The Effects of Dietary Creatine Supplementation on Renal Function: A Meta-Analysis of Studies Using Renal Function Markers

by

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Abstract

Over the past few decades the use of dietary creatine monohydrate has emerged as one of the most popular dietary ergogenic supplements. But some researchers have warned that such supplementation may not be entirely safe. This is based on multiple case reports that have indicated a possible link between creatine supplementation and renal dysfunction. Yet several additional studies have not supported a link between creatine supplementation and renal function, leaving many athletes to wonder what the risks of supplementation might be.

This review re-examines data associated with methods used to analyze renal function in individuals who supplemented with dietary creatine monohydrate. The emphasis of this review is on the various renal function marker methods [*i.e*, plasma creatinine (mg/dL), plasma urea (mg/dL), estimated creatinine clearance (ml/min), urinary creatinine (g/24hr), ^{51}Cr-EDTA (ml/min), Cystatin C (mg/L), and urinary urea (g/24/hr)], as well influential factors associated with the individuals that may have the potential to impact renal function (*i.e*., exercise, type of exercise, medicated, diseased, daily creatine intake, and length of creatine cycle). The combination of these data was imported into the statistical program Comprehensive Meta-Analysis (CMA). In all, a total of 21 studies were examined, which included 1,620 control subjects and 961 subjects treated with creatine. Data were compared in a variety of ways, including the comparisons of pre- and post-treatment urinary function markers via an unpaired t-test. The results of the unpaired t-tests found that plasma creatinine and estimated creatinine clearance (eCrnCl) were different before and after creatine supplementation ($p<0.05$), while other renal function markers did not differ. The groups assessed with plasma creatinine and estimated creatinine clearance were then evaluated individually against categorical moderators associated with exercise, medications, duration of creatine supplementation and pre-existing disease. Results indicated that the combination of exercise and consumption of high doses of creatine monohydrate for a short period of time, as well as consumption of the recommended dose for an extended period of time, had the greatest influence on levels of plasma creatinine ($p<0.001$) and estimated creatinine clearance ($p<0.001$).

Because both plasma creatinine and estimated creatinine clearance might change because of changes in creatine intake that are unrelated to renal function, it is recommended that additional clinical studies of creatine supplementation use either Cystatin C or ^{51}Cr-EDTA as the measure of renal function. In this review, neither of these markers changed with creatine supplementation, and they would not be expected to be directly influenced by creatine intake. In summary, the determination of the impact of creatine supplementation on renal function may be confounded by the marker used to assess renal function, and choosing a marker that is not directly affected by creatine intake (independent of renal function) would provide the most reliable results.

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Nomenclature

Abbreviations

ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BUN	Blood Urea Nitrogen
CHO	Carbohydrate
CKD	Chronic Kidney Disease
Cr	Creatine
CreaT	Creatine Transporter
^{51}Cr-EDTA	51 Chromium-Ethylenediaminetetraacetic Acid
Crn	Creatinine
Cys-C	Cystatin C
eCrnCl	Estimated Creatinine Clearance
GFR	Glomerular Filtration Rate
GI Tract	Gastrointestinal Tract
GMP	Good Manufacturing Practices
eGFR	Estimated Glomerular Filtration Rate
Igf-1	Insulin Growth Factor 1
MDRD	Modification of Diet in Renal Disease
PCr	Phosphocreatine
Ucr	Urinary Creatinine Concentration
V	Urine Flow Rate

Units of Measurements

µCi	microuries
dL	deciliter
g	gram
g/24hr	grams per 24 hours
g/d	grams per day
kg	kilogram
MBq	mega Becquerel
mg/24hr	milligrams per 24 hours
mg/dL	milligrams per deciliter
mg/L	milligrams per liter
mL	milliliters
mmol	millimoles
mmol/kg	millimoles per kilogram

Chapter 1: Introduction

1.0 Introduction

Creatine (Cr) is a naturally occurring amino acid, synthesized within the body, as well as supplemented through various exogenous sources. When consumed, creatine is absorbed in the gastrointestinal tract (GI tract), taken up in the plasma, and transported to areas of high energy demand (*e.g.*, skeletal muscle). In skeletal muscle, creatine uptake occurs through sodium and chloride-dependent transporters CreaT [1, 2, 3]. Once absorbed, creatine is stored in the form of phosphocreatine (PCr) until periods of high energy turnover utilizes PCr in the production of adenosine triphosphate (ATP). Hence, the primary biological function of creatine is its role in the production of adenosine triphosphate (ATP) within skeletal muscle tissues. Studies have shown that for individuals who supplement with creatine monohydrate, their total PCr concentrations can increase up to 20%, which may allow for faster regeneration of ATP [2, 3]. This particular feature of creatine monohydrate makes it an attractive dietary supplement for both professional and amateur athletes. Despite its widespread use, the safety of creatine monohydrate supplementation is still debated by consumers, researchers, and clinicians. One of the major questions associated with creatine monohydrate supplementation is whether or not its long-term use and over-consumption can lead to renal dysfunction. This concern arose from several case studies as well as research studies that have linked creatine monohydrate supplementation to acute renal failure [4, 5, 6, 7, 8, 9, 10]. In contrast, a large number of other studies have concluded that creatine monohydrate supplementation poses no significant health concerns at recommended supplementation doses [4, 5, 11, 12, 13, 14, 15, 16].

One possible explanation for the varying conclusions is that many studies use direct plasma creatinine levels, the byproduct of creatine metabolism, or a derivative, such as estimated glomerular filtration rate (eGFR) or estimated creatinine clearance (eCrnCl) as their marker for renal function. But the levels of creatine intake might affect creatinine levels, or the urinary handling of creatinine, independent of changes in kidney function. Another possible explanation is that the studies did not adequately address how confounding factors may influence the previously mentioned methods of evaluating renal function, as well as how age, exercise, pregnancy, diet, muscle mass, medications, disease (*e.g.*, diabetes mellitus, acute renal failure), and gender in both creatine and non-creatine supplemented individuals [12, 17, 18, 19, 20] impact these renal function markers.

The aim of this study is to re-examine the data as they pertain to renal health risks associated with the consumption of the dietary supplement creatine monohydrate. This included a review of the methods used in various studies to determine renal function with a discussion of their appropriateness as renal function markers in the creatine monohydrate dietary supplement population. A meta-analysis on pooled data from previous studies was then employed. The analysis included the incorporation of influential factors, such as age, race, medication, resistance training, and pre-existing renal issues, as well as disease. The overall goal of this evaluation was to investigate the hypothesis that creatine supplementation does not have any direct negative effects on the kidneys.

Chapter 2: Literature Review

2.1 Handling of Creatine by the Body

Creatine is a small amino acid that plays a role in cellular energy balance, particularly in skeletal muscles. It can be synthesized endogenously and it can be obtained from diet. A 70 kilogram (kg) adult has approximately 120 grams (g) of creatine in their body [21, 22]. Of this, 95% is distributed within skeletal muscle, with the remaining 5% distributed within the brain, heart, testes, and kidneys [23, 24].

Endogenous production occurs through a multistep process involving the kidney and liver (Figure 1). Through endogenous production, approximately 1 to 2 grams of creatine can be synthesized in a 24-hour period [5, 21, 22]. Once synthesized, creatine is transported from the liver to skeletal muscle. Creatine can also be obtained from the diet, mainly from meat and fish. The average American diet contains approximately 200g of meat per day, which would yield an equivalence of approximately 1g of dietary creatine monohydrate [25], although this value can vary significantly with diet (see Table 1 for creatine content in food). Dietary creatine is well absorbed from the small intestine through an active transporter process that utilizes sodium and chloride-dependent transporters. Together, endogenous production and dietary consumption and absorption contribute about 2 grams per day (g/d) of creatine to the body's pool.

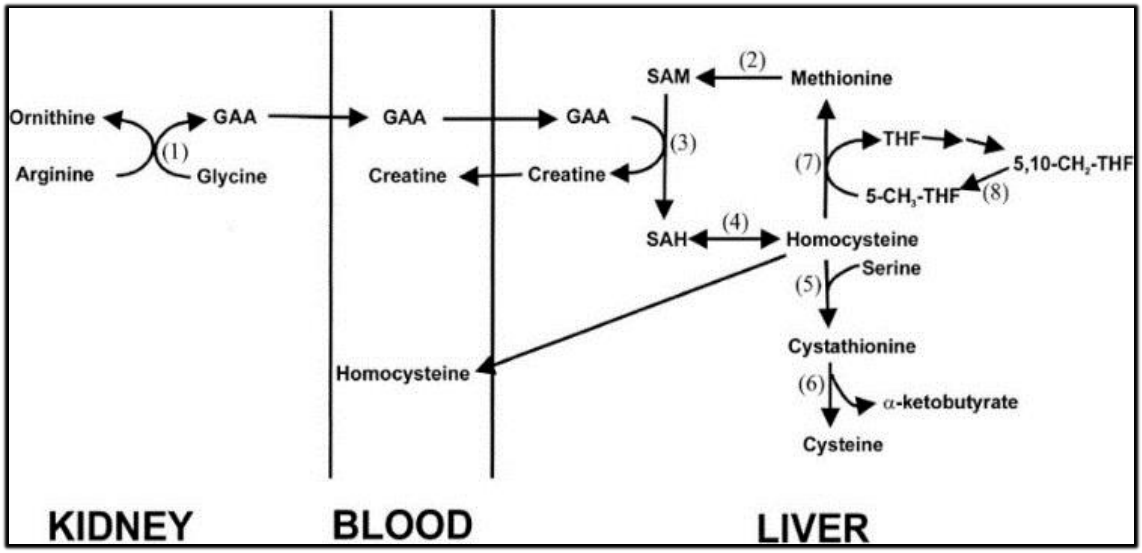

Figure 1: General Overview of Biosynthesis of Creatine [26].

Table 1: Creatine Content in Food [25].

Meat	Creatine Content (g/kg)	Creatine Content (g/lb)
Pork	5	2.3
Beef	4.5	2
Fish/Seafood		
Herring	6.5-10	3-4.5
Salmon	4.5	2
Tuna	4	1.8
Cod	3	1.4
Shrimp	trace	Trace
Other Foods		
Milk	.02	.01
Cranberries	0.1	.05

From the blood plasma, creatine is transported into skeletal muscle cells against a concentration gradient that utilizes the same sodium-chloride-dependent CreaT transporters utilized for absorption within the GI tract [23, 27, 28, 29]. The CreaT

transporter has a high affinity for creatine, where the uptake of creatine is highly reliant on the extracellular concentration of sodium ion (Na^+), with two sodium molecules transported for every creatine molecule [28]. Presently, there are insufficient data to determine the exact regulation of the CreaT transporter, but it has been postulated that the CreaT transporter is likely regulated by fluctuations in extracellular creatine concentrations [30, 31].

Normal creatine storage is approximately 100 to 160 mmol/kg/dm [13, 29, 32]. This value can increase more than 20% after consuming 20g of creatine for five consecutive days [33]. Since skeletal muscle can only absorb a certain amount of creatine from the plasma, 40% to 72% of the original dose in creatine supplementing individuals is excreted in the urine (Table 2). This urinary creatine excretion can be decreased if carbohydrates are consumed with the creatine, because it enhances creatine uptake by skeletal muscle [23, 34, 35] (Table 2, Figure 2). Like carbohydrates, endogenous compounds such as catecholamine, thyroid hormone, and insulin-like growth factor 1 (IGF-1), and exercise have the ability to influence the increased uptake of creatine (1 to 3-fold higher) into skeletal muscle [23, 34, 35]. The subjects in Figure 2 consumed 5g dietary creatine monohydrate with 250mL of hot sugar-free orange juice alone, or followed by 93g of carbohydrates (CHO), which was contained in 500mL of Lucazade sports drink. In summary, Figure 2 depicts that subjects who consumed creatine with carbohydrates excreted a lesser amount of creatine in their urine when compared to subjects who did not consume creatine with carbohydrates.

Table 2: Percentage of Supplemented Creatine that is Excreted via the Kidneys [5].

Dose (g/d)	Duration (days)	Excreted (%)
10	10	73
20	10	67
20	5	67
0.25kg/body weight	5	57
21	5	60
10	5	44
9	5	33
25	5	72
20	1	67
0.1kg/body weight	7	46
20	5	55
20	5	47
21	14	77

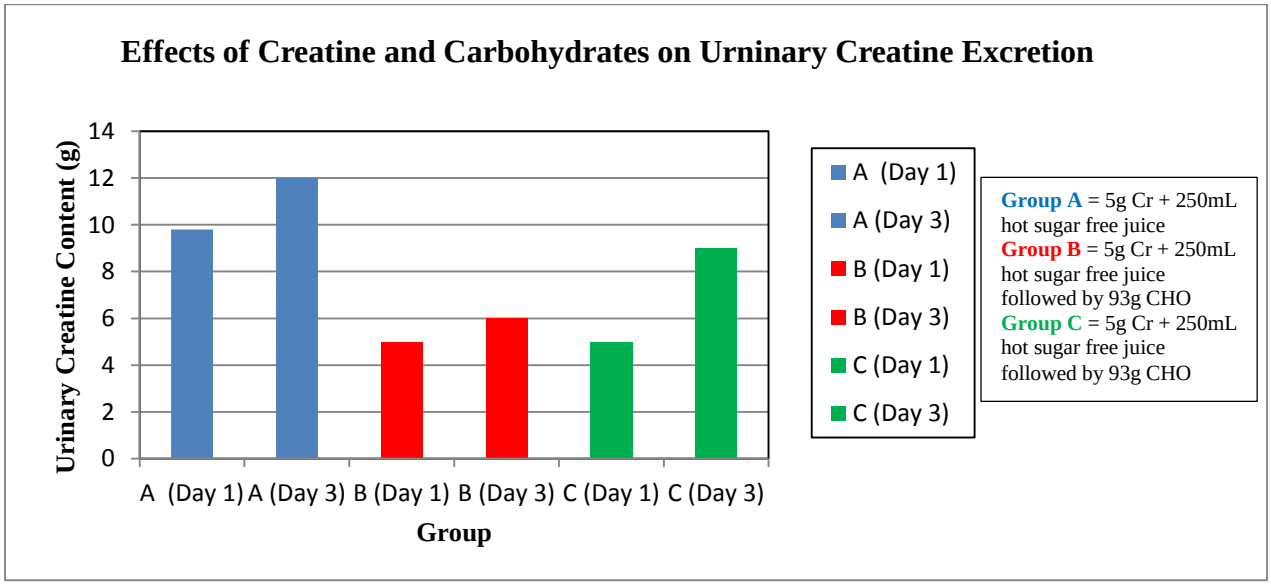

Figure 2: Effects of Creatine and Carbohydrates on Urinary Creatine Excretion [32].

