The Potential Role of Dietary Intake in Explaining Postoperative Muscle Loss in Total Knee Arthroplasty (TKA)

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ABSTRACT

Post-operative muscle loss has been identified as the greatest contributor to osteoarthritis patients' long-term strength deficits, explaining 77% of muscle weakness one to three years after total knee arthroplasty (TKA) for the treatment of osteoarthritis in the knee. Essential amino acid supplementation may help reduce atrophy, but other factors could have an equally influential role. Patients' food intake could likewise affect atrophy, and thus dietary intake must be measured in order to determine whether essential amino acids reduce muscle loss following TKA. Subjects with a minimal dietary intake could exacerbate muscle loss because fasting causes the body to break down skeletal muscle protein to liberate amino acids for use as gluconeogenic precursors in the liver. As a result, individuals with different diets may experience differing degrees of muscle atrophy. This investigation seeks to test the hypothesis that higher rates of muscle atrophy in subject groups could be explained by comparatively poorer dietary intake. For this study, subjects completed a total of three 72-hour food logs before surgery, then two, and six weeks post-TKA. During these periods, bilateral quadriceps muscle volume was determined using magnetic resonance imaging (MRI). Baseline and six-week whole-body dual-energy X-ray (DEXA) scans were also performed to compare changes in lean tissue and fat mass. Data collected indicated there was no significant difference in dietary intake between the control group and treatment group, suggesting that any muscle saved in the treatment group was a result of essential amino acid supplementation.

As the average age of our population increases, we are faced with new problems and pathologies to combat in our search for a higher quality of life. The current average lifespan (including both men and women) is almost 78 years of age; however, evidence suggests that the average lifespan is increasing by almost half of a year annually (Arias, 2007). While such a feat should be celebrated as a marvel of modern health advancements, this increased life expectancy, in combination with the aging "baby boomers" generation, will cause significant growth in the elderly population. Current predictions suggest that by the year 2050, the population of individuals over the age of 65 will more than double from 40 million to 88 million (Johnson,

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2010). Healthcare facilities must be prepared to support this surge and develop techniques to efficiently manage pathologies common to the elderly population.

Osteoarthritis (OA) of the knee involves gradual wear and tear of the articular cartilage in the joint of the knee, which allows for bone on bone rubbing. Osteoarthritis is currently the most prevalent chronic disease in the United States, affecting 60% of Americans over the age of 65, especially women (Parsley et al., 2010). Total knee arthroplasty (TKA) is the most common surgical treatment for osteoarthritis, and due to the prevalence of the disease, it is estimated that by the year 2030, 3.48 million TKAs will be conducted annually in the United States (Kurtz, 2007), with two-thirds of TKAs predicted to be performed on elderly women. Although the surgery has shown success in alleviating chronic knee pain, TKA has not been successful in completely restoring full physical function in women (MacDonald, 2008; Parsley et al., 2010). This inability to recover physical function has been labeled as the "never catch up syndrome" (Lavernia, 2009), the result of quadriceps weakness which is much more pronounced among women; women produce around 40-50% less force than men when tested two years following surgery (Silva, 2003).

Muscle atrophy is the greatest contributor to long-term quadriceps weakness, which can explain 77% of strength deficits one to three years following TKA (Meier, 2009). An interesting aspect of TKA is that muscle atrophy presents in both the operative and the non-operative quadriceps muscle groups. This factor should be considered when developing therapies to prevent muscle loss, because weakness in the non-operative leg is associated with the measured decrease in physical function one to two years following surgery (Zeni, 2010). Furthermore, for the older women that make up the majority of patients, significant muscle loss is especially detrimental because these patients are limited in their ability to increase muscle mass (Bamman, 2003). As a result, it is imperative that therapies are designed to prevent bilateral muscle atrophy following TKA in order to improve long-term functional health.

There has been a growing interest in essential amino acids (EAA's) in relation to muscle protein turnover. Of the 20 total amino acids, ten have been labeled as essential while the remaining 10 are considered non-essential amino acids. An essential amino acid is simply one that the body cannot create on its own and therefore must be obtained by dietary means.

