THE INFLUENCE OF BODY MASS INDEX (BMI) ON THE PROTEIN NEEDS OF CRITICALLY ILL PATIENTS AS EVIDENCED BY URINARY UREA NITROGEN (UUN)

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ABSTRACT

Recommendations for protein needs in critically ill obese individuals are controversial and insufficiently researched. Current guidelines suggest protein needs for the critically ill obese be calculated with predictive equations that are based on energy needs data and incorporate accepted body weight adjustment calculations. There are no known studies that evaluate the alterations in protein needs based on body mass index in acute care patients.

The purpose of this study was to investigate the relationship between BMI and dietary protein needs as measured by 24- hour urinary urea nitrogen (UUN) test to determine if body weight was significantly associated with measured protein needs. The relationship between measured protein needs and estimated protein needs in obese individuals using ideal body weight (IBW) or adjusted body weight (ABW) calculations was also examined.

A retrospective chart review of 150 Veteran Affairs Medical Center patients who had a 24- hour UUN test during a previous admission in the last 5 years was conducted. Exclusion criteria included: less than 19 or greater than 85 years of age, patients receiving hemodialysis, a diagnosis of a gastrointestinal bleed or hepatic encephalopathy at time of urine collection, or insufficient urine volume collection. IBW was calculated using the Hamwi formula and ABW was calculated using the Amato formula. All statistical tests were two-tailed and performed using a significance level of 0.05 using SAS 9.2.

Participants were 82 European Americans and 62 African Americans with a mean age 62 (±10.0) years and a mean BMI 26.9 (±7.7) kg/m². Subjects had a mean of UUN 96 (±35.4) gram

of protein. In the total group, body weight was significantly ($p=0.0012$) associated with measured protein needs. In obese patients estimated protein needs based on either IBW or ABW calculations were significantly ($p<0.0001$) different from measured protein needs.

The results of this study suggest that protein needs for critically ill patients are associated with actual body weight. Additionally, predicting protein needs in the obese, critically ill patient using IBW or ABW for may not be appropriate. In this population, protein requirements should be measured rather than estimated using predictive equations.

DEDICATION

This thesis is dedicated to everyone who assisted and guided me through the process of completing this project. I would especially like to thank my family and friends for their unwavering encouragement and support in my journey to complete this manuscript.

LIST OF ABBREVIATIONS AND SYMBOLS

ABW Adjusted Body Weight

CBW Current Body Weight

DRI Daily Reference Intake

F Fisher's *F* ratio: A ration of two variances

IBW Ideal Body Weight

M Mean: the sum of a set of measurements divided by the number of measurements in the set

p Probability associated with the occurrence under the null hypothesis of a value as extreme as or more extreme than the observed value

r Pearson product-moment correlation

RDA Recommended Dietary Allowance

REE Resting Energy Expenditure

RMR Resting Metabolic Rate

t Computed value of *t* test

UUN Urinary Urea Nitrogen

< Less than

> Greater than

= Equal to

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CHAPTER 1

INTRODUCTION

Protein is one of the three macronutrients essential for the body to function. Protein provides the amino acids necessary for energy metabolism, digestion, blood clotting, vision, antibody formation, acid-base regulation, fluid balance, building muscle and skin, and growth, repair, and replacement of tissue (1). Dietary protein requirements for healthy individuals are well established and documented, however, recommendations for protein needs in individuals who are critically ill are still strongly debated and insufficiently researched.

Nutrition support during times of metabolic stress is a key component of a positive patient outcome. The metabolic changes that take place during critical illness drastically alter the way in which the body functions to provide the materials necessary to promote healing. The body accelerates the breakdown of skeletal muscle for use as energy, resulting in a rapid loss in lean body mass during metabolic stress and illness. Additionally, patients may be prescribed certain medications as part of their routine care that can have the detrimental side effect of accelerating the breakdown of muscle tissue (2). Therefore, the goal of nutrition support is to provide an appropriate intake of energy and amino acids to support healing and decrease the catabolism of body proteins. Amino acids provided during critical illness are utilized to build protein, slow the breakdown of skeletal muscle, assist with the body's natural defense mechanism, and support recovery (3).

Recommendations for nutrition support in critically ill patients are made based on predictive equations that utilize the patient's Body Mass Index (BMI), a ratio of weight in relation to height (1, 4). The energy and protein predictive equations for critical care patients are well-established for those who have a BMI <30.0. However as BMI increases above 30.0, alterations occur in the proportions of body tissue compartments, such that obese patients have a proportionately higher fat-to-muscle ratio than do their normal-weight counterparts. This has implications for calculating nutrition support regimens, as adipose tissue is not as metabolically active as muscle mass. Therefore, adjustments are often made to the predictive equations used to estimate calorie and protein needs to account for the alterations in fat-to-lean mass seen in obese patients (4). Current nutrition guidelines suggest both energy and protein needs for the critically ill be calculated using Ideal Body Weight (IBW) rather than Actual Body Weight (ABW) in order to adapt to the decreased metabolic needs of increased fat mass (5). Although the area of establishing energy prediction equations (or their adjustment factors) appropriate for overweight/obese patients is well-studied, there are no known studies evaluating alterations in protein needs based on BMI in acute care patients. Therefore, by following these common practice guidelines, it is possible that obese patients may be at risk for iatrogenic protein malnutrition.

The purpose of this study wass to investigate the relationship between dietary protein needs (as evidenced by UUN) and BMI. The investigation will use the following hypotheses:

Hyp 1: Body weight is significantly associated with measured protein needs (UUN).

Hyp 2: In overweight/obese adults, estimated protein requirements using adjusted body weight are significantly different from measured protein needs.

The goal of this study wass to provide evidence of protein requirements for improved nutritional guidelines for critically ill hospitalized patients. Improved nutritional support could decrease the risk of protein calorie malnutrition and its related complications and improve the chance of a positive outcome for critically ill patients.