2.2 Intracellular Utilization and Clearance of Creatine

Intracellularly, when creatine enters skeletal muscle tissue, it can exist in either a free or phosphorylated form (PCr) [34]. During periods of high energy usage, ATP levels will be maintained by the creatine kinase catalyzed reaction, where adenosine diphosphate (ADP) becomes phosphorylated by phosphocreatine (PCr) to regenerate ATP and creatine [13, 33, 36, 37] (Figure 3). Both creatine and PCr are spontaneously and irreversibly degraded into creatinine, which is excreted via the kidneys at a rate of approximately 2g per day in healthy, un-supplemented adults [27]. However, the rate of creatinine conversion and the rate at which creatinine is excreted in the urine can vary significantly with changes in exercise level, muscle mass, dosage amount and length of creatine supplementation [23, 35].

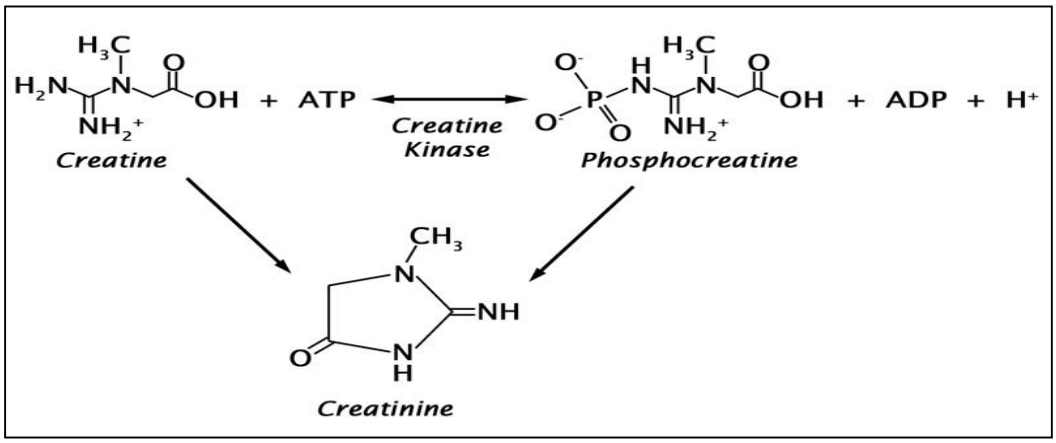

Figure 3: Regeneration of ATP and Creatinine Formation [38].

2.3 Creatine and Creatinine Clearance

Creatine is cleared from the body primarily through its conversion to creatinine and subsequent excretion by the kidneys. This is particularly important because renal function is often assessed using plasma creatinine levels or derivatives of this measure. Under normal conditions, creatinine generation occurs at a constant, predictable rate [23, 28, 29]. However, in supplementing individuals, creatinine generation may not be constant, especially if supplementation levels are high. This is supported by the majority of the data in Figure 4 and Table 3, which is the result of a review study conducted by Poortmans *et al*. [5]. Figure 4 also includes other studies that were utilized in this thesis [39, 40]. As Figure 4 depicts, as creatine supplementation increases, plasma creatinine concentrations generally rise. Additional studies have demonstrated that when individuals exceed the recommended dose (greater than 10g/d) of creatine monohydrate, they may experience a rapid increase in renal elimination of creatine as well as a slight elevation in creatinine clearance [5, 39], both of which are indicative of rising creatinine levels.

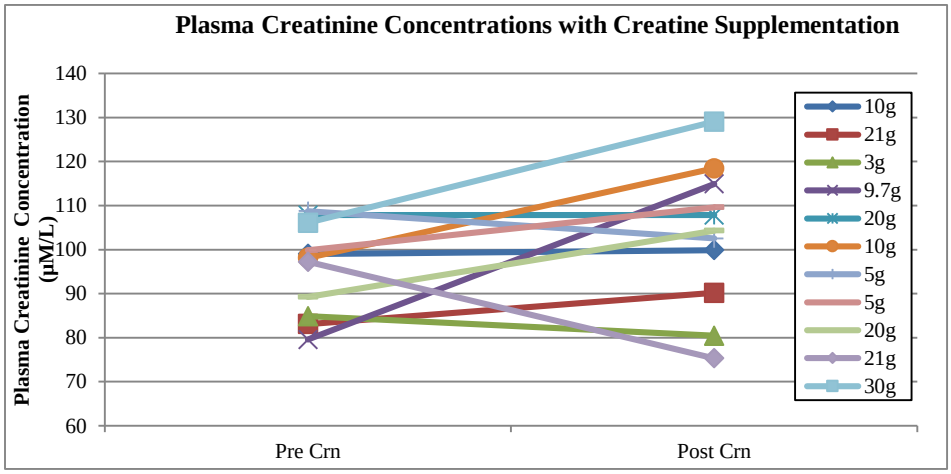

Figure 4: Mean Plasma Creatinine Levels at Various Creatine Doses [5].

Table 3: Mean Plasma Creatinine Levels at Various Creatine Doses and Lengths of Use [5, 40, 41].

				Plasma Crn Level (mg/dL)	
Reference #	Group	Dose (g/d)	Duration (d)	Pre-Cr	Post-Cr
[5]	Cr	20g	5d	0.95	1.03
[5]	Cr	10	5	1.09	1.10
[5]	Cr	21	5	0.91	0.99
[5]	Cr	3	63	0.93	0.88
[5]	Cr	<10	5y	0.86	0.78
[5]	Cr	9.7	4y	0.06	1.26
[5]	Cr	20	7d	0.88	1.19
[5]	Cr	10	56d	1.19	1.30
[5]	Cr	0.3/kg body wt	7	1.08	1.36
[5]	Cr	0.3/kg body wt	7	1.20	1.05
[5]	Cr	5	19m	0.95	1.13
[5]	Cr	5	1y	1.20	1.21
[5]	Cr	5	14w	1.10	0.41
[5]	Cr	0.3/kg body wt	4w	1.23	1.74
[5]	Cr	20	8d	1.60	1.15
[5]	Cr	21	14d	0.98	0.83
[40]	Cr Load	20 + 2000mL of CHO	5d	0.97	1.23
[40]	Cr Load +6	20g Cr + 4g CHO	4d	1.13	1.16
[40]	Cr Maint +Ex	20g Cr (5d), 3g (8w)	n/a	0.76	0.95
[40]	Cr Maint	20g Cr (5d), 3g (8w)	n/a	0.75	1.05
[41]	Cr	30	7	1.07	1.42

2.3.1 Creatinine Clearance

Presently, no established value – nor an accepted estimate – have been determined for the rate at which creatine is converted to creatinine within the skeletal muscle tissue of humans [38, 42]. Factors including dose, body mass of the individual, and exercise may all be contributing factors that influence the amount of creatinine that is excreted in the urine (Table 4 and Table 5) [38, 42]. Though there are insufficient data to support the assumption that creatinine clearance is proportional to muscle mass [42], clinically, it is important that factors such as dose, body mass, and exercise be considered

in order to appropriately estimate the clearance of creatinine within the body. Additionally, studies [32, 35] have shown that consumption of carbohydrates with dietary creatine monohydrate may affect the total amount of creatinine excreted in the urine. It has been postulated that the rate of creatinine that is cleared in the urine is decreased in individuals who consume carbohydrates with dietary creatine monohydrate. These factors can directly affect plasma creatinine levels, which are often used to determine kidney function either through a direct assessment of plasma creatinine, or through calculations of estimated GFR (eGFR) or estimated creatinine clearance.

Table 4: Mean Urinary Creatinine Levels in Creatine Supplemented Subjects [24].

		Urinary Crn (mg/24hrs)		
Dose	**Duration (d (day), m (month), yr (years))**	**Pre-Cr**	**Post-Cr**	**Difference (g/24hr)**
20	6d	990	1360	370
0.5/kg body wt	5d	1410	2090	680
20	4d	1860	2250	390
3	58d	1730	1900	170
9	5d	1630	2210	580
3 to 10	8m-5yr	1800	1530	-270
20	6d	2150	2620	470
10	56d	1380	1850	470
0.3/kg body wt	7d	2340	2720	380
20	4d	1710	1850	140
20	7d	1870	1810	-60
20	6d	1410	2090	680
20	4d	1300	1800	500
5	19m	2820	2670	-150
20	8d	1560	2710	1150
21	14d	1860	2220	360
5	5m	1570	1640	70

2.4 Health Concerns Involving Creatine Supplementation

Though creatine is a naturally produced compound within the human body, several studies have questioned its safety when consumed in high doses (greater than 10g/d) as a dietary supplement [5, 6, 13, 43, 44, 45]. This concern has arisen mainly from case reports in which supplementing individuals have presented with a variety of renal disorders (Table 5) that were determined through the estimation of creatinine clearance. These disorders included acute renal failure (three individuals), interstitial nephritis (three individuals), acute tubular necrosis (one individual), and focal segmental glomerulosclerosis (one individual). Unfortunately, these case reports provide no direct evidence that creatine was the causative agent of the renal failure and it could be that additional factors were involved in some, or all, cases. For example, all subjects in the case studies were on a weight-training regimen that consisted of a high protein diet [4, 8, 9, 46]. Though very vague on the details of these subjects, it was disclosed that in conjunction with a daily exercise regimen, some subjects consumed daily medications [6, 46], multiple dietary supplements besides creatine [9, 46], and some subjects may have had predisposing medical conditions prior to creatine supplementation (*e.g.*, steroid-responsive nephrotic syndrome, and diabetes) [9, 46]. These factors leave open the possibility that creatine itself is not the culprit of renal failure in some, or all, of these case studies.

Table 5: Summary of Case Studies Reporting Renal Dysfunction with Creatine Supplementation [4, 6, 8, 9, 43, 46].

Reference #	Age	Dose	Length	Initial Serum Creatinine (mg/Dl)	Intra-Serum Creatinine (mg/Dl)	Estimated Creatinine Clearance (mL/min)	8 weeks later Estimated Creatinine Clearance	Blood Urea Nitrogen (BUN) (mg/dL)	Diagnosis	Complicating Factors
[4]	X	20g/d x 5d, 3g/d x 5d, 1g/d x 21d	1 month	4.3	6.2	X	X	X	Interstitial Nephritis and Renal Failure	Bodybuilder (high consumption of protein)
[9]	24	5g/d x 3d	6 months	3.8	X	30	X	30	Interstitial Nephritis and Acute Renal Failure	Consumed multiple supplements
[46]	42	5g x 4/day, 5g/d	2 months	1.4	3.50	X	X	77	Acute Renal Failure and lactic acidosis	Bodybuilder Diabetic
[8]	18	20g/d x 5d, 1g/d x 6 weeks	7 weeks	0.45	2.28	X	X	X	Acute Renal Failure, and Acute Tubular Necrosis	Border lin high blood pressure (150/90 mmHg)
[6]	25	15g/d x 7d, 2g/d x 7 weeks	8 Weeks	1.80	2.04	61	54	X	Focal Segmental Glomerulosclerosis	Pre-Existing renal dysfunction, medicated (cyclosporine)
[43]	20	20g/d	4 weeks	1.40	2.30	X	X	X	Acute Interstitial Nephritis	None

Another complicating factor when determining if creatine supplementation negatively affects kidney function is the inconsistency of dose. Creatine monohydrate is a popular supplement, but historically, dosages have varied and are up to the user. Initially, manufacturers proposed that users of creatine monohydrate begin with a loading phase of 5g consumed four times daily for four weeks, followed by a maintenance dose of 5g per day for three weeks [9, 47]. Yet most studies report average daily doses were between 10-15g/d [9, 47]. Further, surveys have found that 80% of collegiate athletes exceeded the recommended dose of creatine monohydrate (greater than 10g/d) [9], while others were unaware of how to properly dose this supplement [47]. This may be of importance because there is the potential for very high doses to alter the body's metabolism of creatine, converting it to toxic compounds, such as formaldehyde and methylamine [24]. Therefore, researchers have proposed that one might expect renal damage could occur in those individuals that supplement with long-term at doses of creatine exceeding 20 g/d [5, 23]. Because most studies likely utilized self-reporting of creatine dosing by the subjects, there is the potential that some were dosing above the amount they were reporting. Although there is a potential that this occurred, this paper is assuming that the reported supplementations are correct, and that if incorrect assessments of kidney function occurred, it was more likely because of the methods used to assess kidney function.