Previous studies have shown support for the hypothesis that EAA supplementation can result in increased muscle protein synthesis, stimulating muscle growth. One such study demonstrated that EAA supplementation after a single bout of exercise led to an increase in muscle protein synthesis when compared to synthesis from the exercise alone (Dreyer, 2008). Previous studies have also shown that as we age, we begin to obtain higher levels of anabolic resistance (resistance to normal muscle growth) to amino acids at low dosages—thus decreasing the stimulatory effect of dietary intake on muscle protein synthesis (Johnson, 2010). Because of this increase in anabolic resistance, many elderly people can remain in a catabolic state even while ingesting the daily-recommended amount of calories and protein. But if the daily-recommended consumption is inadequate, perhaps the solution would be to simply increase patients' essential amino acid intake above previously recommended standards. This dietary

change could then negate the anabolic resistance and eventually lead to a net anabolic state of muscle growth.

These results may have implications that could slow the rate of muscle atrophy in older populations, but EAA supplementation should not be the only focus in this area of research. Instead, the patient's entire diet should be taken into consideration. The amount of fat, carbohydrates, and protein consumed could all have potential effects on the rate of muscle atrophy, with or without EAA supplementation. The following review discusses insufficient dietary intake's potential to accelerate muscle loss due to decreases in blood glucose levels.

BIOLOGICAL REVIEW

GLUCOSE

Glucose is a six-carbon simple sugar that is the end product of carbohydrate digestion (Hall, 2011). Carbohydrate digestion begins as soon as food enters the mouth, when enzymes present in saliva begin to break down complex carbohydrate sugars known as polysaccharides. The food then proceeds through the stomach and on to the small intestine, where any remaining polysaccharides are completely broken down into the monosaccharide glucose (Freeman, 2008). Once carbohydrates are reduced to this form, glucose is absorbed through the small intestine into the bloodstream, where it is circulated throughout the body to be utilized as a substrate in the creation of the body's ubiquitous form of energy: adenosine triphosphate (ATP).

GLUCOSE UTILIZATION IN AEROBIC RESPIRATION

Whether it is the stomach, skeletal muscles, or any other organ in the body, cells require a consistent inflow of glucose to function. The manner in which cells utilize glucose follows a four-stage mechanism that includes glycolysis, pyruvate decarboxylation, the TCA cycle, and oxidative phosphorylation (Freeman, 2008). These processes take place sequentially, and while all four of these processes are important in the overall creation of ATP and glucose utilization, one of the foci of this paper is the TCA cycle and how it may be affected by differing levels of food intake.

GLUCOSE REGULATION

The mechanism of particular interest to this investigation is glucose control and regulation. As stated, the elderly population often experiences difficulty in maintaining a healthy level of food intake. If food intake is low, blood glucose levels will begin to decrease as well. An individual is generally said to be euglycemic when his or her resting blood glucose concentration is within 90 to 108 milligrams glucose per deciliter of blood (mg/dL). If this level rises above 126mg/dL, a person is said to be hyperglycemic; conversely, if this level drops below 70mg/dL, a person is said to be hypoglycemic and may develop symptoms accordingly (Houston, 2006). While these values represent only the resting blood glucose level, the concentration can be augmented or attenuated depending on the state of the individual. Some of the factors that can

influence the blood glucose level include continual fasting, the ingestion of a meal, or exercise. This study is primarily focused on the effects of low dietary intake on future muscle atrophy; therefore, the most relevant factor is the health effects of continual fasting, in which a subject does not ingest adequate amounts of food for extended periods of time.

If an individual is continually unable to maintain an adequate dietary intake, the body will recognize the subsequent low blood glucose level and will begin to defend the normal level by activating several mechanisms. This can include breaking down stores of excess glucose in a process called glycogenolysis, burning excess fat in the form of triglycerides in a process known as lipolysis, or finally, proteolysis, by which muscle protein is broken down into amino acids to be used to generate necessary glucose (Brooks, 2005). While the focus of muscle synthesis is often placed on protein intake, it is apparent that if caloric intake is not maintained, muscle can still deteriorate via amino acid metabolism in order to defend blood glucose levels, even with adequate amounts of protein.

AMINO ACID METABOLISM

Amino acids are the foundation and building blocks of proteins in the body; a single synthesized protein may contain hundreds of amino acids in its structure, and the largest storehouse of proteins in the body is found in the skeletal musculature. Because skeletal muscle is comprised of so many of the body's amino acids, it follows that amino acid metabolism would lead to atrophy of the skeletal muscles.

Like stored glycogen and triglycerides, amino acids can also be used to generate glucose during times of need, such as fasting. Indeed, metabolism of amino acids occurs every morning because the body is in a natural catabolic state after not receiving any form of sustenance since dinner the night before (Brooks, 2005). This catabolic state will continue until the individual ingests his or her first meal of the day—thus providing the body with sufficient glucose to cease amino acid metabolism and muscle atrophy.