CHAPTER 2

LITERATURE REVIEW

The word protein is derived from the Greek “proteose” meaning “primary” or “taking first place” (6). Protein may well be the “primary” of the three macronutrients, nutrients needed in large amounts, required for the body to function (1). Protein is formed from a complex chain of amino acids held together with peptide bonds that are used by the cells in the body to form enzymes, hormones, and antibodies (3). Proteins are part of the immune system, muscle, skin, hair, and nails (1). The body’s ability to grow, repair, and replace tissue and maintain pH and fluid balance is dependent upon protein. Proteins serve as cell receptors, transport vehicles, and as a means for cellular communication (3). Protein is also part of the mechanisms that allow the body to metabolize energy, digest food, and assist in blood clotting and vision (1).

The building blocks of protein are amino acids, molecules that have a common structure formed by an amino group, an acid group, and a hydrogen atom attached to a central carbon atom (1). A fourth group, called a side group, attached to the central carbon is what distinguishes one amino acid from another. The side group gives the molecule its unique shape, size, and signature characteristics that determine the molecules functional role in the body.

There are twenty common amino acids that are capable of combining to form a single protein (1). The body can make eleven of these amino acids; because the body can make these amino acids they are referred to as non-essential amino acids. Essential amino acids are the nine amino acids the body cannot make or cannot make in great enough quantity to meet the body’s

needs. Circumstances can cause a non-essential amino acid to become essential if the body can no longer produce the required amino acid or not produce sufficient amounts to meet demand, the amino acid becomes conditionally essential.

Peptide bonds bind amino acids to one another and can be thought of as the glue that holds them together (1). The peptide bond connects the acid end of one amino acid to the amino end of another forming; dipeptides when two amino acids are linked, tripeptides when three amino acids are combined, and polypeptides when ten or more amino acids are connected. In a process that takes just seconds to initiate and complete, the twenty common amino acids can be combined in a variety of combinations to create the 30,000 different proteins found in the body.

Proteins are commonly categorized by their function. Functional protein categories include; enzymes, hormones, structure, immunoproteins, transporters, buffers, fluid balance, and miscellaneous (3). In the role of an enzyme, protein acts as a catalyst to start chemical reactions in the processes of digestion, anabolism (the process of building large molecules from small ones), catabolism (the process of breaking large molecules into smaller molecules), and transformation (one substance is converted into another). Protein as a hormone is a chemical messenger that assists in regulating the body's metabolic processes. Skeletal muscle contains two vital proteins, actin and myosin, and accounts for 40% of the protein found in the body. The next highest concentration, 25%, of protein is found in the organs and the remainder is located in the blood, skin, bones, teeth, ligament, tendons, collagen, hair, and fingernails. The immune system utilizes protein in the form of antibodies that help protect the body from illness and disease. Protein as a transporter carries material in the blood and helps convey substances in and out of cells. Protein is part of the intricate systems that regulates the body's pH to keep it neutral as a change in pH can lead to coma or death (1, 3). Protein also plays a role in storage of materials,

binding non-protein compounds to form substances such as mucus, transmitting signals in and out of cells, blood clotting and vision.

Protein is provided to the body in two ways; exogenous sources, those outside the body in the form of food and endogenous sources, amino acids and body proteins that are inside the body (1). Protein from the diet is vital because it is the only source of the nine essential amino acids and can provide additional sources for amino acids that become conditionally essential. Dietary protein also reduces the body's need to cannibalize its own tissue to acquire the needed amino acid and protein to function.

The proteins provided by the diet must be broken down into smaller amino acid molecules for the body to be able to make use of them (1, 3). The process of breaking down dietary protein begins in the stomach where hydrochloric acid (HCl) begins to denature the proteins; change the proteins shape by breaking the hydrogen bonds. Then the enzyme pepsin breaks the peptide bonds holding the amino acids together resulting in smaller polypeptides. From the stomach the polypeptides move into the small intestine where new enzymes continue to dismantle the polypeptides into even smaller dipeptides, tripeptides, and free amino acids that can then be absorbed across the intestinal wall.

Once the protein has been broken down and absorbed into the intestinal wall the peptides and free amino acids can be used to build new proteins or other nitrogen containing compounds (3). When there is adequate protein to meet the body's needs, excess amino acids are removed from the body. The unused amino group containing the nitrogen is removed and the end product of the reaction is free nitrogen that forms ammonia. Ammonia is a toxic substance that can cause brain damage and coma if allowed to accumulate. Therefore, the liver filters the ammonia out the blood and converts it to urea. The urea then enters the blood stream and travels to the kidneys

where it is excreted in the urine. In a healthy individual urinary urea nitrogen (UUN) contains approximately 80% of total urea nitrogen (TUN).

The production and elimination of urea provides a way to measure how much protein the body is making and the amount of amino acids being broken down (1). Most healthy individuals are in nitrogen balance, the amount of nitrogen consumed is equal to protein breakdown and there is little excess nitrogen to be excreted as urea. During periods of rapid growth such as pregnancy and childhood the body is in positive nitrogen balance as the amount of protein taken in is greater than the amount being excreted because the protein is being used to support the demands of growth. In times of injury, illness, or starvation protein intake decreases and the body begins breaking down tissue to use for energy causing the amount of nitrogen excreted to exceed intake resulting in negative nitrogen balance.

There are several clinical tests used to measure nitrogen balance, the most common is a 24-hour urinary urea nitrogen (UUN) test. A 24-hour UUN test measures the amount of urea excreted in the urine in 24 hours. The results of the test can be used to determine the rate at which the body is breaking down protein and if intake is sufficient to meet demand (7).

The amount of urea produced varies with intake of dietary protein (3), therefore, intake must be considered when interpreting the result of a 24-hour UUN test (7). Urea production increases with a high protein diet and is reduced with a low protein diet (3). In the case of high protein intake the test results can be used to interpret the protein balance or the difference between intake and breakdown of protein (7). The results of a 24-hour UUN test in combination with a low protein intake, approximately less than 20 grams (g) a day, can be used as a tool to calculate the protein requirements and catabolic rate of an individual.