2.5 Assessing Kidney Function in Creatine Supplementing Individuals

The importance of estimating renal function during clinical studies is that the estimate can be used to examine the effects certain substances may pose on the renal system. Studies reviewed in this thesis assessed renal function through the Jaeffe

Reaction, and the Cockcroft-Gault Equation (Equation 1). The Jaeffe Reaction is utilized to directly measure the serum creatinine concentrations in the subject [36, 40, 41, 48, 49, 50, 51, 52, 53]. Once the serum creatinine concentration is determined through the Jaeffe Reaction, some studies utilized the serum creatinine concentration to estimate the creatinine clearance (eCrnCl or eGFR) by using the Cockcroft-Gault Equation. It should be noted that in order to estimate CrnCl with the Cockcroft-Gault Equation, the subject's weight and age need to be available to the researcher [36, 49, 51, 52]. Equation (1) shows the Cockcroft-Gault Equation:

$$Estimated\ CrnCl\ (\frac{mL}{\min}) = \frac{(140-Age)\times Weight\ (kg)\times 0.85\ (if\ female)}{72\times Serum\ Creatinine\ (\frac{mg}{dL})}. \quad (1)$$

Estimated CrnCl is commonly used to assess renal function because it is easier than measuring the "true" GFR, which requires urine collection and measurements of urinary concentrations of the marker compound. If creatinine is not used as the marker compound, then true GFR measurements also require the IV administration of either inulin or a radioactive compound. The estimation of GFR (CrnCl) via the Cockcroft-Gault formula has been found to produce acceptable values for the estimated GFR under many circumstances [12, 51, 52]. This is because most individuals have a very consistent rate of creatinine formation, keeping plasma creatinine levels constant as long as renal function is normal. In such individuals, the relationship between plasma creatinine levels and GFR is shown in Figure 5. The corresponding stages of renal disease associated with the changes in GFR are shown in Table 6. But as previously discussed, those who supplement may have an increased rate of creatinine production, which could cause the

eGFR to underestimate the true GFR, leading to the incorrect assessment of renal function. The following sections take a closer look at how kidney function can be assessed and the specific methods that were used in the studies reviewed for this thesis.

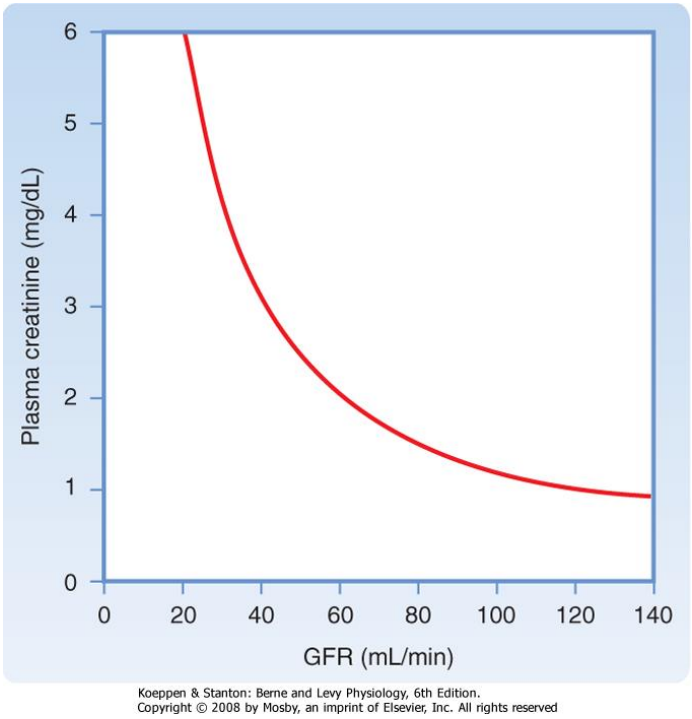

Figure 5: Relationship between GFR and Plasma Creatinine [54].

Table 6: Stages of Kidney Disease [55].

Stage	Description	GFR mL/min/1.73 m^2
1	Kidney damage with normal or increased GFR	90
2	Kidney damage with mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure	<15 (or dialysis)

In the literature review for this thesis, eight of the nine studies that estimated GFR did so by utilizing the Jaffe Reaction [36, 41, 48, 50, 51, 52, 53], while one study [40] utilized an unspecified technique to estimate plasma creatinine levels. The Jaffe Reaction utilizes a blood sample that is suspended into an alkaline solution consisting of picoric acid. In the presence of this solution, the creatinine reacts with the picoric acid, in which the chemical reaction results in a color. Using the solution, the concentration of creatinine in the solution is read through its absorbance in a spectrophotometer [40, 56]. The normal range for plasma creatinine concentration is between 0.5 to 1.0 mg/dL in women and 0.7 to 1.2 mg/dL in men [40, 56]. However, it's to be expected that these values may reach as high as 2.0 mg/dL in subjects with greater muscle mass [40, 56]. Once the plasma creatinine concentration has been determined, it can either be directly used to assess renal function, or it can be taken a step further to be utilized to estimate the GFR through the Cockcroft-Gault Equation -- Equation (1).

Though the Jaffe Reaction is very common in clinical practice, it is associated with some drawbacks. For instance, compounds similar in structure as creatinine, or specific chromogens (as they can relate to certain diseases), have the potential to interfere with true creatinine concentrations. Examples of possible interferents include both glucose and proteins, which are common supplements utilized by consumers who participate in resistance training. The effect of these interferents is the possibility that they can lead to an overestimation of the plasma creatinine, resulting in a decreased eGFR, which may not be reflective of true GFR. Another major drawback of the Jaeffe Reaction – as well as the Cockcroft-Gault Equation (discussed in next section) to estimate GFR, is that those individuals who supplement with creatine monohydrate

exhibit a greater plasma creatinine concentration, and utilizing plasma creatinine concentration as an estimate of renal function therefore may not be the best method to determine renal function, since it may underestimate the true GFR [12, 52].

2.5.1 Blood Urea Nitrogen (BUN)

Blood urea nitrogen (BUN) is another marker that is used clinically to evaluate renal function. Although BUN is not one of the more commonly used methods to evaluate renal function, the idea behind using BUN is that it is a non-creatinine-based renal function marker. More specifically, BUN measures the amount of urea nitrogen in the plasma, which rises with decreased renal function, and low blood flow to the kidneys, as a result of dehydration or heart failure. Because creatine monohydrate has the potential to cause dehydration, the use of BUN as a renal function marker may be affected by individuals who consume dietary creatine monohydrate. In the literature reviewed for this thesis, seven studies utilized BUN to evaluate renal function [11, 40, 48, 50, 52].

Similar to creatinine, urea is an inexpensive estimate marker used to analyze renal function; however, like any creatinine-based marker, it, too, has drawbacks. For instance, during episodes of volume depletion (*e.g.*, dehydration, vomiting, and diarrhea), which are common side effects associated with creatine supplementation, GFR will remain the same, but urea is reabsorbed in the tubules of the kidney, which results in an increase in plasma concentration of urea, which would signify renal dysfunction [57]. Other factors -- such as high protein intake, corticosteroid/medication use, and hyper-catabolism -- have all been shown to increase BUN concentration [57]. Like creatinine clearance, the

use of urea as a marker of renal function may not be the most accurate indicator in this context [5, 13, 15, 40, 44, 48].

2.5.2 ^{51}Cr-EDTA

Clinically, the "gold standard" methods of evaluating renal function include ^{51}Cr-EDTA, and Cystatin C. The major advantages that these methods have over traditional methods (*i.e.*, estimated creatinine clearance, plasma creatinine, and BUN) is that they are non-creatinine-related markers of GFR, they are freely filtered by the kidneys, and they are not known to be impacted by dietary changes, drugs, and volume changes [57].

^{51}Cr-EDTA is an exogenous renal function marker that has the potential to accurately calculate GFR in individuals who supplement with dietary creatine monohydrate [46]. In the literature reviewed for this thesis, it was found that three studies examined renal function using ^{51}Cr-EDTA [12, 50, 52] in which a bolus injection of 3.7MBq (100μCi) was administered, and blood samples were collected and the plasma clearance rate was calculated using a slope-intercept method [16, 34, 58] which is based on the rate that ^{51}Cr-EDTA leaves the blood.

Clinically, when compared to traditional methods, ^{51}Cr-EDTA provides evidence that confounding factors may influence GFR measurements, most notably individuals who consume foods high in creatine concentration or individuals who supplement dietary creatine supplementation [21, 33, 41]. Further, Chaves *et al*. [59] showed that for subjects who suffered from renal artery stenosis while consuming medications, the use of ^{51}Cr-EDTA to measure renal function identified captopril-induced changes in GFR, which normally would not be identified using traditional methods [21] .

One of the drawbacks of using ^{51}Cr-EDTA is that it is a radioactive nucleotide. Other drawbacks include the fact that ^{51}Cr-EDTA administration is invasive and requires a facility that can store and dispose of radioactive material. More important than these drawbacks, Chaves *et al.* [59] concluded that the utilization of ^{51}Cr-EDTA clearance does not have the ability to independently measure the function of individual kidneys. Though ^{51}Cr-EDTA is a potential alternative to traditional renal function measurements, Cystatin C is an endogenous marker that combines all the advantages of ^{51}Cr-EDTA, but limits the possible side effects and drawbacks.

2.5.3 Cystatin C

Another alternative method for estimating GFR is through measurement of the protein Cystatin C in the plasma. For the past several years, there has been an increase in evidence that suggests and supports the use of Cystatin C as an effective alternative marker for measuring proper renal function (GFR) when compared to other traditional and alternative methods. Several factors make Cystatin C an attractive alternative, including the following factors: Cystatin C is produced at a constant rate by nucleated cells; Cystatin C is freely filtered by the glomerulus; Cystatin C is reabsorbed and catabolized, not secreted by the renal tubules; Cystatin C is unaffected by food ingestion [24, 33]. In the literature review for this thesis, two studies were found to have used Cystatin C as a marker for renal function [1, 60]. In these studies, the measurements for Cystatin C were obtained through a plasma sample that was analyzed with a BN II Nephelometer and a particle-enhanced turbidimetric immunoassay [1, 60]. Clinically, the normal ranges for this renal marker are from to be 0.57 to 0.96 mg/L in males, and 0.5 to 0.96 mg/L in females [1].

One of the main advantages of using Cystatin C is that it is more sensitive to actual changes in GFR, especially in the early stages of Chronic Kidney Disease (CKD) when compared to creatine-based GFR estimates [56]. For instance, when kidney function declines, as seen in renal dysfunction/disease, not only does GFR decline, but the levels of Cystatin C rise [56]. Other reviews have claimed that Cystatin C levels are not influenced by such factors such as age, sex, height, and muscle mass [56]. Though these factors may not influence Cystatin C concentrations, Rule *et al*. [61] claimed that thyroid function, the use of corticosteroids, acute kidney injury, Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease (CKD) in diabetics, and medications may have the potential to interfere with accurate measurements of Cystatin C because of the fact that these factors can affect the concentration of circulating Cystatin C. Previous to these claims, no standard measurement was implemented in the calculation of concentrations of Cystatin C. Following these research studies, Rule *et al.* [61] proposed a standard equation for calculating GFR using Cystatin C because Cystatin C was found to be highly correlated with GFR [3, 18]. Equation (2) presents the standard equation:

$$\text{GFR (ml/min)} = 99.43 \times (\text{cys C})^{-1.5837} \ . \qquad (2)$$

2.5.4 Summary of Mechanisms Used to Assess Renal Function

In summary, kidney function can be assessed through a variety of methods that utilize exogenous and endogenous sources to estimate GFR. Though estimated creatinine clearance and plasma creatinine remain the most commonly used markers clinically for

evaluating renal function, other renal function markers have been proposed that may be superior to estimated creatinine clearance and plasma creatinine for GFR measurements. These markers include ^{51}Cr-EDTA, and Cystatin C. However, even though each method poses possible limitations (Table 7), the use of "gold standard" methods for evaluating renal function may lead to more accurate analyses of renal function in individuals who supplement with creatine monohydrate, in part because of specific reasons associated with each method.

Table 7: Renal Function Markers [13].

Marker	Description	Method	Limitations
Blood Urea Nitrogen (BUN)	Nitrogenous end product of protein metabolism	Blood Sampling	Reabsorbed at various rates Variable generation rate Levels dependent on renal and non- renal factors
Creatinine (eGFR, eCrnCl)	Byproduct of Muscle Breakdown Functional marker	Blood sampling eCrnCl	Secreted at variable rates Significant variability in interpersonal generation
Cystatin C	Filtered low molecular weight protein	Blood/Urine sampling	Limited availability
^{51}Cr-EDTA	Radiopharmaceutical agent	Plasma clearance	Requires facilities for storage/disposal of radioactive materials

2.6 Study Goal

There is still some debate as to whether or not creatine supplementation can lead to renal dysfunction, based mainly on correlative case studies. One confounding factor when determining if there is a link between creatine levels and renal dysfunction is how renal function is assessed. As discussed, creatine supplementation, and the characteristics of athletes might confound the most common measures of renal function. The goal of this

project was to revisit the published data related to various methods used to measure renal function as it pertains to renal health risks associated with the consumption of dietary creatine monohydrate. This included a review of standard methods for estimated GFR measurement, specifically creatinine clearance, and plasma creatinine as an appropriate marker of renal dysfunction in these individuals. A meta-analysis on pooled data from previous studies was employed. The analysis included the incorporation of influential factors that may affect various methods used to measure renal function, such as age, race, medication, resistance training, and pre-existing renal issues, as well as disease. The overall goal of this evaluation was to provide evidence for the hypothesis that creatine supplementation does not have any direct negative effects on the kidney.

Chapter 3: Methods

3.0 Studies

All available research was collected on investigations concerning the effects of creatine monohydrate supplementation on renal function. The majority of the research was identified from December 2011 to August 2015, using online databases (PubMed, Science Direct, EBSCOhost, and Google Scholar), with the following keywords: *creatine monohydrate supplementation and renal function*, *renal function and creatine*, *creatine supplementation, the effects of creatine supplementation, renal function, creatine monohydrate,* and *renal function and supplements*. Through this process, 31 articles were collected that evaluated renal function using various renal function markers methods (*i.e.*, plasma creatinine, urinary creatinine, plasma urea, urinary urea, estimated creatinine clearance, ^{51}Cr-EDTA, and Cystatin C) in adult humans who supplemented with creatine monohydrate. However, because of the specifications and criteria associated with the project meta-analysis software, only 21 articles were utilized in this thesis study.

