)**
African American	47 (71%)	124 (55%)	171 (59%)
Caucasian	8 (12%)	25 (11%)	33 (11%)
Latino	9 (14%)	61 (27%)	70 (24%)
Indian/Pakistani	2 (3%)	4 (2%)	6 (2%)
Asian/Pacific Islander	0	5 (2%)	5 (2%)

***Table 8*. – continued**

Race	With CRI n (%)	Without CRI n (%)	Total n (%)
Native American	0	1 (<1%)	1 (<1%)
Other	0	6 (3%)	6 (2%)
Total	66 (100%)	226 (100%)	292 (100%)

***Table 9*. Racial variables associated with CRI estimated by CG**

Race	X^2	df	P	Odds ratio	95% Confidence interval	
					Lower bound	Upper bound
African American	4.810	1	.03	1.895	1.065	3.373
Latino	5.228	1	.02	.42	.196	.898

When Latino patients were examined, there was a significant association of Latino ethnicity with renal insufficiency (see Table 9). Latino ethnicity had a weak protective effect against CRI when GFR was estimated by CG. The correlation was weak at r = -.13. The odds ratio was only .42 and the confidence interval was .196 to .898. When Caucasian, Indian/Pakistani, Asian/Pacific Islander and unidentified patients were examined, there was no significant association between any other racial identity and renal insufficiency estimated by the Cockcroft/Gault formula.

Data on IADLs were available on 265-288 patients, depending on the variable. Table 10 shows that 65% of patients were dependent in cooking, but that only 16% were dependent in medications. As shown in Table 11, for most of these patients (62%), no recreational activity was

noted in the database. Among patients with renal insufficiency, 54% were dependent in cooking compared to 30% of patients without renal insufficiency. When dependence in medications was examined, 29% of patients with renal insufficiency reported dependence, whereas 12% of those without renal insufficiency reported dependence. Among patients with renal insufficiency, 63% were dependent in shopping compared with 39% who did not have renal insufficiency. When recreational participation was analyzed, no reported category was associated with renal insufficiency. When the instrumental activities of daily living contained within this database were analyzed, all impairments were significantly associated with renal insufficiency (see Table 11).

***Table 10*. Percent of patients dependent in IADLs when CRI estimated by CG**

Cooking	With CRI n (%)	Without CRI n (%)	Total n (%)
Dependent in cooking n = 288	35 (34%)	67 (66%)	102 (35%)
Dependent in medication management n = 265	17 (41%)	24 (59%)	41 (15%)
Dependent in shopping n = 278	40 (33%)	82 (67%)	122 (43%)

Table 11. **Percent participation in recreational activities when CRI estimated by CG**

Recreational activity	With CRI n (%)	Without CRI n (%)	Total n (%)
Senior center	3 (5%)	6 (3%)	9 (3%)
Walk	11 (18%)	55 (26%)	66 (24%)
None noted	42 (68%)	129 (61%)	171 (62%)
Other	6 (10%)	23 (11%)	29 (11%)
Total	62 (91%)	213 (100%)	275 (100%)

Table 12. **IADLs associated with CRI estimated by CG.**

IADL	x^2	df	p	Odds ratio
Dependent in cooking	12.465	1	.01	2.716
Dependent in medication management	10.331	1	.01	2.683
Dependent in shopping	11.699	1	.01	3.069

Table 13 provides the means and standard deviations of the physiological variables in the database. When physiologic variables were examined, patients with renal insufficiency were much more likely to weigh less than patients without renal insufficiency (see Table 13). Patients who had renal insufficiency weighed significantly less than did those without CRI. When BMI was calculated, it was significantly related to renal insufficiency estimated by CG (see Table 14). This appears to be logical since measured body weight is a factor in both BMI and estimated GFR by CG.

***Table 13*. Means and standard deviations of physiologic variables associated with CRI estimated by CG**

	With CRI m (SD)	**Without CRI m (SD)**	**Total m (SD)**
BMI n = 294	23 (5)	31 (9)	29 (9)
Diastolic blood pressure n = 293	73 (13)	76 (11)	75 (11)
Height n = 294	65 (4)	64 (4)	64 (4)
Systolic blood pressure n = 293	146 (27)	146 (23)	145 (24)
Weight n = 297	140 (35)	182 (53)	172 (52)

***Table 14*. Physiologic variables associated with CRI estimated by CG**

Variable	X^2	**df**	**P**
Weight	t = 6.108	295	.01
BMI	t = 6.95	292	.001
Left Ventricular Hypertrophy	X^2 = 10.304	3	.01

***Table 15*. Echocardiogram percentages when CRI estimated by CG**

LVH	With CRI n (%)	Without CRI n (%)	Total n (%)
Normal	28 (67%)	96 (81%)	124 (78%)
Mild	6 (14%)	11 (9%)	17 (11%)
Moderate	1 (2%)	7 (6%)	8 (5%)
Severe	7 (17%)	4 (3%)	11 (7)

Table 15 shows the percentage of subjects with and without CRI estimated by CG who had left ventricular hypertrophy as revealed on echocardiography. Normal findings on echocardiography were negatively associated with CRI, while severe findings of left ventricular hypertrophy conferred a 5.7 odds ratio for CRI (see Table 14). Mild or moderate LVH had no association with CRI.

Table 16 provides information on the numbers and percentages of patients who had each co-morbidity and on whom data were available. The most common co-morbidity for all patients was hypertension (78%). Almost half (48%) had diabetes. When comorbid diagnoses were examined, only diagnoses of congestive heart failure, diabetes, dementia, or chronic kidney disease were associated with renal insufficiency (see Table 17). The odds ratio was 2.167 for CHF, 0.554 for diabetes, 4 for dementia, and 7.725 for chronic kidney disease. All other diagnoses were not associated with patients with renal insufficiency. There was also no association between smoking status or history of smoking and renal insufficiency estimated by Cockcroft/Gault. Those identified as having CRI by CG were more likely to have a diagnosis of

CKD, CHF and dementia than those identified as not having CRI, just the opposite is true of diabetes.

***Table 16*. Comorbid diagnosis variable frequencies associated with CRI estimated by CG**

Variable	**With CRI n (%)**	**Without CRI n**	**Total n (%)**
Atrial fibrillation	6 (9%)	13 (7%)	19 (7%)
Benign prostatic hypertrophy	5 (8%)	9 (5%)	14 (5%)
Cancer	6 (10%)	23 (11%)	29 (11%)
Chronic kidney disease	12 (19%)	6 (3%)	18 (7%)
Cirrhosis	1 (2%)	1 (< 1%)	2 (<1%)
Congestive heart failure	13 (20%)	22 (11%)	35 (13%)
Coronary artery disease	16 (28%)	33 (17%)	49 (19%)
Dementia	16 (26%)	16 (8%)	32 (12%)
Diabetes	23 (37%)	108 (51%)	131 (48%)
Gout	4 (7%)	6 (3%)	10 (4%)
Hepatitis C	0	1 (<1%)	1 (<1%)
History of smoking	14 (24%)	54 (29%)	68 (28%)
History of UTIs	4 (7%)	5 (2%)	9 (3%)
Hypertension	57 (83%)	169 (77%)	226 (78%)
Medication nonadherence	8 (14%)	23 (12%)	31 (13%)
Nephrolithiasis	0	4 (2%)	4 (2%)

Table 16. – **continued**

Variable	With CRI n (%)	Without CRI n	Total n (%)
Peripheral vascular disease	3 (5%)	9 (4%)	12 (5%)
Smoker, current	7 (11%)	24 (12%)	31 (12%)
Transient ischemic attack or stroke	7 (11%)	25 (12%)	32 (12%)

***Table 17*. Associated comorbid diagnoses when CRI estimated by CG**

Variable	X^2	df	p	Odds ratio
Chronic kidney disease	19.734	1	.001	7.725
Congestive heart failure	4.198	1	.04	2.167
Dementia	13.996	1	.001	4.000
Diabetes	4.057	1	.04	.554

Table 18 presents the information on the number and percentages of patients prescribed various types of medication classes. The most commonly prescribed medication class for these patients was ACEI (44%). When medication classes were examined for association with renal insufficiency only angiotensin receptor blockers (ARBs), beta blockers, and metformin were associated with renal insufficiency (see Table 19). The association of ARBs to CRI estimated by CG was weakly negative at r = -.13, also weakly positive for beta blockers at r = .12, but moderately stronger for a negative relationship with metformin at r = -22. Those identified as having CRI when GFR is estimated by CG were less likely than those identified without CRI to be prescribed ARBs or metformin. Just the opposite is the case for beta blockers. This may

reflect conscious provider choices of medications in patients with renal insufficiency that are not metabolized in the kidney (beta blocker) or against those that are considered to be unsafe in renal insufficiency (ARB and metformin). All other medication classes were not associated with renal insufficiency.

***Table 18*. Descriptives of medication classes when CRI estimated by CG**

Medications	**With CRI n (%)**	**Without CRI n (%)**	**Total n (%)**
ACEI n = 275	27(44%)	93 (44%)	120 (44%)
Alpha blockers n = 270	4 (6%)	12 (6%)	16 (6%)
ARB n = 259	1 (2%)	20 (10%)	21 (8%)
ASA n = 277	23 (37%)	75 (35%)	98 (35%)
Beta blockers n = 269	24 (39%)	53 (26%)	77 (29%)
Calcium channel blockers n = 266	22 (36%)	73 (36%)	95 (36%)
Clopidogrel n = 267	5 (8%)	15 (7%)	20 (8%)
COX2 drugs n = 262	5 (8%)	32 (16%)	37 (14%)
Insulin n = 273	11 (17%)	33 (16%)	44 (16%)
Iron n = 261	3 (5%)	8 (4%)	11 (4%)
Loop diuretics n = 266	17 (28%)	46 (22%)	63 (24)
Metformin n = 274	2 (3%)	49 (23%)	51 (19%)
NSAID n = 277	6 (9%)	20 (9%)	26 (9%)
SSRI n = 283	8 (13%)	42 (19%)	50 (18%)

Table 18. **- continued**

Medications	**With CRI n (%)**	**Without CRI n (%)**	**Total n (%)**
Statin n = 275	20 (32%)	88 (41%)	108 (39%)
Sulfonylurea n = 271	10 (16%)	42 (20%)	52 (19%)
Thiazide n = 267	15 (25%)	54 (26%)	69 (26%)
thiazolidinediones n = 265	2 (3%)	11 (5%)	13 (5%)
Thyroid replacement hormone n = 277	5 (8%)	23 (11%)	28 (10%
Warfarin n = 269	7 (11%)	13 (6%)	20 (7%)

Table 19. **Medication variables associated with CRI estimated by CG**

Variable	X^2	**Df**	**p**	**Odds ratio**
ARB	4.088	1	.04	.159
Beta blockers	4.011	1	.045	1.835
Metformin	13.578	1	.001	.104

Table 20 presents the means and standard deviations for the available laboratory variables within the database. Of the laboratory variables available for examination only base urea nitrogen (BUN), creatinine, hemoglobin (Hgb) and high density cholesterol (HDL) were associated with renal insufficiency (see Table 21). Both mean BUN, creatinine, and HDL in patients with renal insufficiency were higher than they were in patients without renal insufficiency. Mean hemoglobin in patients with renal insufficiency was lower than it was in patients without renal insufficiency.

***Table 20*. Descriptives of laboratory variables associated with CRI estimated by CG**

Variable	With CRI m (SD)	Without CRI m (SD)	Total m (SD)
BUN n = 293	26 (13)	16 (6)	19 (9)
Bicarbonate n = 282	26 (4)	27 (3)	27 (3)
Chloride n = 282	103(4)	103 (3)	103 (4)
Creatinine n = 297	1.6 (1.09)	0.91 (0.25)	1.08 (0.67)
Glucose n = 250	126 (51)	125 (51)	124 (54)
HgbA1c n = 169	6.58 (1.32)	7.0 (1.8)	6.90 (1.72)
Hemoglobin n = 237	12.27 (1.73)	13.0 (1.63)	12.89 (1.68)
HDL n = 248	57 (15)	51 (17)	53 (17)
LDL n = 231	110 (39)	114 (40)	114 (40)
Potassium n = 291	4.33 (0.47)	4.30 (0.56)	4.30 (0.53)
Sodium n = 290	138 (3.5)	139 (3)	139 (3)
TSH n = 235	4.50 (13)	2.36 (6)	2.8 (7.8)

***Table 20*. - continued**

Variable	With CRI m (SD)	Without CRI m (SD)	Total m (SD)
Total cholesterol n = 248	194 (46)	196 (50)	196 (49)
Triglycerides n = 249	133 (74)	156 (100)	151 (95)
WBC n = 251	6825 (2662)	6933 (2038)	6943 (2222)

***Table 21*. Laboratory variables associated with CRI estimated by CG**

Variable	t	df	p	m (SD) with CRI	m (SD) without CRI
Base Urea Nitrogen (BUN)	-8.600	291	.01	26 (13)	16 (6)
Creatinine	-8.861	295	.01	1.6 (1.08)	.9131 (.25)
Hemoglobin	3.333	235	.01	12.268 (1.73)	13 (1.63)
High Density Lipoprotein	-2.116	246	.04	56.98 (15.4)	51.42 (17.3)

Characteristics of patients identified with and without CRI estimated by MDRD

There were 298 patients available with all of the elements in the database necessary to calculate eGFR by the MDRD formula. Patients with renal insufficiency (n = 69) represented 22% of the sample (see Tables 22). Age was significantly associated with renal insufficiency (t = -5.0; df = 296; p = .01). Patients with renal insufficiency were older (mean age 77, SD 9) than patients without renal insufficiency (mean age 71, SD 7). See Figure 6 for illustration of age

distribution. Most patients with renal insufficiency were female (80%). The proportion of men and women with and without CRI were not significantly different.