Amino acids can be extracted from muscle tissue and carried in the blood to the liver as a precursor to gluconeogenesis (Ruderman, 1975). This process, known as the glucose-alanine cycle, is capable of providing the 130 grams of glucose per day needed to fulfill the minimum glucose requirements of the brain, nerves, and kidneys (Brooks, 2005). This feat is triggered during fasting, when various amino acids in skeletal muscle are subjected to a reaction with α-ketoglutarate—the keto acid of glutamate—in a process catalyzed by an amino acid transaminase (Brooks, 2005). When the reaction is complete, the original amino acid loses its amine group, thereby reducing it to its keto acid form, while α-ketoglutarate accepts the amine group to form glutamate. The newly produced glutamate then experiences another round of transamination with the high levels of pyruvate located in the skeletal muscle. Glutamate loses its amine group to become α-ketoglutarate, while pyruvate accepts the amine group to form the amino acid alanine (Brooks, 2005). This mechanism allows many different amino acids to be transformed into alanine, one of the few amino acids capable of being mobilized from skeletal muscle and released into the bloodstream.

Once alanine reaches the mitochondrial matrix of the liver, it undergoes one of three processes: another round of transamination, oxidative deamination, or gluconeogenesis. Transamination will occur to reform pyruvate—the keto acid of alanine, but perhaps more importantly, pyruvate is a gluconeogenic precursor. If, however, alanine experiences oxidative deamination, the amine group will be removed, and the leftover carbon skeletal of alanine can be utilized in aerobic respiration.

In order to utilize amino acids in the formation of glucose, muscle protein must be broken down, resulting in increased muscle atrophy. But if daily caloric and protein requirements are met, it would seem that there would be enough glucose already present to avoid breaking down large stores of muscle protein. This will be of particular interest to this research, which tests whether muscle atrophy can be reduced after surgery via adequate dietary intake and amino acid supplementation. Non-fasting individuals will show increased levels of insulin, which has the ability to decrease rates of muscle protein catabolism; therefore, a patient with satisfactory dietary intake should be expected to experience decreased rates of muscle atrophy following surgery (Saltiel, 2001).

RELATION TO TCA CYCLE

Although alanine is the primary amino acid extracted from skeletal muscle, it does not represent the overall composition of the amino acids present in the skeletal muscle. This means that there is some form of local metabolism occurring within the muscle that is responsible for the interconversion of amino acids to alanine as described by the glucose-alanine cycle discussed in the previous section (Owen, 2002). Upon completion of transamination, there are remaining carbon skeletons that can produce one of five products—oxaloacetate, α-ketoglutarate, fumarate, succinyl CoA, and pyruvate—depending on the original amino acid being metabolized. Pyruvate can readily be shuttled to the liver as a precursor to gluconeogenesis; however, the first four products of transamination are TCA cycle intermediates necessary for the cycle to function.

The TCA cycle is the third step in the creation of ATP following pyruvate decarboxylation and before oxidative phosphorylation. This process is composed of eight steps, each using a distinct enzyme or intermediate to carry out reactions necessary to propagate the cycle (Hall, 2011). The steps most relevant to this research are the induction of acetyl CoA—the end product of pyruvate decarboxylation—to the cycle and the use of the intermediates that are provided during amino acid metabolism. During times of fasting, TCA intermediates are removed from the TCA cycle and used in the liver to create glucose via gluconeogenesis. As the various intermediates are used and taken out of the cycle, the reactions ongoing in the TCA cycle cannot be completed; this leads to a buildup of acetyl-CoA that is unable to enter the cycle. Such buildup stresses the system and can lead to further muscle loss.

AMINO ACID SUPPLEMENTATION

It will be of interest to observe the effects of the amino acid supplementation on the rate of muscle atrophy. Essential amino acids have been shown to increase muscle synthesis, and therefore, should be able to slow down muscle atrophy by offsetting muscle loss due to fasting. Conversely, a nonessential amino acid supplement could also decrease muscle atrophy because, instead of skeletal muscle breaking down in order to supply alanine to the liver, the supplement would take its place. An increase in nonessential amino acids should therefore decrease demand for the breakdown of muscle protein. With this in mind, both patients receiving nonessential amino acid supplementation and patients receiving essential amino acid supplementation should be expected to show decreased muscle atrophy following surgery as compared to an untreated patient. It is only the degree to which each supplement attenuates muscle atrophy that is left to be determined.

