Prediction of clinical outcome with serum transthyretin level of early post-burn period in massive burn patients: retrospective observational study

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Abstract

Introduction: We observed serum transthyretin (TTR) constantly maintained low even with adequate nutritional support if the patients' general conditions are poor. We conducted this study to analyze the change of serum TTR with time from injury in massive burn patient and verify the validity of prediction of clinical outcome with serum TTR of early post-burn period.

Methods: From January of 2005 to December of 2010, serum TTR of 471 burn patients (% total body surface area (TBSA) burned, mean 51±20%) analyzed with time from injury retrospectively.

Results: Serum TTR decreased significantly during period of day 5 to 10 after the injury in both survivors (n = 290, mean %TBSA burned 42.9±14.2%) and non-survivors (n = 181, mean %TBSA burned 64.6±20.8%). After this period, the serum TTR constantly increased in survivors, however, remained low in non-survivors. At all time, serum TTR levels of survivors were significantly higher than non-survivors (1-4 day, \( P = 0.019 \); 5-10 day, \( P = 0.019 \); 11-20 day, \( P = 0.000 \); 21-30 day, \( P = 0.000 \); 31-40 day, \( P = 0.000 \)). The serum TTR had weak correlation with the extent of the burn injury (\( r = -0.234 \)). Survival rates of the patients increased significantly by the increase of the serum TTR of early post-burn period (1-10 day, \( P = 0.000 \); 1-4 day, \( P = 0.003 \); 5-10 day, \( P = 0.001 \)).

Conclusions: The serum TTR of early post burn period can be used as a prognostic indicator. And low serum TTR is a signal for screening the patient at risk who requires careful assessment and monitoring in massive burn patient. So it can be a useful option to measure the serum TTR level periodically in massive burn patients.
Introduction

After massive burn injury, dramatic metabolic response which can be as high as 120-150% of normal metabolic rate occurs. This hyper metabolic response results in increases in oxygen consumption, urinary nitrogen excretion, lipolysis, and weight loss. Early active nutritional support reduces the mortality rates, complications and accelerates wound healing. However, lack of nutrition leads to delayed wound healing, compromised immune defense and eventually it can cause morbidity. Therefore, the adequate nutritional support is more important and critical in massive burn treatments [1].

For this reason, our burn center has operated a Nutritional Support Team (NST) organized by burn surgeons, pharmacists, clinical nutritionists and burn dedicated nurses since 2003. Patients admitted to our burn centers generally starts with high calorie and protein diet within 24 hours from the injury. If the oral intake is not sufficient to meet the calorie required for the patient, we provide naso-enteral tube feeding and parenteral nutrition to the patient. Since Curreri formula (25kcal/kg usual body weight + 40kcal/%TBSA burns) has a tendency to over-calculate the calorie required, we determined the total calorie required for patients by using average result of Milner (1994), Zawacki (1970), Xie (1993) formula [2]. The respiratory quotient of patient is measured by using indirect calorimetry(Vmax Series 29n, U.S.A.) and it yields the resting energy expenditure of patient using Consolazio formula [3].

The average calorie required for the patient obtained from using Milner (1994), Zawacki (1970), and Xie (1993) formula is very close to the resting energy expenditure measured from the indirect calorimetry. This result is reflected in determining the calorie level required for each patient.

Daily total calorie intake, protein intake and total output of patient is monitored and recorded. Patient weight was measured once a week using a bed scale. Serological test for nutritional assessment including total blood cell count, routine chemistry, lipid profile, total iron-binding capacity, transthyretin (TTR, previously called prealbumin) and transferrin was conducted once or twice a week. We evaluated the condition of patient such as burn wound status and systemic organ function using the serological parameters we obtained previously (e.g. acute renal failure, acute respiratory distress syndrome, sepsis). And the management methods for each patient are established and revised through the weekly discussion. Since the NST activity, mortality rates of massive burned patients have decreased and mean lowest serum TTR level of these patients has increased consistently every year [4].
But, in spite of adequate nutritional support, we observed serum TTR levels constantly maintained very low when the patients’ general conditions were poor. This made us to believe the serum TTR level can be a useful indicator for measuring patient’s condition. We conducted this study to analyze the change of serum TTR with time from injury in massive burn patient and verify the validity of prediction of clinical outcome with serum TTR of early post-burn period.

