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Original article

Observational study to assess the relationship between enteral nutrition delivery and nutritional biomarkers among mechanically ventilated critically ill patients

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ABSTRACT

Background: Biochemical assessment is considered a useful tool in assessing the patient's nutritional status and intake. However, during critical illness, nutritional biomarkers, such as albumin, and haemoglobin (HB) may reflect the severity of acute illness. The aim of this study is to assess the relationship between energy and protein delivery with the change in albumin, HB, "mean corpuscular volume" (MCV), and "mean corpuscular haemoglobin concentration" (MCHC) levels in critically ill patients.
Method: In this prospective observational study we monitored the intake of energy and protein in a group critically ill patients for 6 consecutive days. Biochemical data including albumin, HB, MCV and MCHC was measured on admission and on day 6 of the follow-up. The variation in the biomarkers between admission and day 6 was calculated as the follow-up reading minus the reading obtained upon admission to (Intensive Care Unit) ICU.
Results: This study included 43 patients. There was a significant difference in the albumin and HB levels between admission and follow up readings. No statistical association was recorded between the intake and the changes in albumin, MCV and MCHC level during ICU stay. The results showed a significant association between the intake of energy (R = 0.393), and protein (R = 0.385), with the increase in HB level during hospitalisation.
Conclusion: Overall, this study showed that most nutritional biomarkers were not influenced by nutritional therapy during the acute phase of illness. These findings may directly undermine the usefulness of the serial measurements of these biomarkers in the early phase of ICU admission.

1. Introduction

Nutritional status is highly relevant to the disease outcome among critically ill patients. Since the majority of critically ill patients have previous pre-existing chronic illness and co-morbidity; they are more likely to be malnourished upon admission to ICU (Zaher et al., 2020). A recent systematic review revealed that about 38 % to 78 % of critically ill patients were malnourished on admission to ICU (Lew et al., 2017), another study have shown that 84 % of the critically ill patients developed malnutrition during hospitalisation (Osooli et al., 2019). It is particularly important to prevent further deterioration of their nutritional status, thus regular monitoring of the nutritional status is crucial for this group of patients (Lew et al., 2017).

In the context of nutritional assessment in ICU settings, physical examination, anthropometric data including body mass index (BMI) as well as biochemical assessment all are considered tools to assess the patient's nutritional status (Osooli et al., 2019). Serum albumin, prealbumin and HB are frequently used to assess the nutritional adequacy and status among hospitalised patients (Higgins et al., 2006; Parent et al., 2016; Davis et al., 2012; Rodriguez et al., 2001; Ramel et al., 2008; Shahriari et al., 2015; Ferrie and Tsang, 2017). The low levels of these biomarkers do not only reflect the nutritional status of the patients, but it also reflects the level of the physiological stress associated with the disease process. Thus, they must be considered as indicators of both the patient's nutritional status and the degree of the disease severity (Parent et al., 2016).

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Underfeeding is a common yet under-recognized problem among hospitalized critically ill patients (Zaher et al., 2018; Heyland et al., 2015). Reduced levels of nutritional biomarkers may suggest inadequate nutritional delivery. However, in critically ill patients, a variety of biomarkers, such as serum lactate, albumin, and HB may reflect the severity of acute illness such as resuscitation and inflammation (Parent et al., 2016). For this reason, the use of these parameters as markers of nutritional status was widely questioned. Nevertheless, the magnitude of inflammatory stimuli varies among individual patients and when the inflammation process is stable, the rate of hepatic protein synthesis may respond to nutrition therapy (Yeh et al., 2018). It is still not clear whether these biomarkers can be used to assess the effectiveness of artificial nutrition support. In the current study we investigated the association between enteral caloric and protein intake with the variation in albumin, HB, MCV, and MCHC levels between day 1 and day 6 of admission in critically ill adult patients.

2. Methods

In this study energy and protein intake were prospectively monitored for a period of 6 consecutive days in a group of mechanically ventilated patients admitted to ICU. The study was undertaken at King Fahad Hospital (KFH) in AL Madinah AL-Munawara, and the data was collected between January and March 2020. This study was approved by the ethical committee in KFH and "Taibah University" (Certificate number: "SREC/AMS 2019/12/CND"). Since this was a pilot study, we aimed for a target enrollment of 40 critically ill patients over a period of three months. Patients who were older than 18 years of age, mechanically ventilated with endotracheal tube, having multiple or single organ failure, exclusively enterally fed and were expected to stay in the ICU for at least 6 days were included in this study. Terminally-ill patients and those diagnosed as brain dead on admission to ICU were excluded from the study.

