



Prognostic Value of Transthyretin Levels in Maxillofacial Infection

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ABSTRACT

Introduction: The Nutritional status in hospitalized maxillofacial infection patients is of great importance. These patients may develop rapidly various deficiencies and wasting. Unfortunately, most of these deficiencies go unrecognized. Considerable efforts have therefore been made to identify patients at risk of malnutrition, with a view to the early provision of nutritional support. Determining the level of Transthyretin, a hepatic protein, is the earliest laboratory indicator of nutritional status and has emerged as the preferred marker for malnutrition. **Objectives:** The objective of the study is to assess the transthyretin level in the patient with infections in the maxillofacial region and correlate between transthyretin concentration and length of hospital stay. **Study design:** A prospective study done on 80 patients who were admitted for maxillofacial infections between 2011 and 2013. We recorded the number of infected spaces and transthyretin. Correlations between the duration of hospital stay, number of facial spaces involved and the variation in transthyretin concentration during the time of admission and discharge were assessed. **Results:** A total of 80 patients (44 males and 36 females) based on the transthyretin level during admission were grouped into high risk (5%), moderate risk (37.5%) and no risk (57.5%). As the severity increased the transthyretin levels decreased. The severity of the infection which was determined by the transthyretin levels has statistical significance with hospital stay during admission and discharge which shows that 78% of the patients were in no risk category who were admitted for 1 to 3 days and the patients who were admitted for more than 3 days have shown 63.3% in moderate risk and 13.3% in high-risk category. The study also shows how the variation seen in transthyretin levels during the time of admission and discharge has shown a significant correlation with hospital stay (0.549) and the no. of spaces (0.442). **Conclusion:** Transthyretin can be used as a diagnostic tool in assessing the nutritional status in patients with a maxillofacial infection which helps in improving the prognosis and reduce the duration of hospital stay.

Keywords: Transthyretin, Nutritional status, Maxillofacial infections

INTRODUCTION

A grave public health concern in rural Indian populations lacking, medical knowledge, awareness, and access to health care is maxillofacial infection following dental infections. Though treated routinely with antimicrobial and/or surgical intervention, the spread of these infections to the vital structures in proximity is inevitable. Resultant extended periods of hospitalization can be a great financial burden on both patients and society alike [1,2].

The nutritional status in odontogenic infection in hospitalized patients is of great importance. Decreased levels of plasma proteins such as albumin, transferrin, and retinol-binding proteins is a common feature of such infections usually also associated with various deficiencies and muscle wasting [3]. Unfortunately, most of these insufficiencies are hardly recognized. Healthy and well-nourished patients usually have sufficient body stores to withstand surgical stress and starvation for a week to 10 days [4]. Undernourished patients, however, are at an increased risk of clinical complications with increased length of stay (LOS) and higher mortality and morbidity. Optimum nutritional supplementation reduces the complication rate and improves treatment results. Hence identification of high-risk malnutrition patients and swift provision of nutritional therapy is essential [5-7].

Transthyretin is a hepatic protein also known as Prealbumin, with a half-life in plasma of less than two days, as compared to the half-life of three weeks of albumin [8]. Hence transthyretin more sensitive to changes in protein-energy status than the later; its concentration reflecting recent nutritional status rather than overall. Measurement of transthyretin levels is a sensitive, effective and earliest method of assessing the severity of illness resulting from malnutrition in critically ill patients or those with chronic infections. Transthyretin levels have been shown to correlate with patient outcomes and are an accurate predictor of patient recovery since it can alert the physician to declining nutritional status thereby improving patient outcome and shorten hospitalization in an increasingly cost-conscious economy [9-11].

Over the years a strong link between poor nutrition and ill health has been established. However, a quick, objective and sensitive method to evaluate nutritional risk is lacking. Determination of the transthyretin level is an effective and objective method of assessing the severity of malnutrition in the critically or chronically ill [10]. This study suggests that early detection of protein malnourishment and timely introduction of nutritional therapy can patient prognosis and decrease the hospital stay.

MATERIALS AND METHODS

A prospective study was conducted in the Department of Oral and Maxillofacial Surgery, A.B. Shetty Memorial Institute of Dental Sciences, Mangalore from December 2011 to September 2013. Ethical clearance was obtained from our institution's ethical board.