Materials and methods

Patient selection
From January of 2005 to December of 2010, a total of 635 burn patients consulted to NST were reviewed. As exclusion criteria, we excluded the patients with total body surface area burned less than 20% and those patients who did not check the serum TTR level within 10 days from admission. Therefore, a total of 471 patients were selected and reviewed retrospectively. Demographics of patients are described in Table 1. The study was performed according to the declaration of Helsinki. Because measured serum TTR (at least once a week) is a part of the routine medical care of the NST consultation patients, there was no change in our current clinical practice. No randomization was performed. As it was an observational retrospective study, neither approval of the ethics committee nor informed consent was required.

Blood samples
As described above, serum TTR was checked once or twice a week for NST activity. Serum TTR was measured by image 800 Immunochemistry system (Beckman Coulter Inc., USA) using dedicated Prealbumin reagent (Beckman Coulter Inc., USA).

Statistical analyses
In this study, we analyzed the serum TTR level with time from injury, total body surface area burned and patient’s progress status. Statistical analysis was performed with t-test, Pearson correlation coefficient, Chi-Square test and ANOVA test in SPSS 17.0.
Results

We compared the serial serum TTR level changes of survivors and non-survivors since the burn injury (Figure 1). The serum TTR level decreased significantly during period of day 5 to 10 after the injury in both survivors and non-survivors (survivors, \( P = 0.000 \); non-survivors, \( P = 0.000 \)). After this period, the serum TTR level constantly increased in survivors, however, remained low in non-survivors. In each period, serum TTR levels of survivors were significantly higher than non-survivors (1-4 day, \( P = 0.019 \); 5-10 day, \( P = 0.019 \); 11-20 day, \( P = 0.000 \); 21-30 day, \( P = 0.000 \); 31-40 day, \( P = 0.000 \)).

We divided patients into 4 groups according to the total body surface area burned by increment of 20% and analyzed the change of serum TTR level at each period for each group (20-39% : \( n = 149 \); 40-59% : \( n = 168 \); 60-79% : \( n = 94 \); 80-100% : \( n = 60 \)) (Figure 2). The serum TTR levels decreased during day 5 to 10 in all groups. After 10 days from injury, the serum TTR level increased except with the group of over 80% (\( n = 5 \)) of total body surface area burned in survivors. In each period, the group with more severe burn injury showed lower serum TTR level (1-4 day, \( P = 0.004 \); 5-10 day, \( P = 0.000 \); 11-20 day, \( P = 0.000 \); 21-30 day, \( P = 0.001 \); 31-40 day, \( P = 0.001 \)) (Figure 2A). It took more time to normalize the serum TTR level in survivors if the total body surface area burned is higher (Figure 2B). In the other hand, every group of non-survivors showed the serum TTR level decreased or maintained low after 10 days from the injury (Figure 2C).

The serum TTR level was significantly related to the extent of the burn injury (\( P = 0.000 \)) but the correlation was not strong in all and each period (Total period, \( r = -0.234 \); 1-4 days, \( r = -0.207 \); 5-10 days, \( r = -0.233 \); 11-20 days, \( r = -0.284 \); 21-30 days, \( r = -0.313 \); 31-40 days, \( r = -0.266 \)) (Figure 3).

There was no significant difference in length of hospital stay (LOS) according to the serum TTR level of early post-burn period (1-4 days, \( P = 0.99 \); 5-10 days, \( P = 0.38 \) in survivors) (Figure 4).

Survival rates of the patients increased significantly by the increase of the serum TTR level during early post-burn period (1-10 day, \( P = 0.000 \); 1-4 day, \( P = 0.003 \); 5-10 day, \( P = 0.001 \)) (Figure 5).
Discussion

Transthyretin (TTR) is a plasma protein synthesized in the liver and its main function is transporting thyroxine (T4) and retinol. Its hepatic synthesis is sensitive to protein and energy intake. And it has relatively short half-life of 2-4 days [5, 6]. For this reason, the serum TTR is known as affected by nutritional status and acute stress such as inflammation, malignancy and trauma. Therefore, we have been using the serum TTR level as a biochemical marker of nutritional status and general condition of the patient.

In the presence of inflammation, it is reported that the serum TTR level drops regardless of adequate calorie intake [7]. In 2004, Fuhrman MP et al. reported that the serum TTR level correlates with morbidity and mortality which can serve as a useful indicator for severity of illness. They reported that failure of serum TTR levels to increase with nutrition support does not indicate inadequate nutrition support, rather than a patient is not recovering from the primary problem that caused inflammatory metabolism or has developed a secondary problem such as infection [8]. However, in 2005, Lim SH et al. reported that in critically ill patients, the serum TTR level did not respond sensitively to nutritional support and the increases of the TTR level does not indicate a better prognosis for critically ill patients [9].

