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A Retrospective Study of Energy and Protein Intake

Among Intensive Care Unit Patients

By

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Dedication Page

To my guardian angel, my dad

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A Retrospective Study of Energy and Protein Intake Among Intensive Care Unit Patients

May Annie Chalhoub

ABSTRACT

Critically ill patients admitted to the intensive care unit (ICU) are subjected to catabolic stress. To compensate for the severe loss of muscles, international guidelines stress on the importance of supplementing ICU patients with higher protein and energy. There is however a controversy about the adequate amount and progression of protein and energy administration. The present study therefore aimed to investigate the association between protein and energy intake and ICU length of stay (LOS). A retrospective data analysis was conducted on ICU patients (53.6% males and 46.4% females, age 70.43±14.74) who resided in the intensive care of the LAU Medical Center Rizk Hospital for more than three days. Day to day protein and caloric intakes, clinical, and demographic information were collected from the patients' charts. Binary logistic regressions were used to examine the relationship between LOS and intakes, as well as other covariates. Protein and caloric intake on days three and five showed no significant association with LOS. However, intakes on day five showed a significant inverse association with sepsis (p=0.019 for protein and p=0.042 for energy). Logistic regression analyses assessing the determinants

of sepsis showed that it was significantly associated with protein and energy intake (R^2=5.9%), mechanical ventilation, and presence ulcers. The present study findings suggest that sepsis could be a possible mediator in how protein and energy intake can affect ICU LOS.

Keywords: Intensive care unit, Protein intake, Energy intake, Length of Stay, Sepsis, Pressure Ulcer, Lebanon

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LIST OF ABBREVIATIONS

LOS: length of stay

ICU: intensive care unit

PU: pressure ulcer

MV: mechanical ventilation

PMH: previous medical history

CI: confidence interval

SD: standard deviation

IBW: Ideal body weight

ROA: reason of admission

BMI: body mass index

NPO: nothing by mouth

Chapter One

Literature Review

1.1 Intensive Care Unit Patients

1.1.1 Critically ill patients in ICU

The intensive care unit (ICU) is a specific ward in hospitals that provides extensive observational and invasive services to critically ill patients that cannot be provided in general wards (Smith & Nielsen, 1999).

Patients admitted to the ICU present a number of metabolic and nutritional challenges. These critically ill patients require more time to be physiologically independent in order to recover. The main characteristics of critically ill patients are episodes of infection and shock during their stay at the ICU. Medically speaking, being critically ill encloses complex manifestations: metabolic, immunologic, and neuroendocrine complications (Boniatti et al., 2011). All of the latter heighten the pro-inflammatory state of patients (Lew et al., 2016). Pro-inflammation can significantly worsen the nutritional status which, in case of critically ill patients, is already characterized by being malnourished (Lew et al., 2016).

1.1.2 Metabolic Changes

As a survival response to illness, the body undergoes metabolic changes for energy provision to provide for vital tissues (Figure 1). Changes include activation of the sympathetic nervous system, pituitary hormone release, and peripheral resistance to accommodate for anabolism. Because of these changes, the body does not only rely on

energy substrate availability. Thus, the body alters energy production pathways in order to find alternative substrates. Under these complex metabolic stressors, the body undergoes an increase in energy expenditure (EE), hyperglycemia, and muscle wasting (Preiser et al 2015).

Stress induced hyperglycemia increases production and/or expression of pro-inflammatory markers: leukocyte release, suppressed chemotaxis and phagocytosis, and reactive oxygen species release (Preiser et al 2015). In return, the excessive release of counter-regulatory hormones, pro-inflammatory mediators, and exogenous administration of drugs (corticosteroids and vasopressors) can furthermore exacerbate hyperglycemia (Figure 1). In this viscous cycle, the body's immunity and inflammatory response becomes unbalanced, increasing oxidative stress and ultimately causing organ dysfunction. (Viana et al, 2014). One of the most common adaptive mechanisms is peripheral insulin resistance and hepatic gluconeogenesis. The severity of insulin resistance is directly related to the severity of the disease (Preiser et al 2016), although studies are showing that hyperglycemia has more of a protective role in survival (Ndahimana et al, 2018). Moderate hyperglycemia has been shown to maximize glucose uptake by enhancing the expressions of plasma membrane glucose transporters (GLUTs). Hyperglycemia and GLUT expression both aid in the activation of macrophages and neutrophils. Hyperglycemia also plays a protective role in promoting angiogenesis and improving systolic function. (Marik & Bellomo, 2013)

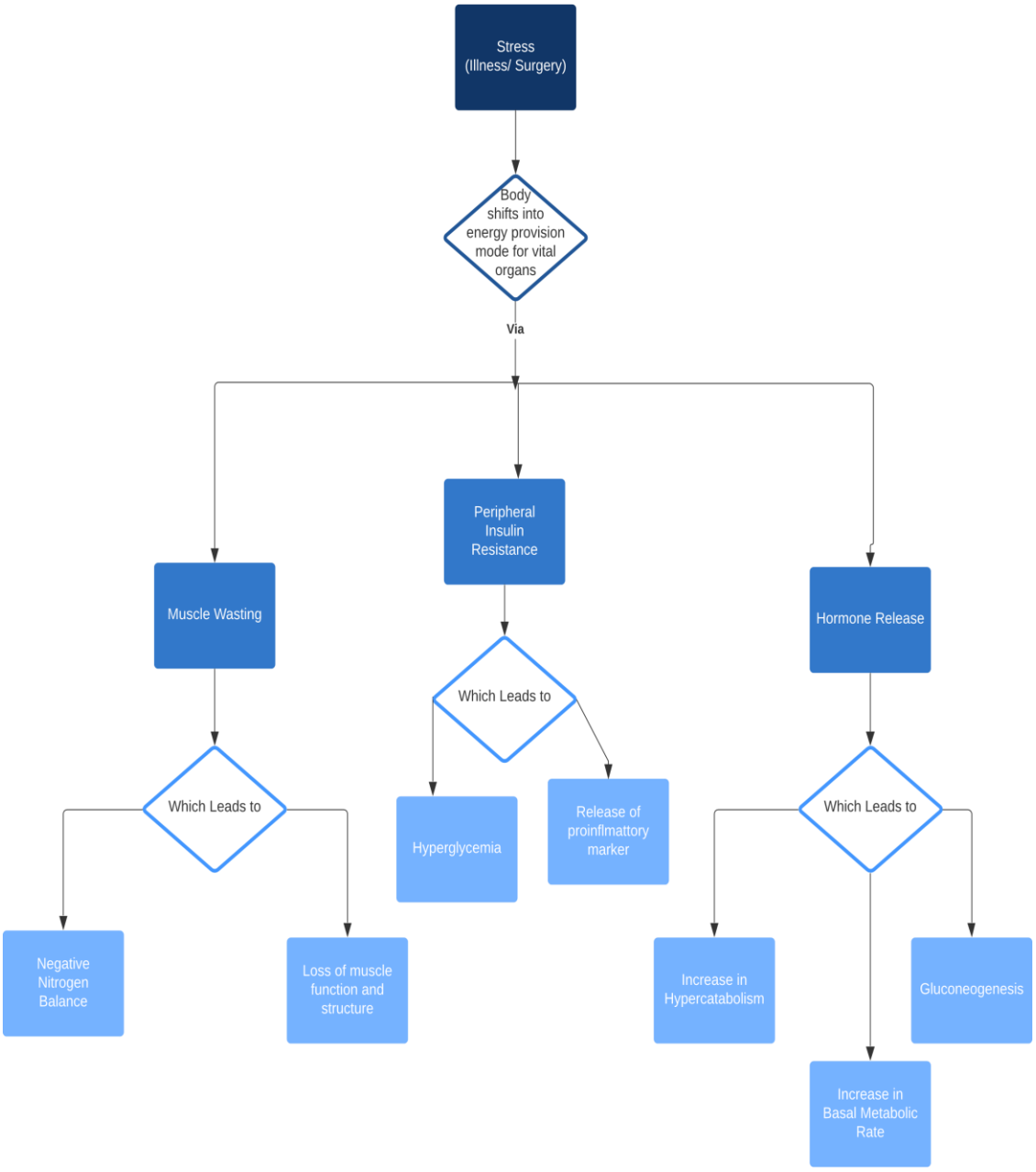
Hormones are also part of the adaptive mechanisms, whereby glucagon, norepinephrine, epinephrine, cortisol, and thyroid hormones accelerate hyper-catabolism. Other physiological conditions also exacerbate the energy expenditure such as fever, hypothermia, and tachycardia (Preiser et al 2016). Catecholamines not only increase

metabolic rate, but also stimulate gluconeogenesis, fatty acid breakdown, and glucagon secretion (Ndahimana et al, 2018).