A complete case history was recorded for all the patients. All patients reported with maxillofacial infection were treated based on clinical examination and radiographic evidence and underwent routine investigation and culture sensitivity after which the patient was administered antimicrobial therapy and other surgical treatment such as extraction of teeth, intraoral and extraoral incision and drainage along with intravenous antimicrobial therapy.

All patients aged between 15-60 years reported with a maxillofacial infection on clinical examination and radiographic evidence. Patients who were medically compromised, pregnant, chronic alcoholics, on steroid therapy or had any occult infection were excluded from the study.

All blood samples were collected during the time of admission and discharge for accessing the human transthyretin level in 4 ml of the vacutainer tube. Serum was coagulated at room temperature for 10-20 mins, with centrifugation done for 20 mins at the speed of 2000-3000 rpm. Blank wells were set separately. A sample dilution of 40 μ l was added to the testing sample well. Then testing sample 101 (sample final dilution is 5-fold) was added and gently mixed. After closing the plate with the Closure plate membrane it was incubated for 30 min at 37°C. The incubation mixture was aspirated into a sink or proper waste container. Using a squirt bottle, each well was completely filled with wash solution, and contents of the plate were aspirated into a sink or proper waste container. A total of five washes was done in all. After the final wash, the plate was inverted and blot dried until no moisture was present. The enzyme, HRP-Conjugate reagent 50111 was added to each well, except blank well. Chromogen Solution A 50 l and Chromogen Solution B 50l were added to each well and light preservation evaded for 15 min at 37°C. Stop Solution of 50 ul was added to each well. The stoppage of the reaction was indicated by the blue colour changing to yellow.

Taking blank well as zero, absorbance is read at 450 nm after adding Stop Solution within 15 min. Taking the standard density as the horizontal, the OD (Optical Density) value for the vertical, the standard curve was drawn on graph paper. The corresponding density was found out according to the sample OD value by the sample curve, multiplied by the dilution multiple, or the straight-line regression equation of the standard curve was calculated with the standard density and the OD value. With the sample OD value in the equation, the sample density was calculated and multiplied by the dilution factor, giving us the sample actual density. The normal assay range is 0.07 mg/dl-20 mg/dl.

Transthyretin levels were assessed for determining its diagnostic value in maxillofacial injury. Correlation between the hospital stay duration, the number of spaces and the variation in transthyretin level during the hospital stay is done using Spearman's correlation Coefficient. The significance of transthyretin level with the severity of the infection was done using Man Whitney's U test.

RESULTS

Of 80 patients (44 males and 36 females) (Graph 1) 56.2% patients were in the age group 15 to 30 years, 20% patients in the age group of 31 to 45 years and 23.8% of the patients were in the age group of 46 to 60 years (Table 1). All patients were clinically examined and brief history was recorded. Each patient was treated as in-patients, transthyretin levels were recorded at the time of admission and discharge to assess the nutritional status of the patient and its effect on the hospital stay (Table 2).

The patients were grouped based on transthyretin level on admission with values <10 mg/dl being regarded as indicative of the severe risk of protein-energy malnutrition, 10 mg/dl-17 mg/dl as moderate risk and >17 mg/dl no risk groups respectively. During the time of admission, 5% of the people were at high risk, 37.5% of the people showed moderate risk 57.5% were under no risk category (Table 3), but during the time of discharge the high and the moderate risk patients came down to 1.2% and 31.2% respectively, the no-risk category showed 67.5% of the patient (Table 4 and Graph 2). This was done to assess the severity of the infection.

The severity of the infection as denoted by the transthyretin levels has statistical significance with hospital stay during admission and discharge (Tables 5-8) which shows that 78% of the patients were in no risk category who were admitted for 1 to 3 days and the patients who were admitted for more than 3 days have shown 63.3% in moderate risk and 13.3% in high-risk category. The study also shows how the variation seen in transthyretin levels during the time of admission and discharge has shown a significant correlation with hospital stay (0.549) and the number of spaces (0.442) (Graph 3).