In 1982, Moody et al. studied 16 burn patients whose total body surface area burned was between 2 to 37% and reported that the serum TTR levels dropped to lowest levels after 6 days from burn injury. Patients who had more severe burn injury needed longer time to return to normal serum TTR level and the lowest level of serum TTR had association with the size of total body surface area burned [10]. In 1989, Boosalis et al. reported that burn patients had decreased albumin and TTR concentrations over the duration of hospitalization that related to the severity of thermal injury but not to adequacy of nutritional support and the serum TTR level reflects severity of injury and prognosis but it cannot accurately reflect nutritional status or adequacy of nutritional support [11]. In 1991, Cynober et al. studied 61 burn patients who received continuous enteral nutrition and whose mean total body surface area burned was 25.8% and mortality rate was 37.7%. Their results showed that the serum TTR decreased maximally during 6 and 8 days after burn injury and it remained low in non-survivors [12]. In 1992, Rettmer et al. studied 15 burn patients whose total body surface area burned was in between 16% to 80%. He supplied nutritional support with calculated calorie and checked serum nutritional markers including TTR after 15 days from burn injury. Result showed all serum level of nutritional markers including TTR was below normal range after 15 days from burn injury. So he concluded that the laboratory results of nutritional status must be interpreted cautiously [13].
In our results, the serum TTR level decreased significantly during the period of day 5 to 10 after injury in both survivors and non-survivors. After 10 days from injury, the serum TTR level constantly increased in survivors, however, remained low in non-survivors. Survivors showed significantly higher serum TTR level than non-survivors at each period. These results correspond with the previous reports described above.

The serum TTR level increased in all groups after 10 days from injury except the group whose total body surface area burned was over 80%. The group with more severe burn injury needed more time to return to normal serum TTR level. The survivor group with total body surface area burned over 80% showed constantly low serum TTR level until 40 days of the study. The study showed the TTR curve of the survivors with more than 80% TBSA burned did not normalize even after the post burn 40 days. Further investigation showed all of these subjects (n = 5) have increased more than 10mg/dl during the post burn 60 to 90 days. Moreover, the C-reactive protein level which indicates the status of inflammation maintained at higher than 100mg/L after the post burn 40 days and dramatically decreased to 50mg/L during the post burn 60 to 90 days. We think this is primarily due to the fact that it takes much longer time to close the wound of the survivors with more than 80% TBSA burned (Figure 2B). Actually Cynober et al. reported that survivors with sepsis had very low serum TTR levels after 28 days from burn injury compared with survivors without sepsis and there was no significant difference in transthyretin levels between the patients who died in a state of sepsis and the patients who died of other causes [12]. So the serum TTR levels decreased or maintained low in patients who do not reach the recovery phase yet or patients who are in sepsis.

In each period, the group which had more severe burn injury showed lower serum TTR level. So we analyzed the correlation between burn extent and serum TTR level by time. Serum TTR level was significantly related to the extent of the burn injury but the correlation was very weak in each period. Similarly to this result, Cynober et al. reported that the maximum decrease in serum transthyretin concentration was not significantly related to the extent of the burn injury in survivors without complications [12]. Therefore, the serum transthyretin levels are only slightly dependent on the extent of the burn injury.

Shenkin A. et al. reported adequate nutritional support reduces length of hospital stay (LOS) [14]. So we investigated the relation between serum TTR level at early post-burn period and length of hospital stay. We found there was no significant differences of length of hospital stay (LOS) according to serum TTR level during the period of day 1 to 4 ($P = 0.99$) and day 5 to 10 ($P = 0.38$) after injury. Kyle, U. G. et al. reported that low
serum albumin levels correlated with longer LOS, but TTR was not associated with length of hospital stay due to its short half-life [15].

In 1995 consensus statement, a panel agreed that patients with serum TTR levels below 5mg/dl had poor prognosis and recommended that patients with TTR levels below 15 mg/dl received a consultation from the hospital’s nutritional team [16]. And there were many reports about the association between serum TTR level and prognosis of patients in end-stage renal disease [17-20], end-stage liver disease [21] and organ transplantation patients [7]. These reports concluded that serum TTR level have association with patients prognosis. Regarding burn patients Cynober et al. reported that low serum level of transthyretin levels appear to be predictive of a fatal outcome and indicative of sepsis. In our results, the survival rates of patients increase when the serum TTR levels increase during early post-burn period. So the serum TTR level of early post-burn period has predictive value to the prognosis of burn patient.