Rapid muscle wasting is a common phenomenon in catabolic stress that can result in a negative protein balance. Resistance is found at the level of the periphery (muscles) in order to shunt the amino acids towards the liver for gluconeogenesis to preserve vital organ function. Severe muscle loss is furthermore exacerbated by insulin resistance and physical inactivity (Preiser et al 2015). The state of muscular atrophy indicates loss of appropriate structure and therefore function of muscles. Sepsis, medications, and systematic inflammation are all confounders in muscle loss, not to mention the bed-ridden state of ICU patients, rendering them incapable of mobilization, which can exacerbate muscle atrophy (Koukourikos et al., 2014)

As for septic patients, muscle wasting is also considered to be a prominent consequence due to increases in proteolysis and decreases in protein synthesis pathways. The main line of action of how sepsis triggers muscle weakness is via mitochondrial alterations. It has been shown that sepsis induces dysfunctions at the level of mitochondria of both respiratory and limb muscles by reducing respiratory chain complex activity and energy production, respectively. (Callahan & Supinski, 2009). Excessive damage to the powerhouse of the muscle cells triggers muscle weakness by the loss of muscle quality rather than just wasting (Owen et al., 2019).

Figure 1. *Metabolic Changes that the body undergoes during illness*



1.2 Nutrition in Critically Ill Patients

1.2.1 Malnutrition: Definition, Prevalence, and Triggers

With all the uncontrollable stress that the body is under, an external crucial factor can mediate the clinical outcomes of ICU patients; this factor being nutrition. Inappropriate nutritional therapy can exacerbate physiological disequilibrium by increasing the risk of infections, metabolic alterations, or even muscular abnormalities (Berger, et al. 2018).

The European Society of Enteral and Parenteral Nutrition (ESPEN) defines malnutrition as a "state of imbalance between nutrition intake and requirements that ultimately leads to alterations in body composition that affect physical and mental function and impair clinical outcome from disease" (Cederholm, et al., 2017). According to Berger et al, the prevalence of malnourished patients in ICU ranges from 17 to 78% (Berger, et al. 2018). In general, ICU patients have higher odds of being malnourished compared to general ward patients. This high prevalence of malnutrition is attributed to inadequate feeding practices (Lew et al., 2016). A worldwide cross-sectional study on 880 ICUs revealed that patients are either:

(1) Being administered calories independently from their actual body weight

(2) Receiving slightly less calories than their needs in case of a body mass index (BMI) less than 18.5 or over 40 kg/m^2

(3) Waiting longer than 24 hours to be fed; over 40% of patients were not fed within the first day of admission (Bendavid et al., 2017).

Several other factors can contribute to the prognosis of malnutrition. For instance, two-thirds of differences in requirement and delivery are due to under-prescription of the needed energy and protein compared to the recommendations, whereas one-third is due to

under-delivery of energy and protein. Even among the prescribed protein and calories, the consumed amount is significantly lower ($p<0.001$). Other factors also include the reason of admission, whereby surgical patients have higher needs making them more prone to underfeeding compared to medical patients (Osooli et al., 2019). Septic patients are also considered hypermetabolic, whereby their total energy expenditure to resting energy expenditure ratio is 1.0 while it's 1.1 for trauma patients (Wischmeyer, 2018).

1.2.2 Diagnosis and Effects of Malnutrition

Malnutrition increases patients' length of stay (LOS) in both ICU and hospital. (Lew et al., 2016). In a systematic review, Lew et al found that malnutrition alone can be an independent factor that can extend the LOS in the ICU of patients, partly by increasing their incidence of infection in the ICU (Lew et al., 2016). Malnutrition also impairs cellular immunity, which increases ICU mortality and prolong general hospital stays (Hung et al., 2019). In their prospective cohort, Lew et al furthermore showed that malnutrition was solely responsible for increasing the risk of 28-day mortality by 33% (Lew et al., 2017). In their study, they aimed to associate malnutrition and mortality among ICU patients by using the subjective global assessment (SGA) parameter. The study showed a dose dependent relationship between SGA and mortality; each one- point increase in SGA was associated with an eight percent higher risk of 28-day mortality (Lew et al., 2017). Similarly, severe underfeeding was associated with both ICU and hospital mortality ($p=0.005$ and $p=0.003$, respectively) (Osooli et al., 2019).

ESPEN diagnosis criteria for the risk of malnutrition include diseases related to malnutrition with risk of inflammation, which can be either acute or chronic (like cancer cachexia). It also encompasses developing diseases related malnutrition without having a risk of developing an inflammation. High risk of malnutrition could also involve patients

who do not have a disease, yet their socioeconomic or psychological status can contribute to the prognosis of malnutrition. As for the clinical setting, ESPEN clearly emphasizes than any critically ill patient residing more than 48 hours in the ICU is a high malnutrition risk patient (ESPEN, 2019).

However, ASPEN guidelines are currently being updated regarding nutrition support and diagnosis for critically ill patients. The last guidelines stress on nutritional screening for all ICU patients upon admission. High risk patients are those with a nutritional risk screening (NRS) or The Nutrition Risk in Critically ill (NUTRIC) scores exceeding five (ASPEN, 2016).

1.2.3 Nutritional Requirements

With the physiological complications of catabolic stress, predictive equations fail to estimate energy expenditure in about 80% of patients. This is translated into having a higher incidence of unintentional underfeeding. Low protein and energy intake affects outcome variables, be it ICU LOS or mortality. Conversely, higher protein intake was shown to go in parallel with better survival rates (Preiser et al 2015). As for resorting to indirect calorimetry, preliminary studies are showing it as a superior to equations for the long-term clinical outcomes of patients. However, further studies are needed in order to validate this claim in randomized clinical trials (RCTs) (Moonen et al., 2021). ESPEN has a high consensus on resorting to indirect calorimetry, especially among mechanically ventilated patients (ESPEN, 2019). ASPEN guidelines however have a weak consensus regarding resorting to indirect calorimetry in determining energy requirements (ASPEN, 2016).

To avoid complications, the Medical Nutrition Therapy (MNT) Goals in the ICU shed light on assuring that adequate nutritional support is being met by reaching estimated

protein and energy needs. It also recommends that close assessment is performed to feeding response and potential deficiency risks (Hasanloei, et al 2018).

Protein intake is one of the most important nutritional parameters among critically ill patients. Protein is not only important in the provision of substrates to maintain muscle mass, but also in controlling infection rate during the ICU stay. This, in return, would be reflected on clinical outcomes (Weijs, 2014). Low protein intake exacerbates muscle wasting, lowers immunity, and increases the risk of infection. On the other hand, excessive protein intake increases load on kidneys and delays the much-needed autophagy that clears the body from toxins and provides it with substrates (Weijes et al, 2014).