INTRODUCTION

As discussed, TKA surgery is becoming more and more prevalent, and by the year 2030, it is estimated that 3.48 million surgeries will be conducted every year (Kurtz, 2007). Thus it is imperative to find methods to decrease the associated muscle atrophy following surgery. Recent studies have shown that the quadriceps muscle group may atrophy more than 10% following surgery (Meier, 2008). Under normal muscle atrophy rates, an elderly individual will lose 10% muscle mass in approximately two decades; therefore, the equivalent of two decades of muscle mass may be lost following a single surgical procedure. Because the majority of patients receiving total knee surgery are both overweight and elderly, it is often the case that this muscle will never be regained. Consequently, the focus must be on preventing atrophy from occurring at all following surgery, since it cannot be corrected easily.

As noted, essential amino acid supplementation is currently being studied as a possible preventative measure for muscle atrophy following TKA surgery. Essential amino acids, leucine in particular, are anabolic and stimulate muscle protein synthesis. Conversely, non-essential amino acids are not anabolic, thus providing the rationale for supplemental groups. However, dietary intake by each subject within the study is a key component that may influence the eventual total muscle loss regardless of whether the subject receives essential or nonessential amino acids. Essential amino acid supplementation has been shown to activate anabolic pathways for muscle synthesis, but it might not have a large impact if the subject is not ingesting an adequate amount of calories, because muscle protein will be broken down via proteolysis to supply a substrate for the synthesis of glucose. Therefore, to optimally reduce the rate of muscle atrophy following surgery, the subject should ingest adequate amounts of both calories and protein.

One problem that arises in this study is the investigators' inability to dictate the subjects' diets during testing, which could impact the magnitude of muscle atrophy. All subjects were allowed to eat as they chose during the testing period as long as they recorded it in the food logs during the selected recording times. As a result, it is reasonably plausible that there will be no

significant differences in dietary intake found between two groups of subjects. This study, however, is not intended to be taken as exhaustive by any means. Instead, if there are no significant differences found in dietary intake, any differences in muscle atrophy rates between groups following surgery could be attributed to whether or not the subject was ingesting essential amino acids or nonessential amino acids. Such a conclusion would then have future implications for the implementation of essential amino acids in the surgical protocol for TKA.

The general hypotheses for this study is that there will be a significant difference in dietary intake that will partially explain differences in muscle atrophy following surgery between a placebo group with a nonessential amino acid supplementation (non-anabolic) and a treatment group with an essential amino acid supplementation (anabolic). Furthermore, a secondary hypothesis is that either form of supplementation will allow for the majority of subjects to reach the recommended protein intake of at least 0.8g/kg/day with a caloric intake of at least 2000 calories per day.

Subjects were tested according to the following specific hypothesis: Lean muscle mass in both the TKA leg and the untreated leg for subjects who meet the nutritional standards above will remain closer to preoperative muscle mass after surgery. This specific hypothesis will be tested with the implementation of the following measure: The total mass, lean muscle mass, and fat mass of both the TKA leg and the untreated leg will be measured before and after surgery and at specifically selected intervals.

METHODS

For this study, 18 subjects (12 women and six men) were selected in the range of 60-80 years of age, who were all relatively healthy older men and women, and who were scheduled to have elective total knee replacement surgery with orthopedic surgeons at the Slocum Center for Orthopedics and Sports Medicine in Eugene, Oregon. Subjects were excluded from the study if they matched any of the following exclusion criteria:

1. Dementia or related mental issues that could potentially put subject at risk as determined by the surgeon.
2. Previous TKA and/or THA surgery.
3. Untreated endocrine disease.
4. Significant heart, liver, kidney, blood, or respiratory disease.
5. Peripheral vascular disease.
6. Active cancer.
7. Recent (within six months) treatment with anabolic steroids or corticosteroids.
8. Alcohol or drug abuse.
9. Inability to have MRI.

Once selected, the subjects were placed in either an experimental group or a control group using a double blind methodology. The experimental group received 20g of mixed essential amino acids twice daily for a period of seven days before surgery and 14 days after surgery. The

control group received 20g non-essential amino acids in the form of alanine twice daily given at the same time intervals. The first 20g for both groups of subjects was taken at 10:00 a.m., and the second was taken at 2:00 p.m.

Subjects were also required to fill out three 72-hour food logs - one seven days before surgery, one 14 days after surgery, and once 42 days after surgery. These logs accounted for all food eaten within the 24 hour period, and specific notes were taken describing what was consumed with the supplement. The amount of fat, carbohydrate, and protein consumed by each individual was calculated from these logs.