Data from the papers were entered into Microsoft Excel™. This included the number of subjects in both the control and treatment groups (Table 8), and a breakdown of the types of studies with respect to each renal function marker. All of the studies utilized in this meta-analysis review reported their results for estimated creatinine clearance through the use of the Cockcroft-Gault equation, and the Jaeffe Reaction was employed to evaluate plasma creatinine when it was used as a marker.

Table 8: Summary of Publications Used in the Current Study. In all studies, the control groups represent individuals who did not take creatine, while the treatment groups were those who ingested creatine supplements.

Reference Number	Renal Function Analysis Method	Method Used to estimate GFR	# Individuals in Group	# Treated Group
[41]	Plasma Creatinine, Urinary Creatinine	Jaeffe Reaction	5	5
[5]	Plasma Creatinine, Plasma Urea, estimated Creatinine Clearance	Jaeffe Reaction, Cockcroft-Gault	85	9
[50]	Plasma Creatinine, Plasma Urea, Cr-EDTA	Jaeffe Reaction	14	12
[15]	Plasma Creatinine, estimated Creatinine Clearance	Jaeffe Reaction, Cockcroft-Gault	13	10
[40]	Plasma Creatinine, Plasma Urea	Jaeffe Reaction	19	29
[48]	Plasma Creatinine, Plasma Urea, Urinary Creatinine, Cystatin C	Jaeffe Reaction	17	31
[53]	Plasma Creatinine, Urinary Creatinine	Jaeffe Reaction	10	10
[34]	Plasma Creatinine, Urinary Urea, estimated Creatinine Clearance, Urinary Creatinine, Cr-EDTA	Jaeffe Reaction, Cockcroft-Gault	12	13
[47]	Plasma Creatinine, Plasma Urea, Urinary Urea, Urinary Creatinine	Jaeffe Reaction, Cockcroft-Gault	11	12
[52]	Plasma Creatinine, Plasma Urea, Urinary Urea, estimated Creatinine Clearance, Urinary Creatinine, Cr-EDTA	Jaeffe Reaction, Cockcroft-Gault	11	13
[49]	Plasma Creatinine, Plasma Urea, estimated Creatinine Clearance, Urinary Creatinine	Jaeffe Reaction, Cockcroft-Gault	44	54
[51]	Plasma Creatinine, estimated Creatinine Clearance	Jaeffe Reaction, Cockcroft-Gault	15	15
[11]	Plasma Urea		6	88
[62]	Urinary Urea, Urinary Creatinine		9	19
[14]	Urinary Urea, Urinary Creatinine		10	10
[13]	Urinary Urea		19	15
[63]	Urinary Creatinine		11	20
[35]	Urinary Creatinine		12	12
[60]	Urinary Creatinine		10	9
[58]	Urinary Creatinine		9	8
[64]	Cystatin C		9	9

3.1 Statistical Analysis

Multiple statistical tests were performed using the statistical program Comprehensive Meta-Analysis as summarized in Figure 6 [65]. The first analysis involved the evaluation of individual group means between each renal function marker (*i.e.*, pre-treatment, post-treatment, pre-control, and post-control). In order to perform these statistical tests, the information entered into Comprehensive Meta-Analysis incorporated the following data: renal function data for each marker for pre- and post-treatment, pre- and post-control, standard deviation for each group, and numbers of subjects in each group (Appendix A). Using the entered data, the Comprehensive Meta-Analysis software calculated a corresponding p-value and standard error between each individual group mean. Data were graphed in Microsoft Excel.

The second analysis compared the pre- and post-group means of the treatment and control group for each renal function marker. The analysis between these groups utilized an unpaired t-test that evaluated the groups based on a calculated p-value. If the data between the group means presented any significant difference ($p<0.05$), it was further analyzed by incorporating the data for several categorical moderators that were common amongst the studies. Similar to the comparison between group means, the group means that indicated a significant difference utilizing categorical moderators were evaluated based on the calculated p-value. The categorical moderators utilized included: (1) whether or not the test subjects exercised, (2) the type of exercise performed (no exercise, cardio, resistance training, or a combination of both), (3) whether or not the test subjects consumed medication during the trials, (4) whether or not the test subjects suffered from any disease, (5) the amount of creatine consumed daily, and (6) length of time the test

subjects consumed creatine (creatine cycle) (Appendix D). In order to make the data for the categorical moderators compatible with the Comprehensive Meta-Analysis program, they were coded as shown in Table 9.

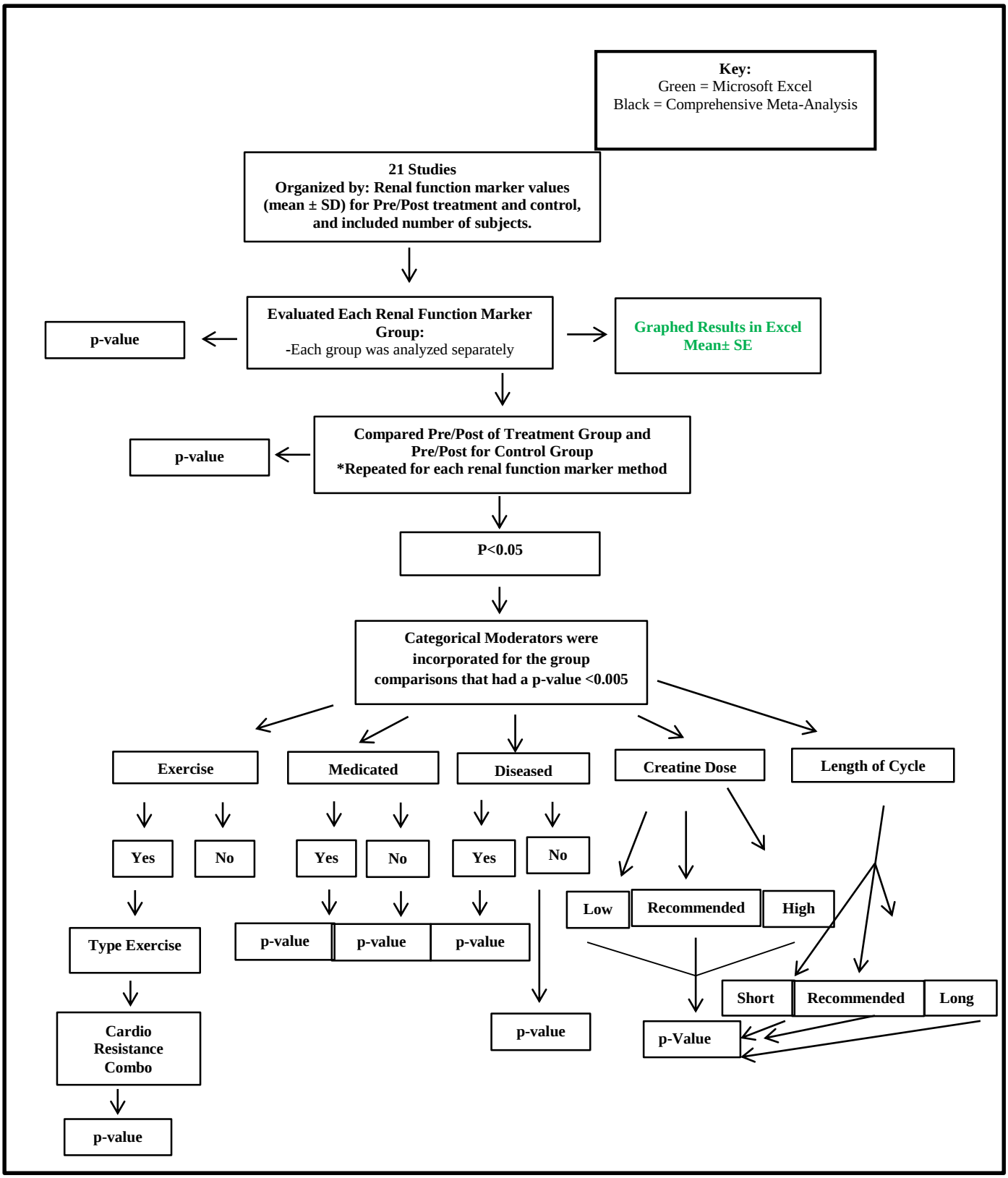

Figure 6: Process Used for Determining which Statistical Tests were Performed.

Table 9: Coded Categorical Moderators for Meta-Analysis Statistical Program.

Variable	Original Data	Coded Data
Exercise	Yes	Yes
	No	No
Type of Exercise	None	None
	Cardio	Cardio
	Resistance and Cardio	Res/Card
	Resistance	
Medicated	Yes	Yes
	No	No
Diseased	Yes	Yes
	No	No
Daily Creatine Intake (g)	0-5	Low Dose
	5.1-10	Recommended
	10+	High Dose
Length of Cycle (days)	0-29	Short
	30-45	Recommended
	45+	Long

Chapter 4: Results and Discussion

4.0 Comparison of Renal Function Markers in Comprehensive Meta-Analysis

The data and the results from the 21 studies included in the group means analysis are presented in Table 10. This analysis found significant differences ($p<0.05$) among the Pre-Treatment and Post-Treatment groups when plasma creatinine and eGFR were used as the renal function markers. When other measures were used to assess renal function, there were no significant differences between pre- and post-supplementation. Graphically, these data are presented in Figure 7 by means of boxplots, which represent ranges of data with respect to each renal function indicator and each group. For example when ^{51}Cr-EDTA was employed as the marker, the pre-treatment group was associated with ranges of approximately 88 milliliters per minute (ml/min) up to approximately 98 ml/min. The post-treatment group was associated with a higher range, from approximately 92 ml/min to approximately 104 ml/min. Table 10 indicates statistically significant differences in the ranges for the pre- and post-treatment groups associated with the plasma creatinine and estimated creatinine clearance markers. Consistent with previous studies [1, 9, 43, 44, 50, 58] there is significant difference between pre-and post-treatment urinary creatinine. Since urinary creatinine is not one of the popular methods used to measure renal function (*i.e.*, plasma creatinine, estimated creatine clearance), it is a creatinine-based marker that can be used as a reference point to compare plasma creatinine and estimated creatinine clearance.

Table 10: Summary of Renal Function Marker Data.

	Plasma Creatinine (mg/dL)	**Plasma Urea (mg/dL)**	**Estimated Creatinine Clearance (ml/min)**	**Urinary Creatinine (g/24hr)**	**^{51}Cr-EDTA (ml/min)**	**Cystatin C (mg/L)**	**Urinary Urea (g/24hr)**
Pre-Treatment Mean/SD	N=194 1.17±0.07	N=239 15.79±1.02	N=95 134.16±11.05	N=241 1.07±0.11	N=38 92.79±4.84	N=71 0.80±0.01	N=83 17.65±2.23
Post-Treatment Mean/SD	N=194 1.28±0.13	N=157 15.65±0.97	N=95 112.01±4.45	N=241 1.26±0.15	N=38 97.57±6.14	N=71 0.77±0.03	N=83 18.62±1.68
Pre-Control Mean/SD	N=253 1.16±0.10	N=298 15.03±0.74	N=170 163.15±16.32	N=292 1.04±0.10	N=37 94.87±6.46	N=43 0.83±0.03	N=81 17.79±3.55
Post-Control Mean/SD	N=253 1.89±0.10	N=217 14.31±0.83	N=170 134.04±9.84	N=292 1.07±0.09	N=37 96.53±7.10	N=43 0.85±0.06	N=81 18.68±3.06
Group Comparison p-Values	**Plasma Creatinine**	**Plasma Urea**	**Estimated Creatinine Clearance**	**Urinary Creatinine**	**^{51}Cr-EDTA**	**Cystatin C**	**Urinary Urea**
Pre-Treatment Pre vs Post-Treatment	<0.001	0.708	0.001	0.003	0.199	0.194	0.054
Pre-Control vs Post-Control	0.391	0.08	0.059	0.183	0.250	0.756	0.277