ESPEN categorizes protein feedings into: low if intake is <0.8g/kg body weight, normal if intake ranges between 0.8-1.2 g/kg body weight, and high when intake >1.2g/kg body weight. And since ICU patients are subjected to severe catabolic stress, the latter protein intake is said to be the desired amount among ICU patients. Actual weight of patients is used unless patients are obese, whereby ideal body weight is used for the calculation (ESPEN,2019).

The American Society of Parenteral and Enteral Nutrition (ASPEN), however, based their recommendations on BMI. According to ASPEN, patients with BMI < 30 kg/m^2 should be given 1.2-2 g/kg actual body weight. For BMI 30-50 kg/m^2 and BMI> 50 kg/m^2, protein intakes should be 2 g/kg/ideal body weight and 2.6 g/kg/ideal body weight, respectively (ASPEN,2010).

With excess catabolic stress, increase in basal metabolic rate (BMR), infection, and muscle wasting, the body lacks enough supply of energy to fight the illness, hence the importance of energy intake and the administered calories (Singer, 2019). Undernutrition can result in a higher LOS, infection, dependence on mechanical ventilation, and/or

mortality, while overnutrition would result in prolonged dependence on mechanical ventilation (MV), infection, higher hyperglycemia, urea excretion, and/or mortality (Singer, 2019).

ESPEN recommendations state that during the acute phase of illness, feedings should not exceed 20-25 kcal/kg/body weight, while during recovery feedings can reach 25-30 kcal/kg/actual body weight (Hasanloei, et al 2018). Moreover, according to ESPEN, any energy feeding below 70% of the target is referred to as hypocaloric feeding, whereas energy administration around the target is defined as isocaloric feeding.

ASPEN also has energy recommendations based on BMI, whereby patients with BMI < 30 kg/m^2, BMI 30-50 kg/m^2, and BMI> 50 kg/m^2, should receive 25-30 kcals/kg actual body weight, 22-25 kcals/kg actual body weight, and11 – 14 kcals/kg ideal body weight, respectively (ASPEN,2010).

As for mechanically ventilated patients, neither guideline has specific recommendations for either protein or energy, meaning that these patients abide by the critically ill patients guidelines (ESPEN, 2019; ASPEN, 2016).

Guidelines by ESPEN clearly emphasize that patients who are not expected to receive their diet orally within the first 48 hours of admission, should be placed on enteral nutritional feeding within said timeframe of ICU admission (ESPEN, 2019). This may be implemented, if possible, within the first 24 hours after ICU admission (Kreymann et al., 2006) after ensuring hemodynamic stability. The American Society of Parenteral and Enteral Nutrition (ASPEN) also recommends initiation of feedings within the first 24-48 hours, while ensuring that at least 80% of the patient's energy and protein needs are met within the first 48-72 hours of admission.

1.3 Recent observational studies and clinical trials

Despite the existence of nutritional guidelines, discrepancies exist between research and clinical practice.

1.3.1 Early High Intake

As per ESPEN guidelines, a high-energy intake was associated with lower mortality risk but a higher length of stay in the ICU (Singer et al, 2011). A prospective study in Malaysia showed that patients receiving over two-thirds of their prescribed energy and protein, showed a higher 60-day mortality risk (Lee, Airini, & Barakatun-Nisak, 2018). Wang et al observed a higher mortality rate among patients who received less than 65% of their energy requirement (Ndahimana & Kim, 2018). A retrospective cross-sectional study categorized patients as high or low nutrition risk via Nutrition Risk in Critically Ill score. Among patients defined as having high nutritional risk, higher energy intake lowered LOS, 14 and 28-day mortality rates, while no effect was detected among the low-risk group (Wang et al., 2018). A retrospective study revealed lower 6-month mortality among patients with early protein feedings of 1.2g/kg (Looijaard, et al., 2019), while high protein intake of 1.5 g/kg led to significantly low mortality among septic patients. Moreover, feedings more than 0.7g/kg body weight compared to lower intakes during early days have shown better rates of survival ($p = 0.017$) (de Koning, Koekkoek, Kars, & Van Zanten 2019).

In a single center cohort in Amsterdam, ICU patients were studied retrospectively to reveal that the higher the protein delivery, the lower the mortality 90 days post discharge. In a dose dependent manner, each daily increase in protein intake by 1g/kg was accompanied by an 18% lower risk (OR 0.82, 95% CI 0.73–0.92). Among patients

diagnosed with malnutrition, the mortality risk was furthermore lowered to reach 30% with each daily increase of 1g/kg of protein (Weijs et al., 2019). A prospective database among mechanically ventilated ICU patients showed that among overfed, non-septic patients mortality decreased with the increase in protein intake. Patients receiving <0.8g/kg had a 37% mortality risk, intakes from 0.8-1g/kg were associated with 27% risk, while the lowest mortality risk (19%) was detected among patients having a protein intake equal to or exceeding 1.2g/kg. This indicates that protein intake ≥ 1.2g/kg was significantly associated with lower mortality (p=0.013) (Weijs et al., 2014).

1.3.2 Late High Intake

Studies have shown that delaying the increase of protein intake until days three and four of ICU admission increases survival. Septic patients showed a low mortality rate with high-energy intake (>110% of needs) in days 4-7 while late medium energy intake (80-110%) among non-septic patients showed similar results (de Koning, Koekkoek, Kars, & Van Zanten 2019).

In a randomized clinical trial (RCT) conducted by Arabi et al, patients who were permissively underfed (receiving 60-70% of their caloric intake) showed a 30% hospital mortality risk compared to a 42.5% risk in the those receiving their needs (p=0.04). However, the same study showed that septic patients with early protein intake higher than 1.2g/kg body weight showed higher risk of mortality and that late high protein initiation (0.8-1.2 g/kg body weight) showed low mortality (de Koning, Koekkoek, Kars, & Van Zanten 2019). Thus, despite ESPEN guidelines, septic patients with a medium protein intake of 0.8-1.2 g/kg body weight of protein showed a lower 6-month mortality rate. In non-septic patients, early (within the first three days of admission) high protein intake increased mortality. In specific, higher 6-month mortality rate was observed when early

protein feedings were high (>1.2g/kg) or when they were low (<0.8g/kg) during the late phase (days 4-7) (de Koning, Koekkoek, Kars, & Van Zanten 2019). Consistently, lower protein intake within the first days of admissions and increasing them after three days was associated with lower 6-month mortality compared to patients with overall high protein intake ($p < 0.001$). (Lambell, Tatucu-Babet, Chapple, Gantner, & Ridley, 2020)

1.3.3 Protein intake and muscle wasting

Not only does nutritional status affect mortality and LOS, it surpasses them to affect muscle wasting. A retrospective study in Japan aimed to associate protein intake with physical abilities among patients admitted to the ICU. Patients were divided as low protein group (receiving less than 1 g/kg/day) or high protein group (receiving more than 1 g/kg/day). The high protein group had significantly better upper body score and handgrip strength ($p=0.004$ and $0=0.035$). Moreover, only 10% in the high protein group were diagnosed to have ICU acquired weakness, whereas the prevalence among the low protein group reached 35%. Independent walk pre-hospital discharge was detected among 80% of the high protein group, while that of the low protein group reached 40% ($p=0.032$). Differences in other clinical outcomes however were not detected. (Matsushima et al., 2021). In another attempt for associating protein intake with muscle wasting and mortality, Looijaard et al conducted a retrospective study on mechanically ventilated ICU patients. No association with protein intake was detected among patients with normal skeletal muscle. However, high early protein intake decreased both 60-day mortality and six-month mortality risk (adjusted hazard ratio per 0.1g/kg/day 0.82 95%CI 0.73–0.94) (HR 0.88, 95%CI 0.79–0.98) among low skeletal muscle patients. Additionally, among patients with low skeletal muscle and density, lower 60-day mortality (HR 0.76, 95%CI 0.64–0.90)

and six-month mortality was detected (HR 0.80, 95%CI 0.68–0.93) (Looijaard et al., 2020).