***Table 22*. Gender percentages of patients with CRI estimated by MDRD**

	Women	**Men**	**Total n (%)**
With CRI n = 69	45 (66%)	23 (34%)	68 (23%)
Without CRI n (%)	178 (77%)	51 (22%)	229 (77%)
Totals	223 (75%)	74 (25%)	297 (100%)

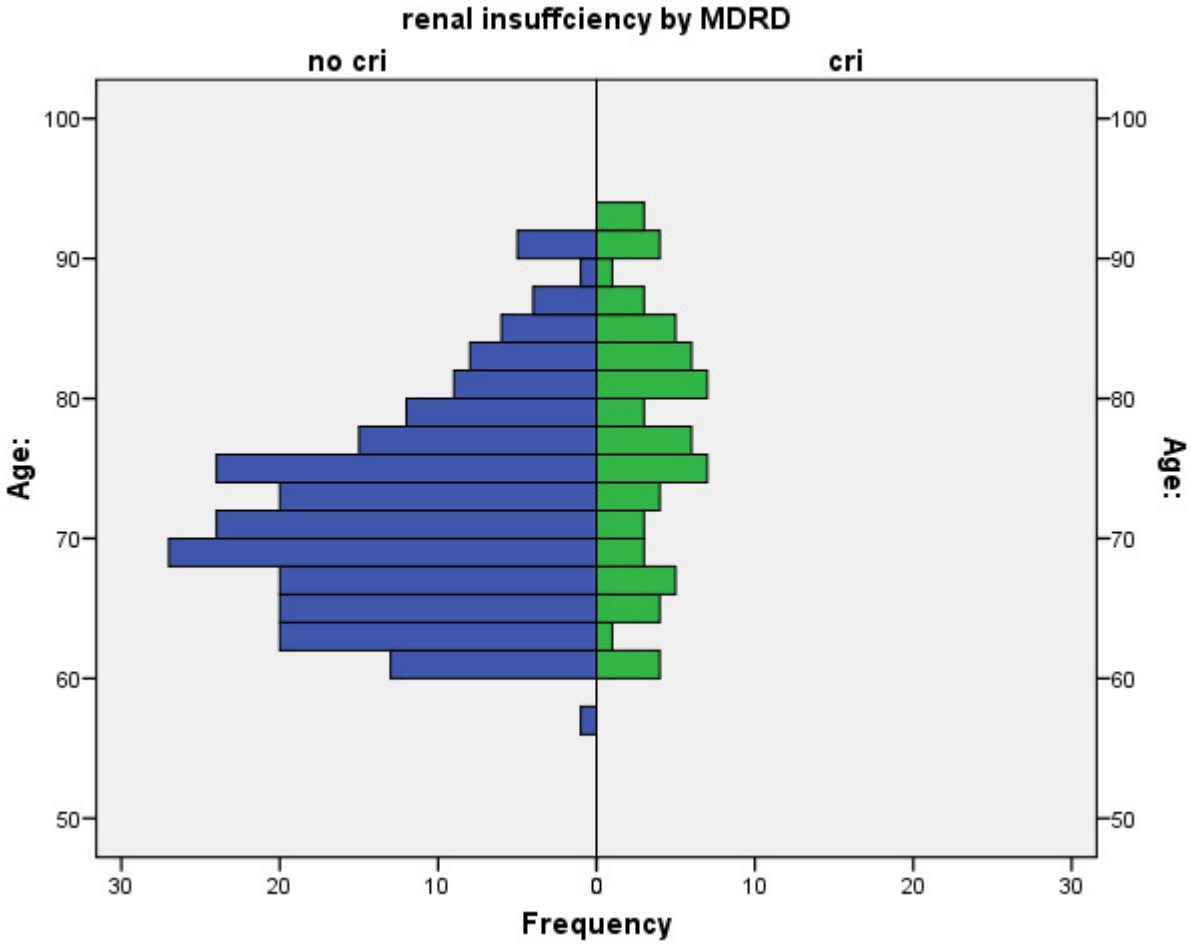

Figure 6. Age distribution by renal status estimated by the MDRD formula

Racial distribution within patients who had renal insufficiency identified by the MDRD formula was 67% African American, 14% Caucasian, 15% Latino, 1.5% each of Indian/Pakistani, Asian/Pacific Islander and also in those subjects who were of unidentified race (see Table 23). Patients whose race was not identified in the database could not be examined when the MDRD formula was used for estimation since the formula requires information about race. The chi square statistic was only significant for the association of Latino racial/ethnic identity with renal insufficiency identified by the MDRD formula ($X^2 = 4$; df = 1; p = .04). This association was weakly negative ($r = -.116$) with an odds ratio of 0.477 indicating a mild protective association of Latino ethnic identity with CRI identified by MDRD.

***Table 23*. Descriptives of race of patients with CRI estimated by MDRD**

Ethnicity	With CRI n (%)	Without CRI n (%)	Total n (%)
African American	44 (67%)	128 (56%)	172 (59%)
Caucasian	9 (14%)	24 (11%)	33 (11%)
Latino	10 (15%)	60 (26%)	70 (24%)
Indian/Pakistani	1 (2%)	5 (2%)	6 (2%)
Asian/Pacific Islander	1 (2%)	4 (2%)	5 (2%)
Native American	0	1 (<1%)	1 (<1%)
Other	1 (2%)	5 (2%)	6 (2%)
Total	66 (100%)	227 (100%)	293 (100%)

Table 24 presented the number and percentage of patients dependent in IADLs. Table 25 reveals that relatively few patients engaged in recreational activities. When the instrumental

activities of daily living (IADLs) contained within the database were analyzed for association with renal insufficiency identified by the MDRD formula, all the variables were significantly positively associated (see Table 26). Patients with renal insufficiency were more likely to be dependent in cooking, dependent in medication administration, and dependent in shopping than were patients identified as not having CRI by MDRD. When recreational participation was analyzed, no category was associated with renal insufficiency.

***Table 24*. Percentages of IADLs in patients with CRI estimated by MDRD**

IADLs	With CRI n (%)	Without CRI n (%)	Total n (%)
Dependent in cooking	32 (49%)	71 (32%)	103 (36%)
Dependent in medication management	15 (26%)	27 (13%)	42 (16%)
Dependent in shopping	39 (60%)	84 (39%)	123 (44%)

***Table 25*. Percentages of participation in recreational activities in patients with CRI estimated by MDRD**

Recreational activity	With CRI n (%)	Without CRI n (%)	Total n (%)
Senior center	2 (3%)	7 (3%)	9 (3%)
Walk	9 (15%)	57 (27%)	66 (24%)
None noted	47 (76%)	125 (58%)	172 (62%)
Other	4 (7%)	25 (12%)	29 (11%)
Totals	62 (100%)	214 (100%)	276 (100%)

***Table 26*. IADLs associated with CRI estimated by MDRD**

Variable	X^2	df	p
Dependent in cooking	6.152	1	.01
Dependent in shopping	8.706	1	.01
Dependent in medication management	5.660	1	.01

Table 27 presents the means and standard deviations for physiologic variables. When the physiologic variables were examined by independent sample t-test for association with renal insufficiency estimated by MDRD, only diastolic blood pressure was associated with the presence of renal insufficiency (t = 1.2; df = 292; p = .05). Patients who had renal insufficiency had a lower mean diastolic blood pressure than did patients who did not have renal insufficiency. BMI was not significantly related to eGFR estimated by MDRD.

***Table 27*. Means and standard deviations of physiologic variables when CRI estimated by MDRD**

Variable	With CRI m (SD)	Without CRI m (SD)	Total m (SD)
BMI n = 294	30 (11)	29 (8)	29 (9)
Diastolic blood pressure n = 294	73 (14)	76 (11)	75 (11)
Height n = 295	65 (4)	64(4)	64 (4)

***Table 27*. – continued**

Variable	With CRI m (SD)	Without CRI m (SD)	Total m (SD)
Systolic blood pressure n = 294	148 (28)	145 (23)	145 (24)
Weight n = 297	177 (65)	171 (48)	172 (52)

When patients were examined for prevalence of LVH by echocardiogram, the largest percentage of patients had a grade of normal (77%) or mild (11%) cardiac function (see Table 28). Patients with moderate function were the smallest percentage (5 %), while patients with severe cardiac function represented 8% of the available sample of patients who had CRI estimated by MDRD. None were significantly associated with CRI estimated by MDRD.

***Table 28*. LVH prevalence by CRI estimated with MDRD**

Left Ventricular Hypertrophy	With CRI n (%)	Without CRI n (%)	Total n (%)
Normal	31 (67%)	93 (81%)	124 (77%)
Mild	6 (13%)	11 (10%)	17 (11%)
Moderate	3 (7%)	5 (4%)	8 (5%)
Severe	6 (13%)	6 (5%)	12 (8%)
Totals	115 (100%)	46 (100%)	161 (100%)

Table 29 presents the number and percentage of patients' comorbid diseases. The most commonly occurring one is hypertension (78%). When comorbid diagnoses variables were examined, only diagnoses of hypertension, congestive heart failure, history of urinary tract

infection, coronary artery disease, or chronic kidney disease were associated with renal insufficiency identified by MDRD (see Table 30). Hypertension had a weak positive relationship at $r = .173$ and odds ratio of 3.5; CKD moderate at $r = .387$, odds ratio of 21.957; congestive heart failure moderate at $r = .27$, odds ratio of 4.8; coronary artery disease moderate at $r = .21$, odds ratio of 3; history of UTI weak at $r = .143$, but an odds ratio of 4.46 risk of CRI for those with CRI identified by MDRD. All other diagnoses were not associated with patients with renal insufficiency. There was also no association between smoking status or history of smoking and renal insufficiency. When GFR was estimated by MDRD, patients identified as having CRI were more likely than patients identified as not having CRI to have hypertension, CHF, history of UTIs, CAD, and CKD.

***Table 29*. Frequencies of comorbid disease in patients with CRI estimated by MDRD**

Variable	With CRI n (%)	Without CRI n (%)	Total n (%)
Atrial fibrillation	6 (9%)	13 (6%)	19 (7%)
BPH	3 (5%)	11 (6%)	14 (5%)
Cancer	4 (7%)	25 (12%)	29 (11%)
Chronic kidney disease	15 (25%)	3 (2%)	18 (7%)
Cirrhosis	0	2 (1%)	2 (<1%)
Congestive heart failure	19 (30%)	17 (8%)	36 (13%)
Coronary artery disease	21 (34%)	29 (15%)	50 (20%)
Dementia	11 (19%)	22 (11%)	33 (13%)
Diabetes	32 (50%)	99 (47%)	131 (48%)

Table 29. – **continued**

Variable	With CRI n (%)	Without CRI n (%)	Total n (%)
Gout	4 (7%)	6 (3%)	10 (4%)
Hepatitis C	0	1 (<1%)	1 (<1%)
History of smoking	14 (24%)	54 (29%)	68 (28%)
History of UTIs	5 (8%)	4 (2%)	9 (3%)
Hypertension	62 (91%)	165 (74%)	227 (78%)
Medication nonadherence	11 (19%)	21 (11%)	32 (13%)
Nephrolithiasis	0	4 (2%)	4 (2%)
Peripheral vascular disease	3 (5%)	9 (4%)	12 (5%)
Smoker, current	6 (10%)	25 (13%)	31 (12%)
Transient ischemic attack or stroke	10 (16%)	23 (11%)	33 (13%)

Table 30. **Comorbid diagnoses associated with CRI when estimated by MDRD**

Variable	X^2	df	p	Odds ratio
Chronic kidney disease	39.854	1	.01	21.957
Congestive heart failure	20.039	1	.01	4.8
Coronary artery disease	11.440	1	.01	3
History of UTIs	5.573	1	.02	4.46
Hypertension	8.694	1	.01	3.5

Table 31 presents the number and percentages of patients prescribed various medication classes. When medication classes were examined for association with renal insufficiency estimated by MDRD, only beta blockers (r = .26), insulin (r = .186), loop diuretics (r = .259), metformin (r = -.193), and thiazolidinediones (r = .182) were associated with renal insufficiency (see Table 32). Metformin was negatively associated with renal insufficiency (patients were less likely to be on metformin), while the association of beta blockers, loop diuretics, thiazolidinediones, and insulin was positively associated with renal insufficiency. All other medication classes were not associated with renal insufficiency. When GFR was estimated by MDRD, those identified as having CRI were more likely than were patients identified as not having CRI to be prescribed beta blockers, insulin, loop diuretics, and the thiazolindinediones. They were less likely to be prescribed metformin.

***Table 31*. Descriptives of medications associated with CRI estimated by MDRD**

Variable	**With CRI n (%)**	**Without CRI n (%)**	**Total n (%)**
ACEI n = 276	32 (50%)	88 (42%)	120 (44%)
Alpha blockers n = 271	4 (6%)	12 (6%)	16 (6%)
ARB n = 260	6 (10%)	15 (8%)	21 (8%)
ASA n = 278	24 (37%)	75 (35%)	99 (36%)
Beta blockers n = 270	32 (50%)	46 (22%)	78 (29%)
Calcium channel blockers n = 267	25 (40%)	70 (34%)	95 (36%)
Clopidogrel n = 268	6 (10%)	14 (7%)	20 (8%)
COX2 drugs n = 263	4 (7%)	33 (16%)	37 (14%)

Table 31. – **continued**

Variable	With CRI n (%)	Without CRI n (%)	Total n (%)
Insulin n = 274	18 (29%)	26 (12%)	44 (16%)
Iron n = 262	2 (3%)	9 (5%)	11 (4 %)
Loop diuretics n = 267	27 (44%)	37 (18%)	64 (24%)
Metformin n = 275	3 (5%)	48 (23%)	51 (19%)
NSAID n = 278	5 (8%)	21 (10%)	26 (9%)
SSRI n = 284	11 (18%)	40 (18%)	51 (18%)
Statin n = 276	31 (49%)	77 (36%)	108 (39%)
Sulfonylurea n = 272	10 (16%)	42 (20%)	52 (19%)
Thiazide diuretics n = 268	14 (24%)	55 (26%)	69 (26%)
thiazolidinediones n = 266	7 (13%)	6 (3%)	13 (5%)
Thyroid replacement hormone n = 278	8 (13%)	20 (9%)	28 (10%)
Warfarin n = 270	7 (11%)	13 (6%)	20 (7%)

***Table 32*. Medication classes associated with CRI estimated by MDRD**

Variable	X^2	df	p	Odds ratio
Beta blockers	18.198	1	.01	3.478
Insulin	9.503	1	.01	2.846
Loop diuretics	17.864	1	.01	3.627
Metformin	10.278	1	.01	.171
thiazolidinediones	8.844	1	.01	4.857

Table 33 provides the means and standard deviations for the laboratory variables within the database. Of the laboratory variables available for examination, only BUN, creatinine and hemoglobin were associated with renal insufficiency (see Table 34). Mean BUN and creatinine of patients with renal insufficiency identified with the MDRD formula were higher than they were for patients without renal insufficiency. Mean hemoglobin of patients with renal insufficiency was 12.466 (SD 1.7333). Mean hemoglobin of patients without renal insufficiency was lower than it was for patients without renal insufficiency. All other laboratory variables were not associated with renal insufficiency.