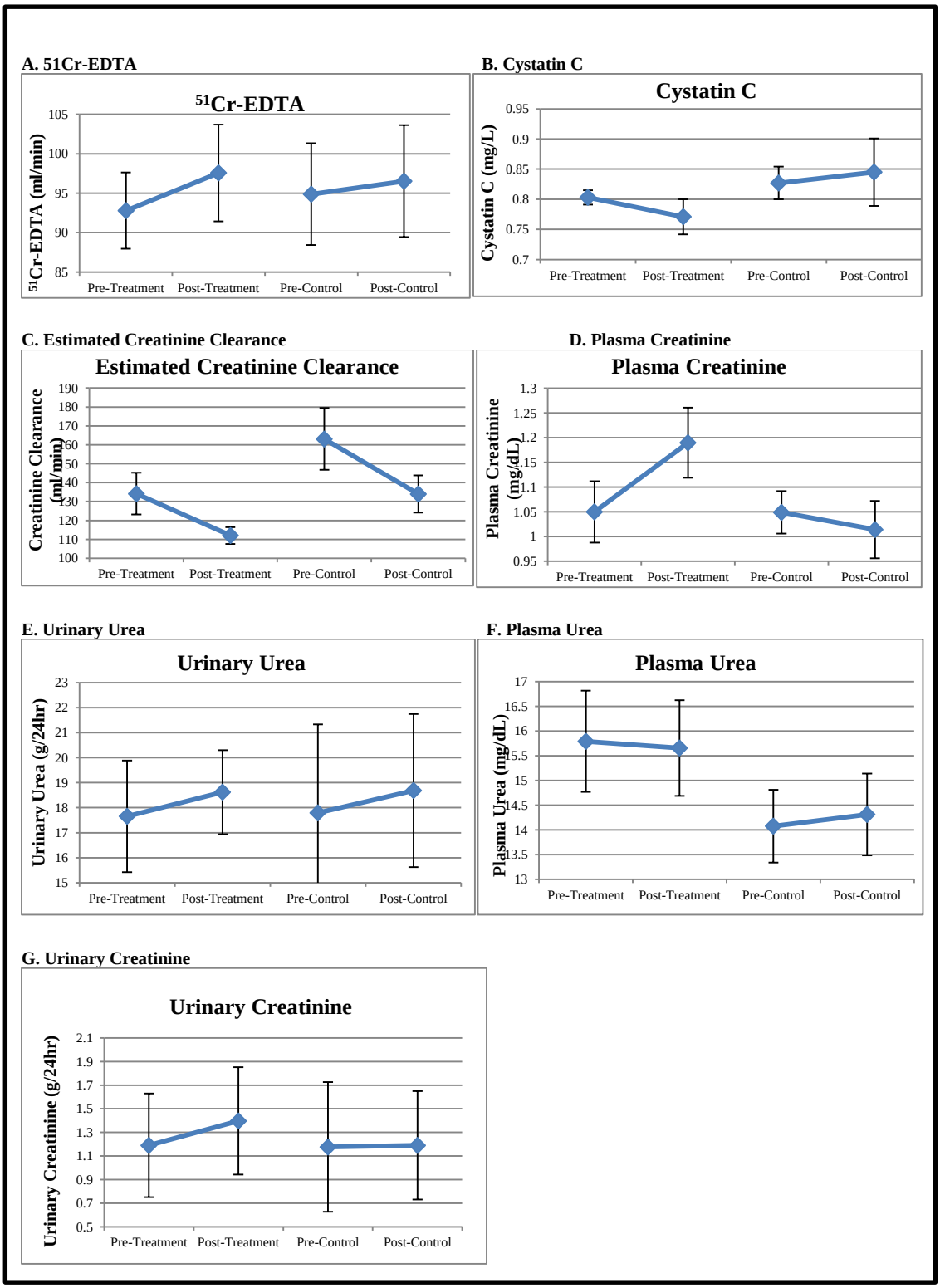

Figure 7: Summary of Graphed Data from Microsoft Excel.

4.0.1 Statistical Analysis: The Use of Categorical Moderators in Comprehensive Meta-Analysis

The incorporation of categorical moderators was utilized and applied specifically to the two renal function markers that featured significant differences between the mean values in Table 10: Plasma Creatinine and estimated Creatinine Clearance. The results of incorporating categorical moderators into the analysis and their significance on the mean data can be seen in Table 11 along with their corresponding p-value. If the categorical moderator information was not available for analysis, it is represented by an X.

Table 11: Summary of the Effects of Categorical Moderators on Data.

	Plasma Creatinine	Estimated Creatinine Clearance
Overall p-Value	<0.001	0.001
Moderators:		
Exercise		
Yes	<0.001	0.001
No	<0.001	X
Type of Exercise		
None	0.30	X
Resistance	0.003	0.783
Cardio	<0.001	X
Res/Card	<0.001	<0.001
Medicated		
Yes	X	X
No	<0.001	0.001
Diseased		
Yes	0.152	0.783
No	<0.001	<0.001
Creatine Dose		
Low Dose	0.239	0.610
Recommended	0.012	0.014
High Dose	<0.001	0.143
Length of Cycle		
Short	<0.001	0.114
Recommended	0.210	X
Long	<0.001	0.007

The data presented in Table 11 display the effects each categorical moderator had on the pre- and post-data values for the Treatment and Control groups for plasma creatinine and estimated creatinine clearance. As the data indicate, certain categorical moderators, or the combination of several moderators, had a profound effect on the mean data. Though exercise and non-exercise were significant in plasma creatinine, it can be concluded that healthy adult individuals who consumed a high dose of creatine for both

short and an extended period of time were associated with the most significant effect on the mean data, whether or not the individuals were subjected to an exercise regimen. Further, healthy adult individuals who were engaged in resistance and cardio training, and who consumed the recommended amount of creatine for an extended period of time, were associated with the greatest impact on the mean data for estimated creatinine clearance.

4.1 Discussion of Results

The overall aim of this thesis project was to conduct a meta-analysis that reviewed renal function markers in test subjects who supplemented with dietary creatine monohydrate. This study differs from most other studies that have investigated the effects of creatine supplementation on kidney function by evaluating each type of renal function marker independently and then comparing the renal function markers to each other. The analysis further incorporated influential factors that provided further insight into non-supplementation factors that may also have an impact on renal function markers. The results from this study provide evidence that the use of dietary creatine monohydrate in healthy adults who were subjected to resistance and cardio training caused an increase in estimated creatinine clearance and plasma creatinine, but not in other renal function markers that are not directly linked with the creatine metabolic pathways.

As expected with a meta-analysis, the results found in this thesis project were in agreement with other investigations that examined the effects of creatine supplementation on kidney function when using the renal function markers plasma creatinine and estimated creatinine clearance [1, 9, 43, 44, 47, 50, 58]. Interestingly, the individual studies utilized for the meta-analysis found significant difference between six treatment

groups that evaluated renal function with the marker plasma creatinine. Two of the six treatment groups consumed dietary creatine monohydrate mixed with carbohydrates for their testing [1]. A deeper investigation of these studies found that the subjects utilized by Bender *et al*. [48] consumed the recommended dosage of creatine with carbohydrates for a period of time that was greater than the recommended cycle. Subjects tested in Juhn *et al*. [47] consumed 10g of creatine daily with carbohydrates, but they also consumed dietary supplements other than creatine monohydrate. More importantly, since creatine monohydrate spontaneously degrades into creatinine, it could be argued that the significantly elevated plasma creatinine concentrations found in Juhn *et al*. [47] may be attributed to the consumed creatine solution, which was consumed the day of clinical testing, and which was pre-mixed and stored overnight. These findings contradict other studies that claim the uptake of creatine monohydrate into skeletal muscle is enhanced when consumed with creatine carbohydrates [18, 40]. However, these studies only evaluated plasma creatinine, and not estimated creatinine clearance.

This thesis investigation found no significant difference in renal function in test subjects who consumed dietary creatine monohydrate, and whose renal function was evaluated with the "gold standard" methods ^{51}Cr-EDTA and Cystatin C [1, 16, 58]. Though the use of "gold standard" methods was limited to five studies [48, 50, 52, 64], these studies also utilized estimated creatinine clearance and plasma creatinine as additional renal function markers for their creatine-supplemented subjects. Analysis of these two studies found no significant differences in estimated creatinine clearance ($p=0.783$) and plasma creatinine ($p=0.500$) (Appendix E).

Ever since creatine supplementation gained popularity, there have been concerns about its safety, especially in regard to renal function. Much of this concern has been derived from case studies that report increased renal function markers in single individuals [4, 8, 38, 42, 53]. A challenge with these reports is that the subjects had other potentially complicating factors including previous medical history, use of anabolic steroids, as well as consumption of extremely high doses of creatine monohydrate [42, 53]. For these reasons, along with the fact that case studies do not include a control group, these papers were not statistically evaluated in the current meta-analysis.

As this current study indicates, and as might be expected from the metabolic pathway of creatine, the use of estimated creatinine clearance and plasma creatinine may not be an accurate indicator of renal function in creatine-supplementing individuals. This has been previously explored by others, who reported that these markers may provide false-positive diagnosis of decreased renal function [1, 9, 44, 50, 58]. The cause of false-positive diagnosis has been attributed to creatine supplementation directly leading to increased levels of plasma creatinine through its metabolic pathway, and which can be independent of renal function. This is analogous to the condition of rhabdomyolysis, where an increased rate of muscle cell breakdown drives up plasma creatinine levels, making the subject look like they have renal dysfunction [42].

Another complicating factor when using creatinine as a renal function marker is that individuals with increased muscle mass, or those who participate in resistance training, or both can also show elevated plasma creatinine [7, 12, 17, 18, 40]. It has been shown that creatinine degradation is directly proportional to muscle creatine content [49]. Though some of the background information was limited for the meta-analysis, it could

reasonably be expected that individuals who supplement with creatine would have a greater muscle mass, and participate in a greater level of resistance training than the general population.

Based on evidence that creatine supplementation can likely impact plasma creatinine levels independent of renal function, the use of either plasma creatinine or creatinine clearance as a marker of renal function in such individuals is not recommended. The use of non-creatinine-related GFR markers, such as Cystatin C, and ^{51}Cr-EDTA is instead recommended.

Though the use of Cystatin C and ^{51}Cr-EDTA methods to measure renal function markers is a more attractive way to evaluate renal function in individuals who supplement with dietary creatine monohydrate, the analysis of these markers does pose some possible disadvantages. For example, the analysis of each marker is time consuming, costly, requires intravenous administration, and is labor intensive [60]. However, in order to get an accurate renal function measurement in these individuals, the use of these “gold standard” methods is strongly recommended.

Chapter 5: Conclusion and Recommendations

5.0 Conclusion and Future Recommendations

In conclusion, when renal function markers utilizing creatinine are excluded from analysis because of direct effect of creatine on their plasma levels, the limited data set in this thesis investigation indicates that the use of dietary creatine monohydrate poses no significant effects on renal function. Therefore, it is recommended that health care professionals evaluate renal function in individuals who supplement with dietary creatine monohydrate by using either Cystatin C or ^{51}Cr-EDTA.

It is further recommended that future studies focus on establishing a dosing regimen with respect to individual muscle mass. There is a strong connection between muscle mass and creatine-to-creatinine concentration. There may be a possibility that the use of traditional renal function markers may be utilized, but only if dietary creatine monohydrate is dosed according to muscle mass, and utilized by the body accordingly, and not over-dosed so that the concentrations of plasma creatinine and urinary creatinine become elevated outside the normal range.

References

[1] Brault JJ, Abraham KA, Terjung RL. Muscle creatine uptake and creatine transporter expression in response to creatine supplementation and depletion. *J Appl Physiol (1985)*. 2003;94(6):2173-2180.

[2] Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. *Pharmacol Rev*. 2001;53(2):161-176.

[3] Sora I, Richman J, Santoro G *et al*. The cloning and expression of a human creatine transporter. *Biochem Biophys Res Commun*. 1994;204(1):419-427.

[4] Ardalan M, Samadifar Z, Vahedi A. Creatine monohydrate supplement induced interstitial nephritis. *J Nephropathol*. 2012;1(2):117-120.

[5] Poortmans, Jacques R., Francaux, M. Creatine consumption in health. *In Essentials of Creatine in Sports and Health*. 2008. Start, JR, Antonio J, Kalman D (eds): 127-172.

[6] Pritchard NR, Kalra PA. Renal dysfunction accompanying oral creatine supplements. *Lancet*. 1998;351(9111):1252-1253.

[7] Sale C, Harris RC, Florance J, Kumps A, Sanvura R, Poortmans JR. Urinary creatine and methylamine excretion following 4 x 5 g x day(-1) or 20 x 1 g x day(-1) of creatine monohydrate for 5 days. *J Sports Sci*. 2009;27(7):759-766.

[8] Taner B, Aysim O, Abdulkadir U. The effects of the recommended dose of creatine monohydrate on kidney function. *NDT Plus*. 2011;4(1):23-24.

[9] Thorsteinsdottir B, Grande JP, Garovic VD. Acute renal failure in a young weight lifter taking multiple food supplements, including creatine monohydrate. *J Ren Nutr*. 2006;16(4):341-345.

[10] Velema MS, de Ronde W. Elevated plasma creatinine due to creatine ethyl ester use. *Neth J Med*. 2011;69(2):79-81.

[11] Groeneveld GJ, Beijer C, Veldink JH, Kalmijn S, Wokke JH, van den Berg LH. Few adverse effects of long-term creatine supplementation in a placebo-controlled trial. *Int J Sports Med*. 2005;26(4):307-313.

[12] Gualano B, de Salles Painelli V, Roschel H *et al*. Creatine supplementation does not impair kidney function in type 2 diabetic patients: A randomized, double-blind, placebo-controlled, clinical trial. *Eur J Appl Physiol*. 2011;111(5):749-756.

[13] Gualano B, Lugaresi R, de Salles Painelli V *et al*. Creatine supplementation does not augment muscle carnosine content in type 2 diabetic patients. *Appl Physiol Nutr Metab*. 2011;36(5):764-767.

[14] Huso ME, Hampl JS, Johnston CS, Swan PD. Creatine supplementation influences substrate utilization at rest. *J Appl Physiol (1985)*. 2002;93(6):2018-2022.

[15] Mayhew DL, Mayhew JL, Ware JS. Effects of long-term creatine supplementation on liver and kidney functions in American college football players. *Int J Sport Nutr Exerc Metab*. 2002;12(4):453-460.

[16] Poortmans JR, Francaux M. Long-term oral creatine supplementation does not impair renal function in healthy athletes. *Med Sci Sports Exerc*. 1999;31(8):1108-1110.

[17] Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: Validity of the 24-hour urinary creatinine method. *The American Journal of Clinical Nutrition*. 1983(37):478-494.

[18] Hsu J, Johansen KL, Hsu C, Kaysen GA, Chertow GM. 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*. 2008;3(4):992-997.

[19] Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: New insights into old concepts. *Clin Chem*. 1992;38(10):1933-1953.

[20] Samra M, Abcar AC. False estimates of elevated creatinine. *The Permanente Journal*. 2012;16(2):51-52.

[21] da Silva RP, Nissim I, Brosnan ME, Brosnan JT. Creatine synthesis: Hepatic metabolism of guanidinoacetate and creatine in the rat in vitro and in vivo. *Am J Physiol Endocrinol Metab*. 2009;296(2):E256-61.