1.4 Pathophysiology

1.4.1 Pros of Delay in High Intakes:

Septic patients have higher catabolic stress compared to non-septic ones. Other than a variation in the degree of catabolism, difference in absorption rate is also detected, rendering them to have a different timing in the activation of autophagy. (Koning et al., 2019)

Nutrition inhibits autophagy, the housekeeping system that aims in cleansing the body from toxic proteins and providing the body with substrates for energy production. Septic patients have different autophagy behavior that leads to clearing the body from intracellular microorganisms (Weijes et al, 2014). Impairments in autophagy activation have shown to diminish the expression of chaperones related to protein synthesis, which in return exacerbates proteolysis and diseases progression. Blunting autophagy also means no clearance of the body from cellular damage (Preiser et al., 2015). When patients are calorically deprived, the cell activates a survival mechanism via regulating inflammatory pathways. Thus, during the acute phase of infection, low caloric intake can relieve inflammatory response and its damage by altering the metabolic, hormonal, and inflammatory pathways. During the early phase, hyper catabolism ensures production of endogenous energy and pro-inflammatory mediators. This will cause chronic state of hyperglycemia, which is controlled under caloric restriction feedings. (Looijaard et al., 2018). According to the EAT-ICU trial, early high protein increases ureagenesis, which adds more load on the kidneys. It was proposed that high protein intake has no effect on

muscle breakdown in the early critical phase, during which the body is blunted to anabolic stimulus in order to support gluconeogenesis to stop auto digestion (Preiser, 2018)

1.4.2 Pros of Early in High Intakes:

Early high protein intake shows more pronounced advantages among patients with low skeletal muscle density that already have a high risk of myostetosis. This condition can not only cause a low-grade inflammation but also insulin resistance than can blunt any anabolic response. Early high protein can control the body's resistance to anabolic stimulus. (Looiijaard et al, 2020), therefore lowering insulin resistance and inflammation. Providing catabolic patients high protein regimens early on provides the body with the required amino acids, thus, downgrading the rate of muscle turnover and promoting muscle synthesis, and, on the long run, lowering the risk of developing ICU acquired muscle weakness (Preiser, 2018). In prospective RCTs, an early protein intake of 1.2g/kg/d has been shown to not only preserve muscle mass, but also, a positive nitrogen balance. No associations were detected among higher levels. Moreover, intakes from 0.8-1.2g/kg/d were associated with lower overall handgrip strength and thigh muscle thickness (Rooyackers et al., 2017). Moreover, early high protein intake provides support to the immune system and aids in wound healing and signal regulation (Sweify, 2016).

As previously mentioned, malnutrition among ICU patients entails either under or over feeding, which irrespective of feeding initiations, can also cause adverse effects. Thus, quoting Yatabe "it is important to switch from the strategy of "defense" (underfeeding) to that of "offense" (adequate feeding) at the right time"

1.4.3 Cons of overfeeding:

One of the most prominent clinical features of overfeeding is hypercapnia and re-feeding syndrome. High protein particularly promotes dehydration and metabolic acidosis, while

high caloric intake promotes hyperglycemia, hepatic steatosis, and lower immunity (Preiser et al., 2015) (Yatabe,2019). The normal suppression of fat and muscle breakdown post-prandially is blunted during catabolic stress, which can cause furthermore stressful load on the body. Excess calories can cause damage to the mitochondria by the increase in oxygen radical production and gastrointestinal intolerance which increases the risk of infection. (Al-Dorzi et al., 2016)

1.4.4 Cons of underfeeding*:*

Not only does it cause hypoglycemia and hypothermia, but underfeeding can also alter the LOS by lowering immunity, increasing infection risk, and delaying wound healing. Underfeeding can also increase catabolism of muscles leading to impairment in muscle function. (Yatabe, 2019)

Chapter Two

Relevance to the Field, Aim, and Study Hypothesis

2.1 Relevance to the Field

Several studies have shown the benefits of high protein and energy regimens in decreasing mortality, infection, and length of hospitalization among ICU patients. There is however a controversy about the adequate amount, initiation and progression of protein and energy administration.

2.2 Research Question

The main question to be answered in this research is “can high protein and energy intake within the early phase of admission alter the LOS of patients in the ICU?”.

2.3 Objective

The objective of the present study is to investigate the association of protein and energy quantity and timing administration with LOS and other clinical parameters in the ICU. The aims are:

1. To describe the protein and caloric intake, initiation, and progression of patients in the ICU
2. To, primarily, investigate the association of these intakes with LOS
3. To, secondarily, examine the impact of these intakes on other clinical outcomes (sepsis, pressure ulcer)

Chapter Three
Methodology

3.1 Study Design and Sample Size Calculation

A retrospective analytical study was conducted among 140 patients admitted or transferred to the ICU at the Lebanese American University Medical Center-Rizk Hospital. Based on sample size calculations, the desired sample size would be 140 participants (at a confidence interval of 95%, margin of error at 5, and population proportion at 10%) (Daniel, 1995).

3.2 Population:

All patients who were hospitalized at LAUMC ICU from March to July 2020 were retrospectively assessed.

Exclusion criteria included patients who:

- Resided less than 3 days in the ICU
- Had their length of stay related to their underlying condition (head trauma), pregnancy, and paresis.
- Received their dietary intake orally
- Infected with the novel coronavirus (COVID-19)

Eligibility criteria included:

- ≥18 years old
- Received enteral and/or parenteral nutritional feeding
- Resided more than 3 days at the ICU.

3.3 Research Procedure

Data was drawn from a computerized patient record system (Laserfiche, 2020). Patients' charts and medical records from the nursing daily monitoring sheets were retrospectively revised to extract data on demographics, reason of ICU admission and medical progress (mechanical ventilation days, sepsis, infection). Anonymity was ensured whereby each patient was given a code enclosed by the researcher.

Demographic data collected included age, sex, height, and weight. ICU scores (SOFA, BRADEN, APACHE, and NUTRIC), and admission diagnosis were also retrieved. Nutritional parameters included route of feeding and daily protein and energy administered from admission until ICU transfer, discharge, or death.

3.4 Nutritional Assessment

Based on the given anthropometry, BMI was calculated by dividing the weight (Kg) by the height (meter^2). Then it was categorized as either underweight (>18 kg/m^2), normal (18-24.9 kg/m^2), overweight (25-30 kg/m^2), and obese (>30 kg/m^2).

Manufacturers' information of the formulas from Nutrison were used to calculate the amount of protein and energy in the given enteral nutrition formula. Non-nutritional calories such as propofol was also included in the daily intake calculations.

The received amounts of protein and energy /kg of actual body weight for normal and overweight and Ideal body weight (IBW) for obese/ day were calculated for days one, three, and five of feeding initiations, irrespective of day of admission. In case patients had discontinued feedings on days three and five, their data was excluded from the analysis.

3.5 Outcomes:

Primary outcome was the total length of stay (LOS) of patients in ICU before being transferred to a regular floor or discharged home. The count of length of stay started at the first day of arrival or transfer to ICU.

Secondary outcomes were sepsis and pressure ulcers.

3.6 Ethics:

The study was approved by the LAU institutional review board who waived the requirement for consent (IRB #: LAU.SAS.MB2.11/May/2020). Prior to conducting the study, all researchers had completed the Collaborative Institutional Training Initiative (CITI) training.