A standard formula, (24hr UUN(g) +4g) x 6.25, is used to calculate protein loss using the results of a 24-hour UUN test (8). Results between 5-10 grams a day imply the catabolic rate is normal for a healthy person or that mild protein breakdown is occurring but is not of concern. Results of 10-15 grams a day suggest a moderate state of protein catabolism and losses of 15 grams or more a day suggest severe protein breakdown (7).

Urea is not exclusively excreted in urine; it is also expelled through feces, sweat, hair, skin, and nails. Non-urinary urea losses are accounted for in the protein loss equation by the addition of two grams of nitrogen to the UUN test results (3). The average nitrogen lost in the feces is one gram and insensible losses through skin, hair, and nails are averaged at one gram. Two additional grams of non-urea nitrogen are lost in the urine as creatinine, uric acid, and ammonia and are added to the protein loss equation. The sum of the UUN test and the additional four grams of nitrogen must be multiplied by 6.25; nitrogen is one sixth the weight of dietary protein, to convert grams of nitrogen into grams of protein (7).

While 24-hour UUN tests are the most available laboratory test in a clinical setting, they are not always the most accurate (7). Two of the most important methodological aspects of conducting a 24-hour UUN test are timing and accuracy of sample collection. In a hospital setting over a 24-hour period there are two to three shifts of nurses who must coordinate the collection of the sample (9). There is also the possibility of spillage during collection or transport or leaking of catheters. These errors reduce the sample volume which could produce unreliable test results.

Additionally, there are several metabolic factors that can affect the accuracy of a 24-hour UUN test. The amount of water in the body, renal insufficiency, dialysis, and a gastrointestinal (GI) bleed can skew test results (3). Body water content is associated with edema that results in

rapid changes in body weight (7). To remove the excess fluid, rapid diuresis may be used which produces a swift reduction in body weight and available body water. Dialysis can alter fluid balance and blood urea nitrogen (BUN) which changes the results of a 24-hour UUN test. Although there is no way to correct the results of a UUN test for a GI bleed, it must be taken into account when interpreting the results and determining treatment.

Stress, as defined by Webster, is a force that tends to strain or deform (10). When the body experiences stress in the form of physical injury, alterations in chemical balance, disruption of a physical process, or an emotional impact the body's natural equilibrium is upset. The body's response to stress is to attempt to re-establish the delicate physical and chemical balance of a healthy state (11).

Immediately following a traumatic event a number of triggers send a signal to the hypothalamus which controls the sympathetic nervous system (SNS), the nervous system that controls the fight or flight response. The SNS sets in motion a series of reactions that are intended to prevent further damage from occurring to the body by stopping blood loss and increasing blood flow to the tissue. Increasing blood flow to the tissue stimulates recovery and repair and initiates wound healing by increasing the amount of nutrients carried to the tissue and removing waste and dead cells (11).

The magnitude of the stress response is determined by the severity and duration of the stressor, the individual's nutrition status, and other diseases afflicting the patient (11). The more severe the stressor the more intense and prolonged the stress response. The individual's nutrition status is key in determining the patient's ability to cope with and recover from the stress and a poor nutritional status can indicate poor recovery. Illnesses that were present prior to the immediate stress complicate the situation and increase of the risk of morbidity and mortality.

During times of stress, metabolic functions are altered to support recovery and repair of the body. This metabolic response occurs in two stages, the ebb phase and the flow phase (3). The ebb phase is the body's immediate response to stress and continues for twelve to twenty-four hours, however, it can last longer if the event is severe (3,11). In the ebb phase the body systems slow down their processes; metabolic rate declines, blood pressure falls, body temperature drops, oxygen consumption decreases, and blood flow to the tissue decreases (3). The decreased blood flow to the tissues means that the cells are not receiving the needed nutrients and waste is not being removed.

The ebb phase evolves into the flow phase which typically lasts seven to ten days; cresting during days three to five (11). During the flow phase, the body becomes hypermetabolic with increased cardiac output, oxygen consumption, and energy expenditure and a rise in body temperature (3). The initial stage of the flow phase, the acute response, is marked by a change in hormone production and blood cell count, and an increase in protein turnover, all of which cause a fever (6). Hormonal balance shifts as the body begins to produce acute phase response proteins (APRP) to help the body respond to stress through blood clotting, increased immune response, and the prevention of further tissue damage. The APRP also assist with repairing and reconstructing damaged tissue. Despite the release of APRP in an attempt to prevent further damage to the body the breakdown of skeletal muscle remains greater than anabolic activity of protein production for use by the body.

In a healthy body when nutrient needs are increased hunger cues are initiated and intake increases, thereby satisfying both hunger and nutrient needs (4). In injury or illness the appetite is suppressed even though the need for energy and protein is greatly increased. Without

exogenous sources of energy and protein the body begins to use internal sources to meet its needs.

A dramatic increase in the demand for energy in the form of glucose, the body's main energy source, is a hallmark of stress (3). The increase in the demand for glucose during stress is thought to be related to the process required to repair damaged tissue (11). However, one of the hormonal changes that take place during stress is an increase in the release of the hormone insulin. Insulin prevents the formation of ketone bodies which are required for the body to make glucose (3, 6). Without ketones to make glucose the body begins to breakdown skeletal muscle to meet the increased demand for energy (6).

Skeletal muscle is the largest source of free amino acids in the body and it is catabolized to provide energy, boost immunity, and as a source of free amino acids (11). Free amino acids are also used to keep a constant pool of total available free amino acids for use by the entire body. Free amino acids from the muscle tissue are utilized by the internal organs to maintain their function.

The assault on the skeletal tissue leads to the loss of lean body mass, wasting, and weakness seen in critical illness (6). The significant loss of body proteins results in negative nitrogen balance as intake decreases and catabolism increases (3). It has been noted that, during the first week of treatment in an intensive care unit (ICU), patients can lose 10-20% their total lean body mass (4). Wasting associated with stress can be gradual in events such as mild injury, malnutrition, cancer, and immobilization or rapid, as with severe injury, burns, and infection (11). Loss of muscle mass, whether slow or quick, further complicates recovery by decreasing the bodies' already-weakened defenses and thereby increasing the risk of morbidity and mortality.