***Table 33*. Descriptives of laboratory variables associated with CRI by MDRD**

Variable	With CRI m (SD)	Without CRI m (SD)	Total m (SD)
BUN n = 294	28 (11)	16 (5)	19 (9)
Bicarbonate n = 283	26 (4)	27 (3)	27 (3)
Chloride n = 290	103 (4)	102 (3)	103 (4)
Creatinine n = 298	1.69 (1.04)	0.88 (0.20)	1.08 (0.67)
Glucose n = 251	134 (56)	122 (49)	124 (54)
HgbA1c n = 169	6.83 (1.75)	6.9 (1.73)	6.9 (1.7)
Hemoglobin n = 238	12.7 (1.7)	13.02 (1.7)	12.89 (1.7)
HDL n = 249	54 (15)	52 (18)	53 (17)
LDL n = 232	118 (39)	112 (40)	114 (40)
Potassium n = 292	4.3 (0.45)	4.3 (0.56)	4.3 (0.53)
Sodium n = 291	139 (3)	138 (3)	139 (3)
TSH n = 236	4.58 (13)	2.32 (5)	2.8 (8)

Table 33. – **continued**

Variable	With CRI m (SD)	Without CRI m (SD)	Total m (SD)
Total cholesterol n = 249	202 (48)	194 (49)	196 (49)
Triglycerides n = 250	136 (66)	154 (102)	151 (95)
WBC n = 198	7311 (2630)	6777 (2045)	6943 (2222)

***Table 34*. Descriptives of laboratory variables associated with CRI when estimated by MDRD**

Variable	t	df	p
Base Urea Nitrogen (BUN)	-12.518	292	.01
Creatinine	-11.048	296	.01
Hemoglobin	2.207	236	.03

Differences and commonalities of patients with CRI identified by CG and MDRD

As shown in Table 35, each of the estimation formulas includes age, gender, and serum creatinine. CG includes weight. MDRD includes Black race (yes/no). A total of 44 patients in the database were identified to have CRI by both estimation formulas. Table 36 provides a summary of variables associated with CRI by each formula.

***Table 35*. Variables included in estimating GFR**

CG	**MDRD**
Age	age
Gender	gender
Serum creatinine	Serum creatinine
Weight	Black (yes/no)

As expected, age was strongly associated with CRI regardless of method of estimation. In both formulas, increasing age is associated with decreasing GFR and increased risk of CRI. Gender, a variable in both estimation formula, should not still be significant in this analysis. It was when GFR was estimated by CG. This implies that the factor weight in the CG formula may be too small. The factor weighting for female gender within the CG equation was intended to compensate for smaller body size and muscle mass of women (Cockcroft, 1976). The original Cockcroft/Gault sample from which the equation was developed had only 4% (nine) women and may account for the misweighting of this factor.

African American race was significantly associated with CRI only when estimated by the Cockcroft/Gault formula. This reflects that in the MDRD formula, there is a factor for African American race, thus compensating for this racial identity.

In this dataset, Latino ethnic identity was significantly correlated with renal insufficiency, but it had a protective effect when the formula used to estimate GFR was MDRD or CG with measured body weight. Those patients of Latino identity were only .42 times as likely when

calculated by CG and .47 times as likely when calculated by MDRD as any other patient to experience CRI.

***Table 36*. Summary of variables associated with CRI by each formula**

	CG	**MDRD**
	n with CRI 68	n with CRI 69
Demographic variables	Age	age
	Gender	_
	African American race	_
	Latino ethnicity	Latino ethnicity
Functional variables	Dependence in cooking	Dependence in cooking
	Dependence in medication management	Dependence in medication management
	Dependence in shopping	Dependence in shopping
Physiologic variables	weight	_
	_	Diastolic BP
	LVH	-
Comorbidity variables	Chronic kidney disease	Chronic kidney disease
	Congestive heart failure	Congestive heart failure
	_	Coronary artery disease
	Dementia	_
	Diabetes	_

***Table 36*. – continued**

	CG	**MDRD**
	_	History of UTI
	_	Hypertension
Medication variables	ARB	_
	Beta blockers	Beta blockers
	_	Insulin
	_	Loop diuretics
	Metformin	Metformin
	_	Thiazolidinediones
Laboratory variables	BUN	BUN
	Creatinine	Creatinine
	HDL	_
	Hemoglobin	Hemoglobin

Dependence in cooking, shopping and medication management were each associated with the presence of CRI by both formula. These variables most likely reflect the physical frailty and disability that results as sequelae of the disease process. This is congruent with Odden (2006) and Fried (2006) who each separately found that frailty and functional impairments increase as eGFR decline.

The physiologic variables associated with GFRs indicating CRI were weight and diastolic blood pressure. Lower diastolic blood pressure was associated with patients with CRI estimated

by MDRD. Although this seems counterintuitive at first glance, patients' GFR is believed to be an end result of years of hypertension which providers may have been struggling to manage for many years. There may have been many years of uncontrolled hypertension prior to its recognition and treatment. Other studies have found that control of hypertension can slow the progression of CRI (Ostchega, Dillon, Hughes, Carroll, & Yoon, 2007).

Weight was significantly related to CRI but only by the CG formula. Weight is a variable in the Cockcroft/Gault formula, but not in the MDRD formula. In this sample, patients who had CRI identified by CG weighed, on average, 42 lbs less than patients without CRI. Again, understanding of this phenomena may be that weight loss is a consequence of the disease, rather than a cause. Multiple studies have found a strong relationship of high BMI or weight to risk of CKD (Chertow, Hsu, & Johansen, 2006; Ejerblad et al., 2006; Hsu, McCulloch, Iribarren, Darbinian, & Go, 2006; Johansen, Young, Kaysen, & Chertow, 2004).

Comorbid diseases and lifestyle habits such as smoking status and recreation were examined which are often associated with renal insufficiency. As shown in Table 23, the data revealed different associations according to the formula used to estimate GFR. The Cockcroft/Gault formula tended to identify patients with fewer comorbid diseases (n = 4) than did the MDRD (n = 5). This is also consistent with new information that suggests CG produces a more conservative estimate of GFR, thus identifying patients with CRI that might otherwise be missed (Melloni, 2008). CRI by both formulas was significantly associated with a diagnosis of CKD. The providers who cared for these patients were appropriately recognizing renal insufficiency in their patients. Both formulas also were associated with congestive heart failure

which has been observed in other studies (National Kidney Foundation, 2007) and is part of the model of CKD.

Dementia and diabetes were significantly associated with CRI when estimated by CG. Each comorbidity is also often associated with weight and may be the reason for the association when CRI is computed by CG, a formula that uses weight in its estimation of GFR. CRI by MDRD was significantly associated with coronary artery disease, history of UTI, and hypertension. MDRD. This is may occur because of the study population used to develop the MDRD formula who had known kidney disease (Levey, 1999).

In this database, patients identified by the CG formula as having CRI had fewer associated medications. This also fits with other information (Melloni, 2008) that the CG formula is more conservative and identifies patients earlier in the disease trajectory.

There were only three medications associated with CRI identified by CG. They were angiotensin receptor blockers, beta blockers, and metformin. This reflects that even though the diagnoses of hypertension and diabetes were not associated with CRI identified by CG, the medications used to manage these conditions were associated. Both metformin ($r = -.223$) and ARBs ($r = -.126$) were negatively associated with CRI, indicating that patients with CRI identified by CG were less likely to be on these drugs than patients without CRI identified by CG. Beta blocker drugs were weakly correlated with CRI identified by CG ($r = .122$). Clinicians know that beta blocker drugs are first line drugs recommended by JNC 7 for initial management of hypertension and that they are not metabolized in the kidney(Bakris, Hart, & Ritz, 2006; Chobanian et al., 2003).

Five drugs were associated with CRI identified by MDRD. They were beta blockers (r = .26), insulin (r = .17), loop diuretics (r = .26), metformin (r = -.19), and thiazolidinediones (r = .18). As with CRI identified by CG, the correlation with metformin was negative. This reflects clinician awareness of renal status and avoidance of this medication which can be unsafe when used in patients with CRI. All other associations were mild to moderate positive associations with CRI identified by MDRD. These drug classes are all used to treat the common comordid conditions of hypertension or diabetes. The medications are all very appropriate in the way they are being used with patients with CRI with the one questionable use of thiazolidinediones. In recent years, clinicians have learned through post marketing surveillance that this class of medications can cause fluid retention in some patients (Macfarlane and Fisher, 2006). Careful monitoring and judicious patient selection are indicated.

The laboratory variables associated with CRI identified by the formulas were very similar. Both formula identified BUN, creatinine and hemoglobin as significantly associated. BUN and creatinine rise with CRI (McCance and Heuther, 2006) and hemoglobin declines as the kidney declines in function. Only the CG identified HDL as significantly associated. The mean HDL of patients with CRI was actually higher than in patients without CRI, which is counterintuitive. The significance of this difference is unknown. HDL levels have not been associated with renal disease in previous study. HDL levels are unrelated to the function of the kidney. Further work needs to be done to determine if this result can be replicated.

Exploration of data

A large portion of patients in the database (65%) were either overweight or obese when classified by BMI category (see Figure 7). According to data published on the CDC website

derived from NHANES data, 33% of the overall American population can be classified as obese. In this sample, 41% were obese. Because a large portion of this sample was either overweight or obese, GFR was also estimated using CG and ideal body weight. In their original publication, Cockcroft and Gault (1976) recommended that for patients who are obese, use of ideal body weight might produce a more reliable estimate of GFR especially in older, overweight patients.

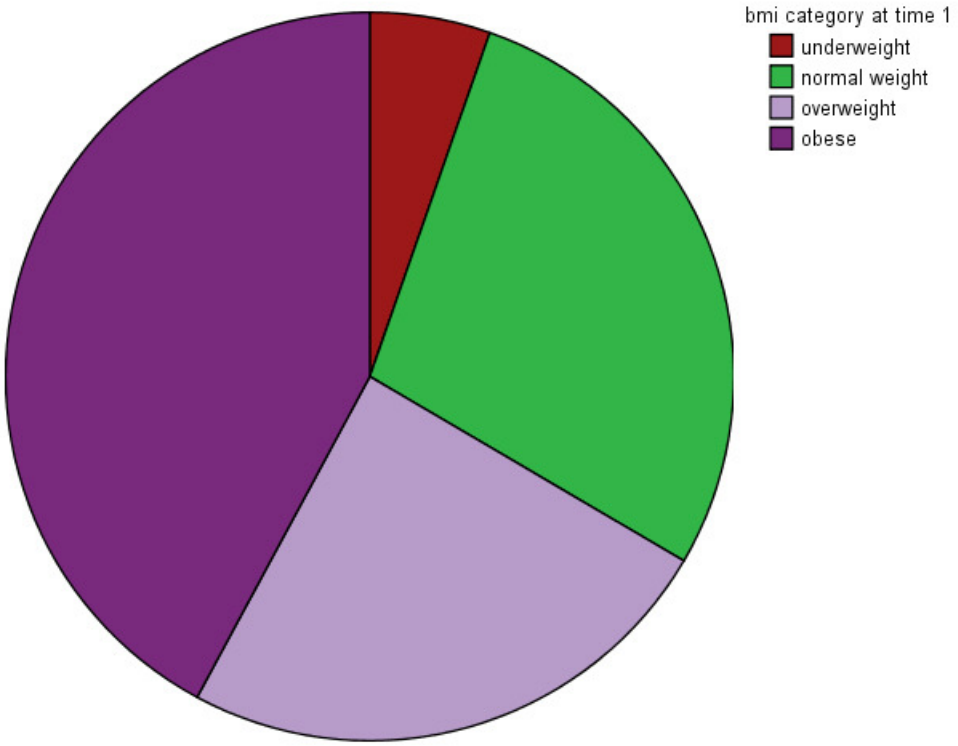

Figure 7. BMI categories of the sample

When the GFRs derived from each formula were compared, estimates from CG IBW were highly correlated with estimates from the MDRD (r = .89). The correlation between eGFRs from CG IBW and CG using measured body weight were moderate with r = .75. The lowest

correlation occurred between eGFRs from the CG using measured body weight and MDRD (r = .61).

GFR estimated by CG using IBW was least likely to underestimate GFR. The implication of this finding is that GFR using ideal body weight may be the most conservative way of estimating GFR, especially in older, overweight patients. When height is measured, Cockcroft/Gault estimation using ideal body weight based on height yielded significantly different estimated GFR which correlates more closely to the estimate by MDRD (Daniel, 2008).

Characteristics of patients who experience rapid declines in GFR identified by CG and MDRD formulas

Rapid decline in eGFR estimated by Cockcroft/Gault

Rapid decline in GFR was calculated by subtracting the eGFR estimated on entry into the study from the same patients eGFR calculated from data collected at 2 years after entry into the study. Patients who had 20cc or more decline in the two year study period were considered to have rapid decline. Characteristics of patients on entry into the database who did experience this rapid decline were then compared with patients who did not experience a rapid decline. all data reported below were obtained at the time of entry into the study (the visit to the clinic dietician).

Only 37 patients (12%) of the total sample experienced a decline of 20cc or more in estimated GFR by Cockcroft/Gault. As shown in Table 37, those with rapid decline in GFR were 51% African American and 43% Latino. The sample of patients with rapidly declining eGFR by CG was 84% female and 16% male (see Table 38). The mean amount of change of all patients when estimated by CG was eight cc of change (SD 37) over the two year study period. The mean amount of change of patients with rapidly declining eGFR by CG was 50 cc of change (SD 80).

This small group of patients had a mean age of 72 (SD 7) and was not statistically different in age from those patients who did not experience a rapid decline in GFR. The only significantly associated variable with rapid decline estimated by CG was Latino ethnicity. There was a weak positive relationship of $r = .172$ indicating that Latino patients were more likely to experience rapid decline than any other racial or ethnic group.