Chapter Four

Statistics

4.1 Variables, Outcome, Exposures, and Confounders

At the beginning of the study, intake was to be assessed in relation with LOS. Both protein and energy intake were the independent variables, whereas the LOS in the ICU was the dependent variable. This association was adjusted for gender, age, previous medical condition (PMH), sepsis, and ventilation.

When assessing the development of sepsis as the dependent variable, energy and protein intake (calculated as an interaction factor), mechanical ventilation (MV), and pressure ulcer (PU) were adjusted for.

4.2 Statistical analysis

Data was analyzed using SPSS software version 26 (SPSS Inc., Chicago, IL, USA). For the descriptive analysis, categorical data were reported as frequencies and percentages. As for continuous data, the normality was assessed using the Shapiro-Wilk test. Normally distributed data were reported in terms of mean ± standard deviation (SD), whereas skewed data were reported as median (interquartile range). After accounting for BMI and before conducting bivariate analysis, received energy and protein were divided by body weight to calculate the received grams of protein and calorie per actual kg body weight of normal and overweight subjects. However, for obese patients, intakes were divided by their ideal body weight. Ideal body weight was based on ESPEN that recommends using

the patient's height calculated at BMI= 25kg/m^2 (ESPEN,2019). Then, the intakes of the cohort were categorized based on ESPEN and ASPEN guidelines in order to detect abidance to guidelines.

Protein and energy intake were analyzed as both categorical and continuous. Previous observational studies categorize time intervals as early if within day one to three and late for days four to seven after ICU admission (de Koning, Koekkoek, Kars, & Van Zanten 2019). Categorical stratifications were based on the mentioned ASPEN and ESPEN guidelines.

In the bivariate analysis, our primary outcome was to detect an association between LOS and intakes. As two ordinal continuous variables, the spearman correlation test showed no association between the intended independent variable and LOS. Thus, LOS was converted into a categorical data as per the median of the collected LOS which was eight days. Patients were categorized as either residing less or more than eight days at the ICU. After resorting to LOS as categorical in the bivariate analysis, the Mann Whitney test showed no associations with intakes on either day three and five. Thus, energy and protein intake were categorized as per both ASPEN and ESPEN guidelines and compared with LOS as a categorical variable via Chi square.

The secondary outcomes of interest were sepsis and PU. Patients were categorized whether they developed sepsis or not during their ICU stay. Bivariate analysis used Chi square tests to compare sepsis and LOS, gender, PU, MV, reason of admission (ROA), PMH, and BMI. As for the intakes, Mann Whitney was used to compare sepsis development with protein and energy intake on the third day and protein intake on the fifth, whereas Independent T- test was used for the fifth day of energy intake. Variables

with a p-value < 0.2 at the bivariate level were considered eligible to be included in the logistic regression model. For variables less than five in the model, the Fischer's exact p-value was used. Sepsis was the dependent variable and protein and energy intakes on the fifth day, MV, and PU development were the independent variables. An interaction was observed between energy and protein intakes in the logistic regression model. Accordingly, an interaction term (energy intake* protein intake) was created and used in the analysis. In the multiple logistic regression model, significance was set at $p<0.05$. Furthermore, in order to assess the goodness of fit of the model, area under the curve was calculated.

As for PU, patients were categorized as either developing PU or not during their ICU stay. Bivariate analysis used Chi square to compare PU and LOS, gender, sepsis, MV, ROA, PMH, and BMI. As for the intakes, Mann Whitney was used to compare sepsis development with protein and energy intake on the third day and protein intake on the fifth, whereas Independent T- test was used for the fifth day of energy intake. Variables with a p-value < 0.2 at the bivariate level were considered eligible to be included in the logistic regression model. PU was the dependent variable and energy and protein intakes at day five were the independent variables. An interaction was observed between energy and protein intakes when both entered the model separately. Accordingly, the interaction term was used alone in the model and how much it explained in terms of PU development was reported.

Chapter Five

Results

5.1 Population Characteristics

A total of 210 patients were admitted to the ICU during the study period. After excluding patients with a LOS less than 3 days, head traumas, and COVID; a total 140 patients fulfilled the inclusion criteria.

Table 1 shows the characteristics of the study participants. The mean age of the admitted patients was 70.43 (±14.74) years with 53.6% being males. Half of the patients suffered from two or more chronic non-communicable comorbidities: diabetes, hypertension, hyperlipidemia, coronary heart disease, cancer, and thalassemia. Pulmonary complications were the main ICU reasons of admission (35.7%). The majority of patients suffered from pressure ulcer (66.4%) but only 34.3% developed sepsis during their ICU stay. A total of 65% of patients admitted to the ICU required the assistance of mechanical ventilation during their stay. As for anthropometrics, admitted patients had a mean height and weight of 166.19 (±9.04) cm and 75.068 (±18.02) kg respectively. The majority of patients had a BMI ranging from 18.5-24.9 kg/m^2.

5.2 Energy and Protein Intake:

5.2.1 Initiation

The majority (87.1%) of participants were hemodynamically stable to have their feedings initiated within the first 72 hours of admission to the ICU, as per guideline recommendations. (Table 2)

Table 1: *Characteristics of study participants*

Gender	Male	75 (53.6)
	Female	65 (46.4)
ROA	Pulmonary	51 (36)
	Cardiac	20(14.3)
	General Status Alterations	48(34.3)
	Gastrointestinal	12 (8.6)
	Cancer	3 (2.1)
	Fracture	1 (0.7)
PMH	PH	18 (12.9)
	One NCD/ Cancer/ Rare Disease	52(36.7)
	Two or more NCDs	70 (50.4)
Mortality	No	92 (65.7)
	Yes	48 (34.3)
Ventilation	No	49(35)
	Yes	91(65)
Sepsis	No	92 (65.7)
	Yes	48 (34.3)
Ulcer	No	47 (33.6)
	Yes	93 (66.4)
BMI	>18.5 18.5-24.9 25-29.9 >30	2 (33.3) 28 (58.3) 25 (55.6) 19 (46.3)
Age [a]		70.43 (14.74)

All values are reported as n(%) except for age that was reported as mean (±SD)
ROA: reason of admission PMH: previous medical history PH: previously healthy
NCD: non-communicable disease

Table 2: *Timings of initiation of feeding of patients*

	N=140	Feeding Initiation N(%)
Day	1-3	122 (87.1)
	3+	18 (12.9)

5.2.2 Intake

Irrespective on what day feeding was initiated, intakes were assessed at days one, three, and five. On the first day participants received on average 0.59 (0.23) g/kg of actual or IBW/d of proteins and 11.53 (6.78) kcal/kg/d of energy. The amounts were gradually increased to reach 0.97 (±0.34) g/kg/d of proteins and 20.86 (10.56) kcal/kg/d of energy on day 3 and 1.15 (± 0.40) g/kg/d of proteins and 23.75 (± 7.70) kcals/kg/d of energy on day 5 respectively. (Table 3)

Table 3: *Average intake of patients on one, three, and five of feeding initiation*

			N	Protein (g/kg)	Energy
Day of Feeding	1		140	0.59 (0.23)	11.53 (6.78)
	3		94	0.97 (±0.34)	20.86 (10.56)
	5		71	1.15 (± 0.40)	23.75 (± 7.70)

Normal values were reported as M **(**±SD) while skewed data was presented as median (Q3-Q1)

5.2.3 Intake vs ESPEN

On days three and five respectively, 34% and 21.1% of the ICU patients had a low protein intake while 27.9% and 49.3% had an optimal protein intake.