As the acute response begins to subside, the body moves into the adaptive response of the flow phase (11). The adaptive response is associated with anabolism and recovery (3). The body begins to decrease the production of APRP, hormonal balance returns, and metabolic rate begins to return to pre-stress levels. The body's gradual return to homeostasis allows it to utilize nutrients efficiently promoting the rebuilding of lean body mass and repair of damaged tissue.

Protein needs during illness and injury are defined very differently than in a healthy state. In healthy individuals the required amount of protein is that which maintains a zero nitrogen balance (12). In illness protein requirements are defined as the amount necessary to prevent as much breakdown of body proteins as possible. Non-essential amino acids may become conditionally essential as the definition of essential amino acid changes from what the body can or cannot make to become a question of supply and demand (11). Since the role of catabolism is much higher in illness, it stands to reason the protein requirements will be greater in illness than health (12).

The goal of medical nutritional therapy during stress is to provide the body with another source of energy and protein other than skeletal tissue during illness to lessen the loss of lean body mass (12). A favorable protein intake will increase immune function, decrease insulin resistance and oxidation-reduction reaction imbalance, and decrease the loss of amino acids. Amino acids given during illness provide the liver another source other than skeletal muscle from which to make protein in-turn improving nitrogen balance (3). However, even optimal levels of protein do not slow down the rate of protein breakdown during the acute phase response. Even if positive nitrogen balance is achieved, it is not a sign that the breakdown of body proteins has stopped.

While it is agreed that protein needs increase during times of stress, the magnitude of the increase and how much exogenous protein must be provided to meet the increased demand is a subject of contention (13, 14). It has been shown that providing 1.5 grams of protein per kilogram (kg) of body weight a day is sufficient to promote whole body protein synthesis and 2.2 grams of protein per kilogram of body weight per day increase both protein synthesis and catabolism in all stressed patients. If the goal of nutrition support in critical illness is to increase protein synthesis then both low and high protein diets are adequate. The question is then "which practice will benefit the patient the most?" the low protein diet that promotes anabolism or the high protein diet that has the added benefit of improving nitrogen balance but increases both catabolism and anabolism (15).

Lambert Adolphe Jacques Quetelet, a 19^{th} century mathematician, developed a formula that is used to estimated body fat percentage (BF%) using the relationship between height and weight (16, 17). The Quetelet Index, or Body Mass Index (BMI), has become a globally recognized tool to begin to assess health and nutrition status (18). Calculating BMI has become widely used because it can be done in any setting and requires very little equipment. The tools to collect the necessary data include a balance or a scale to obtain weight and a stadiometer to measure height (16). The data is then plugged into the formula, weight in kilograms divided by height in meters squared, and the calculation can easily be computed by hand or with a basic calculator (18).

BMI results are divided into classes which are used to estimate the possible risk for developing a disease or weight-related comorbidity (18). A BMI of less than 18.5 kg/m^2 is considered underweight and is associated with a risk of increased illness, a decline in reproductive capabilities, and decreased overall function (1). A normal BMI, between 18.5 kg/m^2

and 24.9 kg/m^2, is linked with optimal health, immune function, and disease resistance. Increased risk of disease and illness begins in the category defined as overweight, a BMI of 25.0 - 29.9 kg/m^2 (18). The cutoff point between a healthy BMI and an unhealthy BMI was established because, at a BMI of 25.0 kg/m^2, there is a significant increase in the ratio of adipose tissue to muscle mass (1). A BMI of 25.0 kg/m^2 is a marker for healthy individuals not to surpass and a goal for those with a BMI greater than 25.0 kg/m^2 to strive for. Obesity classification begins at a BMI of greater than or equal to 30.0 kg/m^2 and has three categories. Obesity I is a BMI from 30.0 - 34.9 kg/m^2, Obesity II is a BMI of 35.0 - 39.9 kg/m^2, and Obesity III is a BMI greater than or equal to 40.0 kg/m^2 (19). The risk of developing a weight related illness or disease increases with the progression of the obesity category.

Current nutrition support guidelines for the critically ill recommend 1.2 – 2.0 grams of protein per kilogram of actual body weight for those with a BMI of less than 30.0 kg/m^2 (5). The recommendation for protein intake for patients with a BMI of 30.0 – 40.0 kg/m^2 is ≥2.0 grams of protein per kilogram of ideal body weight (IBW) and for those with a BMI greater than 40.0 kg/m^2, ≥2.5 grams of protein per kilogram of IBW should be administered. The increase in adipose tissue renders use of actual body weight to determine protein needs inappropriate and likely overestimates needs (20). To reach the higher protein goals, protein supplements are often used because standard enteral and parenteral formals do not contain enough protein.

There are numerous formulas for calculating IBW; the Hamwi equation is the most commonly used formula in the United States (21). The Hamwi method of calculating IBW was developed in 1964 but it is unknown how it was derived or if and how it was validated. The formula for IBW uses height and gender which does not take into account the increased muscle mass that is seen in obesity (22). The use of IBW to calculate protein needs of obese patients is

also controversial because the predictive equations used to estimate protein needs are based on normal weight patients (20). Therefore, it is suspected that use of IBW in predicting protein requirements underestimate the needs of obese individuals.

Adjusted body weight is another well-known predictive equation used to estimate nutrition needs in obese patients. Like IBW, there are several formulas to calculate ABW. The original formula, IBW + [(actual body weight-IBW) x 0.25), appeared in the 1984 *Renal Dietitian's Newsletter* without any apparent original research (23). The 25% adjustment factor was designed to account for the portion of the excess body weight in the obese that was believed to be metabolically inactive. A variation on the ABW formula uses a 50% adjustment factor to account for the excess body weight in obesity. Adjusted body weight was used for a short time to estimate nutritional needs of the obese but because the method was never validated it is not recommended for use (5, 20).