***Table 37*. Racial distribution among patients with rapid decline estimated by CG**

Race	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
African American	19 (51%)	120 (60%)	139 (59%)
Caucasian	1 (3%)	23 (12%)	24 (10%)
Latino	16 (43%)	45 (27%)	61 (26%)
Indian/Pakistani	1 (3%)	2 (1%)	3 (1%)
Asian/Pacific Islander	0	4 (2%)	4 (2%)
Native American	0	1 (<1%)	1 (<1%)
Other	0	4 (2%)	4 (2%)
Totals	37 (100%)	199 (100%)	236 (100%)

Table 38. **Gender distribution among patients with rapid decline by CG**

Gender	With rapid decline n (%)	Without rapid decline n (%)	Total n (%)
Women	31 (84%)	145 (73%)	176 (74%)
Men	6 (16%)	55 (28%)	61 (26%)
Totals	37 (100%)	200 (100%)	237 (100%)

As shown in Table 39, a larger proportion of patients with a rapid decline in GFR were dependent in IADLs than were those without rapid decline. Table 40 shows the recreational activities of these patients. Functional variables associated with rapid decline in eGFR by CG were dependence in cooking and dependence in shopping (see Table 41). There was an association of patients who indicated they walked for recreation upon entry into the study as well as an association of patients who did not note any type of recreational activity. The association with walking was a negative association (r = - .176) possibly meaning that walking had a modest protective effect. The association of patients who did not note any activity at all was positive at *r* = .214.

***Table 39*. IADLs in patients who experienced rapid decline estimated by CG**

Functional variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Dependent in cooking	19 (53%)	61 (31%)	80 (35%)
Dependent in medication management	6 (17%)	24 (14%)	30 (14%)
Dependent in shopping	22 (61%)	73 (40%)	95 (43%)

***Table 40*. Recreational activities of patients who experienced a rapid decline estimated by CG**

Recreational activities	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Senior center	1 (3%)	6 (3%)	7 (3%)
Walks for recreation	3 (8%)	53 (28%)	56 (25%)
None noted	30 (83%)	106 (57%)	136 (61%)
"other" recreation	2 (6%)	22 (12%)	24 (11%)
Totals	36 (100%)	187 (100%)	223 (100%)

***Table 41*. Functional variables associated with rapid decline estimated by CG**

Functional variables	X^2	df	p	Odds ratio
Dependent in cooking	6.093	1	.02	2.437
Dependent in shopping	5.764	1	.02	2.411
Walks for recreation	5.853	1	.02	.245
No recreation noted	10.068	1	.002	3.801

When the physiologic variables upon entry into the study were examined, patients with rapid decline in GFR estimated by CG over the subsequent two year period were more likely to weigh more, have a higher BMI, be shorter and have higher systolic and diastolic blood pressure than were patients who did not experience a rapid decline (see Table 42). Physiologic variables upon entry into the study associated with rapid decline in eGFR by CG were BMI, diastolic blood pressure, height, and weight. There was no association with left ventricular hypertrophy or systolic blood pressure.

***Table 42*. Means and standard deviations of physiologic variables associated with rapid decline estimated by CG**

Physiologic variables	With rapid decline m (SD)	Without rapid decline m (SD)	Total m (SD)
BMI n = 235	36 (12)	28 (7)	29 (9)
Diastolic blood pressure n = 235	78 (16)	74 (10)	75 (11)

Table 42. – **continued**

Physiologic variables	**With rapid decline m (SD)**	**Without rapid decline m (SD)**	**Total m (SD)**
Height n = 235	63 (3)	65 (4)	64 (4)
Systolic blood pressure n = 235	148 (23)	145 (24)	145 (24)
Weight n = 237	200 (70)	169 (47)	172 (52)

Table 43. **Physiologic variables associated with rapid decline estimated by CG**

Physiologic variables	***t***	**df**	**p**
BMI	-4.935	233	.000
Diastolic blood pressure	-1.700	235	.001
Height	2.170	233	.031
Weight	-3.423	235	.001

When comorbid disease variables were examined, patients with rapid decline in GFR estimated by CG over the subsequent two year period were more likely to have a history of lower urinary tract problems than patients without rapid decline. Variables associated with rapid decline in eGFR by CG were very few (see Table 45). Only nephrolithiasis and history of UTIs

revealed any association with rapidly declining eGFR by CG. Neprolithiasis had a weak correlation with rapid deline at $r = .240$. History of UTIs had an even weaker relationship at $r = .152$. No other variables had any relationship to rapid decline when eGFR was estimated by CG.

***Table 44*. Percentage of comorbid diagnosis occurrence in patients with rapid decline when estimated by CG**

comorbid variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Atrial fibrillation	2 (6%)	11 (6%)	13 (6%)
BPH	1 (3%)	11 (6%)	12 (6%)
Cancer	3 (8%)	15 (9%)	18 (9%)
Chronic kidney disease	0	12 (7%)	12 (6%)
Cirrhosis	0	2 (1%)	2 (1%)
Congestive heart failure	5 (14%)	21 (11%)	26 (12%)
Coronary artery disease	3 (10%)	33 (19%)	36 (18%)
Dementia	2 (6%)	21 (12%)	23 (11%)
Diabetes	18 (50%)	88 (49%)	106 (49%)

Table 44. – **continued**

comorbid variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Gout	3 (9%)	7 (4%)	10 (5%)
Hepatitis C	0	1 (<1%)	1 (<1%)
History of smoking	11 (37%)	40 (24%)	51 (26%)
History of UTIs	3 (8%)	3 (2%)	6 (3%)
Hypertension	28 (78%)	150 (77%)	178 (77%)
Medication nonadherence	4 (13%)	17 (10%)	21 (11%)
Nephrolithiasis	2 (7%)	0	2 (1%)
Peripheral vascular disease	2 (6%)	6 (3%)	8 (4%)
Smoker, current	5 (19%)	21 (81%)	26 (12%)
Transient ischemic attack or stroke	7 (21%)	17 (10%)	24 (11%)

***Table 45*. Diagnostic and comorbid variables associated with rapid decline in GFR when estimated by CG**

Diagnostic and comorbid variables	X^2	**df**	**p**	**Odds ratio**
History of UTIs	5.018	1	.03	5.425
Nephrolithiasis	11.715	1	.001	1.071

When medications were examined which were prescribed to patients before they experienced a rapid decline in estimated GFR by CG, there were multiple medications of interest (see Table 46). The most prescribed medication to patients who experienced a rapid decline was ACEI (60%). The second most prescribed medication was ASA (52%). Medication variables that were associated with rapid decline in eGFR by CG were ACEI, aspirin, iron supplements, and loop diuretics (see Table 47). The association of rapid decline in eGFR estimated by CG with ACEI was weak at $r = .141$, aspirin was $r = .161$, iron was $r = .141$, and loop diuretics was strongest at $r = .171$.

***Table 46*. Medication descriptives associated with rapid decline in eGFR when estimated by CG**

Medication variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
ACEI n = 218	21 (60%)	75 (41%)	96 (44%)
Alpha blockers n = 214	0	14 (8%)	14 (7%)
ARB n = 202	3 (10%)	13 (8%)	16 (8%)
ASA n = 218	17 (52%)	56 (30%)	73 (34%)
Beta blockers n = 214	8 (23%)	50 (28%)	58 (27%)
Calcium channel blockers n = 214	15 (44%)	57 (32%)	72 (34%)
Clopidogrel n = 211	4 (13%)	10 (6%)	14 (7%)
COX2 drugs n = 204	5 (16%)	26 (15%)	31 (15%)

Table 46. – **continued**

Medication variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Insulin n = 216	7 (19%)	25 (14%)	32 (15%)
Iron n = 203	3 (9%)	4 (2%)	7 (3%)
Loop diuretics n = 211	13 (39%)	35 (20%)	48 (23%)
Metformin n = 216	6 (19%)	34 (18%)	40 (19%)
NSAID n = 219	2 (5%)	18 (10%)	20 (9%)
SSRI n = 225	8 (22%)	30 (16%)	38 (17%)
Statin n = 217	11 (33%)	73 (40%)	84 (39%)
Sulfonylurea n = 215	10 (29%)	33 (18%)	43 (20%)
Thiazide n = 209	8 (24%)	49 (28%)	57 (27%)
thiazolidinediones n = 208	0	10 (6%)	10 (5%)
Thyroid replacement hormone n = 217	5 (15%)	16 (9%)	21 (10%)
Warfarin n = 212	1 (3%)	11 (6%)	12 (6%)

***Table 47*. Medication variables associated with rapid decline in GFR when estimated by CG.**

Medication variables	X^2	Df	p	Odds ratio
ACEI	4.311	1	.04	2.160
ASA	5.675	1	.02	2.448
Iron	4.008	1	.045	4.319
Loop diuretics	6.167	1	.013	2.656

When laboratory variables of patients at the beginning of the study period were examined, there was very little difference in any variables that was associated with rapid decline (see Table 48). The laboratory variables associated with rapid decline in eGFR estimated by CG were bicarbonate (t = -1.990; df = 224; p = .05) and creatinine (t = 1.995; df = 235; p = .05). These laboratory values represent the patients' initial values at the beginning of the two year study period.

***Table 48*. Descriptives of laboratory variables associated with rapid decline in GFR when estimated by CG**

Laboratory variables	With rapid decline m (SD)	Without rapid decline m (SD)	Total m (SD)
BUN n = 233	17 (6)	19 (9)	19 (9)
Bicarbonate n = 226	27 (3)	26 (3)	27 (3)
Chloride n = 230	102 (3)	103 (4)	103 (4)

Table 48. – **continued**

Laboratory variables	**With rapid decline m (SD)**	**Without rapid decline m (SD)**	**Total m (SD)**
Creatinine n = 237	0.89 (.24)	1.12 (0.72)	1.08 (0.67)
Glucose n = 198	131 (66)	124 (51)	124 (54)
HgbA1c n = 141	7.22 (1.70)	6.78 (1.79)	6.9 (1.72)
Hemoglobin n = 185	13.0 (1.6)	12.9 (1.6)	12.9 (1.68)
HDL n = 200	52 (16)	53 (18)	53 (17)
LDL n = 185	122 (37)	113 (41)	114 (40)
Potassium n = 231	4.22 (0.41)	4.34 (0.58)	4.30 (0.53)
Sodium n = 230	139 (3)	138 (3)	139 (3)
TSH n = 185	4.38 (16)	2.29 (2.3)	2.79 (7.8)
Total cholesterol n = 200	208 (44)	194 (47)	196.28 (49)
Triglycerides n = 200	169 (123)	145 (83)	151 (95)
WBC n = 196	7350 (1652)	6850 (2299)	6943 (2222)

Characteristics of patients who experience rapid decline in GFR identified by MDRD formula

When patient characteristics present at the start of the study period were examined who experienced a rapid decline according to estimates produced by the MDRD formula, there were 23 patients. There was no significant difference in age between those who experienced a decline and those who did not. The patients who experienced the rapid decline were 74% female and 26% male (see Table 49).

When racial characteristics of the patients who experienced rapid decline estimated by MDRD were examined, they were 52% African American and 48% Latino (see Table 50). No other racial or ethnic groups were part of the patients identified with rapid decline by MDRD. The mean amount of change in eGFR in the group who experienced rapid decline was 31 cc of change (SD11). The only demographic variable to be significantly associated with rapid decline when eGFR was estimated by MDRD was Latino ethnic identity ($X^2 = 6.966$; df = 1; p = .008). The association was weak at $r = .168$.

***Table 49*. Gender distribution of patients who experienced a rapid decline in GFR when estimated by MDRD**

	With rapid decline n (%)	**Without rapid decline n (%)**	**Total n (%)**
Women	17 (74%)	171 (76%)	188 (76%)
Men	6 (26%)	53 (24%)	59 (24%)
Totals	23 (100%)	224 (100%)	247 (100%)

***Table 50*. Racial characteristics of patients with rapid decline in GFR when estimated by MDRD**

Race	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
African American	12 (52%)	133 (60%)	145 (59%)
Caucasian	0	27 (12%)	27 (11%)
Latino	11 (48%)	51 (23%)	62 (25%)
Indian/Pakistani	0	3 (1%)	3 (1%)
Asian/Pacific Islander	0	4 (2%)	4 (2%)
Native American	0	1 (<1%)	1 (<1%)
Other	0	4 (2%)	4 (2%)
Totals	23 (100%)	223 (100%)	246 (100%)

Functional variables associated with rapid decline in eGFR estimated by MDRD included the IADLs of dependency in cooking, medication management, and shopping (see Table 51). Dependency in cooking was strongest at $r = .210$, dependency in medication management was $r = .152$, and dependency in shopping was $r = .196$. Dependency in all IADLs at the start of the study period was significantly associated with rapid decline estimated by MDRD (see Table 53).

Table 51. **IADLs in patients with rapid decline in GFR when estimated by MDRD**

Functional variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Dependent in cooking	15 (65%)	68 (31%)	83 (35%)
Dependent in medication management	7 (32%)	27 (14%)	34 (15%)
Dependent in shopping	16 (73%)	83 (40%)	99 (43%)

When recreational participation was examined, the preponderance of patients did not report any recreational activity (see Table 52). Ninety-six percent of the sample who experienced a rapid decline estimated by MDRD reported no recreational activity at the start of the study period. Patients with rapid decline did not report attending a senior center or walking. Once again, patients who reported walking had a mildly protective effect at $r = -.176$, while no activity noted was positively associated at $r = .214$.

Table 52. **Recreational activity of patients with rapid decline in GFR when estimated by MDRD**

	With rapid decline n (%)	**Without rapid decline n (%)**	**Total n (%)**
Senior center	0	8 (4%)	8 (3%)
Walks for recreation	0	57 (27%)	57 (25%)
None noted	21 (96%)	123 (59%)	144 (62%)
"other" recreation	1 (5%)	22 (11%)	23 (10%)
Totals	22 (100%)	210 (100%)	232 (100%)

***Table 53*. Functional variables associated with rapid decline in GFR when estimated by MDRD**

Functional variables	X^2	df	p	Odds ratio
Dependent in cooking	10.552	1	.002	4.108
Dependent in shopping	8.859	1	.003	4.048
Dependent in medication management	5.128	1	.024	2.990
Walks for recreation	7.608	1	.006	.746
No recreation noted	11.364	1	.001	8.622

A very different picture of associated variables emerges when physiologic variables are examined for association with rapid decline in eGFR estimated by MDRD. In contrast to the CG, when multiple variables exhibited an association, there were no physiologic variables associated with rapid decline of eGFR estimated by MDRD (see Table 54). No echocardiographic findings were associated with rapid decline estimated by the MDRD formula.