As for the energy intake, ESPEN categorizes energy intakes based on days of feeding initiations. Within the first three days, energy intake should range from 20-25 kcal/kg body weight: 32.7% of patients' feeding abided by these guidelines. However, energy intake should increase after 72 hours to range from 25-30 kcal/kg body weight, whereby 29.6% received it. (Table 4)

5.2.4 Intake vs ASPEN:

From our cohort, among patients with BMI <30 g/m^2, 73.8% were consuming less than the recommended amount of 1.2-2g of protein/kg and 76.9% were not given the recommended 22-25 kcals/kg on the third day. On the fifth day, 42% were consuming the recommended amount of 1.2-2g of protein/kg and 30.6% reached the recommended 22-25 kcals/kg (Table 4).

As for patients with 30<BMI<50 BMI g/m^2, all patients did not reach the recommended intake of protein on both days three and five. On the other hand, 25.8% followed the recommended energy intake on day three and 18.2% on day five (Table 4)..

Table 4: *Actual intakes of protein and energy compared to guidelines*

Protein and Energy intake as per guidelines		**Day 3**	**Day 5**
ESPEN *Protein g/kg*	<0.8	33 (44)	15 (21.1)
	0.8-1.2	37 (38.1)	21 (29.6)
	>1.2	27 (17.9)	35 (49.3)
Energy Kcal/kg	<20	45 (46.6)	20 (28.2)
	20-25	29 (32.7)	18 (25.4)
	25-30	23 (29.9)	21 (29.6)

ASPEN *Protein g/kg BMI <30*	<1.2 1.2-2 >2	48 (73.8) 17 (26.2) 0(0)	26 (53.0) 21 (42.8) 2 (4.2)
Protein g/kg 30<BMI <50	<2	32 (100)	22 (100)
Energy *Kcal/kg BMI <30*	>25 25-30 >30	47 (72.3) 15(23.1) 4(4.6)	24 (48.9) 15(30.6) 10(20.4)
Kcal/kg 30< BMI<50	<22 22-25 >25	18 (58.1) 8(25.8) 5(16.1)	10 (45.5) 4(18.2) 8(36.4)

All values are reported as n(%)

5.3 Length of stay and clinical characteristics:

A statistically significant difference was detected between length of stay and gender, whereby the longer stay in the ICU was associated with males more than females ($p=0.028$). A total of 70% of septic patients resided in the ICU for more than eight days, whereas 66.3% of those MV had a similar LOS. Both were significantly different from non-septic patients and patients that did not require MV ($p<0.001$). No difference, however, was found between the different BMI categories or pressure ulcer with LOS ($p=0.45$ and 0.32 respectively). (Table 5)

Table 5: *Clinical characteristics of participants based on their length of stay*

		<8 days	>8 days	P value[§]
Gender	Male	33 (44)	42 (56)	0.028 *
	Female	41 (63.1)	24 (36.9)	
PMH	Previously Healthy	10(55.6)	8(44.4)	0.14*
	1 NCD/ Cancer/ Rare Disease	42(60)	28(40)	
	2+ NCD	22(42.3)	30(57.7)	
Sepsis	No	59(65.6)	31(34.4)	<0.001*
	Yes	15(30.0)	35(70.0)	
Ulcer	No	24(51.1)	23(48.9)	0.45
	Yes	50(53.8)	43(46.2)	
Ventilation	No	44(86.3)	7(13.7)	<0.001*
	Yes	30(33.7)	59(66.3)	
Age [a]		74	66	0.2*
BMI	>18.5 18.5-24.9 25-29.9 >30	2 (33.3) 28 (58.3) 25 (55.6) 19 (46.3)	4 (66.7) 20 (41.7) 20 (44.4) 22 (53.7)	0.32
Day 3	Protein Energy	0.95 (0.55) 20.04 (+/ 6.22)	1.01(0.54) 20.36 (6.89)	0.38 0.821
Day 5	Protein	1.13 (+/-0.42)	1.15 (0.41)	0.90

	Energy	24.08 (8.23)	23.71 (7.72)	0.88

All data are presented as n (%) except for age where mean (SD) was presented.
§ Differences were tested by Mann-Whitney or chi square tests depending on the type of the variable. *: eligible to be entered into the model, $p<0.2$

5.4 Sepsis and clinical characteristics:

As shown in table 6, intakes of protein and energy on the third day of feeding showed no associations with the risk of sepsis development ($p=0.54$ and $p=0.72$). However, five days into feeding initiation, differences between protein and energy intake among septic and non-septic patients was detected. Septic patients were consuming fewer grams of protein per kg body weight per day compared to non-septic patients (1.02±0.36 and 1.25±0.41 respectively, $p=0.019$ *). The received caloric intake per kg body weight was also lower among septic patients (21.72±7.25) compared to non-septic patients (25.4±7.70) ($p=0.042$).

Developing pressure ulcer during ICU stay was significantly associated with the risk of sepsis ($p<0.001$). The usage of mechanical ventilation during the ICU stay also showed a positive association with sepsis ($p=0.003$).

No difference between gender and previous medical history was detected between septic and non-septic patients ($p=0.21$ and $p=0.28$ respectively). Among patients who developed sepsis, on the fifth day of feeding initiation, 54.5% died. As for the goodness of the fit of the model, the area under the curve of the model was 0.652.

Table 6: *Unadjusted Clinical characteristics of participants based on the existence or absence of sepsis* diagnosis

		Non-Septic	Septic	P value[§]
Gender	Male	52 (69.3)	23 (30.7)	0.21
	Female	38 (58.5)	2 7(41.5)	
PMH	Previously Healthy	13 (72.2)	5(27.8)	0.28
	1 NCD/ Cancer/ Rare Disease	32 (71.1)	13 (28.9)	
	2+ NCD	45(58.4)	32(41.6)	
LOS	Below 8 days	61 (82.4)	13 (17.6)	<0.001*
	Above 8 days	31 (47)	35 (66)	
Ulcer	No	43(91.5)	4(8.5)	<0.001*
	Yes	46(49.5)	47(50.5)	
Ventilation	No	41(80.4)	10(19.6)	0.003*
	Yes	40(44.9)	49(55.1)	
Age [a]		67.57	75.77	0.25
BMI	>18.5 18.5-24.9 25-29.9 >30	3 (50) 34 (70.8) 27 (60) 26 (63.4)	3 (50) 14 (29.2) 18 (40) 15 (36.6)	0.57

Day 3	Protein	1.00 (0.50)	0.90 (0.59)	0.54
	Energy	20.05 (+/- 6.54)	19.55 (+/-6.88)	0.72
Day 5	Protein	1.25 (+/-0.41)	1.02 (+/- 0.36)	0.019 *
	Energy	25.4 (+/- 7.7)	21.72 (+/-7.25)	0.042 *

All data are presented as n (%) except for age where mean (SD) was presented.
§ Differences were tested by Mann-Whitney or chi square tests depending on the type of the variable. *: eligible to be entered into the model, $p<0.2$

5.5 Association between Sepsis, protein and energy intake, mechanical ventilation, and ulcer

The interaction factor (energy x protein) showed a significant negative influence on sepsis development ($p=0.023$), whereby the higher the energy and protein intake, the lower the risk of developing sepsis. After entering mechanical ventilation in the model, the significant influence of both energy and protein remained ($p=0.025$) with the positive influence of sepsis from mechanical ventilation ($p=0.017$). Thus, dependence on MV increases the risk of sepsis. However, when ulcer was entered in the final model, both the interaction factor and mechanical ventilation lost their significant influence with respect to sepsis ($p=0.13$ and $p=0.096$ respectively), while ulcer showed a positive significant association with sepsis development ($p<0.001$). (Table 7)