All subjects in the study received an MRI preoperatively and again at two and six weeks following total knee replacement surgery. Images for the MRI were taken from the Anterior Superior Iliac Spine (ASIS) to the tibial plateau. Total muscle volume of the quadriceps muscle group as well as total fat, subcutaneous fat, and intermuscular fat were determined from these images.

Additionally, subjects were required to receive two DEXA scans—one seven days before surgery and one six weeks following surgery. These scans were used to find the body composition (fat, lean, and total tissue volume) at each point and to calculate percent change between the two.

Separate analysis of covariance (ANCOVA) were conducted to test for the effects of the treatment for four primary outcomes: six-week TKA leg lean mass, six-week control leg lean mass, six-week TKA leg mid-section five-slice value, and six-week control leg mid-section five-slice value. This test compares measured variables to determine whether they change significantly during the course of the study. Subject characteristics that were found in univariate correlations to be significantly related to outcomes were included as covariates in all models: gender, age, body mass index, tourniquet time; and baseline values of dietary fat intake, carbohydrate intake, and protein intake. Baseline values for each outcome were also included as a covariate for analysis. The effect sizes (Cohen's d) were found using covariate-adjusted values from the ANCOVAs at each time point (d =absolute value [(mean1-mean2) / pooled standard deviation)]). Models were conducted using data from all of the subjects (N=18), and then again using data from only females (N=12) in order to generate statistics for future research on female-only elderly populations. The procedure for analyzing the secondary outcomes was the same as the one used for the primary outcomes.

RESULTS

Table 1. Baseline values

	Placebo Group Mean±SE (N=9)	Treatment Group Mean±SE (N=9)	Sig1
Subject Characteristics			
# Females	6 (66.7%)	6 (66.7%)	1
Age	70.4±1.6	69.3±1.6	0.63
Body Mass Index	28.8±0.8	33.8±1.8	0.02
Tourniquet Time (min)	43.6±4.9	44.0±1.5	0.39
Fat Intake	48.7±5.3	60.2±4.6	0.12
Carbohydrate Intake	169.7±13.5	180.0±18.8	0.66
Protein Intake	63.2±10.6	73.2±3.4	0.38
Calorie Intake	1,358.4±113.3	1,573.0±102.3	0.18
Baseline Values			
TKA leg tissue (g)	13,328±863.7	15,803.3±1,053.8	0.1
TKA leg lean mass (g)	7,938.3±909.0	8,614±658.1	0.55
TKA leg fat (g)	5,390.0±547.8	7,187.9±853.1	0.11
Control leg tissue (g)	13,315±978.9	15,653.8±1,184.2	0.16
Control leg lean mass (g)	7,954.3±990.6	8,485.1±600.2	0.65

Significant values from chi-squared or t test, as appropriate. Observed (unadjusted) values are presented.

Preliminary data were collected for each subject within the placebo group and the EAA group. Baseline values were recorded and the significance value between groups was found. The only significant difference between the groups was Body Mass Index (BMI) but both groups had a BMI high enough to indicate the subjects were overweight. None of the other baseline values were significantly different, suggesting that all subjects as a whole were similar, and any deviations in baseline numbers could not be used to suggest they had influence on significant differences in muscle atrophy following surgery.

Table 2. Dietary intake

|	Control Group Mean±SE	Treatment Group Mean±SE	Sig1
Fat Intake			
Baseline (g)	47.5±5.3	61.4±5.3	0.12
2 Weeks (g)	33.5±5.8	51.6±5.8	0.08
6 Weeks (g)	59.0±7.0	52.0±7.0	0.55
Carbohydrate Intake			
Baseline (g)	187.9±17.7	161.8±17.7	0.37
2 Weeks (g)	146.7±22.7	165.3±25.8	0.62
6 Weeks (g)	202.3±25.8	166.7±25.8	0.41
Protein Intake			
Baseline	62.6±9.7	73.8±9.7	0.48
2 Weeks	51.4±6.0	62.5±6.0	0.26
6 Weeks	79.4±6.8	63.4±6.7	0.16
Protein Intake g/kg body mass			
Baseline	.743±0.109	.910±0.109	0.35
2 Weeks	.628±0.070	.742±0.070	0.33
6 Weeks	.993±0.080	.785±0.080	0.13
Calorie Intake			
Baseline	1,436.2±129.2	1,495.2±129.2	0.78
2 Weeks	1,086.1±127.3	1,376.1±127.3	0.18
6 Weeks	1,625.6±180.0	1,527.7±180.0	0.74

Separate ANCOVA models specified for each time point. Covariates in all models were age, sex, BMI, and tourniquet time. Also covaried in two-week and six-week models were baselines scores of the outcomes. Covariate-adjusted values are presented in the table.