***Table 54*. Physiologic variables associated with rapid decline in GFR when estimated by MDRD**

Physiologic variables	With rapid decline m (SD)	Without rapid decline m (SD)	Total m (SD)
BMI n = 244	30 (8)	29 (9)	29 (9)
Diastolic blood pressure n = 245	76 (12)	75 (11)	75 (11)
Height n = 245	63 (3)	64 (4)	64 (4)

Table 54. **– continued**

Physiologic variables	**With rapid decline m (SD)**	**Without rapid decline m (SD)**	**Total m (SD)**
Systolic blood pressure n = 245	142 (19)	146 (24)	145 (24)
Weight n = 246	169 (47)	173 (54)	172 (52)

When comorbid variables from the start of the study period of patients who experienced a rapid decline by MDRD were examined, the most common comorbid diagnoses was hypertension (83%), followed by diabetes (39%) (See Table 55). Diagnostic and comorbid variables associated with rapid decline in eGFR estimated by MDRD included atrial fibrillation, dementia, gout, and history of smoking (see Table 56). Atrial fibrillation had a weak positive association with rapid decline in eGFR by MDRD with $r = .143$; dementia was $r = .142$, gout was $r = .153$, and history of smoking was a stronger negative association at $r = -.224$.

Table 55. **Comorbid diagnoses of patients when rapid decline in GFR estimated by MDRD**

Diagnostic and comorbid variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Atrial fibrillation	4 (17%)	11 (6%)	15 (7%)
BPH	1 (5%)	11 (6%)	12 (6%)
Cancer	1 (5%)	19 (10%)	20 (9%)

Table 55. – **continued**

Diagnostic and comorbid variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Chronic kidney disease	0	13 (7%)	13 (6%)
Cirrhosis	0	1 (<1%)	1 (<1%)
Congestive heart failure	5 (24%)	24 (12%)	29 (13%)
Coronary artery disease	5 (23%)	33 (18%)	38 (18%)
Dementia	6 (26%)	21 (11%)	27 (12%)
Diabetes	9 (39%)	103 (51%)	112 (50%)
Gout	3 (14%)	7 (3%)	10 (4%)
Hepatitis C	0	1 (<1%)	1 (<1 %)
History of smoking	11 (55%)	41 (22%)	52 (25%)
History of UTIs	1 (5%)	5 (2%)	6 (3%)
Hypertension	19 (83%)	169 (78%)	188 (78.3%)
Medication nonadherence	2 (11%)	21 (11%)	23 (11%)
Nephrolithiasis	1 (5%)	1 (<1%)	2 (<1%)
Peripheral vascular disease	1 (4%)	8 (4%)	9 (4%)
Smoker, current	3 (13%)	21 (88%)	24 (11%)
Transient ischemic attack or stroke	5 (22%)	23 (12%)	28 (13%)

***Table 56*. Diagnostic and comorbid diagnoses associated with rapid decline in GFR when estimated by MDRD**

Diagnostic and comorbid variables	X^2	df	p	Odds ratio
Atrial fibrillation	4.433	1	.035	3.522
Dementia	4.396	1	.036	2.908
Gout	5.282	1	.022	4.690
History of smoking	10.280	1	.005	.233

Table 57 presents the prevalence of medication classes prescribed to patients who experienced rapid decline in GFR when estimated by MDRD. There was only one medication variable associated with rapid decline in eGFR estimated by MDRD which was iron (X^2 = 4.789; df = 1; p = .029). The relationship was weak at r = .150.

***Table 57*. Medications prescribed to patients who experienced rapid decline in GFR when estimated by MDRD**

Medication variables	With rapid decline n (%)	Without rapid decline n (%)	Total n (%)
ACEI n = 227	14 (61%)	86 (42%)	100 (44%)
Alpha blockers n = 222	0	14 (7%)	14 (6%)
ARB n = 212	1 (5%)	18 (9%)	19 (9%)
ASA n = 228	9 (39%)	73 (36%)	82 (36%)
Beta blockers n = 222	8 (36%)	54 (27%)	62 (28%)

Table 57. **– continued**

Medication variables	**With rapid decline n (%)**	**Without rapid decline n (%)**	**Total n (%)**
Calcium channel blockers n = 221	8 (36%)	66 (33%)	74 (34%)
Clopidogrel n = 219	2 (9%)	13 (7%)	15 (7%)
COX2 drugs n = 215	2 (10%)	31 (16%)	33 (15%)
Insulin n = 226	1 (4%)	33 (16%)	34 (15%)
Iron n = 213	3 (14%)	7 (4%)	10 (5%)
Loop diuretics n = 221	6 (26%)	45 (23%)	51 (23%)
Metformin n = 226	4 (17%)	40 (20%)	44 (20%)
NSAID n = 229	1 (4%)	20 (10%)	21 (9%)
SSRI n = 235	4 (18%)	37 (17%)	41 (17%)
Statin n = 226	6 (28%)	81 (40%)	87 (39%)
Sulfonylurea n = 224	6 (26%)	38 (19%)	44 (20%)
Thiazide n = 218	6 (26%)	53 (27%)	59 (27%)
Thiazolidinediones n = 219	0	11 (6%)	11 (5%)
Thyroid replacement hormone n = 227	2 (9%)	22 (11%)	24(11%)
Warfarin n = 221	2 (9%)	11 (6%)	13 (6%)

When initial study laboratory variables were examined, patients who experienced rapid decline when estimated by MDRD were very similar to patients who did not experience rapid decline (see Table 58). Only creatinine was associated with rapid decline in eGFR estimated by MDRD ($t = 2.174$; $df = 245$; $p = .03$). The mean value of creatinine of patients identified with rapid decline by MDRD was lower than the mean value of creatinine of patients without rapid decline.

***Table 58*. Laboratory variables of patients who experienced a rapid decline in GFR when estimated by MDRD**

Laboratory variables	**With rapid decline m (SD)**	**Without rapid decline m (SD)**	**Total m (SD)**
BUN n = 243	17 (5)	19 (9)	19 (9)
Bicarbonate n =235	27 (3)	27 (3)	27 (3)
Chloride n = 240	102 (4)	103 (4)	103 (4)
Creatinine = 247	0.79 (.22)	1.10 (.69)	1.08 (0.67)
Glucose n = 206	116 (39)	126 (53)	124 (54)
HgbA1c n = 144	7.3 (1.5)	6.8 (1.79)	6.90 (1.7)
Hemoglobin n = 193	12.8 (1.5)	12.9 (1.6)	12.9 (1.7)
HDL n = 206	55 (19)	53 (17)	53 (17)

Table 58. – **continued**

Laboratory variables	**With rapid decline m (SD)**	**Without rapid decline m (SD)**	**Total m (SD)**
LDL n = 191	114 (37)	114 (40)	114 (40)
Potassium n = 241	4.3 (0.37)	4.3 (0.57)	4.3 (0.5)
Sodium n = 240	138 (4)	139 (3)	139 (3)
TSH n = 195	1.6 (1.4)	2.8 (7.4)	2.8 (7.7)
Total cholesterol n = 206	203 (46)	197 (46)	196 (49)
Triglycerides n = 206	172 (157)	147 (84)	151 (95)
WBC n = 207	7410 (1628)	6845 (2240)	6943 (2222)

Summary of Variables Associated with Rapid Decline

The variables associated with rapid decline of eGFR when estimated with each formula are presented in Table 59. Variables common to each and positively associated with decline were dependence in cooking, dependence in shopping, having no recreation, receiving iron supplementation, and having low creatinine levels. The only variable negatively associated with rapid decline with both formulas was walking for recreation.

***Table 59*. Variables associated with rapid decline in GFR by each formula**

Variable	**CG**	**MDRD**
Demographic variables	-	-
Functional variables	Dependent in cooking	Dependent in cooking
	Dependent in shopping	Dependent in shopping
	-	Dependent in medication administration
	Walks for recreation	Walks for recreation
	No recreation noted	No recreation noted
Physiologic variables	BMI	-
	Diastolic blood pressure	-
	Height	-
	Weight	-
	CG	MDRD
	Nephrolithiasis	
	-	Atrial fibrillation
	-	Dementia
	-	Gout
	-	History of smoking

Table 59. **– continued**

Variable	**CG**	**MDRD**
Medication variables	Angiotensin Converting Enzyme Inhibitors	-
	ASA	-
	Iron	Iron
	Loop diuretics	-
	Bicarbonate	-
	Creatinine	Creatinine

When logistic regression was applied to the variables present upon entry into the study associated with rapid decline in GFR by CG over the two year study period, the resulting model suggested that bicarbonate, creatinine, dependence in cooking and dependence in shopping, as well as iron were predictive of rapid decline estimated by CG. The overall model is significant at the .008 level according to the model of chi-square statistic. The model predicts 85% of the variance. The Nagelkerke R^2 is .143.

When logistic regression was applied to the variables present upon entry into the study associated with rapid decline in GFR by MDRD over the two year study period, the resulting model suggested that bicarbonate, creatinine, dependence in cooking, and iron were predictive of rapid decline in GFR. The overall model is significant at the .001 level according to the model of chi-square statistic. The model predicts 91% of the variance. The Nagelkerke R^2 is .292.

The fact that both of these models are very similar and are based on functional and laboratory variables as well as a common supplement, from variables all present at the start of

the study period, suggests more study needs to be undertaken to better understand the initiating conditions that set the stage for a rapid decline in renal function. Why did otherwise healthy patients, before they had a rapid decline in renal function, need to take an iron supplement?

Summary of Results

Characteristics of patients with CRI

Age

Advancing age was significantly associated with decreasing GFR and increasing risk of CRI by both formulas. This is expected given documented decline associated with age (Lindeman & Goldman, 1986).

Gender

With CG, females were more likely than males to have CRI. No difference was associated with gender when estimated by MDRD. The study sample from which the Cockcroft/Gault formula was derived had only 4% women. The percent of women in this study sample was 74%. Because the Cockcroft/Gault formula includes a weighted factor for female gender and there were so few women in the Cockcroft/Gault study sample, perhaps this formula should be revisited with a larger sample of women in hopes of improving its sensitivity.

Race

With CG there is no variable for race, yet there are documented differences in creatinine production and excretion when race and national origin are examined that cannot be explained by muscle mass (Hsu, Johansen, Hsu, Kaysen and Chertow, 2008). With MDRD only one race is included in the formula. Other races besides “Black” also have demonstrated differences in

creatinine that can affect formula estimates (Rodriguez, Hernandez, O'Hare, Glidden, and Perez-Stable, 2004).

Functional status

Physical frailty appears to be significantly associated with CRI as estimated by both formulas. The phenomena of physical frailty and disability have been observed in patients with CRI by others (Odden, 2006; Fried, 2006). This is not surprising considering the mild anemia that can occur with CRI which can lead to fatigue and deconditioning.

Physiologic variables

Weight was significantly related to CRI, but only when the CG formula was used. In this database, patients who had CRI identified by CG weighed, on average, 42 lbs less than patients without CRI. In this database 41% of the patients in the study were obese. According to data published on the CDC website derived from NHANES data, 33% of the overall American population can be classified as obese. There is a growing body of evidence that obesity is linked to CRI (Ejerblad, 2006; Chertow, 2006).

Because the CG formula includes weight as a proxy for muscle mass, it is subject to unreliability as relative body compartment proportions become distorted in conditions such as obesity or severe sarcopenia that occurs when patients are dependent in all ADLs. The proportion of muscle/lean mass to adipose tissue is not normal. Use of ideal body weight rather than measured body weight with estimates of GFR by CG should be considered in obese patients. In patients who are severely debilitated, but not overweight the decision of which formula to use is dependent on available information about the patient, such as height. When height and/or weight are not available, the MDRD formula can be substituted. The MDRD

however is not as sensitive for the identification of CRI and tends to identify patients later in the trajectory of their disease. Results suggest use of IBW when using CG.

Comorbid diseases

CRI by both formulas was significantly associated with CHF and CKD. These conditions are parallel on the national kidney foundation's model for chronic kidney disease (National Kidney Foundation, 2007). An inability to manage fluid volumes in either the heart or the kidney affects the ability of other organs to do so as well.

Additionally, the CG formula was also associated with dementia and diabetes. Severe LVH on echocardiogram was associated with CRI only by CG.

The MDRD had three additional diagnoses which were significantly associated with CRI which were CAD, history of UTI and hypertension. It is unclear why CAD and hypertension are not identified by both formulas.

Medications

Beta blockers were significantly positively associated with CRI by both formulas. This is not surprising since beta blockers are a first line recommendation of JNC7 for hypertension and the drug class is not metabolized in the kidney. Metformin was also significantly negatively associated with both formulas. Metformin is specifically not recommended for use in patients with CKD because of the risk of potentially life threatening complications associated with its use when renal function is compromised. If clinicians are aware of compromised renal function, beta blocker drugs may be their first choice. Likewise, with metformin, because clinicians know of the potential serious adverse drug effect that it can have in the setting of renal insufficiency, careful monitoring of renal function of patients on metformin is required.

ARBs were also significantly negatively associated with CRI identified CG. ARBs function in the renin-angiotensin system of the kidney and because of their site of action, use in CKD is controversial.

Insulin, loop diuretics and thiazolidinediones were uniquely positively associated with the MDRD formula. Loop diuretics are most often used in management of hypertension and CHF. Both of these diagnoses are associated with this formula. Insulin and TZDs are used to manage diabetes, which was not associated with the MDRD formula, but was associated with the CG formula. The most common form of diabetes is diabetes mellitus type 2 which often has an insidious and subtle presentation in maturity. It is by far the most common form of diabetes in the elderly. The usual management of diabetes is with oral agents until they are unable to manage the hyperglycemia. Insulin is added after the diagnosis has been established and oral agents are no longer effective. The presence of insulin associated with the MDRD formula and not the CG formula implies that patients identified by the MDRD formula may have had the diagnosis of diabetes longer. TZDs are also a medication used to manage diabetes, often as an adjunct to other medications. It is not clear why this medication has an association to CRI since one of the possible side effects can be fluid retention and aggravation of CHF. Since these side effects have only come to light in the last few years, it is possible that clinicians were unaware of the potential side effects of the medication when they were on the drug at the start of the study period.

Laboratory variables

BUN, creatinine, and hemoglobin were positively associated with CRI by both formulas. This is expected due the build up of unexcreted creatinine and BUN in the serum as the kidney

declines in its abilty to filter these wasteproducts. Erythropoesis is the result of the stimulation of erythropoietin on the bone marrow. As the kidney declines in function, it produces less erythropoietin as well, which will eventually negatively impact hemoglobin.

HDL was associated with CRI only when estimated by CG. The level of HDL in patients with CRI identified by CG was higher (57) than patients without CRI (51). Low HDL, defined as less than 40 in women or 50 in men by the ATEP 3, is an independent risk factor for heart disease, so an explanation for this association is not clear and requires further study. In contrast, a recent study from China found an association of CRI to low HDL, defined as less than 40 ((Zhang et al., 2008).