Table 7: *Adjusted Association between sepsis, MV, ulcer, and intake*

Model		B	95% Confidence Interval for B: Lower Bound	95% Confidence Interval for B: Upper Bound	P value§
1	Constant	1.669	1.449	1.889	<0.001*
	Interaction Factor	-.007	-.013	-0.001	0.023*
2	Constant	.930	0.291	1.569	0.005*

	Interaction Factor Mechanical Ventilation	-.007 .392	-0.013 0.73	-0.001 0.712	0.025* 0.017*
3	Constant Interaction Factor Mechanical Ventilation	0.867 -0.007 0.356	0.204 -0.013 0.020	1.531 -0.001 0.692	0.05 0.025 0.017
4	Constant Interaction Factor Mechanical Ventilation Ulcer	.224 -.004 .207 .560	-.0354 -0.009 -0.073 0.366	0.821 0.001 0.488 0.754	0.358 0.130 0.096 <0.001*

p-values: one-way analysis of variance (ANOVA) as appropriate; ***p*-value** < 0.05 was considered significant

R^2 model 1: 7.3%

R^2 model 2: 14.8%

R^2 model 3: 43.6%

5.6 Ulcer and clinical characteristics:

Patients were categorized as developing PU or not during their ICU stay. Intakes of energy and protein on the fifth day of feeding initiation, showed borderline association with the risk of PU (p=0.057 and p=0.099). PU patient were consuming 1.02±0.36 g/kg/d of proteins and 21.72±7.25 kcal/kg/day versus 1.25± 0.41g/kg/d and 25.4±7.7 kcals/kg/d for patients with no PU. Significant difference among patients with PU and no PU was detected among sepsis (p<0.001). (Table 8)

Table 8: *Unadjusted Clinical characteristics of patients based on the existence or absence of PU on the fifth day of feedings*

		No PU	PU	
LOS	Below 8 days	5 (38.5)	8 (61.5)	0.764
	Above 8 days	26 (44.8)	32 (55.2)	
Sepsis	No	28 (71.8)	11 (28.2)	<0.001*
	Yes	3 (9.4)	29 (90.6)	
Ventilation	No	9(90.0)	1 (10)	0.092*
	Yes	30 (49.2)	31 (50.8)	
Day 5	Protein	1.25 (±0.41)	1.02 (± 0.36)	0.057 *
	Energy	25.4 (± 7.7)	21.72 (±7.25)	0.099 *

All data are presented as n (%) except for age where mean (SD) was presented.
§ Differences were tested by Mann-Whitney or chi square tests depending on the type of the variable. *: eligible to be entered into the model, p=0.2

In the model summary, the interaction factor was able to explain 4.5% of the development of pressure ulcer (R^2=4.5%).

Chapter Six
Discussion

6.1 Summary of Results

Although, the majority of literature reviews detected controversial associations, our results, unexpectedly, showed an absence in association between LOS and both energy and protein intakes. This might be due to the small sample size that was not sufficient to show an association or lack of variability of intake among patients. Moreover, on the fifth day of feeding initiation, the average amount of protein intake the patients were receiving 1.15(± 0.40) g/kg was less than what the guidelines recommend, which is a minimum of 1.2g/kg.

At the beginning of the study, the main aim was to detect an association between LOS at the ICU with protein and energy intake patients were receiving. However, LOS showed a significant association ($p<0.001$) with sepsis development during ICU stay, which was a secondary outcome in the study. Thus, the study shifted from detecting an association between energy and protein intake with LOS to sepsis and PU development.

The combined effect of protein and energy intake, the interaction factor, showed a significant association with sepsis with or without mechanical ventilation. However, when ulcer was entered, both the interaction factor and mechanical ventilation lost their significance to PU, indicating a confounding effect. In other words, deficiencies in energy and protein intake leads to PU development, which might increase LOS.

6.2 Sepsis:

Sepsis is an unregulated response by the body due to infection that causes severe abnormalities in immunity, metabolism, and hemodynamic parameters. Septic patients have a longer and more complex stay at the ICU. Nutritionally speaking, sepsis goes hand in hand with severe protein catabolism and cachexia. Septic patients can have either a hypo or hyper-metabolic activity. (De Waele et al., 2020). To our knowledge, minimal studies have ventured into ICU septic patients and clinical associations, even more so, such studies had a small representative sample size.

In our cohort, protein and energy intake have shown beneficial effects in the prognosis of sepsis, even after adjusting for MV. Comparing the intakes of septic to non-septic patients, our cohort revealed a significant difference in the protein and caloric intakes on the fifth day. Non-septic patients were on a high protein (1.25±0.41 g/kg/d) and energy (25.4±7.7kcal/kg/d) regimen, whereas septic patients were on a moderate protein (1.02±0.36g/kg/d) and energy (21.72±7.25kcal/kg/d) regimen (Table 6). This was translated into having significant differences in the clinical outcomes, LOS and MV (Table 6). In other studies, PROCASPT study specifically, septic patients receiving amounts within the same range of our cohort (0.8-1.2 g/kg/d) on the same day showed a significant lower six-month mortality compared to protein intakes exceeding 1.2g/kg/d ($p=0.048$). Even better survival rates ($p=0.015$), lower MV days, and in hospital mortality were recorded. Moreover, patients who had a protein intake of 0.8-1.2 g/kg/d during the entire week had better survival rates compared to those on an overall low intake ($p=0.015$). (Koning et al., 2019). In the PROCASPT study, day four and onward, medium and high energy intake showed better results compared to low intakes ($p=0.046$ and $p=0.002$,

receptively) (Koning et al., 2019). A post-hoc observational study showed that in the presence of sepsis, the mean intake on day four of 1g/kg/d was not associated with mortality, neither did caloric overfeeding (Weijes et al, 2014). In line with this, the PROTINVENT retrospective cohort also showed no effect on LOS in the ICU with neither quantity of protein nor its feeding initiation. However, they depicted better clinical outcomes among non-septic patients who had their protein feedings advanced on the fourth day compared to those who had an overall high intake (Looijaard et al., 2018). Such progression was detected in our cohort. Furthermore, they compared patients who had less than 0.8g/kg/day feeding for a week, to those who had advanced on the fourth day. Patients in the latter group had better clinical outcomes. (Looijaard et al., 2018). They also revealed a time dependent trend whereby increasing protein intakes at the rate of 0.8 g/kg/d on days one to two, to 0.8-1.2g/kg/d on days three to five, to reach intakes >1.2g/kg/d showed superior long-term outcomes (Looijaard et al., 2018). In our cohort, patients that did not develop sepsis reached 1.25 (+/-0.41) g/kg actual or ideal body weight/day. The PROTINVENT retrospective cohort showed a lower six-month survival rate (65.6%) among patients consuming 0.8g/kg/day of protein compared to patients consuming 0.8-1.2g/kg/d and more (68.9% and 55.6%, respectively) in the early phase. In our cohort, on the third day of feeding initiation, patients were receiving 1g/kg/d.