2.1. Clinical, biochemical and anthropometric data

The clinical and biochemical data was collected from the hospital electronic system and the patient's files. We recorded the primary diagnosis that necessitated the ICU admission for each patient then it was categorized into multiple or single organ failure diagnosis (Goldstein et al., 2005).

Biochemical data including albumin, HB, MCV and MCHC was measured on admission and on day 6 of the follow-up. The variation in the biomarkers between admission and day 6 was calculated as the follow-up reading minus the reading obtained upon admission to ICU. Information related to blood transfusion were recorded for each patient, they were then categorized in to two groups either they received transfusion or did not receive transfusion. Lactate level was recorded daily, and the highest value was used as a marker of disease severity.

The anthropometry data like weight, height were obtained and used to calculate the BMI for the studied population. Patient's weight was measured using the bed-scale in ICU. Height was recorded from the patient's chart, in the absence of the height readings, demi-span measurements were performed to estimate the patient's height (Cirillo et al., 2018). In few cases, the weight and height were estimated by one of the ICU medical staff, obtained from the patient's family member or the nearest recorded weight in the hospital records was utilised.

2.2. Enteral nutrition (EN) prescription and delivery

The EN prescription at KFH was based on the "American Society for Parenteral and Enteral Nutrition" (ASPEN) guidelines published in 2016 (McClave et al., 2016). For patients with normal BMI, the energy requirement was estimated based on their actual body weight using the quick method [25–30 kcal/kg/day]. For patients undergoing dialysis, energy requirement was estimated based on their dry weight. The protein prescription was also based on ASPEN guidelines and was individualised for each patient according to their weight and BMI category (BMI <30: 1.2–2 g/kg/d; BMI 30–40: 2 g/kg/d; and BMI $\geq$40: 2.5 g/kg/d).

The initiation rate of EN was 20 ml/hour, advanced by 20 ml/hour every 4 h if the patient is tolerating the feed in accordance with hospital protocol. The actual amount of enteral intake was monitored and recorded daily (1 day = 24 completed hours) for all patients from admission up to day 6 of the follow up. The type of formulae and the total volume of EN received was then calculated and used to determine the amount of energy and protein intake based on the nutritional data card of the formulas. The nutritional intake was expressed as percentages of the patient's estimated requirements.

2.3. Statistical analysis

Data was analysed using the "Statistical Package for Social Sciences" (SPSS) version 20. The normality of the data was tested using the Shapiro-Wilk test. Quantitative variables such as population characteristics, biochemical parameters as well as caloric and protein intake) were expressed as a median with interquartile range (IQR). Wilcoxon signed ranked test was used to test the variation in biochemical markers between admission and follow up. Enter linear-regression analysis was performed to assess the association between the cumulative energy and protein intake during the study period and the variation in the measured biomarkers between admission and follow up. All regression analysis models were adjusted for the age, transfusion status and the disease severity. All the performed tests were two-tailed, with a significant level of 95 %.

3. Results

A total of 43 critically ill patients were recruited in this study. Around 56 % (n = 24) of the patients were males. The inpatient mortality was about 16 % (n = 7 patients), but all patients survived during the study period. The clinical and demographic characteristics of the studied population is presented in Table 1. The actual nutritional intake was recorded daily for the whole period of the study (first 6 days of ICU admission). We have recorded a gradual increase in the enteral intake of both energy and protein from admission to day 6 of the follow up. The cumulative intake of energy and protein over the 6 days was 39 % (16–61) and 31 % (11–45) respectively of the calculated requirements.

Among our cohort, serum albumin decreased in most patients (68 %) during hospitalisation and the difference between the admission reading and the follow up reading (day 6) was statistically significant (P value = 0.001*). Similarly, serum HB decreased in 72 % of our patients and we recorded a statistically significant difference between the admission reading and the follow up reading (P value = 0.00*). No statistically significant difference was recorded in the level of MCV and MCHC between admission and the follow up reading (P value > 0.05).

Table 1
Characteristics of the studied population.

