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Original Research Article

# Thyroid Hormone Dysfunction and CRP Levels in children with Sepsis

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## Abstract

**Introduction**: A hormonal disorder that often affected in sepsis is thyroid hormones. CRP (C-reactive protein) one of the best biomarker to rule out sepsis, and also CRP-guided duration of antibiotic therapy associated with a decreased duration of therapy. The aim of study was to find out association between thyroid hormones and CRP level in children with sepsis.

**Materials and Methods**: Present study is hospital based observational cohort study.70 children with diagnosed sepsis were required in sample size. Serum free T3, free T4, TSH and CRP level was measured on day one and also on follow up (7th day).

**Result**: There was positive correlation in CRP and culture positivity with negative outcome (Death). CRP positivity was more in patient with low FT3 (75%) and FT4 (91.7%) as compared those with normal FT3 (70%) and FT4 (69%) and same result in follow up also. On day one Serum FT3 level was low in 40 (57.2%) subjects and Serum FT4 level was low in 12 (17.2%) subjects. TSH was normal in most 66 (94.2%) of subjects.

**Conclusion**: CRP and culture positivity has positive correlation with negative outcome. There is an inverse relationship of thyroid hormones with CRP levels; it supports the interplay between thyroid hormones and the immune system. So Thyroid hormones dysfunctions with increase CRP could be an indicator of disease severity with possible need for hormone supplementation.

**Keywords:** CRP, Thyroid hormones, Serum free T3, free T4, TSH, sepsis

# INTRODUCTION

Sepsis is the most common cause of mortality in infants and children. The incidence of sepsis and septic shock were increasing in the last 30 to 40 years[1]. Sepsis is SIRS (Systemic Inflammatory Response Syndrome) plus a suspected or proven infection. To define sepsis a child must have a confirmed or suspected infection and signs of that infection. Severe sepsis requires diagnosis of end organ system involvement. Septic shock requires cardiovascular dysfunction that is not resolved by initial fluid resuscitation. These definitions are aimed at identifying sepsis in an early stage to facilitate early intervention, with the goal of stopping further spread of infection and preventing.[2]

Determination of altered physiology is specific to age dependent vital Signs. The timely diagnosis of sepsis in neonates is important as the illness can be rapidly progressive and in some instances fatal[3]. Sepsis in newborn continues to be serious problem leading to significant amount of morbidity and mortality[4]. The inability of neonates to completely suppress the minimum inflammatory response makes them more susceptible to bacterial invasion of the blood stream than older adults and the risks are even higher in preterm infants[5].

Sepsis might cause hemodynamic and cardiovascular disorders and hormonal imbalance. A hormonal disorder that often affected in sepsis is thyroid hormones which occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome. (NTIS) [6]

Euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) is a condition of decreased thyroid hormone levels without disruption of thyroid hormone function that occurs in severe systemic non-thyroid disease. Changes in thyroid hormone will later result in disruption of oxygen consumption, cardiovascular, sympathetic nerves, respiration, digestive, and hematopoiesis which in turn will lead to organ system failure and ended in death.[7, 8]

The critical disease is characterized by complex and multiple changes in the thyroid pathway. Along with worsening of a critical illness, the decrease occurs in not only triiodothyronine (T3) levels but also thyroxine (T4) and thyroid stimulating hormone (TSH). Decreased levels of T4 and TSH showed an indication of worsening of disease and poor prognosis.[9, 10]

World Health Organization (WHO) reported 70% in eight million children under five years' mortalities in developing countries caused by infection diseases which commonly ended in sepsis condition. The incidence of sepsis was 0.56% of 1000 children and 5.6% of 1000 infants with the highest mortality rate as 10.6% 7There are few studies about thyroid hormone level changes in sepsis, so we a planned this study to evaluate thyroid hormone changes and the clinical outcomes in children with sepsis.

IL-1 and IL-6 are inflammatory cytokines implicated in the pathogenesis of non-thyroidal illness. C-reactive protein (CRP) is an acute phase reactant produced in the liver, induced by cytokine IL-6 and its levels are commonly assayed for diagnosis of neonatal sepsis.[11]

CRP one of the best biomarker to rule out sepsis, On the other hand CRP-guided duration of antibiotic therapy showed a decreased duration of therapy for the neonatal population.[12] CRP also performed slightly better than Procalcitonin (PCT). PCT has the disadvantage to be more expensive and to have the need to use a nomogram due to PCT kinetics.

# Materials and Methods

Present study is hospital based observational cohort study which was conducted in Department of Pediatrics, SMS Medical College & Hospitals Jaipur from July 2020 to June 2022. Sample sizes were calculated at 95% confidence level expecting 71.2% of low T3 levels among children with sepsis. At 11% absolute allowable error the require sample size were 70 cases of children suffering from sepsis. The study was conducted on children with sepsis fulfilling the inclusion and exclusion criteria.