The PROCASPT cohort, however, showed that early high protein feedings was related to higher six month mortality compared to low intake (p=0.005). Nevertheless, better overall survival outcomes were detected among patients who had feedings below 0.8g/kg/d on the first three days that was advanced to above 0.8g/kg/d from days four to seven compared to those on an overall low intake (p=0.065). The post hoc analysis by Wejis et al showed that non-overfed patients had a lower mortality rate on day four as the protein intake was

higher. The highest end of intake (1.2g/kg/d) was significantly associated with low mortality (p=0.013) (Weijes et al, 2014)

As for energy intake, non-septic patients in our study were consuming a borderline high caloric intake (25.4kcal/kg/d). The PROCASPT study showed that energy intake of 80-110% (medium to high) of needs on days four to seven were associated with a lower six-month mortality compared to low energy intake (p=0.014) (Koning et al., 2019). Similar to our study, a multicentre double blinded RCT in Australia and New Zealand showed no significant difference among mortality, LOS, and survival between high calorie vs. moderate energy delivery. (New England Journal of Medicine, 2018). Additionally, a systematic review and meta-analysis aimed to compare the difference in outcomes between low and high caloric intake patients. No difference was detected between caloric restriction and high caloric intake on mortality (p=0.19). However, the risk of bloodstream infection and pneumonia were lower among caloric restricted patients. Hospital LOS was significantly longer among patients who were underfed (Al-Dorzi et al., 2016)

6.3 Pressure Ulcer

It is defined as skin ulcerations that are not only linked to higher LOS in hospitals, but also morbidity and premature mortality. Epidemiological studies revealed that 12-50% of hospitalized patients with ulcer are malnourished. Weight loss, dehydration, and protein energy malnutrition are all risk factors that increase susceptibility in developing pressure ulcer. In general, patients with pressure ulcers (PU) are already in hypercatabolic state, but that doesn't necessitate having a high REE than those who do not have PU. Another independent risk factor is age, whereby people above the age of 65 have a higher risk of developing PU. (Mahmoodpoor et al., 2018). In our cohort the mean age of the participants

was 70.3 (Table 1) making them already prone to PU development irrespective of other clinical variables. Patients on bed rest have a 17-fold higher prevalence of developing PU (Tsaousi et al, 2014), which is evident in our cohort.

The Cochrane review on eight RCTs targeting nutritional interventions as treatments or preventative measure of PU showed no promising results. However, a trial was mentioned that showed improved wound healing time (twelve weeks) among tube fed patients with high protein and energy intake. (Little, 2012). In a prospective cohort, patients with PU had a significantly longer hospital LOS compared to patients without PU. Protein recommendations for PU are 1.25-1.5 g/kg/day since high protein improves healing rates (Mahmoodpoor et al., 2018). In our cohort, PU patients were consuming less than the recommended amounts (Table 8).

In their prospective cohort study in Brazil, Wenzel et al assessed development of press injuries according to nutritional parameters. The frequency of developing PU was 31.5%, which is much less than our cohort (66.5%). They managed to find an association between patients who did not achieve their nutritional requirements and PU development (Wenzel & Whitaker, 2021). In our cohort, in the absence of sepsis, energy and protein intake showed a significant negative association with PU development. Moreover, patients who had their intakes initiated after 48 hours had higher risks of developing PU. Unlike our study, ROA showed no associations with PU development in the bivariate model. In the Brazilian cohort, readmission for surgery, orthopedic surgeries, and surgeries lasting over four hours were considered as risk factors for they promote immobility (Wenzel & Whitaker, 2021). Such association were not detected in our study since only 0.7% was admitted for similar reasons. However, they also found a correlation between cardiac complications and PU development, which was not detected in our cohort. Cardiovascular

diseases increase the susceptibility of ischemia which can discontinue blood supply to the tissue causing tissue necrosis. (Wenzel & Whitaker, 2021). However, to date, a full disclosure on the relationship between nutrition and PU is still lacking for studies are still preliminary. (Tatucu-Babet & Ridley, 2021)

6.4 Interpretation

In our cohort, whether sepsis or PU was considered as the outcome, both showed significant associations ($p<0.001$) that outranked associations with other clinical parameters.

PU development in our cohort might be linked to a low energy and protein intake. Such intakes can lead to weight loss, particularly fat loss (blowing the cushioning effect of fat on the bones) and physical weakness. (Tsaousi et al, 2014) (Mahmoodpoor et al, 2018) Edema is another effect that causes loss of elasticity of the skin and thus mobility and immunity (Tsaousi et al, 2014). Dehydration interferes with appropriate cell metabolism and wound healing. (Mahmoodpoor et al, 2018) Nutrient insufficiency is a key factor in PU development and disable wound healing. It also interferes in immunity, collagen synthesis and integrity. Development of PU went in parallel with sepsis development in our cohort ($p<0.001$). According to John Hopkins Medicine, at the level of the body, sepsis is a complication that arises from PU development. When PU is detected, aerobic and/or anaerobic bacteraemia is detected, which is the primary cause of infection related PU. Other than localized infections, cellulites and osteomyelitis can trigger infections, both of which cause sepsis. (Sullivan & de Barra, 2018) (Momodu & Savaliya, 2021). In our cohort, sepsis was significantly positively associated with LOS ($p<0.001$), in line with the literature where development of sepsis was shown to elongate the hospital and ICU stay

of patients (Sakr et al., 2018). In summary, undernutrition can prolong LOS and this could be mediated though PU development that may trigger sepsis in patients.

6.5 Strength, Limitations, and Future Implications

Our cohort had several strengths. To start with, patients were on enteral feedings meaning that precise calculations of intake were measured. Timings and quantities of feedings were calculated based on the time of feeding initiation, irrespective of how many days the patient resided at the ICU before feeding was started. When we calculated energy and protein intakes on days three and five, patients that were NPO for surgery were excluded from the analysis. Another strength is that we limited bias regarding LOS, for the eligibility criteria clearly stated that patients should be residing in the ICU for more than three days. We also corrected for various confounders in the logistic regression.

Our study also had several limitations with the small sample size being the most prominent one. Based on our sample size calculations regarding intakes and LOS, 140 participants were needed. However, when we reached the fifth day of feeding initiation, the remaining eligible participants dropped to 71. Having a small sample limited the detection of variability between intakes among ICU patients and could have led to type 2 error. As for the study design, a retrospective cohort doesn't infer causation. Additionally, weight and BMI were the only markers that were used to assess weight loss or weight gain. More reliable markers would have provided a more comprehensive look on how the body composition was affected, including skinfold thickness, percent body fat, and percent muscle mass. Lastly, the collected data were taken during the period when the COVID crisis was prominent, which was reflected in missing ICU related scores, such as the

sequential organ failure assessment (SOFA) score that tracks a person's status in ICU to determine the extent of organ failure. The higher the SOFA score, the higher the risk of mortality (Vasilevskis, et al 2016). Another parameter that could have been used, if available, is the acute physiological and chronic health evaluation (APACHE), which is a validated score that shows severity of disease classification system. The higher the scores the higher the risk of death. (Akavipat, Thinkhamrop, Thinkhamrop, & Sriraj, 2019). Another specific nutrition parameter that wasn't collected properly is the nutritional risk assessment tool (NUTRIC) that detects malnutrition among ICU patients. The lower the score, the lower the risk of being malnourished. (de Vries, Koekkoek, Opdam, van Blokland, & van Zanten 2018)

Future implications include replication of the study results with a bigger sample size. Moreover, a prospective study should be conducted in order to establish a potential cause/effect relationship. Future studies should also include non-invasive physical examinations and/or bioelectrical impedance usage to get a clearer idea on how the composition of the body is changing as the intakes progress.

Chapter Seven

Conclusion

In conclusion, our study showed that sepsis development could be a potential mediator between how protein and energy intake can either increase or shorten the LOS of patients in the ICU. Moreover, we showed a significant difference between the intakes of septic and non-septic patients; whereby non-septic patients were consuming higher intakes of protein and energy. This was also reflected in the PU development, which might have in turn affected MV days and sepsis development. A major finding in the study is the fact that patients are not being delayed with their feeding initiations as per recommendations. Most importantly, we detected a favorable gradual progression in energy and protein intake among the population.

Nevertheless, the study failed to show the association between protein and energy intake with LOS. Further research, preferably a longitudinal multicentre study with a large sample, is needed to detect the presence or lack of association between these variables.

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