Characteristics of those with Rapid decline

Latino race

Latino ethnic identity was significantly positively associated with rapid decline by both formulas. A possible explanation for this is the prevalence of obesity within this cultural group. Obesity is an independent predictor of CRI, but could also obscure the early identification of CRI if the CG formula using measured body weight is used to estimate GFR.

Variables that predict

Two functional variables were common to both estimation formulas, dependence in cooking and shopping. Both of these activities require more physical and cognitive stamina than medication administration. It is significant that the physical frailty revealed in dependence in these IADLs is present before the rapid decline has occurred. Walking for recreation prior to the onset of rapid decline is negatively associated with rapid decline and no recreation was positively

associated with decline. Are patients with less functional reserve more vulnerable to a rapid decline in renal function?

Iron supplementation was part of both prediction models. Bansal and colleagues (2007), in seeking an answer to the relationship of CKD, anemia and heart failure, studied data from the SOLVED trial and concluded that anemia is associated with a rapid decrease in kidney function in patients with heart failure (Bansal et al., 2007).

The final variable that was part of both models is bicarbonate. The relevance of this finding suggests that perhaps these patients had a relative fluid volume deficit or were mildly and chronically dehydrated at the start of the study period. Fluid issues in the setting of anemia requiring iron supplementation could be the scenario described by the model.

CHAPTER 5

DISCUSSION, CONCLUSIONS, and RECOMMENDATIONS

Discussion

Twenty three per cent of this study sample was estimated to have CRI. When compared to USRDS report this exceeds the estimate of 7.7 - 9.8 % of the Medicare eligible population in the southeastern US including Texas (US Renal Data System, 2007). From the USRDS report, Texas spent $957,122,038 in 2007 alone on estimated costs for CKD in the Medicare/Medicaid population. In almost every population parameter measured by the USRDS, the prevalence of and risk factors for CKD are increasing. Persons of Black race and/or Hispanic identity are at increased risk of developing CKD (Boyle et al., 2001; Chiapella & Feldman, 1995). The geographic locations and predicted population growth of Blacks and Hispanics point to the need for a reliable and accurate method for screening for CKD among elderly, most minority, ambulatory care patients. Even though the original sample selection method (dietary referral) may have skewed the sample, the prevalence of CRI in the study sample exceeds USRDS projections.

The two most popular formulas, the Cockcroft/Gault and MDRD, were developed from study populations that were neither elderly nor minority. Both formulas contain the elements of age, gender, and serum creatinine. The Cockcroft/Gault formula also contains measured body weight. The MDRD formula

does not contain body weight, but instead requires information about race: Black, yes/no.

Advancing age is associated with gradually increasing GFR and increasing prevalence of CRI. Although Baracskay (1997) did not think the CG formula was sufficiently accurate for use in the elderly, he was able to show that iothalamate clearance (a gold standard) decreased by 1ml/year for every year of age in the elderly (Baracskay et al., 1997). All of his subjects were over age 65. Erikson (2006) in Norway and Fehrman-Ekholm (2004) in Sweden also observed the same rate of decline (Eriksen & Ingebretsen, 2006; Fehrman-Ekholm & Skeppholm, 2004). In this study sample, the mean decline in eGFR exceeded 1ml/year.

Female gender carries increased risk in both estimation formulas. The hypothesis for this occurrence has long been the smaller body habitus and muscle mass of women. This occurrence is well supported throughout the literature (Guan, 2006). Results of this study suggest that the weighting of gender in the CG formula needs re-evaluation. The original study sample upon which the regression equation was built had only 4% women. Eriksen (2006) also observed that women have a slower rate of decline and have better survival.

Serum creatinine is the best current measure of CKD available to primary care clinicians in the US. Used in isolation, serum creatinine is an unreliable and crude estimate of renal function especially in those who may have impaired creatinine production or clearance such as the elderly (Giannelli et al., 2007). It is widely available

in laboratories throughout the US. When used in an estimating formula with other necessary variables, it significantly improves the sensitivity of CKD detection.

Weight is a variable only in the Cockcroft/Gault formula. For most Americans, weight increases gradually throughout their adult lives until the final few years of decline before death not caused by trauma. Weight in the Cockcroft/Gault formula is intended to capture a crude estimate of an individual's muscle mass and creatinine production.

Race is a non modifiable demographic variable, but is becoming more and more difficult to separate as immigrants acculturate and intermarry with other backgrounds in today's world. Other race/ethnic groups have been identified as having differences in the prevalence of creatinine and CKD which are not considered in our current popular formulas. At the same time, the USRDS report based on NHANES 1998 -2004 data, reveal an increasing prevalence among almost every segment of the population. At the same time there are differences in survival and mortality of patients who progress to ESRD unexplained by prevalence of CKD. Xue, Herzog, Foley, and Collins (2007) found that in spite of a higher prevalence of CKD among Blacks, Caucasian patients are more likely to die (Xue, Frazier, Herzog, & Collins, 2005). Black patients are more likely to progress to ESRD than whites regardless of additional comorbidity. Since NHANES data uses US Census definitions and only distinguishes Hispanic or Latino ethnic identity as a modifier and not a unique group, data about these peoples are difficult to analyze.

In this study Latino ethnic identity was identified as a unique group separate from Black or Caucasian. Prevalence of CKD within the Latino subgroup of this study was measured as 13% by CG and 14% by MDRD which is significantly less than the prevalence in the total sample which was 23%. The association of Latino ethnic identity as a protective factor has not been reported before. The fact that this association is not present when ideal body weight is used suggests that the observed prevalence of higher weight in this group is a covariant.

Prevalence of ESRD in Hispanic Americans has been very difficult to measure. Authors have resorted to counting Hispanic surnames on dialysis registries for lack of more accurate measures. Prevalence of ESRD is reported to be flattening as other ethnic groups continue to climb, yet many Hispanics have an increased prevalence of multiple risk factors for CKD, such as diabetes, hypertension and obesity (US Renal Data System, 2007).

Studies which compared the clinical usefulness of the two formulas have found CG estimations to be more sensitive and conservative when the patient population is elderly (Melloni, 2008). Comorbid history and treatment history suggests that for these patients CG with MBW is more conservative than is MDRD. Garcia-Navelro (2005) found CG produces lower estimations of GFR which is especially obvious in the elderly and those with poor nutritional condition. He recommended CG in this population as a more conservative and safe approach (Garcia-Naveiro, Rodriguez-Carmona, & Pérez-Fontán, 2005).

The same result of CG producing lower estimates of GFR was found in this study, primarily with normal or underweight patients. When CG was estimated using measured body weight the CG estimates exceeded MDRD estimates in patients whose BMI was 25 or more. This study and others have reported that CG with IBW produces the most conservative estimates for use in older ambulatory care persons. Because the population most at risk for the development of CKD are older and often minority, modifications in estimation formulas are needed to fit population of interest. Most older persons are also female and many are overweight. Specific characteristics of older patients require consideration when an estimation formula is considered. Neither of the two most popular formulas used for estimation were developed in such a population.

Limitations

This study is limited by the study design which was a secondary analysis of an existing database. The researcher has little control over the variables chosen for collection. There is no "gold standard" of renal function within the database such as iohexal clearance or 24 hour urinary creatinine clearance. The database itself was a retrospective review of medical records. Being a retrospective rather than prospective study implies a greater proportion of missing data which may not reflect the variable of interest as accurately as possible. Some of the subgroups of patients within certain diagnostic categories are very small, so conclusions based on these data are not substantive, but merely suggestive.

It is also limited by the way in which patients were selected for inclusion in the study. The initial design was to measure protein intake from existing chart records of patients who had been referred to the dietician in the clinic. This sample has a skewed prevalence of comorbid diagnoses that are appropriate for dietary interventions, such as diabetes, hyperlipidemia, hypertension, and obesity which are also associated with CKD which may explain the higher prevalence of CRI within the study sample. The findings of this study are limited to similar populations and should not be generalized to unlike populations such as nursing home residents.

Conclusions

From the data in this database, the Cockcroft/Gault formula using ideal body weight identified elderly patients most conservatively with the least comorbidity. Patients with less comorbidity allow clinicians more opportunity for renal preserving interventions, especially if those patients were overweight or obese.

In this set of data about older patients in a publicly funded clinic who were primarily women and minority, the Cockcroft/Gault formula identified patients earlier in their disease with less comorbidity than did the MDRD formula. A hypothesis to consider to explain this difference in sensitivity between formulas could be the differences in study sample characteristics between the sample selected for the MDRD and the CG.

Patients who experienced rapid decline of GFR were most likely to be Latino, whereas African American patients did not experience rapid decline. Because Latino

patients have a high prevalence of overweight and obesity, perhaps their renal insufficiency was not recognized at an earlier stage.

From the data contained within this database, there is a significant association of Latino ethnic identity with CRI which has not been identified before. It may be related to nutritional status. Within the cohort of patients identified as Latino, 75% of the sample was either overweight or obese. Patients of Latino ethnicity were also associated with rapid decline. This informs clinicians who care for such patients to consider renal insufficiency in their Latino patients.

Clinical significance of chronic kidney disease is that it most often occurs in a patient of advanced age, who is dependent in IADLs, and may also have congestive heart failure. Additional comorbid conditions to consider are hypertension, dementia, diabetes and coronary artery disease. Although these diagnoses were not necessarily associated with both estimations of renal insufficiency, the medications used to manage these diagnoses often were (beta blockers, metformin). Laboratory values that were associated with chronic kidney disease were BUN, creatinine and hemoglobin. When clinicians can recognize these clusters of functional and physiologic status, patients can benefit from earlier and more appropriate interventions. The profile of patients who experience CRI not only helps clinicians to identify similar patients, but also helps clinicians to be alert for emerging functional deficits in patients with known CRI.

Recommendations

To gain more clarity about this issue, a prospective study is indicated. Laboratory variables to consider for inclusion in a prospective study in addition to those

already in the database, would be serum protein and albumin, urine protein, a measure of socioeconomic status, a more accurate measure of lean body mass as well as a more accurate and reliable measure of dietary protein intake. Inclusion of a gold standard measure such as iohexal or iothalamate clearance is recommended. Patients should be asked for their racial and ethnic identity because clinician observations may be inaccurate. Latino patients should be asked about national origin so that subgroups can be evaluated. This naturally leads to a need for information about genes which might be involved in transmission of risk for CKD to subsequent generations. The sample for such an ideal study should be randomly chosen without bias for nutritional or renal risk factors.

Examination of renal and nutritional parameters within the Latino population needs to be investigated. This segment of the US population is diverse and reflects many cultures and ethnic origins. In Texas, the largest percent are of Mexican origin and many are diabetic and obese. Longer exposure to traditional western diet and lifestyle appears to be connected to poorer outcomes in many ethnic groups (Chiapella & Feldman, 1995).

People of Latino identity come from many continents and backgrounds. A recent publication by Rodriguez (2004) describes creatinine levels of various Latino subgroups (Rodriguez, Hernandez, O'Hare, Glidden, & Pérez-Stable, 2004). There were significant differences between Latino subgroups with Cuban Americans having the highest serum creatinines. Further research needs to be done to discover the relationship of renal

function to level of acculturation in the US as well as genetic transmission of CKD risk factors.

Variance in culture almost by definition also means variance in diet. The missing ingredient in many of the published descriptive studies reviewed is nutritional intake. Serum creatinine is the result of protein intake, muscle mass and renal clearance. Without better knowledge of protein intake and measures of muscle mass, only crude measures of measured total body weight can proxy for the root cause. Future studies should include measured protein intake over time, muscle mass, serum protein, serum albumin, serum creatinine, as well as urinary protein and albumin. Patients of all ethnic groups should be evaluated including their diet content.

There are also other unanswered questions that arise from this data. What is the nature of the relationship of CRI by CG to HDL? Other studies have found a relationship of low HDL to CKD (Zhang et al., 2008).

Why were patients with rapid decline by both formulas on iron supplements at the beginning of the two year study period? Did the iron itself have a negative effect on their renal function? Bansal (2007) did find an association of anemia with a rapid decrease in GFR in patients with heart failure (Bansal et al., 2007). This requires further investigation.

From the data available in this database, reflective of older minority patients, it appears that the Cockcroft/Gault estimations of GFR may identify patients at an earlier stage of their kidney disease and thus allow clinicians more opportunity to recognize the need for medication adjustment at an earlier stage of deterioration to prolong kidney

viability and function. When eGFR is calculated by CG with IBW, patients who are overweight or obese may have a much more accurate estimation. Further study needs to be done which can examine the nutritional and racial/ethnic contributions to renal insufficiency.

This study bears repeating in a more frail population such as a nursing home population. Because of the circumstances of institutional living and nursing home regulations, many of the variables such as dietary protein intake may be much more easily measured than in outpatient ambulatory patients.

As our aging population grows in number and diversity, information to guide clinicians in providing the safest care for their patients is critically needed. Specific information about which formulas have the greatest sensitivity and specificity for patients based on patient characteristics such as race, BMI, gender, and age gives clinicians greater ability to provide the safest, most conservative care for their patients.

APPENDIX A

LETTER OF PERMISSION FROM DATABASE OWNER

UT SOUTHWESTERN
MEDICAL CENTER
UNIVERSITY HOSPITALS & CLINICS

Belinda A. Vicioso, M.D.
Associate Professor
Jose Garcia, M.D. Professorship in
Internal Medicine

Mildred Wyatt and Ivor P. Wold
Center for Geriatric Care
Department of Internal Medicine

February 29, 2008

University of Texas at Arlington
Institutional Review Board
701 S. Nedderman Drive
Arlington, TX 76019

Dear Sirs,

I am pleased to offer permission to analyze the data from my database, "Determinants of Renal Function", to Kathryn Daniel, MS, ANP-BC, GNP-BC for her dissertation work entitled "Clinical Significance of Chronic Kidney Disease in the Elderly". The database will be delivered as a SPSS data file and is de-identified. I look forward to reviewing the analysis with her for the insights and knowledge that can be gained from this database to improve care provided to similar patients.

Sincerely,

Belinda Vicioso, M.D., F.A.C.P.