The current body of research suggests that providing a hypocaloric, high-protein diet for the obese critically ill patient encourages a positive clinical outcome (4, 20). Although there are no standard guidelines for a hypocaloric high-protein diet, common practice provides 30-70% of estimated energy needs and 50-60% of total calories from protein (4). Restriction of calories increases insulin sensitivity which improves glycemic control and decreases the risk of overfeeding. Additional benefits include decreased levels of carbon dioxide, a reduction in fluid retention, hypertriglyceridemia, time spent on the ventilator and in the intensive care unit (ICU), and an increase in prealbumin levels (20).

Piatti et. al. (24) found that a hypocaloric high-protein diet had greater benefit than a hypocaloric, high-carbohydrate diet in healthy, obese women. The hypocaloric high-protein subjects maintained their fat free mass and positive nitrogen balance and decreased their fat

mass. The individuals on a hypocaloric, high-carbohydrate diet also had a decrease in fat mass but had a significant loss of LBM, and developed a negative nitrogen balance. A hypocaloric high-protein diet has also been shown to promote a decrease in serum insulin, cholesterol, HDL cholesterol, and triglycerides.

In the obese patient a low calorie, high-protein diet increases the use of adipose tissue for energy (4). The use of adipose tissue for fuel has a two-fold benefit; it decreases the catabolism of skeletal muscle while promoting a decrease in excess fat mass and improving body composition. It should be noted that individuals with a BMI greater than 40.0 kg/m^2may have different needs than those in Obesity Class I and Class II and a hypocaloric, high protein diet has not been proven appropriate for this group (22).

Although guidelines and recommendations are in place for nutrition support based on BMI it is common to find that ICU patients are given similar nutrition prescriptions regardless of BMI (25). In an international prospective, observational study Alberda et. al (25) reported obese ICU patients receive an average of 0.4 grams of protein per kilogram of actual body weight and no protein supplementation despite The American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines and recommendations for a high protein diet. The significant gap between protein needs and intake may accelerate loss of lean body mass, vital amino acids, and micronutrients, and lead to the development of malnutrition that was not present prior to illness. Increased protein intake in the obese, critically ill patient could improve nitrogen balance, retention of skeletal muscle, and improve the overall patient outcome (20, 25).

Obesity is a worldwide health epidemic. In the United States alone, the rates of obesity have doubled in the past thirty years (4). Currently, two-thirds of the US population is overweight and one-third, or 100 million people, is obese. There are variations in the predictions

on the future rates of obesity; some predict the prevalence of obesity beginning to level off while others predict seventy-five percent of Americans will be overweight by 2015. With this in mind, it is essential to adequately study optimal methods to provide nutrition support to this rapidly growing population.

It is known that an insufficient amount of protein during times of metabolic stress could accelerate muscle wasting and promote poor wound healing. It is also common knowledge that current practice guidelines for protein provision are based on theoretical models and previous data from non-overweight/obese patients. Therefore, the goal of this study was to provide evidence to improve nutritional support guidelines in the provision of protein to critically ill patients in hopes of improving patient outcome.

CHAPTER 3

METHODOLOGY

INTRODUCTION

This study was a retrospective chart review of previously hospitalized Birmingham Veteran Affairs Medical Center (BVAMC) patients who have had a 24 hour UUN collection. BVAMC utilizes an electronic medical records program, VISTA, which is employed daily for routine patient care was used to generate a data set of patients who had a 24 hour UUN test during a previous hospital admission within the past five years. The Institutional Review Boards at the BVAMC and The University of Alabama have reviewed and approved this study.

SUBJECTS

Beginning with the most recent admission date, subjects were selected on their ability to meet the study criteria. Exclusion criteria included <19 or >85 years of age, patients receiving hemodialysis, insufficient urine volume collection for a UUN test, and/or a diagnosis of a GI bleed or hepatic encephalopathy. Data collected from the medical record included the medical record number (MRN) which is the patient's Social Security Number (SSN), name, age at time of specimen collection, gender, ethnicity, weight, height, UUN test results and date of collection, unit location at time of UUN, feeding method, medications (specifically steroids and diuretics), comorbidities, and admitting diagnosis.

ANALYSES

Descriptive statistics compiled included age at time of 24-hour UUN test, race, gender, BMI, unit location at time of 24-hour UUN, feeding method, weight in kilograms at time of 24-hour UUN, and 24-hour UUN results in grams of protein. Descriptive statistics were expressed as mean, total number, standard deviation, minimum, maximum, and percent. Correlational analysis was used to evaluate the relationship of measured body weight with protein needs (hypothesis 1). Body weight at time of 24-hour UUN collection was the most current body weight (CBW) available and was utilized for calculations. The data was run with and without outliers. As outcomes did not change, all subjects were included in the final analysis.

T-tests and Pearson's coefficients were used to assess the relationship between estimated protein requirements using IBW, ABW, and measured protein utilization (UUN) in overweight/obese individuals (hypothesis 2). All statistical tests were two-tailed and performed using a significance level of < 0.05. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

IBW was calculated using the Hamwi formula (Males – 106 pounds for the first 60 inches + 6 pounds for every inch after 60 inches, Females – 100 pounds for the first 60 inches + 5 pounds for every inch after 60 inches) and ABW was calculated using the Amato formula (actual weight – IBW) x0.5 + IBW). BMI (kg/m^2) was divided into the BMI classifications established by the World Health Organization. The results of the 24-hour UUN test were converted into grams of protein using the standard formula (24hr $UUN_{(g)}$ +4g) x 6.25. Measured grams of protein per kilogram were calculated for weight at time of 24-hour UUN ((24hr $UUN_{(g)}$ +4g) x 6.25/ weight in kilograms at time of 24-hour UUN collection), IBW ((24hr $UUN_{(g)}$ +4g) x 6.25/ IBW in kilograms), and ABW ((24hr $UUN_{(g)}$ +4g) x 6.25/ ABW kilograms).