[22] Pline KA, Smith CL. The effect of creatine intake on renal function. *Ann Pharmacother*. 2005;39(6):1093-1096.

[23] Smith, Rachel N., Amruta S. Agharkar, and Eric B. Gonzales. A review of creatine supplementation in age-related diseases: More than a supplement for athletes. 2014: 222. *PMC*. Web. 28 May 2016.

[24] Poortmans JR, Kumps A, Duez P, Fofonka A, Carpentier A, Francaux M. Effect of oral creatine supplementation on urinary methylamine, formaldehyde, and formate. *Med Sci Sports Exerc*. 2005;37(10):1717-1720.

[25] Casey S. Daily dose of creatine from meat? Nucleo blog. http://blog.nutribodies.com/19/dail-dose-of-creatine-from-meat

[26] Stead LM, Au KP, Jacobs RL, Brosnan ME, Brosnan JT. Methylation demand and homocysteine metabolism: Effects of dietary provision of creatine and guanidinoacetate. *American Journal of Physiology - Endocrinology and Metabolism*. 2001;281(5):E1095-E1100.

[27] Loike JD, Somes M, Silverstein SC. Creatine uptake, metabolism, and efflux in human monocytes and macrophages. *Am J Physiol*. 1986;251(1 Pt 1):C128-35.

[28] Moller A, Hamprecht B. Creatine transport in cultured cells of rat and mouse brain. *J Neurochem*. 1989;52(2):544-550.

[29] Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. *Clin Pharmacokinet*. 2003;42(6):557-574.

[30] Clark JF, Odoom J Tracey I *et al*. 3 - experimental observations of creatine phosphate and creatine metabolism. In: Conway MA, Clark JF, eds. *Creatine and creatine phosphate.* San Diego: Academic Press; 1996:33-50. http://dx.doi.org/10.1016/B978-012186340-1/50006-0.

[31] Persky AM, Muller M, Derendorf H, Grant M, Brazeau GA, Hochhaus G. Single- and multiple-dose pharmacokinetics of oral creatine. *J Clin Pharmacol*. 2003;43(1):29-37.

[32] Green AL, Simpson EJ, Littlewood JJ, Macdonald IA, Greenhaff PL. Carbohydrate ingestion augments creatine retention during creatine feeding in humans. *Acta Physiol Scand*. 1996;158(2):195-202.

[33] Greenhaff PL, Bodin K, Soderlund K, Hultman E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. *Am J Physiol*. 1994;266(5 Pt 1):E725-30.

[34] Gualano B, Roschel H, Lancha-Jr AH, Brightbill CE, Rawson ES. In sickness and in health: The widespread application of creatine supplementation. *Amino Acids*. 2012;43(2)8519-529.

[35] Steenge GR, Simpson EJ, Greenhaff PL. Protein- and carbohydrate-induced augmentation of whole body creatine retention in humans. *J Appl Physiol (1985)*. 2000;89(3):1165-1171.

[36] Gualano B, Ferreira DC, Sapienza MT, Seguro AC, Lancha AH, Jr. Effect of short-term high-dose creatine supplementation on measured GFR in a young man with a single kidney. *Am J Kidney Dis*. 2010;55(3):e7-9.

[37] Walker JB. Metabolic control of creatine biosynthesis I. Effect of dietary creatine. *Journal of Biological Chemistry*. 1960;235(8):2357-2361.

[38] Mccall W, Persky AM. Pharmacokinetics of creatine. In: *Creatine and creatine kinase in health and disease.* Springer; 2007:262-273.

[39] Williams MH, Kreider RB, Branch JD. *Creatine: The power supplement.* Human Kinetics; 1999. https://books.google.com/books?id=BNA3sYQ38dIC.

[40] Robinson TM, Sewell DA, Casey A, Steenge G, Greenhaff PL. Dietary creatine supplementation does not affect some haematological indices, or indices of muscle damage and hepatic and renal function. *Br J Sports Med*. 2000;34(4):284-288.

[41] Schedel JM, Tanaka H, Kiyonaga A, Shindo M, Schutz Y. Acute creatine ingestion in human: Consequences on serum creatine and creatinine concentrations. *Life Sci*. 1999;65(23):2463-2470.

[42] Willott CA, Young ME, Leighton B *et al*. Creatine uptake in isolated soleus muscle: Kinetics and dependence on sodium, but not on insulin. *Acta Physiol Scand*. 1999;166(2):99-104.

[43] Koshy KM, Griswold E, Schneeberger EE. Interstitial nephritis in a patient taking creatine. *N Engl J Med*. 1999;340(10):814-815.

[44] Poortmans J, Auquier H, Renaut V, Durussel A, Saugy M, Brisson G. Effect of short-term creatine supplementation on renal responses in men. *Eur J Appl Physiol Occup Physiol*. 1997;76(6):566-567.

[45] Sandhu RS, Como JJ, Scalea TS, Betts JM. Renal failure and exercise-induced rhabdomyolysis in patients taking performance-enhancing compounds. *J Trauma*. 2002;53(4):761-3; discussion 763-4.

[46] Saidi H, Mani M. Severe metabolic acidosis secondary to coadministration of creatine and metformin, a case report. *Am J Emerg Med*. 2010;28(3):388.e5-388.e6.

[47] Juhn MS, Tarnopolsky M. Potential side effects of oral creatine supplementation: A critical review. *Clin J Sport Med*. 1998;8(4):298-304.

[48] Bender A, Samtleben W, Elstner M, Klopstock T. Long-term creatine supplementation is safe in aged patients with Parkinson disease. *Nutr Res*. 2008;28(3):172-178.

[49] Kreider, Richard B., Melton, Charles, Rasmussen, Christopher J. *et al*. Long-term creatine supplementation does not significantly affect clinical markers of health in athletes. *Mol Cell Biochem.* 2003; 244(1-2): 95-104

[50] Lugaresi R, Leme M, de Salles Painelli V *et al*. Does long-term creatine supplementation impair kidney function in resistance-trained individuals consuming a high-protein diet? *J Int Soc Sports Nutr*. 2013;10(1):26-2783-10-26.

[51] Mihic S, MacDonald JR, McKenzie S, Tarnopolsky MA. Acute creatine loading increases fat-free mass, but does not affect blood pressure, plasma creatinine, or CK activity in men and women. *Med Sci Sports Exerc*. 2000;32(2):291-296.

[52] Neves M, Jr, Gualano B, Roschel H *et al*. Effect of creatine supplementation on measured glomerular filtration rate in postmenopausal women. *Appl Physiol Nutr Metab*. 2011;36(3):419-422.

[53] Volek JS, Mazzetti SA, Farquhar WB, Barnes BR, Gomez AL, Kraemer WJ. Physiological responses to short-term exercise in the heat after creatine loading. *Med Sci Sports Exerc*. 2001;33(7):1101-1108.

[54] Koeppen, Bruce M., Bruce A. Stanton. *Berne and Levy physiology*. 6th ed. Philadelphia, PA: Mosby Elsevier; 2008. http://users.atw.hu/blp6/BLP6/HTML/S7.htm.

[55] Mayo Foundation for Medical Education and Research. No Date. Creatinine estimated GFR (MDRD), serum. http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/8472. Accessed January 28, 2016.

[56] Galindo S. Creatinine. [Jaffe Reaction]. August 25, 2009; Standard Operating Procedure CHOO5. http://www2.isu.edu/~galisusa/creatineSOP.html

[57] Ferguson MA, Waikar SS. Established and emerging markers of kidney function. *Clin Chem*. 2012;58(4):680-689.

[58] Mujika I, Padilla S, Ibanez J, Izquierdo M, Gorostiaga E. Creatine supplementation and sprint performance in soccer players. *Med Sci Sports Exerc*. 2000;32(2):518-525.

[59] Chaves A.A.R., Buchpiguel C.A., Praxedes J.N., Bortolotto L.A., Sapienza M.T. 2010. Glomerular filtration rate measured by ^{51}Cr-EDTA of catrophil-induced changes in hypertensive patients with renal artery stenosis. *Clinics* Vol. 65(6), pp. 607-612. http://www.scielo.br/pdf/clin/v65n6/08.pdf

[60] Izquierdo M, Ibanez J, Gonzalez-Badillo JJ, Gorostiaga EM. Effects of creatine supplementation on muscle power, endurance, and sprint performance. *Med Sci Sports Exerc*. 2002;34(2):332-343.

[61] Rule AD, Bergstralh EJ, Slezak JM, Bergert J, Larson TS. Glomerular filtration rate estimated by Cystatin C among different clinical presentations. *Kidney Int*. 2006;69(2):399-405.

[62] Vandenberghe K, Goris M, Van Hecke P, Van Leemputte M, Vangerven L, Hespel P. Long-term creatine intake is beneficial to muscle performance during resistance training. *J Appl Physiol*. 1997;83(6):2055-2063.

[63] Hultman E, Greenhaff PL, Ren J-, Soderlund K. *Biochem Soc Trans*. 1991;19:347.

[64] Gualano B, Ugrinowitsch C, Novaes RB *et al*. Effects of creatine supplementation on renal function: A randomized, double-blind, placebo-controlled clinical trial. *Eur J Appl Physiol*. 2008;103(1):33-40.

[65] Comprehensive Meta-Analysis (Version 3) [Computer Software]. (2015). Englewood, NJ: Biostat. Available from http://www.meta-analysis.com

Appendix A

Individual Data Utilized For Means ± Standard Error in Comprehensive Meta-Analysis

Appendix A provides pre- and post-data (the mean, the standard deviation, and the sample size) for control groups and treatment groups (*i.e.*, groups receiving creatine) with respect to each renal function marker as reported in each study. Renal function markers include (1) plasma creatinine, (2) plasma urea, (3) urinary urea, (4) estimated creatinine clearance, (5) urinary creatinine, (6) Cystatin C, and (7) ^{51}Cr-EDTA.

Plasma Creatinine (mg/dL)

Table A-1: Pre-Treatment Result for Studies Using Plasma Creatinine (mg/dL) as a Renal Function Marker.

Reference #	Treated Pre Mean	Treated Pre SD	Treated Sample size
[41]	1.2	0.14	5
[49]	1.1	0.1	12
[40]	0.995	0.17	7
[40]	1.17	0.113	6
[40]	0.78	0.068	9
[40]	0.769	0.05	7
[47]	0.995	0.101	31
[52]	1.27	0.019	10
[34]	0.9	0.2	13
[46]	1.14	0.31	12
[51]	0.77	0.12	13
[48]	1.29	0.2	12
[49]	1.26	0.1	25
[49]	1.16	0.2	17
[51]	0.97	0.15	15

Table A-2: Post-Treatment Results for Studies Using Plasma Creatinine (mg/dL) as a Renal Function Marker.

Reference #	Treated Post Mean	Treated Post SD	Treated Sample size
[41]	1.23	0.15	5
[49]	1.2	0.2	12
[40]	1.27	0.34	7
[40]	1.19	0.113	6
[40]	0.97	0.17	9
[40]	1.07	0.19	7
[47]	1.1	0.204	31
[52]	1.44	0.04	10
[34]	1	0.3	13
[46]	1.38	0.34	12
[51]	0.78	0.1	13
[48]	1.41	0.2	12
[49]	1.42	0.2	25
[49]	1.35	0.2	17
[51]	1.06	0.17	15

Table A-3: Pre-Control Results for Studies Using Plasma Creatinine (mg/dL) as a Renal Function Marker.

Reference #	Pre-Control Mean	Pre-Control SD	Control Sample size
[41]	1.02	0.04	5
[49]	1	0.1	14
[40]	1.09	0.16	7
[40]	0.93	0.09	6
[40]	0.88	0.102	6
[40]	1.09	0.16	7
[47]	0.995	0.101	17
[52]	1.3	0.036	10
[34]	0.8	0.1	12
[46]	1.13	0.25	11
[51]	0.76	0.13	11
[48]	1.23	0.1	44
[49]	1.23	0.1	44
[49]	1.23	0.1	44
[51]	1.04	0.25	15

Table A-4: Post Control Results for Studies Using Plasma Creatinine (mg/dL) as a Renal Function Marker.

Reference #	Post-Control Mean	Post-Control SD	Control Sample size
[41]	0.96	0.05	5
[49]	1.1	0.1	14
[40]	1.04	0.2	7
[40]	0.96	0.14	6
[40]	0.81	0.06	6
[40]	1.04	0.2	7
[47]	1.1	0.204	17
[52]	1.25	0.046	10
[34]	0.8	0.1001	12
[46]	1.17	0.38	11
[51]	0.78	0.09	11
[48]	1.35	0.1	44
[49]	1.35	0.1	44
[49]	1.35	0.1	44
[51]	1.04	0.25	15

Plasma Urea (mg/dL)

Table A-5: Pre-Treatment Results for Studies Using Plasma Urea (mg/dL) as a Renal Function Marker.

Reference #	Treated Pre Mean	Treated Pre SD	Treated Sample Size
[11]	15.94	4.12	88
[40]	12.32	3.08	7
[40]	11.48	1.12	6
[40]	10.08	1.96	9
[40]	11.76	1.96	7
[48]	12.00	2.9	31
[50]	19.41	4.96	12
[49]	15.2	3	12
[49]	15.5	3.8	25
[49]	15.6	3.7	17
[47]	19.2	4.8	12
[53]	39.46	9.08	13

Table A-6: Post-Treatment Results for Studies Using Plasma Urea (mg/dL) as a Renal Function Marker.