Conclusions

In major burn patients, there are numerous possible complications including malnutrition, acute renal failure, and acute respiratory distress syndrome and wound sepsis. It is important to find out hidden septic causes and complications to manage massive burn patients. In our results, serum TTR level of early post burn period can be used as a prognostic indicator. And low serum TTR level is a signal for screening the patient at risk who requires careful assessment in massive burn patient. So it can be a useful option to measure the serum TTR level periodically in massive burn patients.
Key Messages

- In massive burn patients, serum TTR decreased significantly during period of day 5 to 10 after the injury in both survivors and non-survivors compared to day 1 to 4.
- After 10 days from burn injury, the serum TTR level constantly increased in survivors, however, remained low in non-survivors.
- The serum TTR level was significantly related to the extent of the burn injury, but the correlation was not strong in all and each period.
- Survival rates of the patients increased significantly by the increase of the serum TTR level during early post-burn period.
- Serum TTR of early post burn period can be used as a prognostic indicator. And low serum TTR is a signal for screening the patient at risk who requires careful assessment in massive burn patient.

Abbreviations

NST: Nutritional Support Team; TTR: transthyretin; FB: Flame Burn; SB: Scalding burn; EB: Electrical burn;
CoB: Contact burn; ChB: Chemical burn; TBSA: Total Body Surface Area

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

YSC and HJY conceived of and designed the study. JH and DHK helped collecting data and analysis. BCL and DKS carried out statistical analysis. HSK and JHK draft the manuscript. WC coordinated the study. All authors read and approved the final manuscript.

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### Table 1

Patient Demographics \((n = 471)\)

<table>
<thead>
<tr>
<th></th>
<th>Survivors ((n = 290))</th>
<th>Non-survivors ((n = 181))</th>
<th>Total patients ((n=471))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean</td>
<td>42±13</td>
<td>47±13</td>
<td>44±14</td>
</tr>
<tr>
<td>Male:Female ratio</td>
<td>242:47</td>
<td>136:46</td>
<td>378:93</td>
</tr>
<tr>
<td>% TBSA burned, mean</td>
<td>42.9±14.2</td>
<td>64.6±20.8</td>
<td>51±20</td>
</tr>
</tbody>
</table>

All values calculated as means ± standard deviation. FB = Flame Burn; SB = Scalding burn; EB = Electrical burn; CoB = Contact burn; ChB = Chemical burn; TBSA = Total Body Surface Area.
Figure Legends

Figure 1
Variations of serum transthyretin (TTR) levels according to outcome and the time between injury and assay in total patients

Figure 2
Variations of serum transthyretin (TTR) levels according to total body surface area burned and the time between injury and assay in total patients (A), survivors (B), non-survivors (C)

Figure 3
Correlation between serum transthyretin (TTR) and total body surface area burned by the time after burn injury. (A)Total period (B) 1-4 days (C) 5-10 days (D) 11-20 days (E) 21-30 days (F) 31-40 days after burn injury

Figure 4
Length of hospital stay according to serum transthyretin (TTR) level during the period of day 1 to 4 (A) and day 5 to 10 (B) in survivors

Figure 5
Survival rate according to serum TTR level during the period of day 1-10, day 1-4, day 5-10 after injury
References


13. Rettmer RL, Williamson JC, Labbe RF, Heimbach DM: Laboratory monitoring of nutritional status


Figure 1
Variations of serum transthyretin levels according to outcome and the time between injury and assay in total patients
Figure 2

Variations of serum transthyretin levels according to total body surface area burned and the time between injury and assay in (A) total patients, (B) survivors, (C) non-survivors.
Figure 3

Correlation between serum TTR and total body surface area burned by the time after burn injury.

(A) Total period, $r = -0.234$ (B) 1-4 days, $r = -0.207$ (C) 5-10 days, $r = -0.233$ (D) 11-20 days, $r = -0.284$ (E) 21-30 days, $r = -0.313$ (F) 31-40 days, $r = -0.266$
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Length of hospital stay according to serum TTR level during the period of (A) day 1-4, $P = 0.99$ and (B) day 5-10, $P = 0.38$ in survivors.
Figure 5

Survival rate according to serum TTR level during the period of day 1-10 ($P = 0.000$), day 1-4 ($P = 0.003$), day 5-10 ($P = 0.001$) after injury
Additional files provided with this submission:

Additional file 1: competinginterests.doc, 36K
http://ccforum.com/imedia/4041875845228774/supp1.doc