CHAPTER 4

RESULTS

Participant demographics are listed in Table 1. Subjects were one hundred and fifty previously admitted Birmingham Veteran Affairs Medical Center patients (one hundred and forty-five men), with a mean age of 61.9 (±10.0). Approximately one-half of the population (54.6%) was European American and slightly less than half (41.3%) were African American. The remaining 4.1% were comprised of Native Hawaiian/ Pacific Islander (0.6%), American Indian/ Alaskan Native (1.3%), and unknown (2.0%). The total group mean BMI was 26.9 (±7.7); more than half (55.3%) of the subjects had a BMI greater than or equal to 25.0 kg/m^2 classifying them as overweight/ obese. Subjects with a normal BMI accounted for 31.3% of the population and 13.3% had a BMI that classified them as underweight. The majority (64.0%) of subjects were located in an Intensive Care Unit (ICU) at the time of 24-hour UUN collection. Sources of nutrition at the time of 24-hour UUN collection included parentral nutrition (44.6%), enteral nutrition (26.6%), and an oral diet (15.3%).

The results of the correlational analysis run to evaluate the relationship of measured body weight with protein needs are presented in Table 2. The mean grams of protein excreted as measured by UUN were 95.6g (±35.5) for the total group. The mean weight of the total group was 88.7kg (±26.9).

Paired t-tests and Pearson's correlation coefficients were used to assess the relationship between estimated protein requirements using IBW, ABW, and measured protein utilization

(UUN) in overweight/obese individuals (Table 3). Only subjects with a BMI greater than or equal to 30 kg/m^2 (n=48) were included in the paired t-test as this is the BMI class for whom IBW and ABW would be used to calculate caloric and protein needs. The mean grams of protein per kilogram of CBW were 0.9g (±0.4). The mean grams of protein estimated per kilogram of IBW were 1.4g (±0.5) and 1.1g (±0.4) of protein estimated per kilogram ABW.

Table 1. Demographic Data of Previously Admitted Veteran Affairs Patients with a UUN Collection during Admission (n=150)

Variable	% Total	Range	Mean (±SD)
Age (years)	n (%)	25-82	61.95 (10.08)
Race			
White	82 (54.6%)		
Black or African American	62 (41.3%)		
Unknown	3 (2.0%)		
Hispanic/Latino	0 (0%)		
Asian	0 (0%)		
American Indian or Alaskan Native	2 (1.3%)		
Native Hawaiian or other Pacific Islander	1 (0.6%)		
Gender			
Male	145 (96.6%)		
Female	5 (3.3%)		
BMI		14.5 – 60.6	26.9 (±7.7)
Underweight	20 (13.3%)		
Normal weight	47 (31.3%)		
Overweight	35 (23.3%)		
Obese	48 (32.0%)		
Location at time of 24-hour UUN collection			
SICU[a]	72 (48.0%)		
MICU [b]	23 (15.3%)		
CVICU[c]	1 (0.7%)		
CCU[d]	5 (3.3%)		
Surgery	6 (4.0%)		
Medicine Floor	24 (16.0%)		
Palliative Care	0 (0%)		
Feeding Method			
PO[e]	23 (15.3%)		
TF[f]	40 (26.6%)		
TPN[g]	67 (44.6%)		
PO and TF	1 (0.7%)		
PO and TPN	1 (0.7%)		
TF and TPN	5 (15.3%)		
No nutrition support	13 (8.7%)		
Weight (kg) at time of 24-hour UUN, grams		41.3 – 202.0	88.8 (±26.9)
24-hour UUN results (grams of protein)		35.7 – 198.8	95.6 (±35.4)

[a]SICU – Surgical Intensive Care Unit
[b]MICU – Medical Intensive Care Unit
[c]CVICU – Cardio Vascular Intensive Care Unit
[d]CCU – Critical Care Unit
[e]PO – By mouth (per os)
[f]TF – Tube feed
[g]TPN – Total Parenteral Nutrition

Figure 1. Pearson's product moment correlation coefficient between body weight and measured protein excretion in hospitalized patients (N=150; r= 0.26, p= 0.002)

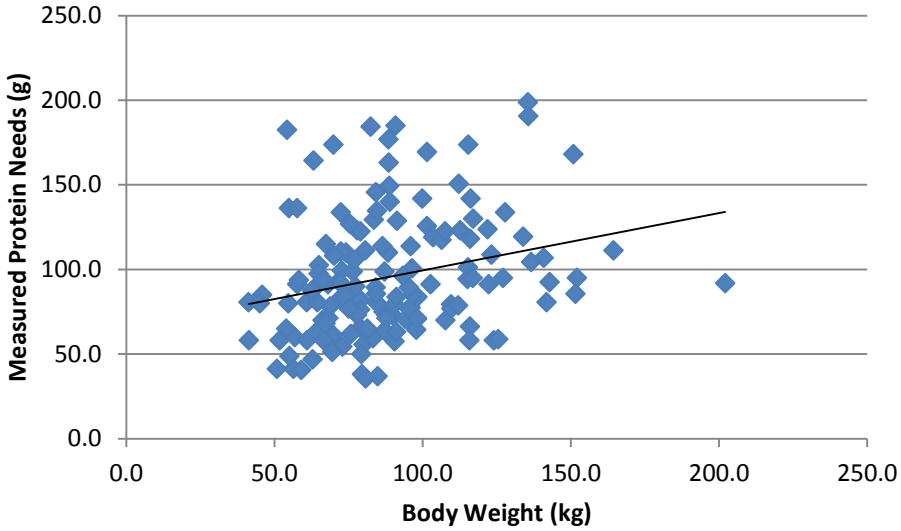

Table 2. Correlation between measured protein needs for current body weight (CBW) and ideal body weight (IBW) or adjusted body weight (ABW) in obese, hospitalized patients (n=48)

	Mean (±SD)	***Range***	***r(p)****
Grams of Protein per kg CBW	0.9 (0.3)	0.4 – 2.0	
Grams of Protein per kg IBW	1.4 (0.51)	0.7 – 2.6	0.90, (<0.0001)*
Grams of Protein per kg ABW	1.1 (0.4)	0.5 – 2.2	1.0, (<0.0001)*

*significant value for difference from measured protein needs using g/kg/CBW

CHAPTER 5

DISCUSSION

The purpose of this study was to investigate the relationship between BMI and dietary protein needs as measured by 24- hour UUN test to determine if body weight was significantly associated with measured protein needs. The relationship between measured protein needs and estimated protein needs in obese individuals using IBW or ABW calculations was also examined. The results of this investigation confirm the study hypotheses which were:

Hyp 1: Body weight is significantly associated with measured protein needs (UUN).