Reference #	Post-Treatment Mean	Post-Treatment SD	Treated Sample Size
[11]	14.17	4.09	6
[40]	10.64	3.64	7
[40]	14.85	1.68	6
[40]	10.08	2.24	9
[40]	10.64	1.12	7
[48]	12.10	2.50	31
[50]	18.24	5.43	12
[49]	15.90	3.40	12
[49]	15.20	2.60	25
[49]	15.60	3.70	17
[47]	21.90	7.50	12
[53]	36.83	8.09	13

Table A-7: Pre-Control Results for Studies Using Plasma Urea (mg/dL) as a Renal Function Marker.

Reference #	Pre-Control Mean	Pre-Control SD	Control Sample Size
[11]	13.28	37.19	87
[40]	13.73	38.45	7
[40]	13.17	36.88	6
[40]	12.04	33.74	6
[40]	13.73	38.45	7
[48]	11.00	30.81	17
[50]	15.55	43.55	14
[49]	15.20	3.80	44
[49]	15.20	3.80	44
[49]	15.20	3.80	44
[47]	17.40	6.20	11
[53]	36.64	8.71	11

Table A-8: Post-Control Results for Studies Using Plasma Urea (mg/dL) as a Renal Function Marker.

Reference #	Post-Control Mean	Post-Control SD	Control Sample Size
[11]	15.13	42.37	6
[40]	9.80	27.46	7
[40]	11.76	32.95	6
[40]	10.08	28.25	6
[40]	9.80	27.46	7
[48]	11.10	31.09	17
[50]	15.52	43.47	14
[49]	15.00	2.90	44
[49]	15.00	2.90	44
[49]	15.00	2.90	44
[47]	15.20	3.50	11
[53]	36.27	8.03	11

Urinary Urea (g/24hr)

Table A-9: Pre-Treatment Results for Studies Using Urinary Urea (g/24hr) as a Renal Function Marker.

Reference #	Pre-Treatment Mean	Pre-Treatment SD	Treatment Sample Size
[62]	18.82	2.27	10
[62]	18.82	2.27	10
[14]	9.70	1.30	10
[34]	26.00	5.60	13
[13]	18.80	2.30	15
[47]	9.66	6.50	12
[52]	21.81	5.21	13

Table A-10: Post-Treatment Results for Studies Using Urinary Urea (g/24hr) as a Renal Function Marker.

Reference #	Post-Treatment Mean	Post-Treatment SD	Treatment Sample Size
[62]	22.17	1.06	10
[62]	19.94	2.01	10
[14]	10.60	2.10	10
[34]	26.80	7.30	13
[13]	22.20	1.10	15
[47]	10.10	5.40	12
[52]	18.94	6.36	13

Table A-11: Pre-Control Results for Studies Using Urinary Urea (g/24hr) as a Renal Function Marker.

Reference #	Pre-Control Mean	Pre-Control SD	Control Sample Size
[62]	18.43	1.61	9
[62]	18.43	1.61	9
[14]	8.00	1.40	10
[34]	22.40	6.60	12
[13]	27.50	1.10	19
[47]	10.30	2.10	11
[52]	19.64	4.67	11

Table A-12: Post-Control Results for Studies Using Urinary Urea (g/24hr) as a Renal Function Marker.

Reference #	Post-Control Mean	Post-Control SD	Control Sample Size
[62]	18.02	1.97	9
[62]	19.36	2.43	9
[14]	10.90	1.40	10
[34]	27.70	8.80	12
[13]	26.80	1.80	19
[47]	9.20	3.90	11
[52]	19.45	4.41	11

Estimated Creatinine Clearance (mL/min)

Table A-13: Pre-Treatment Results for Studies Using Estimated Creatinine Clearance (mL/min) as a Renal Function Marker.

Reference #	Pre-Treatment Mean	Pre-Treatment SD	Treatment Sample Size
[51]	119.00	17.7	15
[34]	112.30	37.7	13
[49]	171.00	117.00	12
[49]	234.00	165.00	25
[49]	213.00	150.00	17
[52]	106.68	23.73	13

Table A-14: Post-Treatment Results for Studies Using Estimated Creatinine Clearance (mL/min) as a Renal Function Marker.

Reference #	Post-Treatment Mean	Post-Treatment SD	Treatment Sample Size
[51]	112.20	23.10	15
[34]	108.30	31.70	13
[49]	120.00	63.00	12
[49]	168.00	165.00	25
[49]	177.00	185.00	17
[52]	107.71	24.36	13

Table A-15: Pre-Control Results for Studies Using Estimated Creatinine Clearance (mL/min) as a Renal Function Marker.

Reference #	Pre-Control Mean	Pre-Control SD	Control Sample Size
[51]	99.50	14.00	15
[34]	118.40	33.90	12
[49]	269.00	241.00	44
[49]	269.00	241.00	44
[49]	269.00	241.00	44
[52]	119.00	21.23	11

Table A-16: Post-Control Results for Studies Using Estimated Creatinine Clearance (mL/min) as a Renal Function Marker.

Reference #	Post-Control Mean	Post-Control SD	Control Sample Size
[51]	103.90	17.3	15
[34]	120.10	32.9	12
[49]	162.00	100.00	44
[49]	162.00	100.00	44
[49]	162.00	100.00	44
[52]	117.23	20.69	11

Urinary Creatinine (g/24hr)

Table A-17: Pre-Treatment Results for Studies Using Urinary Creatinine (g/24hr) as a Renal Function Marker.

Reference #	Pre-Treatment Mean	Pre-Treatment SD	Treated Sample Size
[48]	2.40	1.20	31
[48]	2.40	1.20	31
[41]	1.75	0.71	5
[63]	1.13	0.44	11
[54]	0.82	0.60	10
[62]	1.19	0.08	9
[62]	1.19	0.08	9
[14]	1.30	0.20	10
[47]	1.38	0.67	12
[34]	1.40	0.40	13
[49]	1.23	0.68	12
[49]	1.28	0.60	25
[49]	1.34	0.55	17
[8]	2.39	0.78	8
[52]	1.05	0.16	13
[60]	1.70	0.19	9

Table A-18: Post-Treatment Results for Studies Using Urinary Creatinine (g/24hr) as a Renal Function Marker.

Reference #	Post-Treatment Mean	Post-Treatment SD	Treated Sample Size
[48]	2.00	1.20	31
[48]	2.20	1.00	31
[41]	1.86	0.44	5
[63]	0.98	0.47	11
[54]	1.18	2.25	10
[62]	1.56	0.23	9
[62]	1.53	0.05	9
[14]	1.80	0.20	10
[47]	1.85	0.77	12
[34]	1.40	0.60	13
[49]	1.07	0.40	12
[49]	1.24	0.60	25
[49]	1.14	0.90	17
[8]	2.47	0.57	8
[52]	1.05	0.26	13
[60]	2.48	0.27	9

Table A-19: Pre-Control Results for Studies Using Urinary Creatinine (g/24hr) as a Renal Function Marker.

Reference #	Pre-Control Mean	Pre-Control SD	Control Sample Size
[48]	2.00	1.20	17
[48]	2.00	1.20	17
[41]	1.78	0.24	5
[63]	0.37	0.54	20
[54]	1.36	2.77	10
[62]	1.17	0.08	10
[62]	1.17	0.08	10
[14]	1.10	0.20	10
[47]	1.47	0.53	11
[34]	1.40	0.30	12
[49]	1.41	0.80	44
[49]	1.41	0.80	44
[49]	1.41	0.80	44
[8]	2.68	0.73	9
[52]	0.98	0.20	11
[60]	1.70	0.41	10

Table A-20: Post-Control Results for Studies Using Urinary Creatinine (g/24hr) as a Renal Function Marker.

Reference #	Post-Control Mean	Post-Control SD	Control Sample Size
[48]	1.80	0.80	17
[48]	2.60	1.80	17
[41]	1.56	0.26	5
[63]	0.90	0.46	20
[54]	0.96	0.83	10
[62]	1.13	0.10	10
[62]	1.14	0.09	10
[14]	1.50	0.20	10
[47]	1.51	0.49	11
[34]	1.40	0.40	12
[49]	1.15	1.07	44
[49]	1.15	1.07	44
[49]	1.15	1.07	44
[8]	2.33	0.70	9
[52]	1.14	0.18	11
[60]	2.14	0.28	10

Cystatin C (mg/L)

Table A-21: Pre-Treatment Results for Studies Using Cystatin C (mg/L) as a Renal Function Marker.

Reference #	Pre-Treatment Mean	Pre-Treatment SD	Treatment Sample Size
[48]	0.80	0.10	31
[48]	0.80	0.10	31
[64]	0.82	0.09	9

Table A-22: Post-Treatment Results for Studies Using Cystatin C (mg/L) as a Renal Function Marker.

Reference #	Post-Treatment Mean	Post-Treatment SD	Treatment Sample Size
[48]	0.80	0.10	31
[48]	0.80	0.10	31
[64]	0.71	0.06	9

Table A-23: Pre-Control Results for Studies Using Cystatin C (mg/L) as a Renal Function Marker.

Reference #	Pre-Control Mean	Pre-Control SD	Control Sample Size
[48]	0.80	0.10	17
[48]	0.80	0.10	17
[64]	0.88	0.07	9

Table A-24: Post-Control Results for Studies Using Cystatin C (mg/L) as a Renal Function Marker.

Reference #	Post-Control Mean	Post-Control SD	Control Sample Size
[48]	0.90	0.20	17
[48]	0.90	0.20	17
[64]	0.75	0.09	9

^{51}Cr-EDTA (mL/min)

Table A-25: Pre-Treatment Results for Studies Using ^{51}Cr-EDTA (mL/min) as a Renal Function Marker.

Reference #	Pre-Treatment Mean	Pre-Treatment SD	Treated Sample Size
[34]	90.4	16.9	13
[50]	101.42	13.11	12
[52]	86.16	14.36	13

Table A-26: Post-Treatment Results for Studies Using ^{51}Cr-EDTA (mL/min) as a Renal Function Marker.

Reference #	Post-Treatment Mean	Post-Treatment SD	Treatment Sample Size
[34]	96.1	15	13
[50]	108.78	14.41	12
[52]	87.25	17.6	13

Table A-27: Pre-Control Results for Studies Using ^{51}Cr-EDTA (mL/min) as a Renal Function Marker.

Reference #	Pre-Control Mean	Pre-Control SD	Control Sample Size
[34]	97.9	21.6	12
[50]	103.29	17.64	14
[52]	85.15	8.54	11

Table A-28: Post-Control Results for Studies Using ^{51}Cr-EDTA (mL/min)as a Renal Function Marker.

Reference #	Post-Control Mean	Post-Control SD	Control Sample Size
[34]	96.4	26.8	12
[50]	106.68	16.05	14
[52]	87.18	9.64	11

Appendix B
Data Summary for Plots

Appendix B features tables that summarize the mean and the standard error of the mean (SEM) for the control groups and treatment groups (*i.e.*, groups receiving creatine) with respect to each renal function marker.

Table B-1: Mean and Standard Error of the Mean (SEM) for Control and Treatment Groups that were Evaluated with the Plasma Creatinine (mg/dL) Renal Function Marker.

Group	Mean	SEM
Pre-Treatment	1.05	0.06
Post-Treatment	1.19	0.07
Pre-Control	1.05	0.04
Post-Control	1.01	0.0.06

Table B-2: Mean and Standard Error of the Mean (SEM) for Control and Treatment Groups that were Evaluated with the Plasma Urea (mg/dL) Renal Function Marker.

Group	Mean	SEM
Pre-Treatment	15.79	1.02
Post-Treatment	15.65	0.97
Pre-Control	14.07	0.74
Post-Control	14.31	0.83

Table B-3: Mean and Standard Error of the Mean (SEM) for Control and Treatment Groups that were Evaluated with Estimated Creatinine Clearance (mL/min) Renal Function Marker.

Group	Mean	SEM
Pre-Treatment	134.16	11.05
Post-Treatment	112.01	4.45
Pre-Control	163.15	16.32
Post-Control	134.04	9.84

Table B-4: Mean and Standard Error of the Mean (SEM) for Control and Treatment Groups that were Evaluated with the Urinary Creatinine (g/24hr) Renal Function Marker.

Group	Mean	SEM
Pre-Treatment	1.46	0.08
Post-Treatment	1.64	0.09
Pre-Control	1.39	0.07
Post-Control	1.44	0.09

Table B-5: Mean and Standard Error of the Mean (SEM) for Control and Treatment Groups that were Evaluated with the ^{51}Cr-EDTA (mL/min) Renal Function Marker.

Group	Mean	SEM
Pre-Treatment	92.79	4.84
Post-Treatment	97.57	6.14
Pre-Control	94.87	6.46
Post-Control	96.53	7.10

Table B-6: Mean and Standard Error of the Mean (SEM) for Control and Treatment Groups that were Evaluated with the Cystatin C (mg/L) Renal Function Marker

Group	Mean	SEM
Pre-Treatment	0.80	0.01
Post-Treatment	0.77	0.03
Pre-Control	0.83	0.03
Post-Control	0.85	0.06

Table B-7: Mean and Standard Error of the Mean (SEM) for Control and Treatment Groups that were Evaluated with the Urinary Urea (g/24hr) Renal Function Marker

Group	Mean	SEM
Pre-Treatment	17.65	2.23
Post-Treatment	18.62	1.68
Pre-Control	17.79	3.55
Post-Control	18.68	3.06

Appendix C
Group Comparisons in Comprehensive Meta-Analysis

Appendix C features the summarized data for each renal function marker. The first data table for each marker features a comparison of treatment groups (*i.e.*, groups who received creatine) before and after treatment, as reported in each study that used the marker. The second data table for each marker features a comparison of the control groups in each study, before and after their associated treatment groups were treated. In each table, for each study, the sample size is included, along with pre- and post-mean measurements, pre- and post-standard deviation, and correlation between pre- and post-measurements.