5323 Harry Hines Blvd. / Dallas, Texas 75390-8889 / (214) 648-9012 FAX (214) 648-2087
www.utsouthwestern.edu

APPENDIX B

IRB APPROVAL

THE UNIVERSITY
OF TEXAS
AT ARLINGTON

Office of
Research Administration

Box 19181
202 E. Border St., Suite 201
Arlington, Texas
76019-0181
T 817.272.3723
F 817.272.1111
http://www.uta.edu/research
Expertise at UT Arlington
www.uta.edu/expertise

March 6, 2008

Kathryn M. Daniel
Carolyn Cason, Ph.D.
Nursing
Box 19407

TITLE: *Clinical Significance of Chronic Kidney Disease in the Elderly*
Re: Exempt Approval Letter
IRB No.: 2008.281e

The UT Arlington Institutional Review Board (UTA IRB) Chair (or designee) has reviewed the above-referenced study and found that it qualified as exempt from coverage under the federal guidelines for the protection of human subjects as referenced at Title 45--Part 46.101(b)(1)(4). You are therefore authorized to begin the research as of March 6, 2008.

It is further found that the above referenced study also qualifies for a waiver of the requirement to obtain Informed Consent under the federal guidelines for the protection of human subjects as referenced at Title 45 CFR 46.116(d)(1)-(4). The procedures indicated in the study provide that:

1. the research involves no more than minimal risk to the subjects;
2. the waiver will not adversely affect the rights and welfare of the subjects;
3. the research could not practicably be carried out without the waiver, and
4. whenever appropriate, the subject will be provided with additional pertinent information after participation.

Please be advised that as the principal investigator, you are required to report local adverse (unanticipated) events to this office within 24 hours. In addition, pursuant to Title 45 CFR 46.103(b)(4)(iii), investigators are required to, "promptly report to the IRB ***any*** proposed changes in the research activity, and to ensure that such changes in approved research, during the period for which IRB approval has already been given, are **not initiated without IRB review and approval** except when necessary to eliminate apparent immediate hazards to the subject."

All investigators and key personnel identified in the protocol must have documented *CITI Training* on file with this office. The UT Arlington Office of Research Administration Regulatory Services appreciates your continuing commitment to the protection of human research subjects. Should you have questions or require further assistance, please contact Jan Parker by calling (817) 272-0867.

Yours sincerely,

Patricia Turpin, PhD, RN, CNAA, BC

Patricia Turpin, Ph.D., RN, CNAA, BC
Associate Clinical Professor
UT Arlington IRB Chair

APPENDIX C

SYNTAX FILE FOR COMPUTATION OF eGFR BY COCKCROFT/GAULT UPON ENTRY INTO STUDY

Syntax file for computation of eGFR by Cockcroft/Gault upon entry into study

```
********************* Compute GFR Value by Computing 4 Parts ****************************

compute cgpart1 = 140-age

compute cgpart2 = weight/2.2

compute cgpart3 = 72 * creatini

RECODE
  gender
  (1=.85)  (2=1)  INTO  cgPart4 .
EXECUTE .

compute cg1 = (cgpart1 * cgpart2)/( cgpart3 * cgpart4).
execute.
```

APPENDIX D

SYNTAX FILE FOR COMPUTATION OF eGFR BY MDRD UPON ENTRY INTO THE STUDY

Syntax file for computation of eGFR by MDRD upon entry into the study

```
********** Compute GFR Value by Computing 4 Parts ***************************

compute GFRPart1 = creatini**(-.999).

compute GFRPart2 = age**(-.176).

execute.

RECODE
  gender
  (1=.762)  (2=1)  INTO  GFRPart3 .
EXECUTE .

RECODE
  ethnicit
  (1= 1.18)  (ELSE = 1)  INTO  GFRPart4.
EXECUTE .
```

APPENDIX E

SYNTAX FILE FOR COMPUTATION OF eGFR BY CG WITH IBW UPON ENTRY INTO STUDY

Syntax file for computation of eGFR by CG with IBW upon entry into the study

```
********** Compute GFR Value by Computing 4 Parts ****************************

compute cgpart1 = 140-age

compute cgpart2 = ibw/2.2

compute cgpart3 = 72 * creatini

RECODE
  gender
  (1=.85)  (2=1)  INTO  cgPart4 .
EXECUTE .

compute cg1ibw = (cgpart1 * cgpart2)/( cgpart3 * cgpart4).
execute.
```

APPENDIX F

SYNTAX FILE FOR COMPUTATION OF eGFR BY CG AT TWO YEARS AFTER ENTRY INTO STUDY

Syntax file for computation of eGFR by CG at two years after entry into study

```
********** Compute GFR Value by Computing 4 Parts ****************************

compute cgpart1 = 140-age2

compute cgpart2 = weight2/2.2

compute cgpart3 = 72 * creatin2

RECODE
  gender
  (1=.85)  (2=1)  INTO  cgPart4 .
EXECUTE .

compute cg2 = (cgpart1 * cgpart2) / ( cgpart3 * cgpart4).
execute.
```

APPENDIX G

SYNTAX FILE FOR COMPUTATION OF eGFR BY MDRD AT TWO YEARS AFTER ENTRY INTO STUDY

Syntax file for computation of eGFR by MDRD at two years after entry into study

```
********** Compute GFR Value by Computing 4 Parts ***************************


compute GFRPart1 = creatin2**(-.999).

compute GFRPart2 = age2**(-.176).

execute.

RECODE
  gender
  (1=.762)  (2=1)  INTO  GFRPart3 .
EXECUTE .

RECODE
  ethnicit
  (1= 1.18)  (ELSE = 1)  INTO  GFRPart4.
EXECUTE .



compute MDRD2 = ((170 * GFRPart1) * GFRPart2 * GFRPart3 * GFRPart4).
execute.
```

REFERENCES

Arimoto, T., Takeishi, Y., Niizeki, T., Takabatake, N., Okuyama, H., Fukui, A., et al. (2005). Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *Journal of Cardiac Failure, 11*(8), 595-601.

Bakris, G. L., Hart, P., & Ritz, E. (2006). Beta blockers in the management of chronic kidney disease. *Kidney International, 70*(11), 1905-1913. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=17021610&site=ehost-live

Bansal, N., Tighiouart, H., Weiner, D., Griffith, J., Vlagopoulos, P., Salem, D., et al. (2007). Anemia as a risk factor for kidney function decline in individuals with heart failure. *The American Journal of Cardiology, 99*(8), 1137-1142. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=17437743&site=ehost-live

Baracskay, D., Jarjoura, D., Cugino, A., Blend, D., Rutecki, G. W., & Whittier, F. C. (1997). Geriatric renal function: Estimating glomerular filtration in an ambulatory elderly population. *Clinical Nephrology, 47*(4 (Print)), 222-228.

Boyle, J. P., Honeycutt, A. A., Narayan, K. M., Hoerger, T. J., Geiss, L. S., Chen, H., et al. (2001). Projection of diabetes burden through 2050: Impact of changing demography and disease prevalence in the U.S. *Diabetes Care, 24*(11), 1936-1940.

Brugts, J. J., Knetsch, A. M., Mattace-Raso, F. U. S., Hofman, A., & Witteman, J. C. M. (2005). Renal function and risk of myocardial infarction in an elderly population: The rotterdam study. *Archives of Internal Medicine, 165*(22), 2659-2665.

Bugeja, G., Kumar, A., & Banerjee, A. K. (1997). Exclusion of elderly people from clinical research: A descriptive study of published reports. *BMJ (Clinical Research Ed.), 315*(7115), 1059-1059.

Burkhardt, H., Bojarsky, G., Gretz, N., & Gladisch, R. (2002). Creatinine clearance, cockcroft-gault formula and cystatin C: Estimators of true glomerular filtration rate in the elderly? *Gerontology, 48*(3), 140-146.

Burkhardt, H., Hahn, T., Gretz, N., & Gladisch, R. (2005). Bedside estimation of the glomerular filtration rate in hospitalized elderly patients. *Nephron.Clinical Practice [Electronic Resource], 101*(1 (Electronic)), c1-8.

Cass, A., Cunningham, J., Wang, Z., & Hoy, W. (2001). Social disadvantage and variation in the incidence of end-stage renal disease in australian capital cities. *Australian and New Zealand Journal of Public Health, 25*(4), 322-326.

Centers for Disease Contol. (2007). *Defining obesity and overweight.* Retrieved December 2, 2007, from http://www.cdc.gov/nccdphp/dnpa/bmi/adult_BMI/about_adult_BMI.htm#Interpreted

Chertow, G. M., Hsu, C., & Johansen, K. L. (2006). The enlarging body of evidence: Obesity and chronic kidney disease. *Journal of the American Society of Nephrology: JASN, 17*(6), 1501-1502. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=16672317&site=ehost-live

Chiapella, A. P., & Feldman, H. I. (1995). Renal failure among male hispanics in the united states. *American Journal of Public Health, 85*(7), 1001-1004.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., et al. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA: The Journal of the American Medical Association, 289*(19), 2560-2572.

Cockcroft, D. W., & Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron, 16*(1 (Print)), 31-41.

Coresh, J., Astor, B. C., Greene, T., Eknoyan, G., & Levey, A. S. (2003). Prevalence of chronic kidney disease and decreased kidney function in the adult US population:

Third national health and nutrition examination survey. *American Journal of Kidney Diseases, 41*(1), 1-12.

Couchoud, C., Pozet, N., Labeeuw, M., & Pouteil-Noble, C. (1999). Screening early renal failure: Cut-off values for serum creatinine as an indicator of renal impairment. *Kidney International, 55*(5), 1878-1884.

Daniel, K., Cason, C. L., Vicioso, B., Sesso, R., & Gleason-Wynn. (2008) Differences in GFR calculation: MDRD, Cockcroft/Gault with ideal body weight and Cockcroft/Gault with measured body weight. Poster abstract accepted for presentation at the American Geriatrics Society Annual Meeting in Washington, DC on May 1 & 3, 2008.

Dirks, J. H., de Zeeuw, D., Agarwal, S. K., Atkins, R. C., Correa-Rotter, R., D'Amico, G., et al. (2005). Prevention of chronic kidney and vascular disease: Toward global health equity--the bellagio 2004 declaration. *Kidney International.Supplement,* (98), S1-6.

Drusano, G. L., Muncie, H. L., Hoopes, J. M., Damron, D. J., & Warren, J. W. (1988). Commonly used methods of estimating creatinine clearance are inadequate for elderly debilitated nursing home patients. *Journal of the American Geriatrics Society, 36*(5), 437-441.

Edwards, K. D., & Whyte, H. M. (1959). Plasma creatinine level and creatinine clearance as tests of renal function. *Australasian Annals of Medicine, 8*, 218-224.

Ejerblad, E., Fored, C. M., Lindblad, P., Fryzek, J., McLaughlin, J. K., & Nyrén, O. (2006). Obesity and risk for chronic renal failure. *Journal of the American Society of Nephrology: JASN, 17*(6), 1695-1702. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=16641153&site=ehost-live

Eriksen, B. O., & Ingebretsen, O. C. (2006). The progression of chronic kidney disease: A 10-year population-based study of the effects of gender and age. *Kidney International, 69*(2 (Print)), 375-382.

Fehrman-Ekholm, I., & Skeppholm, L. (2004). Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scandinavian Journal of Urology and Nephrology, 38*(1 (Print)), 73-77.

Ferdinand, K. C., & Saunders, E. (2006). Hypertension-related morbidity and mortality in african americans--why we need to do better. *Journal of Clinical Hypertension (Greenwich, Conn.), 8*(1), 21-30.

Foley, R. N., Murray, A. M., Li, S., Herzog, C. A., McBean, A. M., Eggers, P. W., et al. (2005). Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the united states medicare population, 1998 to 1999. *Journal of the American Society of Nephrology: JASN, 16*(2), 489-495.

Fontseré, N., Bonal, J., Navarro, M., Riba, J., Fraile, M., Torres, F., et al. (2006). A comparison of prediction equations for estimating glomerular filtration rate in adult patients with chronic kidney disease stages 4-5. effect of nutritional status and age. *Nephron.Clinical Practice, 104*(4), c160-8.

Fored, C. M., Ejerblad, E., Fryzek, J. P., Lambe, M., Lindblad, P., Nyrén, O., et al. (2003). Socio-economic status and chronic renal failure: A population-based case-control study in sweden. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association, 18*(1), 82-88.

Freedman, B. I., Volkova, N. V., Satko, S. G., Krisher, J., Jurkovitz, C., Soucie, J. M., et al. (2005). Population-based screening for family history of end-stage renal disease among incident dialysis patients. *American Journal of Nephrology, 25*(6), 529-535.

Fried, L. F., Lee, J. S., Shlipak, M., Chertow, G. M., Green, C., Ding, J., et al. (2006). Chronic kidney disease and functional limitation in older people: health, aging and body composition study. *Journal of the American Geriatrics Society, 54*(5), 750-756.

Fried, L., Solomon, C., Shlipak, M., Seliger, S., Stehman-Breen, C., Bleyer, A. J., et al. (2004). Inflammatory and prothrombotic markers and the progression of renal

disease in elderly individuals. *Journal of the American Society of Nephrology: JASN, 15*(12), 3184-3191.

Friedman, J. R., Norman, D. C., & Yoshikawa, T. T. (1989). Correlation of estimated renal function parameters versus 24-hour creatinine clearance in ambulatory elderly. *Journal of the American Geriatrics Society, 37*(2), 145-149.

From the NIH: Successful diet and exercise therapy is conducted in Vermont for "diabesity".(1980). *JAMA: The Journal of the American Medical Association, 243*(6), 519-520.

Garg, A. X., Blake, P. G., Clark, W. F., Clase, C. M., Haynes, R. B., & Moist, L. M. (2001). Association between renal insufficiency and malnutrition in older adults: Results from the NHANES III. *Kidney International, 60*(5), 1867-1874.

Garcia-Naveiro, R., Rodriguez-Carmona, A., & Pérez-Fontán, M. (2005). Agreement between two routine methods of estimation of glomerular filtration rate in patients with advanced and terminal chronic renal failure. *Clinical Nephrology, 64*(4), 271-280.

Garg, A. X., Papaioannou, A., Ferko, N., Campbell, G., Clarke, J., & Ray, J. G. (2004). Estimating the prevalence of renal insufficiency in seniors requiring long-term care. *Kidney International, 65*(2), 649-653.

Giannelli, S. V., Patel, K. V., Windham, B. G., Pizzarelli, F., Ferrucci, L., & Guralnik, J. M. (2007). Magnitude of underascertainment of impaired kidney function in older adults with normal serum creatinine. *Journal of the American Geriatrics Society, 55*(6), 816-823.

Gral, T., & Young, M. (1980). Measured versus estimated creatinine clearance in the elderly as an index of renal function. *Journal of the American Geriatrics Society, 28*(11), 492-496.

Guan, Y. (2006). Nuclear receptors link gender dimorphism of renal disease progression. *Kidney International, 70*(11), 1889-1890.