Each subject completed food logs for all of his or her dietary intake, and the values for fat, carbohydrates, protein, protein per kilogram mass, and calorie intake at each interval were calculated. When each value between the placebo and EAA group were compared, all values at each time interval were found to be non-significant.

□ Placebo   ■ Treatment

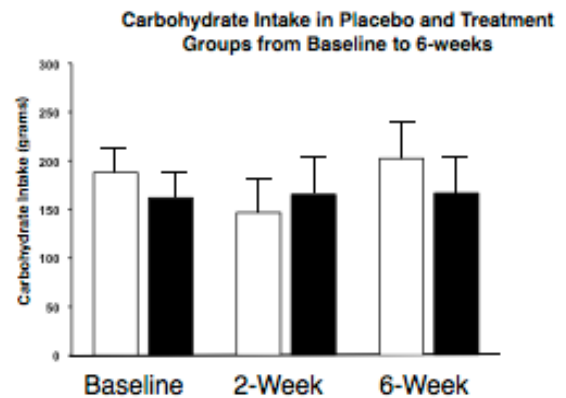**Protein Intake in Placebo and Treatment Groups from Baseline to 6-weeks**
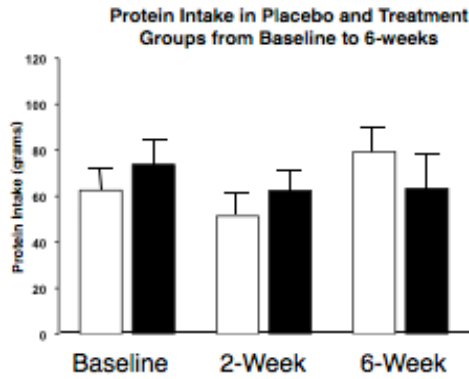
Graph 1: Shows the fluctuations of protein intake throughout the trial for both groups. Differences between the two groups at each time interval were non-significant.

Protein per kilogram mass intake in Placebo and Treatment Groups to 6-weeks
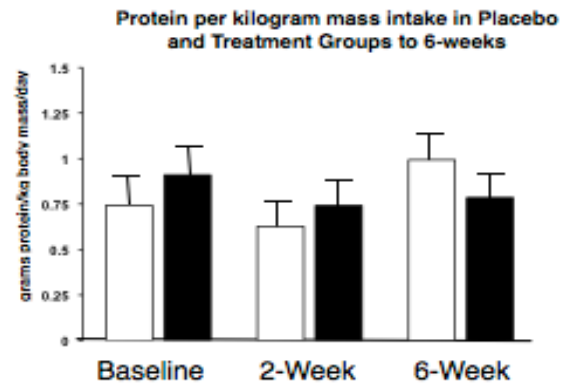
Graph 2: Shows the fluctuations of protein per kilogram mass intake throughout the tiral for both groups. Differences between the two groups at each time interval were non-significant.

Fat intake in Placebo and Treatment Groups from Baseline to 6-weeks
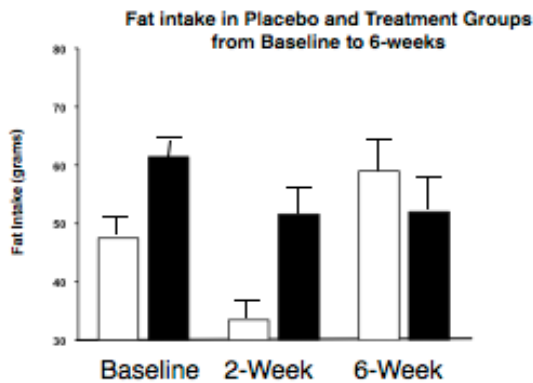
Graph 3: Shows the fluctuations of fat intake throughout the trial for both groups. Differences between the two groups at each time interval were non-significant. Despite a large difference in averages at two weeks post-surgery, large standard error led to differences that were non-significant.