Table C-1: Comparison of Pre- and Post-Treatments Evaluated by Plasma Creatinine (mg/dL) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[41]	1.2	0.14	1.23	0.15	0.8	5
[50]	1.1	0.1	1.2	0.2	0.8	12
[40]	0.995	0.17	1.27	0.34	0.8	7
[40]	1.17	0.113	1.19	0.113	0.8	6
[40]	0.78	0.068	0.97	0.17	0.8	9
[40]	0.769	0.05	1.07	0.19	0.8	7
[48]	0.995	0.101	1.1	0.204	0.8	31
[53]	1.27	0.019	1.44	0.04	0.8	10
[34]	0.9	0.2	1	0.3	0.8	13
[47]	1.14	0.31	1.38	0.34	0.8	12
[52]	0.77	0.12	0.78	0.1	0.8	13
[49]	1.29	0.2	1.41	0.2	0.8	12
[49]	1.26	0.1	1.42	0.2	0.8	25
[49]	1.16	0.2	1.35	0.2	0.8	17
[51]	0.97	0.15	1.06	0.17	0.8	15

Table C-2: Comparison of Pre- and Post-Control Evaluated by Plasma Creatinine (mg/dL) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[41]	1.02	0.04	0.96	0.05	0.8	5
[50]	1	0.1	1.1	0.1	0.8	14
[40]	1.09	0.16	1.04	0.2	0.8	7
[40]	0.93	0.09	0.96	0.14	0.8	6
[40]	0.88	0.102	0.81	0.06	0.8	6
[40]	1.09	0.16	1.04	0.2	0.8	7
[48]	0.995	0.101	1.1	0.204	0.8	17
[53]	1.3	0.036	1.25	0.046	0.8	10
[34]	0.8	0.1	0.8	0.1001	0.8	12
[47]	1.13	0.25	1.17	0.38	0.8	11
[52]	0.76	0.13	0.78	0.09	0.8	11
[49]	1.23	0.1	1.35	0.1	0.8	44
[49]	1.23	0.1	1.35	0.1	0.8	44
[49]	1.23	0.1	1.35	0.1	0.8	44
[51]	1.04	0.25	1.04	0.25	0.8	15

Table C-3: Comparison of Pre- and Post-Treatments Evaluated by Plasma Urea (mg/dL) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[11]	13.73	2.80	9.80	3.08	0.8	7
[40]	13.17	1.96	11.76	1.96	0.8	6
[40]	12.04	1.68	10.08	2.24	0.8	6
[40]	13.73	2.80	9.80	3.081	0.8	7
[40]	11.00	2.90	11.10	1.80	0.8	17
[48]	15.55	3.11	15.52	3.36	0.8	14
[50]	15.20	3.80	15.00	2.90	0.8	44
[49]	15.20	3.80	15.00	2.90	0.8	44
[49]	15.20	3.80	15.00	2.90	0.8	44
[49]	17.40	6.20	15.20	3.50	0.8	11
[47]	36.64	8.71	36.27	8.03	0.8	11

Table C-4: Comparison of Pre- and Post-Control Evaluated by Plasma Urea (mg/dL) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[11]	13.73	2.80	9.80	3.08	0.8	7
[40]	13.17	1.96	11.76	1.96	0.8	6
[40]	12.04	1.68	10.08	2.24	0.8	6
[40]	13.73	2.80	9.80	3.08	0.8	7
[40]	11.00	2.90	11.10	1.80	0.8	17
[48]	15.55	3.11	15.52	3.36	0.8	14
[50]	15.20	3.80	15.00	2.90	0.8	44
[49]	15.20	3.80	15.00	2.90	0.8	44
[49]	15.20	3.80	15.00	2.90	0.8	44
[49]	17.40	6.20	15.20	3.50	0.8	11
[47]	36.64	8.71	36.27	8.03	0.8	11

Table C-5: Comparison of Pre- and Post-Treatments Evaluated by Estimated Creatinine Clearance (mL/min) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[51]	119.00	17.70	112.20	23.10	0.8	15
[34]	112.30	37.70	108.30	31.70	0.8	13
[49]	171.00	117.00	120.00	63.00	0.8	12
[49]	234.00	165.00	168.00	165.00	0.8	25
[49]	213.00	150.00	177.00	185.00	0.8	17
[52]	106.68	23.73	107.71	24.36	0.8	13

Table C-6: Comparison of Pre- and Post-Control Evaluated by Estimated Creatinine Clearance (mL/min) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[51]	99.50	14.00	103.90	17.30	0.8	15
[34]	118.40	33.90	120.10	32.90	0.8	12
[49]	269.00	241.00	162.00	100.00	0.8	44
[49]	269.00	241.00	162.00	100.00	0.8	44
[49]	269.00	241.00	162.00	100.00	0.8	44
[52]	119.00	21.23	117.23	20.69	0.8	11

Table C-7: Comparison of Pre- and Post-Treatments Evaluated by Urinary Creatinine (g/24hr) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[48]	2.40	1.20	2.00	1.20	0.8	31
[48]	2.40	1.20	2.20	1.00	0.8	31
[41]	1.75	0.71	1.86	0.44	0.8	5
[63]	1.13	0.44	0.98	0.47	0.8	11
[53]	0.82	0.60	1.18	2.25	0.8	10
[62]	1.19	0.08	1.56	0.23	0.8	9
[62]	1.19	0.08	1.53	0.05	0.8	9
[14]	1.30	0.20	1.80	0.20	0.8	10
[47]	1.38	0.67	1.85	0.77	0.8	12
[34]	1.40	0.40	1.40	0.60	0.8	13
[49]	1.23	0.68	1.07	0.40	0.8	12
[49]	1.28	0.60	1.24	0.60	0.8	25
[49]	1.34	0.55	1.14	0.90	0.8	17
[8]	2.39	0.78	2.47	0.57	0.8	8
[52]	1.05	0.16	1.05	0.26	0.8	13
[60]	1.70	0.19	2.48	0.27	0.8	9

Table C-8: Comparison of Pre- and Post-Control Evaluated by Urinary Creatinine (g/24hr) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[48]	2.00	1.20	1.80	0.80	0.8	17
[48]	2.00	1.20	2.60	1.80	0.8	17
[41]	1.78	0.24	1.56	0.26	0.8	5
[63]	0.37	0.54	0.90	0.46	0.8	20
[53]	1.36	2.77	0.96	0.83	0.8	10
[62]	1.17	0.08	1.13	0.10	0.8	10
[62]	1.17	0.08	1.14	0.09	0.8	10
[14]	1.10	0.20	1.50	0.20	0.8	10
[47]	1.47	0.53	1.51	0.49	0.8	11
[34]	1.40	0.30	1.40	0.40	0.8	12
[49]	1.41	0.80	1.15	1.065	0.8	44
[49]	1.41	0.80	1.15	1.065	0.8	44
[49]	1.41	0.80	1.15	1.065	0.8	44
[8]	2.68	0.73	2.33	0.70	0.8	9
[52]	0.98	0.20	1.14	0.18	0.8	11
[60]	1.70	0.41	2.14	0.28	0.8	10

Table C-9: Comparison of Pre- and Post-Treatments Evaluated by ^{51}Cr-EDTA (mL/min) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[34]	90.40	16.90	96.10	15	0.00	13
[50]	101.42	13.11	108.78	14.41	0.00	12
[52]	86.16	14.36	87.25	17.6	0.00	13

Table C-10: Comparison of Pre- and Post-Control Evaluated by ^{51}Cr-EDTA (mL/min) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[34]	97.90	21.6	96.40	26.80	0.8	12
[50]	103.29	17.64	106.68	16.05	0.8	14
[52]	85.15	8.54	87.18	9.64	0.8	11

Table C-11: Comparison of Pre- and Post-Treatments Evaluated by Cystatin C (mg/L) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[48]	0.80	0.10	0.80	0.10	0.8	31
[48]	0.80	0.10	0.80	0.10	0.8	31
[64]	0.82	0.09	0.71	0.06	0.8	9

Table C-12: Comparison of Pre- and Post-Control Evaluated by Cystatin C (mg/L) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[48]	0.80	0.10	0.90	0.20	0.8	17
[48]	0.80	0.10	0.90	0.20	0.8	17
[64]	0.88	0.07	0.75	0.09	0.8	9

Table C-13: Comparison of Pre- and Post-Treatments Evaluated by Urinary Urea (g/24hr) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[62]	18.82	2.27	22.17	1.06	0.8	10
[62]	18.82	2.27	19.94	2.01	0.8	10
[14]	9.70	1.30	10.60	2.10	0.8	10
[34]	26.00	5.60	26.80	7.30	0.8	13
[13]	18.80	2.30	22.20	1.10	0.8	15
[47]	9.66	6.50	10.10	5.40	0.8	12
[52]	21.81	5.21	18.94	6.36	0.8	13

Table C-14: Comparison of Pre- and Post-Control Evaluated by Urinary Urea (g/24hr) Output.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[62]	18.43	1.61	18.02	1.97	0.8	9
[62]	18.43	1.61	19.36	2.43	0.8	9
[14]	8.00	1.40	10.90	1.40	0.8	10
[34]	22.40	6.60	27.70	8.80	0.8	12
[13]	27.50	1.10	26.80	1.80	0.8	19
[47]	10.30	2.10	9.20	3.90	0.8	11
[52]	19.64	4.67	19.45	4.41	0.8	11

Appendix D

Data for Studies using Comprehensive Meta-Analysis Statistical Program

Appendix D features detailed data concerning the categorical modulators associated with the plasma creatinine and creatinine clearance renal function markers in creatine studies. Of the seven markers evaluated in this meta-analysis, plasma creatinine and estimated creatinine clearance are the two markers associated with statistically significant differences in pre- and post- evaluations of treatment groups (*i.e.*, groups who received creatine). Table D-1 and D-2 are for plasma creatinine and creatinine clearance, respectively. The meta-analysis found that a combination of exercise and consumption of high doses of creatine for a short period of time, as well as consumption of the recommended dose for an extended period of time, had the greatest influence on plasma creatinine and creatinine clearance measurements.

Table D-1: Categorical Moderator Data Associated with the Plasma Creatinine Renal Function Marker in Creatine Studies.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample Size	Exercise	Type of Exercise	Medication	Disease	Creatine Dose	Length of Cycle
[41]	1.20	0.14	1.23	0.15	0.8	5	Yes	Res/Card	No	No	High Dose	Short
[50]	1.10	0.10	1.20	0.20	0.8	12	Yes	Resistance	No	No	Low Dose	Long
[40]	0.995	0.17	1.27	0.34	0.8	7	Yes	Res/Card	No	No	High Dose	Short
[40]	1.170	0.11	1.19	0.11	0.8	6	Yes	Res/Card	No	No	Recommended	Recommended
[40]	0.78	0.07	0.97	0.17	0.8	9	Yes	Res/Card	No	No	Low Dose	Long
[40]	0.77	0.05	1.07	0.19	0.8	7	Yes	Res/Card	No	No	Recommended	Long
[48]	1.00	0.10	1.10	0.20	0.8	31	No	None	No	Yes	Low Dose	Long
[53]	1.27	0.02	1.44	0.04	0.8	10	Yes	Cardio	No	No	Recommended	Short
[34]	0.90	0.20	1.00	0.30	0.8	13	No	Resistance	No	Yes	Low Dose	Long
[47]	1.14	0.31	1.38	0.34	0.8	12	Yes	Resistance	No	No	Recommended	Long
[52]	0.77	0.12	0.78	0.10	0.8	13	Yes	Resistance	No	Yes	Recommended	Long
[49]	1.29	0.20	1.41	0.20	0.8	12	Yes	Res/Card	No	No	Recommended	Recommended
[49]	1.26	0.10	1.42	0.20	0.8	25	Yes	Res/Card	No	No	Recommended	Long
[49]	1.16	0.20	1.35	0.20	0.8	17	Yes	Res/Card	No	No	Recommended	Long
[51]	0.97	0.15	1.06	0.17	0.8	15	Yes	Res/Card	No	No	High Dose	Short

Table D-2: Categorical Moderator Data Associated with Estimated Creatinine Clearance Renal Function Marker in Creatine Studies.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample Size	Exercise	Type of Exercise	Medication	Disease	Creatine Dose	Length of Cycle
[51]	119.00	17.70	112.20	23.10	0.8	15	Yes	Res/Card	No	No	High Dose	Short
[34]	112.30	37.70	108.30	31.70	0.8	13	Yes	Resistance	No	Yes	Low Dose	Long
[49]	171.00	117.00	120.00	63.00	0.8	12	Yes	Res/Card	No	No	Recommended	Long
[49]	234.00	165.00	168.00	165.00	0.8	25	Yes	Res/Card	No	No	Recommended	Long
[49]	213.00	150.00	177.00	185.00	0.8	17	Yes	Res/Card	No	No	Recommended	Long
[52]	106.68	23.73	107.71	24.36	0.8	13	Yes	Resistance	No	Yes	Recommended	Long

Appendix E
Renal Function Marker Comparisons in ^{51}Cr-EDTA and Cystatin C

Appendix E features a summary of data results associated with ^{51}Cr-EDTA and Cystatin C, the two renal function markers that this meta-analysis recommends for use in creatine studies.

Table E-1: Data Summary for the ^{51}Cr-EDTA (mL/min) Renal Function Marker In Creatine Studies.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[34]	112.3	37.7	108.3	31.7	0.8	13
[52]	106.68	23.73	107.71	24.36	0.8	13

Table E-2: Data Summary for the Cystatin- C (mg/L) Renal Function Marker In Creatine Studies.

Reference #	Pre Mean	Pre SD	Post Mean	Post SD	Pre Post Correlation	Sample size
[50]	1	0.1	1.1	0.1	0.8	14
[48]	0.995	0.101	1.1	0.204	0.8	17
[34]	0.8	0.1	0.8	0.1001	0.8	12
[52]	0.76	0.13	0.78	0.09	0.8	11