Patients characteristics and feeding data (n = 43)	Median (IQR)
Age (years)	53 (35–63)
Admission weight (kg)	65 (55–80)
Height (cm)	161 (158–170)
BMI (kg\m^2)	24 (22–29)
Percentage of cumulative energy intake during the study period(%)	39 (16–61)
Percentage of cumulative protein intake during the study period(%)	31 (11–45)
Time until EN started (hours)	24 (24–48)
Highest lactate during the study period (mmol/L)	3 (2–7)

Biochemical markers	**On Admission (n = 43)**	**Follow up (n = 43)**	**P value**
Albumin (g/liter).	26 (20–31)	22 (18–26)	0.001*
HB (g/dl).	10 (7–13)	9 (7–11)	0.001*
MCV	85 (82–89)	86 (82-89)	0.995
MCHC	32 (32–33)	32 (31–33)	0.287
Primary diagnostic categories		**n**	**(%)**
Multiple organ dysfunction syndrome		11	25%
Nervous system diagnosis		14	32%
Respiratory diagnosis		10	23%
Gastrointestinal diagnosis		3	7%
Cardiovascular diagnosis		3	7%
Endocrine diagnosis		1	2%
Renal diagnosis		1	2%

Data are presented as median (IQR).
* Wilcoxon signed ranked test; P value is significant at 0.05 level.

We assessed the association between the enteral intake of energy/protein and the changes in the biochemical parameters during hospitalisation, no statistical association was recorded between the intake and the changes in albumin, MCV and MCHC level during hospitalisation (Tables 2, 3). Our results showed a significant association between the intake of energy (R = 0.393), and protein (R = 0.385), with the increase in HB level during hospitalisation. The regression models significantly explained 22 % of the variation in HB level (Tables 2, 3). The regression analysis also showed that each increase in caloric and protein intake by 1 % of the calculated requirements predicted an increase in HB level by 0.393 and 0.385 respectively.

4. Discussion

In this pilot study we have recorded under-delivery of both energy and protein among our cohort during the study period. We have also shown that there was a significant difference in the albumin and HB levels between the admission and follow up readings. Finally, this study showed that higher energy and protein intake was associated with increase in HB level during hospitalisation. On the other hand, no statistically significant association was recorded between the intake and the changes in albumin, MCV and MCHC level during hospitalisation.

Despite accumulating evidence demonstrating the unreliability of using serum albumin as a nutrition marker during the course of critical illness, it is still measured serially and utilised to guide the nutrition care plan in many settings (Ferrie and Tsang, 2017; Ferrie and Allman-Farinelli, 2011). The current study clearly demonstrated that the serum albumin level was not influenced by the amount of calories and protein received. Many studies have confirmed that during critical illness, serum albumin is more responsive to inflammation than nutrition therapy in terms of energy or protein intake. In a study by Yeh *et al.* they recoded a negative correlation between the measured serum levels of albumin and CRP, they also indicated that CRP was a significant predictor of the changes observed in albumin levels, suggesting that albumin was increased in response to improvement in inflammation. Similar to our findings, they did not record any association between the rate of change in serum albumin and the amount of calories or protein intake during the first 2 weeks of ICU stay (Yeh et al., 2018). Parent *et al.* also reported that changes in serum albumin levels did not correspond to nutritional intervention and did not correlate with caloric delivery during the first 2 weeks of admission to ICU (Parent et al., 2016). However, by the beginning of the third week, patients who received higher calorie showed greater increase in serum albumin level, which might be related to resolution of inflammation (Parent et al., 2016).

Interestingly, among our cohort we showed an increase in HB level in response to caloric and protein intake. Contradictory to our findings, other studies have shown that nutrition therapy did not improve the level of HB during hospitalisation. In a study by Suzuki *et al.* they have shown that the mean HB values were low at the time of admission and remained low throughout hospitalization regardless of the protein dose received (Suzuki et al., 2020). In another study of patients undergoing dialysis, they have shown that patients with good appetite had higher HB levels compared to patients with poor appetite, implying that nutrition intervention may improve HB status (Kalantar-Zadeh et al., 2004). However, in our study, the improvement showed in the HB level may be related to reduce the rate of catabolism accompanied by increased hepatic protein synthesis in responses to nutritional therapy especially protein intake at adequate levels to reduce endogenous catabolism (Stoppe et al., 2020).