Hemmelgarn, B. R., Zhang, J., Manns, B. J., Tonelli, M., Larsen, E., Ghali, W. A., et al. (2006). Progression of kidney dysfunction in the community-dwelling elderly. *Kidney International, 69*(12), 2155-2161.

Hermida, J., & Tutor, J. C. (2006). Comparison of estimated glomerular filtration rates from serum creatinine and cystatin C in patients with impaired creatinine production. *Clinical Laboratory, 52*(9), 483-490.

Hsu, J., Johansen, K. L., Hsu, C-y., Kaysen, G. A., & Chertow, G. M (2008). Higher serum creatinine concentrations in black patients with chronic kidney disease: beyond nutritional status and body composition. *Clinical Journal of the American Society of Nephrology*, as doi: doi:10.2215/CJN.00090108.

Jelliffe, R. W. (1971). Estimation of creatinine clearance when urine cannot be collected. *Lancet, 1*(7706), 975-976.

Jelliffe, R. W. (1973). Letter: Creatinine clearance: Bedside estimate. *Annals of Internal Medicine, 79*(4), 604-605.

Johansen, K. L., Young, B., Kaysen, G. A., & Chertow, G. M. (2004). Association of body size with outcomes among patients beginning dialysis. *The American Journal of Clinical Nutrition, 80*(2), 324-332. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=15277152&site=ehost-live

Lamb, E. J., Webb, M. C., Simpson, D. E., Coakley, A. J., Newman, D. J., & O'Riordan, S. E. (2003). Estimation of glomerular filtration rate in older patients with chronic renal insufficiency: Is the modification of diet in renal disease formula an improvement? *Journal of the American Geriatrics Society, 51*(7), 1012.

Laroche, M., Charmes, J., Marcheix, A., Bouthier, F., & Merle, L. (2006). Estimation of glomerular filtration rate in the elderly: Cockcroft-gault formula versus modification of diet in renal disease formula. *Pharmacotherapy, 26*(7), 1041-1046.

Levey, A. S. (1989). Use of glomerular filtration rate measurements to assess the progression of renal disease. *Seminars in Nephrology, 9*(4 (Print)), 370-379.

Levey, A. S., & Bosch, J. P. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: A new.. *Annals of Internal Medicine, 130*(6), 461.

Lindeman, R. D., & Goldman, R. (1986). Anatomic and physiologic age changes in the kidney. *Experimental Gerontology, 21*(4-5 (Print)), 379-406.

Lindeman, R. D., Tobin, J. D., & Shock, N. W. (1984a). Association between blood pressure and the rate of decline in renal function with age. *Kidney International, 26*(6 (Print)), 861-868.

Lindeman, R. D., Tobin, J. D., & Shock, N. W. (1984b). Association between blood pressure and the rate of decline in renal function with age. *Kidney International, 26*(6), 861-868.

Lindeman, R. D., Tobin, J., & Shock, N. W. (1985). Longitudinal studies on the rate of decline in renal function with age. *Journal of the American Geriatrics Society, 33*(4), 278-285.

Maaravi, Y., Bursztyn, M., Hammerman-Rozenberg, R., Cohen, A., & Stessman, J. (2006). Moderate renal insufficiency at 70 years predicts mortality. *QJM: Monthly Journal of the Association of Physicians, 99*(2), 97-102.

Macfarlane, D. P., & Fisher, M. (2006). Thiazolidinediones in patients with diabetes mellitus and heart failure : implications of emerging data. *American Journal Of Cardiovascular Drugs: Drugs, Devices, And Other Interventions, 6*(5), 297-304.

Macisaac, R. J., Tsalamandris, C., Thomas, M. C., Premaratne, E., Panagiotopoulos, S., Smith, T. J., et al. (2006). Estimating glomerular filtration rate in diabetes: A comparison of cystatin-C- and creatinine-based methods. *Diabetologia, 49*(7), 1686-1689.

McCance, K. L., & Huether, S. E. (Eds.). (c2006). *Pathophysiology : The biologic basis for disease in adults and children* (5th ed. ed.). St. Louis, MO: Elsevier Mosby.

McManus, D., Shlipak, M., Ix, J. H., Ali, S., & Whooley, M. A. (2007). Association of cystatin C with poor exercise capacity and heart rate recovery: Data from the heart and soul study. *American Journal of Kidney Diseases, 49*(3), 365-372.

Melloni, C., Peterson, E. D., Chen, A. Y., Szczech, L. A., Newby, L. K., Harrington, R. A., et al. (2008). Cockcroft-gault versus modification of diet in renal disease: Importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. *Journal of the American College of Cardiology, 51*(10), 991-996. http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=18325437&site=ehost-live

Menon, V., Shlipak, M. G., Wang, X., Coresh, J., Greene, T., Stevens, L., et al. (2007). Cystatin C as a risk factor for outcomes in chronic kidney disease. *Annals of Internal Medicine, 147*(1), 19-27.

Morales, L. S., Lara, M., Kington, R. S., Valdez, R. O., & Escarce, J. J. (2002). Socioeconomic, cultural, and behavioral factors affecting Hispanic health outcomes. *Journal of Healthcare for the Poor and Underserved 13*(4), 477-523.

Narva, A. S. (2002). Kidney disease in native americans. *Journal of the National Medical Association, 94*(8), 738-742.

National Kidney Foundation. (2007). KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation, 49*(2), S1-S180.

Nordén, G., Björck, S., Granerus, G., & Nyberg, G. (1987). Estimation of renal function in diabetic nephropathy. comparison of five methods. *Nephron, 47*(1 (Print)), 36-42.

Nygaard, H. A., Naik, M., Ruths, S., & Krüger, K. (2004a). Clinically important renal impairment in various groups of old persons. *Scandinavian Journal of Primary Health Care, 22*(3), 152-156.

Nygaard, H. A., Naik, M., Ruths, S., & Krüger, K. (2004b). Clinically important renal impairment in various groups of old persons. *Scandinavian Journal of Primary Health Care, 22*(3), 152-156.

Odden, M. C., Chertow, G. M., Fried, L. F., Newman, A. B., Connelly, S., Angleman, S., et al. (2006). Cystatin C and measures of physical function in elderly adults: The health, aging, and body composition (HABC) study. *American Journal of Epidemiology, 164*(12), 1180-1189.

O'Hare, A. M., Bertenthal, D., Covinsky, K. E., Landefeld, C. S., Sen, S., Mehta, K., et al. (2006). Mortality risk stratification in chronic kidney disease: One size for all ages? *Journal of the American Society of Nephrology: JASN, 17*(3), 846-853.

Oliveira, M. B., Romão, J. E., & Zatz, R. (2005). End-stage renal disease in brazil: Epidemiology, prevention, and treatment. *Kidney International.Supplement,* (97), S82-6.

Ostchega, Y., Dillon, C. F., Hughes, J. P., Carroll, M., & Yoon, S. (2007). Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: Data from the national health and nutrition examination survey 1988 to 2004. *Journal of the American Geriatrics Society, 55*(7), 1056-1065. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=17608879&site=ehost-live

Owens, C. D., Ho, K. J., Kim, S., Schanzer, A., Lin, J., Matros, E., et al. (2007). Refinement of survival prediction in patients undergoing lower extremity bypass surgery: Stratification by chronic kidney disease classification. *J Vasc Surg, 45*(5), 944-952.

Pedone, C., Corsonello, A., & Incalzi, R. A. (2006). Estimating renal function in older people: A comparison of three formulas. *Age & Ageing, 35*(2), 121-126.

Peralta, C. A., Shlipak, M. G., Fan, D., Ordoñez, J., Lash, J. P., Chertow, G. M., et al. (2006). Risks for end-stage renal disease, cardiovascular events, and death in hispanic versus non-hispanic white adults with chronic kidney disease. *Journal of the American Society of Nephrology: JASN, 17*(10), 2892-2899.

Peralta, C. A., Ziv, E., Katz, R., Reiner, A., Burchard, E. G., Fried, L., et al. (2006). African ancestry, socioeconomic status, and kidney function in elderly african americans: A genetic admixture analysis. *Journal of the American Society of Nephrology: JASN, 17*(12), 3491-3496.

Pucci, L., Triscornia, S., Lucchesi, D., Fotino, C., Pellegrini, G., Pardini, E., et al. (2007). Cystatin C and estimates of renal function: Searching for a better measure of kidney function in diabetic patients. *Clinical Chemistry, 53*(3), 480-488.

Rahman, M., Pressel, S., Davis, B. R., Nwachuku, C., Wright, J.,Jr., Whelton, P. K., et al. (2006). Cardiovascular outcomes in high-risk hypertensive patients stratified by baseline glomerular filtration rate. *Annals of Internal Medicine, 144*(3), 172.

Rodondi, N., Yerly, P., Gabriel, A., Riesen, W. F., Burnier, M., Paccaud, F., et al. (2007). Microalbuminuria, but not cystatin C, is associated with carotid atherosclerosis in middle-aged adults. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association, 22*(4), 1107-1114.

Rodriguez, R. A., Hernandez, G. T., O'Hare, A. M., Glidden, D. V., & Perez-Stable, E. J. (2004). Creatinine levels among Mexican Americans, Puerto Ricans, and Cuban Americans in the Hispanic Health and Nutrition Examination Survey. *Kidney International, 66*, 2368-2373.

Rowe, J. W., Andres, R., Tobin, J. D., Norris, A. H., & Shock, N. W. (1976). The effect of age on creatinine clearance in men: A cross-sectional and longitudinal study. *Journal of Gerontology, 31*(2), 155-163.

Rule, A. D., Bergstralh, E. J., Slezak, J. M., Bergert, J., & Larson, T. S. (2006). Glomerular filtration rate estimated by cystatin C among different clinical presentations. *Kidney International, 69*(2), 399-405.

Seedat, Y. K. (1996). Ethnicity, hypertension, coronary heart disease and renal diseases in south africa. *Ethnicity & Health, 1*(4), 349-357.

Shlipak, M. G., Katz, R., Sarnak, M. J., Fried, L. F., Newman, A. B., Stehman-Breen, C., et al. (2006). Cystatin C and prognosis for cardiovascular and kidney outcomes

in elderly persons without chronic kidney disease. *Annals of Internal Medicine, 145*(4), 237.

Shlipak, M. G., Sarnak, M. J., Katz, R., Fried, L. F., Seliger, S. L., Newman, A. B., et al. (2005). Cystatin C and the risk of death and cardiovascular events among elderly persons. *New England Journal of Medicine, 352*(20), 2049.

Singh, D., Whooley, M. A., Ix, J. H., Ali, S., & Shlipak, M. G. (2007). Association of cystatin C and estimated GFR with inflammatory biomarkers: The heart and soul study. *Nephrology, Dialysis, Transplantation: Official Publication of the European Dialysis and Transplant Association - European Renal Association, 22*(4), 1087-1092.

Thylen, P., Klaren, I., End, T., Bergman, U., & Odar-Cederlof. (2007). Do old patients have chronic kidney disease? *Journal of the American Society of Nephrology, 18*(Abstracts), 543A.

Toto, R. D., Mitchell, H. C., Smith, R. D., Lee, H. C., McIntire, D., & Pettinger, W. A. (1995). "Strict" blood pressure control and progression of renal disease in hypertensive nephrosclerosis. *Kidney International, 48*(3), 851-859.

US Renal Data System. (2004). *USRDS 2004 annual data report.* Bethesda, MD: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

US Renal Data System. (2007). *USRDS 2007 annual report: Atlas of chronic kidney disease and end-stage renal disease in the united states*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

Van den Noortgate,N J., Janssens, W. H., Afschrift, M. B., & Lameire, N. H. (2001). Renal function in the oldest-old on an acute geriatric ward. *International Urology and Nephrology, 32*(4 (Print)), 531-537.

Van Den Noortgate,Nele J., Janssens, W. H., Delanghe, J. R., Afschrift, M. B., & Lameire, N. H. (2002). Serum cystatin C concentration compared with other markers of glomerular filtration rate in the old old. *Journal of the American Geriatrics Society, 50*(7), 1278-1282.

Wasén, E., Isoaho, R., Mattila, K., Vahlberg, T., Kivelä, S., & Irjala, K. (2004). Estimation of glomerular filtration rate in the elderly: A comparison of creatinine-based formulae with serum cystatin C. *Journal of Internal Medicine, 256*(1), 70-78.

Wesson, L. G. (1969). *Physiology of the human kidney*. NY: Grune & Stratton.

Wyatt, C., Konduri, V., Eng, J., & Rohatgi, R. (2007). Reporting of estimated GFR in the primary care clinic. *Am J Kidney Dis, 49*(5), 634-641.

Xue, J. L., Frazier, E. T., Herzog, C. A., & Collins, A. J. (2005). Association of heart disease with diabetes and hypertension in patients with ESRD. *American Journal of*

Kidney Diseases: The Official Journal of the National Kidney Foundation, 45(2), 316-323. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=15685510&site=ehost-live

Zhang, L., Zhang, P., Wang, F., Zuo, L., Zhou, Y., Shi, Y., et al. (2008). Prevalence and factors associated with CKD: A population study from beijing. *American Journal of Kidney Diseases: The Official Journal of the National Kidney Foundation, 51*(3), 373-384. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=18295053&site=ehost-live

Zunker, C., & Rutt, C. (2007). Ageless health needs assessment on the U. S.- Mexico border: Ciudad Juarez. *Journal of Cultural Diversity 14*(4), 176-182.

BIOGRAPHICAL INFORMATION

Kathryn Marie Daniel is a native Texan and a product of all Texas schools. She attended public schools in Beaumont, Houston and Richardson, Texas graduating from Pearce High School in Richardson in 1972. She attended Baylor University in Waco, Texas beginning in 1972, graduating first with a BA in Sociology in 1977 followed by a BS in Nursing in 1978. On the Monday following graduation, she began a long and rewarding career working in many settings for Baylor University Medical Center as a Registered Nurse. In the 1980's she attended Texas Woman's University, graduating with a Master of Science in Nursing as a Clinical Nurse Specialist in Medical Surgical Nursing in 1988. After being recruited out of the inpatient acute care setting to work as an advanced practice nurse in a geriatric primary care setting in 1993, Kathryn attended the University of Texas at Arlington from 1995-1997 and completed a post-graduate certificate as an Adult and Gerontologic Nurse Practitioner. Beginning in 2002, she was actively involved in nursing education at Texas Woman's University on the Dallas campus, first on a part time basis and then full time for the following two years. Following almost 10 years of practice in both primary care and long term care, she once again returned to school to complete her PhD at the University of Texas at Arlington.