Table 1 Demographic distribution of patients

Age	Gender		Total
	Male	Female	
15-30 years	23 (51.1%)	22 (48.9%)	45 (56.2%)
31-45 years	7 (43.8%)	9 (56.2%)	16 (20.0%)
46-60 years	14 (73.7%)	5 (26.3%)	19 (23.8%)
Total	44 (55.0%)	36 (45.0%)	80 (100.0%)
Mean age (SD)	35.30 (14.24)	31.92 (12.19)	33.78 (13.38)
Range	16-60 years	17-60 years	16-60 years

Table 2 Comparison of mean transthyretin levels at admission and discharge

Time of Transthyretin Estimation	Gender	Mean Transthyretin level (SD)	Mean Difference (95%CI)	t [#]	df	p-value*
During Admission	Male (n=44)	15.90 (4.36)	-0.56	-0.58	78	0.55 (NS)
	Female (n=36)	16.47 (4.23)	(-2.49-1.35)			
During Discharge	Male (n=44)	16.45 (2.90)	-0.62	-0.86	78	0.39 (NS)
	Female (n=36)	17.08 (3.59)	(-2.07-0.81)			

#Independent samples t-test; *p<0.05 statistically significant

Table 3 Risk assessment based on transthyretin levels representing disease severity

Transthyretin Level (in mg)	During Admission	During Discharge
<10	4 (5.0%)	1 (1.2%)
10-17	30 (37.5%)	25 (31.2%)
>17	46 (57.5%)	54 (67.5%)
Total	80 (100.0%)	80 (100.0%)

Table 4 Correlation between number of spaces involved and duration of hospital stay

No. of Spaces	Duration of Hospital Stay		
	1-3 days	>3 days	Total
1	41 (82.0%)	8 (26.7%)	49 (61.3%)
2	8 (16.0%)	12 (40.0%)	20 (25.0%)
3	1 (2.0%)	10 (33.3%)	11 (13.8%)
Total	50 (62.5%)	30 (37.5%)	80 (100%)
Mann Whitney U test	U statistics=301.000, p<0.001*		

*p<0.001 statistically significant

Table 5 Correlation of duration of hospital stay and transthyretin levels

Hospital Stay	Time of Transthyretin Estimation	Mean Transthyretin Level (SD)	Mean Difference (95%CI)	t [#]	df	p-value
1-3 days	During Admission	17.68 (3.39)	0.12 (-0.60 - 0.85)	0.34	49	0.736
	During Discharge	17.56 (3.08)				
>3 days	During Admission	13.63 (4.48)	-1.73 (-2.65-(-0.80))	-3.83	29	0.001*
	During Discharge	15.36 (3.03)				

#Related samples t-test; *p<0.05 statistically significant

Table 6 Correlation of duration of hospital stay and transthyretin levels during admission

Hospital Stay	Transthyretin Level (During Admission)			Total
	<10	10-17	>17	
1-3 days	0 (0.0%)	11 (22.0%)	39 (78.0%)	50 (62.5%)
>3 days	4 (13.3%)	19 (63.3%)	7 (23.3%)	30 (37.5%)
Total	4 (5.0%)	30 (37.5%)	46 (57.5%)	80 (100%)
Mann Whitney U test	U statistic=318.00, p<0.001*			

*p<0.001 statistically significant

Table 7 Correlation of duration of hospital stay and transthyretin levels at discharge

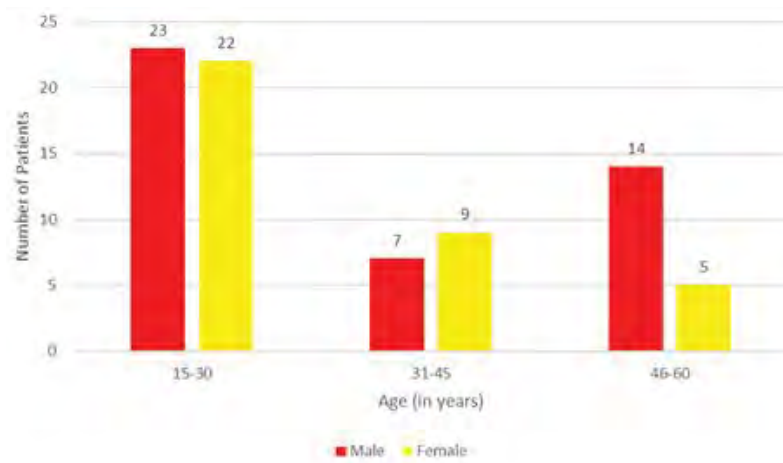
Hospital stay	Transthyretin level (at discharge)			Total
	<10	10-17	>17	
1-3 days	1 (2.0%)	8 (16.0%)	41 (82.0%)	50 (62.5%)
>3 days	0 (0.0%)	17 (56.7%)	13 (43.3%)	30 (37.5%)
Total	1 (1.2%)	25 (31.2%)	54 (67.5%)	80 (100%)
Mann Whitney U test	U statistic=468.500 ,p=0.001*			