Carbohydrate Intake in Placebo and Treatment Groups from Baseline to 6-weeks

Graph 4: Shows the fluctuation of carbohydrate intake throughout the trial for both groups. Differences between the two groups at each time interval were non-significant.
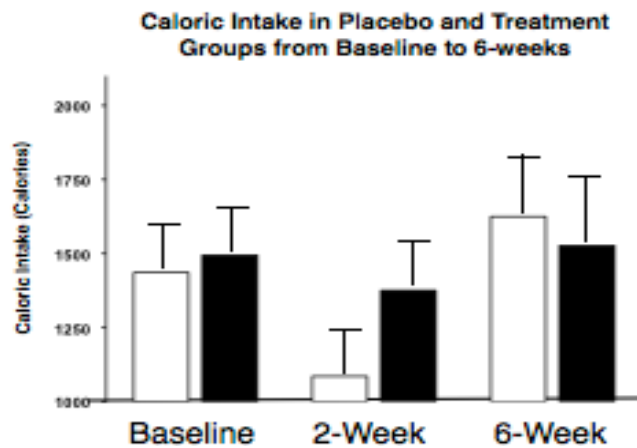
Graph 5: Shows the fluctuations of calorie intake throughout the trial for both groups. Differences between the two groups at each time interval were non-significant.

Table 3. Mean percent change between placebo and treatment group between baseline two weeks.

	Placebo Group (%)	Treatment Group (%)
Fat intake	-26.8*	-7.06
Carbohydrate Intake	-18.2	7.62
Protein Intake	-29.0**	-5.22
Protein/kg mass/day	-27.1**	-4.97
Calorie Intake	-27.4**	-4.32

Shows mean percent change within groups between baseline and two week values.
* indicates a trending value for the placebo group in fat intake.
** indicates significant differences in placebo group for protein intake, protein/kg mass/day, and caloric intake.

The mean percent change was used to find the average difference between the two-week values and the baseline values for each nutritional value that was measured. A negative value demonstrates that value decreased two weeks after surgery within the group. The majority of the percent change values show declines in each nutritional value, except for carbohydrate intake within the EAA group. Significant decreases were found within the placebo group from baseline to two-week values in protein intake, protein per kilogram mass intake, and calorie intake. There also was a trending value found in the fat intake for the placebo group from baseline to the two-week value.

Table 4. Quadriceps data before and after surgery

Outcome Variable	Baseline Mean±SE	2w followup Mean±SE	6w followup mean±SE	Effect Size of 2w	Effect Size of 6w
TKA leg lean mass (g) (n=15)					
Control Group	8,358.7±617.6	NA	6,811.4±192.1	NA	1.74
Treatment group	8,246.3±558.1	NA	7,681.0±173.6		
Control leg lean mass (g) (n=15)					
Control Group	8,915.2±633.8	NA	7,072.5±99.8	NA	3
Treatment Group	7,644.3±572.8	NA	7,848.3±89.7		
TKA leg mid-section 5-slice (g) (n=17)					
Control Group	127.3±9.1	108.6±7.3	105.8±4.7	0.46	0.69
Treatment Group	127.7±9.9	118.7±7.9	115.6±5.1		
Control leg mid-section 5-slice (g) (n=17)					
Control Group	150.6±10.0	133.2±5.2	133.6±3.9	0.31	0.51
Treatment Group	142.2±10.9	138±5.7	139.6±4.2		

Column 2 and column 3 values were adjusted for gender, tourniquet time, age, body mass index, fat intake, carbohydrate intake, protein intake, and baseline values of the outcome variable. Column 1 values were adjusted for gender, age, body mass index, tourniquet time, fat intake, carbohydrate intake, and protein intake. Effect sizes (Cohen's d) were calculated on adjusted values at each time point:d = absolute value [(mean1-mean2) / (pooled standard deviation)]. Analysis of covariance resulted in a statistically significant treatment effect on covariate-adjusted TKA leg lean mass at 6 weeks: $F(1)=7.45$; $p=0.041$. Analysis of covariance resulted in a statistically significant treatment effect on covariate-adjusted control leg lean mass at 6 weeks: $F(1)=21.03$; $p=0.006$.

Whole leg lean mass was taken for both the control and TKA leg for all subjects as well as muscle mass within a small, five-slice section of the quadriceps muscle. Whole leg mass was taken with a DEXA scanner and only recorded at baseline and six weeks after surgery, while the five-slice section was taken with an MRI at baseline, two weeks, and six weeks. The effect size was found between groups for each variable, and an effect size of d=0.2 suggests minor relevance while a value above one suggests strong relevance. Data from both DEXA and MRI scans suggest greater muscle loss in the control group following surgery.