Hyp 2: In overweight/obese adults, estimated protein requirements using adjusted body weight are significantly different from measured protein needs.

In the total group, body weight was significantly ($r=0.26$, $p=0.0012$) associated with measured protein needs. Although the association was low, likely secondary to a large weight range, this would suggest that patients of different body weights would require varying amounts of protein to support metabolic functions. In this study, the mean body weight at time of UUN collection of underweight subjects was 61.5kg and their mean measured protein needs were 1.5g per kilogram of body weight. Subjects of a normal weight had a mean body weight of 71.8kg and mean UUN of 1.2g per kilogram of body weight. Overweight subjects (mean body weight 89.9kg) and obese subjects (mean body weight 116.0kg) both had mean measured protein needs of 0.9g per kilogram of body weight.

While our study enrolled critically ill subjects, a review of the literature could only uncover similar studies that used healthy individuals to examine the relationship between body weight and protein needs. The associations between increasing protein requirements and increasing body weight seen in our study may be explained by research that shows that alteration in body weight is a major factor in changes in lean body mass (26,27). Forbes et al. (26) conducted a longitudinal study and meta-analysis of subjects to monitor body composition and the changes in lean body mass during aging. The individual longitudinal study found a positive relationship between associations in body weight and lean body mass. In the meta-analysis, they found that individuals who maintained or lost weight had a decrease in fat free mass while those who experienced weight gain had an increase in fat free mass. In the Healthy Aging and Body Composition study (Health ABC Study) Newman et al. (27) examined changes in body composition and their relationship to functional decline in old age. Newman found that changes in fat free mass and fat mass were always in the same direction as weight change. They also noted the proportion of change in fat mass was greater than the change in fat free mass.

Nitrogen balance studies have been used for more than forty years to determine adequate grams of protein per kilogram of body weight required to support zero nitrogen balance and optimal health. Bodwell et al. (28) conducted a nitrogen balance study in 1979 to determine the adequacy of the 1973 Food and Agricultural Organization/World Health Organization (FAO/WHO) Recommended Dietary Allowance (RDA) for protein. The FAO/WHO recommendations were based primarily on study results that enrolled mainly young men, raising the question of whether the RDAs were appropriate for other populations. Bodwell found, in a healthy, diverse population, that UUN was significantly correlated with body weight and BMI. The results of Bodwell's study support the theory that the protein needs of healthy obese adults,

whose needs are elevated related to their greater proportion of LBM, would increase even further under the stress of illness or disease as found in our study.

Our study appears to be unique in its assessment of the adequacy of estimation of protein needs based on predictive equations using IBW and ABW for obese patients. There is a dearth of research exploring the use of adjustment factors to calculate protein needs in the obese patient, most research is directed at using adjustment factors to estimate energy needs. Current nutrition support guidelines for protein needs are based on studies which provided a set amount of protein per kilogram of IBW for all obese subjects in an attempt to achieve positive nitrogen balance (29).

Our study showed, in the subset of obese patients, that estimated protein needs based on either IBW or ABW calculations were significantly different from ($p<0.0001$ for each) and positively correlated with measured protein needs (IBW $r^2=0.89011$, $p= <.0001$, ABW $r^2=0.98531$, $p=<0001$). For the patients, mean measured protein needs for body weight at time of UUN collection was 0.9g per kilograms of body weight. When protein needs were estimated using IBW, mean protein needs were 1.4g per kilograms of estimated body weight using ABW, mean protein needs were 1.1g per kilograms of estimated body weight. This suggests that estimated protein needs based on either IBW or ABW will not meet the patient's true protein needs.

Findings from the current study, which showed measured protein needs were significantly different from estimated protein needs when using body weight adjustment factors, are similar to studies which used IBW and ABW to estimate energy needs. When using IBW in conjunction with the Harris-Benedict equation to estimate energy needs for obese patients, two studies found that measured resting energy expenditure (REE) was different than needs estimated

by the predictive equation. In an attempt to validate predictive equations in obese women, Weijs et al. (30) found the 1984 Harris-Benedict equations accurately predicted energy needs 68% of the time. However, when IBW was incorporated into the Harris-Benedict equation, the accuracy of prediction decreased to 23% with 74% of the predictions underestimating energy needs. Feurer et al (31) also found that measured REE was significantly higher than needs estimated by the Harris-Benedict equation when IBW was included.

In a prospective study of obese subjects, an energy prediction equation using ABW and a 25% adjustment factor was evaluated for validation by comparison to results from measured RMR via indirect calorimetry (32). The study found a 74% error rate when using ABW as part of the Harris-Benedict equation to estimate calorie needs, resulting in a significant underestimation of energy needs. Additionally, the needs of 100% of subjects with a BMI >40.0 were underestimated when ABW was used in the Harris-Benedict equation to calculate energy needs. However, the error rate when using actual body weight in the Harris-Benedict equation was only 36%.

We hypothesized that the practice of using predictive equations that utilize actual body weight to estimate protein needs are appropriate for this population. The literature and results of this study do, indeed, support the theory that protein needs are directly associated with body weight. While the results of this study also support the use of actual body weight in calculating protein needs for the obese, literature could only be found to support the use of predictive equations that use actual body weight in the estimation of energy needs for the obese. However, if the use of adjustment factors such as IBW and ABW are considered inappropriate for estimating energy needs in the obese it seems plausible they are also inappropriate for estimating protein needs.