*p<0.01 statistically significant

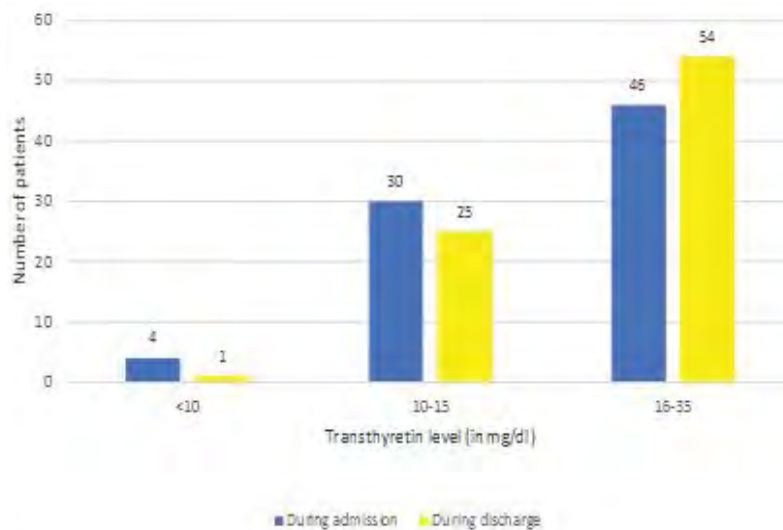
Table 8 Variation in Transthyretin levels during hospital stay

		Hospital Stay	No of Space
Variation in transthyretin level during hospital stay	Spearman's Correlation Coefficient	0.549*	0.442*
	Sig. (2-tailed)	0	0

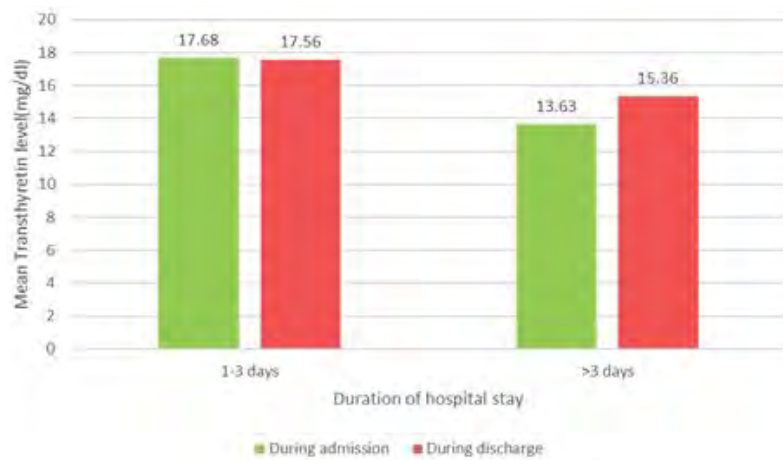
*Correlation is significant at the 0.01 level



Graph 1 Demographic distribution of patients



Graph 2 Transthyretin level in patients



Graph 3 Correlation of duration of hospital stay and transthyretin levels

DISCUSSION

Maxillofacial infections are common in the practice of oral surgery. The outcome of an infection originating from

different areas in the oral cavity can vary considerably [1,2]. Some cases respond well to local treatment and antimicrobial therapy; others need extensive surgical and medical intervention [3]. Surgical intervention is the mainstay of treatment and it should only be deferred when detrimental factors increase the risk of the infection becoming severe. These factors also attribute to the increased hospital stay and added the risk of complications [4,12].

Transthyretin or Prealbumin is extremely sensitive to changes in protein-energy status than albumin. Due to its short half-life, its concentration falls rapidly as a result of the fall in its synthetic rate when there is a reprioritization of synthesis toward acute-phase proteins such as C-reactive protein (CRP), fibrinogen, or α 1-acid glycoprotein [10,13].

This prospective study was done to establish the relationship between the severities of infection, length of hospital stay with transthyretin concentration. 80 patients with maxillofacial infection in the age group of 15 to 30 years were included. Approximately 28.8% of the patients were in the age group of 46 to 60 years and 20% were in the age group of 31 to 45 years. Since the patient with immunosuppressant, diabetics and other age-related complications were not considered in the study, the majority of the patients were between 15 to 30 years of age.