DISCUSSION

Essential amino acids have shown potential to attenuate the rates of muscle atrophy following total knee arthroplasty, but because there are many factors that could potentially influence levels of atrophy, each variable must be accounted for between subjects. Factors including the subjects' activity level, the total time the surgery lasts, and dietary intake before and after surgery could all affect the rate of muscle atrophy. The goal of this study was to

determine whether dietary intake played a part in determining the amount of muscle lost or muscle saved in the quadriceps following total knee arthroplasty. This seemed like a prudent question because skeletal muscle houses the majority of protein within the body, and without adequate caloric intake, the body will begin to break down stores of protein in order to maintain the blood glucose level in circulation. The data, however, failed to support the hypothesis that there would be significant differences in dietary intake between subjects in the placebo group and subjects in the treatment group that could partially explain the differences in muscle mass following surgery.

Through analysis of the food logs, it became apparent that there was no significant difference between the control and treatment group for any of the recorded dietary measurements: fat intake, carbohydrate intake, protein intake, protein per kilogram intake, or caloric intake at any of the selected intervals before and after surgery (all p values >0.05). Despite this lack of significant differences in dietary intake, there are still significant differences between the placebo group and EAA group in regards to the lean mass in the quadriceps and a mid-section five-slice piece in the middle of the quadriceps of the affected leg (effect size of 1.74 & 0.69 respectfully). The five-slice section in the middle of the quadriceps is of particular interest because muscle lost here is less likely to come as a direct loss from the physical surgery. The area proximal to this section is likely to be affected from the tourniquet that prevents blood flow to the quadriceps muscle, while the area distal to this section will accrue ongoing damage from the surgical process.

Although no support was found for the initial hypothesis, these results suggest the administered essential amino acids given to the EAA group were able to spare muscle by limiting the rate of muscle atrophy when compared to the placebo group receiving nonessential amino acids. From previous studies, it appears that essential amino acid supplementation leads to various changes in gene regulation in which muscle protein synthesis is upregulated. Following surgery, the upregulation of muscle protein synthesis would then buffer the rate of muscle atrophy. In order to definitively prove the efficacy of essential amino acid supplementation in reducing muscle loss following TKA, continued research must be conducted to determine whether other variables could possibly account for differences in quadriceps muscle saved or lost following surgery. If there continued to be no significant differences between the two groups in terms of these variables, it would be even more suggestive that essential amino acids were capable of reducing the rate of muscle atrophy following TKA.

For the purpose of this study, dietary intake was not shown to account for any of the differences between groups in terms of muscle lost; however, proper nutrition could still be beneficial in this respect. Dietary intake for both groups had a decreasing trend between baseline and two-week values. For each individual, this could exacerbate muscle loss, but because both groups were subjected to the same decrease at this level, there was no significant difference between the two groups. One particular measurement of interest was the grams of protein per kilogram body mass per day measurement. Even with the added protein supplement for both groups, subjects rarely met the new recommended requirement of one gram of protein per kilogram body mass per day. Although the protein supplement is administered in order to

help reduce muscle loss, subjects should still be practicing healthy nutrition in order to bolster the effects of the supplement.

One interesting finding resulting from this study was that only one of the subjects managed to regularly ingest the recommended 2000 calories a day as demonstrated in the collected food logs, while all other subjects fell short of that requirement. This peculiarity arose from the fact that the majority of the subjects for the study were overweight (average BMI: placebo group: 28.8; TKA group: 33.8); however, this could be attributed to a lack of energy output due to the limited mobility of the subjects both before and after surgery. If energy output is low, then fewer calories would suffice for daily activities while still leading to increases in BMI. Moreover and perhaps more importantly, the lack of energy output before surgery can most likely be credited to pain arising from the damaged knee, thus limiting mobility, while the continued lack of energy output following surgery is a direct result from the surgery itself. This, if nothing else, demonstrates why finding a less deleterious method of TKA surgery is an important step in healthcare. An alternative explanation for a low dietary intake could be the result of inaccuracies in the self-reported food logs. Measures are currently being taken to have healthcare staff record food intake of the subjects following surgery in order to achieve more accurate measures.

It is evident that current protocol for TKA is lacking in its ability to fully restore patients to optimal health because of substantial muscle atrophy. Although the surgery has been proven to be a successful method for eliminating the original pain stemming from osteoarthritis in the knee, there is significant muscle loss in the quadriceps following surgery that leads to ongoing muscle weakness and decreased physical function. Essential amino acid supplementation could be an additional method in the surgical procedure to help reduce this high rate of muscle atrophy. Although essential amino acid supplementation seems to have a positive effect in preventing high levels of muscle loss, it is apparent that other factors could be responsible for part of the differences in muscle loss between a control group receiving nonessential amino acids and a treatment group receiving essential amino acids. Research should continue in this field, but evidence from this preliminary study suggests that dietary intake is not responsible for eliciting any of the differences in muscle saved following surgery.

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