The current study had some limitations. Similar to the FAO/WHO meta-analysis of studies to create the 1973 RDAs, our study was comprised mostly of men; one-hundred and forty five out of a population of one-hundred and fifty. Subjects who had a urinary nitrogen appearance (UNA) test were not excluded from the study. This could be problematic as UNA is calculated to correct UUN results when a rapid change in blood urea nitrogen (BUN) related to a change in body-water content occurs during the 24-hour collection period (7). There were three subjects in the study who had a UNA calculated; all were in the obese category. The sample size for the obese group used to test Hypothesis 2 had 48 subjects including the three subjects with UNA calculations; the small sample size with the addition of three incorrect UUN values could adversely affect the statistical analysis of the data for the obese subjects.

The majority of nitrogen balance studies choose to focus on patients with a particular disease state or stratify the study population by diagnosis, this study did neither. This could contribute to the observed variation in measured protein needs. However, it is believed that not stratifying study subjects by disease state lends strength to the study as it provides a more accurate representation of clinical practice. The results of studies which examine a specific disease state are not necessarily applicable to other illnesses; by not stratifying study subjects the results of this study may be more clinically relevant across a wide range of disease states.

In conclusion, the results of this study suggest that protein needs for critically ill patients are loosely associated with actual body weight. Additionally, in clinical practice the use of IBW or ABW for predicting protein needs in the obese, critically ill patient may not be appropriate. In this population, protein requirements should be measured rather than estimated using predictive equations based on either IBW or ABW.

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APPENDIX

UUN Study Data Sheet **Pt. No** _____

Does participant meet any exclusion criteria?

A. Age <19 or >85 years at time of collection	YES	NO
B. Was patient receiving hemodialysis at time of collection	YES	NO
C. Unspecified urine volume?	YES	NO
D. Was there less than 1.0 liter of urine output for study?	YES	NO
E. Did the Nutrition Support Team note that urine volume was over or under estimated?	YES	NO
F. Was GI bleed present at time of collection?	YES	NO
G. Was the patient's admitting diagnosis hepatic encephalopathy?	YES	NO

Admitted to study (*No* on all above questions)? **YES** **NO**

If admitted, answer the following:

1. Gender M F
2. Ethnicity _____
3. Admission weight (kg) _____ kg
4. Height (cm) _____ cm
5. BMI _____
6. Age (years) at time of study _____ yrs
7. Admitting diagnosis _____
8. UUN results _____ g
9. Date of UUN collection _____
   Use first UUN reported from this admission
10. Location at time of UUN _____
11. Weight at time of UUN _____
12. Feeding method PO TF TPN
13. Medications of interest: Steroids _____
    Diuretics _____
14. Urea Nitrogen Appearance (UNA) (if collected) _____ g

Birmingham VA Institutional Review Board (IRB)
Department of Veterans Affairs Medical Center
VA Research Service (151) • 700 South 19th Street • Birmingham, AL 35233 • 205-933-8101 • Fax: 205-933-4471

IRB APPROVAL - Previously Tabled Protocol

Date: November 23, 2010
From: Kevin W. Harris, MD, PhD, Chairperson
Investigator: Jodie G. Bilbrey, MS, RD
Protocol: The Influence of BMI on the Protein Needs of Critically Ill Patients as Evidenced by UUN
ID: 01384 Prom#: N/A Protocol#: N/A

The following items were reviewed and approved at the 11/22/2010 meeting:

- Research Protocol (11/17/2010)
- Abstract (11/17/2010)
- Financial Disclosure Form (11/03/2010)
- Miscellaneous - Data Privacy and Security Plan Checklist (11/17/2010)
- Miscellaneous - Initial Review Application (11/17/2010)
- Miscellaneous - Current Training Documentation (11/01/2010)
- Miscellaneous - CVs (Bilbrey / Morgan) (11/01/2010)
- Miscellaneous - Letter of Assurance (11/01/2010)
- Miscellaneous - List of Study Personnel (11/01/2010)
- Miscellaneous - Request for Alteration or Waiver of Informed Consent (11/01/2010)
- Miscellaneous - Request for HIPAA Waiver (11/01/2010)
- Miscellaneous - UUN Study Data Sheet

Conditions of Approval are attached. These conditions are further detailed in the HHS, FDA, and VA regulations, which are available in the Research Office.

Approval is granted for a period of 12 months and will expire on 11/21/2011. Your Continuing Review is scheduled for 09/26/2011, and the requirements are attached.

The protocol was determined to have the following level of risk:
Minimal

The protocol was determined to have the following level of benefit to participants:
No prospect for direct benefit to participants, but likely to yield generalizable knowledge

A waiver of HIPAA authorization has been granted for use with this protocol. Approval was granted on November 22, 2010. This waiver was reviewed and approved under full board review procedures (38 CFR 16.108(d). The approval is granted based on this board's determination that the risk to the

Office for Research

Institutional Review Board for the
Protection of Human Subjects

THE UNIVERSITY OF
ALABAMA
RESEARCH

February 24, 2011

Shannon McMahon
Department of Human Nutrition & Hosp. Mgmt.
College of Human Environmental Sciences
Box 870158

Re: IRB#: 11-OR-054-ME "The Influence of Body Mass Index (BMI) on the Protein Needs of Critically Ill Patients as Evidenced by Urinary Urea Nitrogen (UUN)"

Dear Ms. McMahon:

The University of Alabama Medical Institutional Review Board has granted approval for your proposed research.

Your application has been given expedited approval according to 45 CFR part 46. You have also been granted approval for the requested waiver. Approval has been given under expedited review category 5 as outlined below:

(7) Research involving materials (data, documents, records or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatement or diagnosis)

Your application will expire on February 23, 2012. If your research will continue beyond this date, complete the relevant portions of Continuing Review and Closure Form. If you wish to modify the application, complete the Modification of an Approved Protocol. Changes in this study cannot be initiated without IRB approval, except when necessary to eliminate apparent immediate hazards to participants. When the study closes, complete the appropriate portions of the Continuing Review and Closure Form.

Should you need to submit any further correspondence regarding this proposal, please include the above application number.

Good luck with your research.

Sincerely,

Carpantato T. Myles, MSM, CIM
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