In the current study we have also shown that MCV and MCHC levels did not change in response to nutrition therapy in terms of calories and protein. This may be because these biomarkers are generally affected by iron status more that energy and protein intake (Sultana et al., 2013). It is commonly perceived that most EN feed are designed to meet the increased micronutrient requirements, however, some studies have shown that EN formulas may lack essential vitamins and trace elements. Lacone *et al.* compared the micronutrient content of different types of EN formulas available in the market against the dietary reference values and they indicated that the vitamin K requirement was not covered (Iacone et al., 2015). Other study indicated that iron content in some commercially available EN formulas was relatively low. It was also suggested that patients receiving EN feeding for long-term may be at higher risk of developing iron deficiency as the iron

Table 2
Multiple linear regression analysis for the association between the percentage of Cumulative caloric intake from admission to follow up and the changes in nutritional biomarkers

Independent variables	Beta	Standard error	95 % confidence interval	R ^{2}	Adjusted R ^{2}	P value	F
Albumin	−0.05	0.048	−0.113 – 0.083	0.185	0.092	0.761	1.983
HB	0.393	0.014	0.005 – 0.060	0.225	0.141	0.023*	2.696
MCV	−0.010	0.037	−0.077 – 0.73	0.182	0.0.94	0.953	2.058
MCHC	0.067	0.014	−0.022 – 0.032	0.089	0.009	0.710	0.905

All models were adjusted for age, blood transfusion, diseases severity.
* P value is statistically significant at < 0.05 level.

Table 3
Multiple linear regression analysis for the association between the percentage of Cumulative protein intake from admission to follow up and the changes in nutritional biomarkers

Independent variables	Beta	Standard error	95 % confidence interval	R^2	Adjusted R^2	P value	F
Albumin	−0.137	0.065	−0.186 – 0.077	0.199	0.107	0.408	2.169
HB	0.385	0.019	0.006 – 0.082	0.226	0.142	0.023*	2.689
MCV	0.110	0.050	−0.068 – 0.133	0.191	0.104	0.513	2.190
MCHC	0.101	0.018	−0.027 – 0.047	0.094	0.04	0.569	0.960

All **models** were adjusted for age, blood transfusion, diseases severity.
* P value is **statistically** significant at < 0.05 level.

source used in most formulas is inorganic (Bueno, 2013). Additionally, it may be that some components of the EN formulation affect the iron availability in EN feeding (Bueno, 2013). Therefore, studies to evaluate the micronutrient content in the currently available EN formulas requires consideration.

Our findings collectively may suggest that during the early phase of acute illness other tool of nutritional assessment such as measurements of muscle circumference by ultrasound or skinfold thickness might be more effective and provide a better insight on the efficacy of the nutritional therapy. In the weeks following injury when inflammation is starting to resolve, nutritional biomarkers such as albumin may provide valuable information on the adequacy of energy and protein delivery.

This study was limited by the short follow up period and variation in the length of ICU stay between patients. As a result, for the patients who stayed for long time in the ICU, their late reading (day 6) could have been measured during the early phase of illness where the inflammation was not entirely resolved. This made it difficult to exclude the effect of inflammation on the levels of the measured biomarkers, however, to tackle this issue we adjusted our regression models for disease severity. The micronutrient content of the formulas was not analysed in the current study, but, future work aim to investigate the relationship between micronutrient content in EN formulas and nutritional biomarkers such as HB, MCV and MCHC. Finally, our sample size was relatively small and was collected from one hospital, however, this was a pilot study and future work aim to recruit larger cohort from different settings.

5. Conclusion

Overall, this study has shown that the nutritional biomarkers were not influenced by nutritional therapy during the acute phase of illness among our cohort. While their baseline levels may possibly reflect admission nutrition status, during the course of critical illness other factors such as disease severity and inflammation are thought to be the main drive affecting the level of these biomarkers. These findings may directly undermine the usefulness of the serial measurements of these biomarkers to monitor the adequacy of nutritional therapy during the early phase of ICU admission. As a result, this will substantially reduce impact on health care resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None to declare.

Author contribution

S. zaher conceived and designed the study. She collected, analysed and interpretated the data and drafted the manuscript.

Ethics approval and consent for participation

This study was approved by the ethical committee at KFH and Taibah y (Certificate number: "SREC/AMS 2019/12/CND"). Consent for participation in the study, as well as consent for publication of the data was obtained and signed by the patient's families.

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