Patient with alcohol abuse was not considered because studies have shown that chronic alcoholics may be undernourished and serum transthyretin and RBP has shown unreliable index in assessing the nutritional status. Patient with occult infection has also shown fluctuant transthyretin levels after the maxillofacial infection had clinically shown good prognosis. Studies have shown that transthyretin concentration in severe is an unreliable index of nutritional status in patients with the chronic intestinal disease may also indicate dietary intake rather than nutritional status [13-15].

Nutritional assessment in maxillofacial infection is a consideration seen only after the assessment of the severity of the disease. It is always important to assess the severity of the infection not only by clinical consideration but also by a diagnostic tool, previous studies by Cunningham, et al. [8], it is shown that transthyretin can be used to assess the severity of the infection. According to our study site of infection and the number of facial plans involved has shown considerable fall in the transthyretin level. When the duration of hospital stay is less than 3 days it showed transthyretin level well within normal limits that are more than 17 mg/dl with majority of patients had only involvement of one space but as the duration of hospital stay increased the transthyretin concentration showed considerable drop in the levels and severity of infection was also increased with the involvement of more than 2 to 3 facial spaces. This shows from the study that transthyretin concentration had a significant correlation with the severity of the infection and duration of hospital stay. It also shows that transthyretin concentration is indirectly proportionate with the number of spaces and the duration of hospital stay, as the number of spaces increased and the duration of stay increased the transthyretin levels decreased, hence this concludes like the previous studies that transthyretin is a good nutritional marker in assessing the recent dietary intake and can also assess the severity of infection.

The majority of the patients were shown to have an infection with approximately 70% in the mandibular region and rest in the maxillary region. Severity of the diseases increases when there is involvement of the mandibular region as there more deeper facial space involvement which may lead airway compromise and difficulty in normal dietary intake, around 8 patients with such severity of infection needed anesthesia coverage and had longer hospital stay of more than 7 days, in this patient the nutritional status was assessed in the interim period of every 3 days and enteric feeding was also considered to assess the nutritional status of the individual along with intravenous antibiotic coverage. In this patient, there were increased levels of transthyretin concentration from the time of admission to discharge.

Our study has shown that the transthyretin concentration is a good nutritional marker, it is important to use this diagnostic tool in assessing the nutritional status to reduce the clinical cost and also to reduce the duration of hospital stay, clinical studies have shown that estimation of the transthyretin levels aid early identification and intervention for malnutrition. Transthyretin production decreases after 14 days of consuming a diet that provides only 60% of the required protein, synthesis of transthyretin increases above baseline level within 48 hours of protein supplementation with severe protein malnutrition and returns to the normal level within 8 days. This data formulated the hypothesis that transthyretin levels should increase by 2 mg/dl/day with adequate nutritional support [10]. In our study, it shows that the transthyretin concentration has an insignificant correlation with the duration of hospital stay less than 3 days. But shows a significant correlation with transthyretin concentration when the duration of hospital stay is more than three days. This concludes that transthyretin concentration can be used as a diagnostic tool in assessing the nutritional status only after considering the severity of the infection and in cases with increased duration of hospital stay. During the time of admission 78% of the patients were more than 17 mg/dl of transthyretin levels, but as the duration of hospital

stay increased the majority of the patients have shown to have a depreciation of transthyretin concentration less than 17 mg/dl and only 23% the patients with more than 17 mg/dl. But at the time of discharge transthyretin concentration rose in 43% of patients more than 17 mg/dl. Hence transthyretin level at the time of admission and discharge shows a significant correlation with the duration of hospital stays. The variation seen in the concentration during the hospital stay from the time of admission to discharge has also shown a significant correlation with the severity of infection and duration of hospital stay.

CONCLUSION

Hence from our study, we can conclude that transthyretin a hepatic protein, provides good assistance in assessing nutritional status in the patients with maxillofacial infection in regard to the severity of the infection and it helps in improving the prognosis of the patients with maxillofacial infection hence reduce the duration of hospital stay. Further studies will help decide whether augmented nutrition to these patients hasten recovery and shorten the duration of hospital stay. Comparison with other hepatic proteins should be considered with the aim of providing better diagnostic aid in assessing the nutritional status and reduce the length of the hospital stay.

DECLARATIONS

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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