The inclusion criteria were Patients with confirmed diagnosis of sepsis in age group of 1 month to 18 years. Exclusion criteria were Patients with hypothyroid and hyperthyroid diagnosed before admission and mother having hypothyroid/hyperthyroid or taking medication for thyroid disorder.

Sepsis was diagnosed clinically and by lab investigation using The International Pediatric Sepsis Consensus Conference definition. After making diagnosis of sepsis first sample was sent for measuring of free T3, free T4, TSH and CRP level on day one. Then second sample for the same was sent on follow up (7th day). All samples were sent for analysis in central lab in our Hospital. Lab sample analysis by method- Chemiluminescence immunoassay (CLIA) for hormone and CRP levels were determined by immunoturbidimetric assay. Detailed history, clinical examinations & investigations were done in each case and were recorded in the Performa. Data analysis- Data was recorded on a Performa. Analyses of data were done with suitable statistical method. For categorical variables chi-square Test was used. For continuous variables independent samples t-test was used. P-value <0.05 was considered as significant.

# Results

The baseline characteristics of the whole Study cohort are given in Table 1. Majority of the children in the study were aged 1 – 60 months (72.8%) followed by 61-120 months (14.3%). About 54.3% of the children were female and 45.7% of the children were males. The male: female ratio in the study was 1: 1.19.

Table 2 depicts thyroid hormone values on day 1 and follow up, on day 1 Serum FT3 level was low in 40 (57.2%) subjects and Serum FT4 level was low in 12 (17.2%) subjects. TSH was normal in most 66 (94.2%) of subjects and equally low and high 2 (2.9%). On follow up, Serum FT3 level was low in 31 (44.3%) subjects and was normal in 39 (55.7%). Serum FT4 level was low in 5 (7.2%) of the subjects and was normal in most 65 (92.8%) of the subjects. TSH was normal in most 68 (97.2%) of subjects, low in only 1 (1.4%) subject and high in only 1 (1.4%) subject.

Table 3 depicts that 10 children with sepsis died giving a mortality rate of 14.3%. Table 4 shows a positive correlation in CRP and culture positivity with negative outcome (Death).

Table 5 shows that CRP positivity was more in patient with low FT3 (75%) as compared those with normal FT3 (70%), but the difference was not found to be statistically significant (p>0.05). Similarly CRP positivity was more in patient with low FT4 (91.7%) as compared those with normal FT4 (69%), but the difference was not found to be statistically significant (p>0.05). Similarly TSH level was also not associated with CRP status (p>0.05).

Table 6 shows that CRP positivity was more in patient with low FT3 (74.2%) as compared those with normal FT3 (71.8%), but this difference was not found to be statistically significant (p>0.05). Similarly CRP positivity was more in patient with low FT4 (100%) as compared those with normal FT4 (70.8%), but the difference was not found to be statistically significant (p>0.05). Similarly TSH level was also not associated with CRP status (p>0.05).

## TABLES

**Table_1: The baseline characteristics of the whole Study cohort**

| Distribution of subjects according to age group | | |
|---|---|---|
| **Age group(in months)** | **No.** | **%** |
| **1-60** | **51** | **72.8** |
| **61-120** | **10** | **14.3** |
| **121-180** | **8** | **11.5** |
| **>180** | **1** | **1.4** |
| **Total** | **70** | **100** |
| **Distribution of subjects according to gender** | | |
| **Male** | **32** | **45.7** |
| **Female** | **38** | **54.3** |
| **Total** | **70** | **100** |

**Table_2: Thyroid hormone levels on day 1 and follow up**

| Status | Low (%) | Normal (%) | High (%) |
|---|---|---|---|
| **Thyroid hormone levels on day 1** | | | |
| **Serum FT3** | **40(57.2)** | **30(42.8)** | **0(0.0)** |
| **Serum FT4** | **12(17.2)** | **58(82.8)** | **0(0.0)** |
| **TSH** | **2(2.9)** | **66(94.2)** | **2(2.9)** |
| **Thyroid hormone levels on follow up** | | | |
| **Serum FT3** | **31(44.3)** | **39(55.7)** | **0(0.0)** |
| **Serum FT4** | **5(7.2)** | **65(92.8)** | **0(0.0)** |
| **TSH** | **1(1.4)** | **68(97.2)** | **1(1.4)** |

**Table_3: Distribution of subjects according to outcome**

| Outcome | No. | % |
|---|---|---|
| **Death** | **10** | **14.3** |
| **Survived** | **60** | **85.7** |
| **Total** | **70** | **100** |

**Table_4: Association of mortality with CRP and Culture**

| No. of Death | CRP | | Culture | |
|---|---|---|---|---|
| | **Positive** | **Negative** | **Positive** | Sterile |
| **10** | **9 (90%)** | **1 (10%)** | **7 (70%)** | 3 (30%) |
| **Total** | **10** | | **10** | |

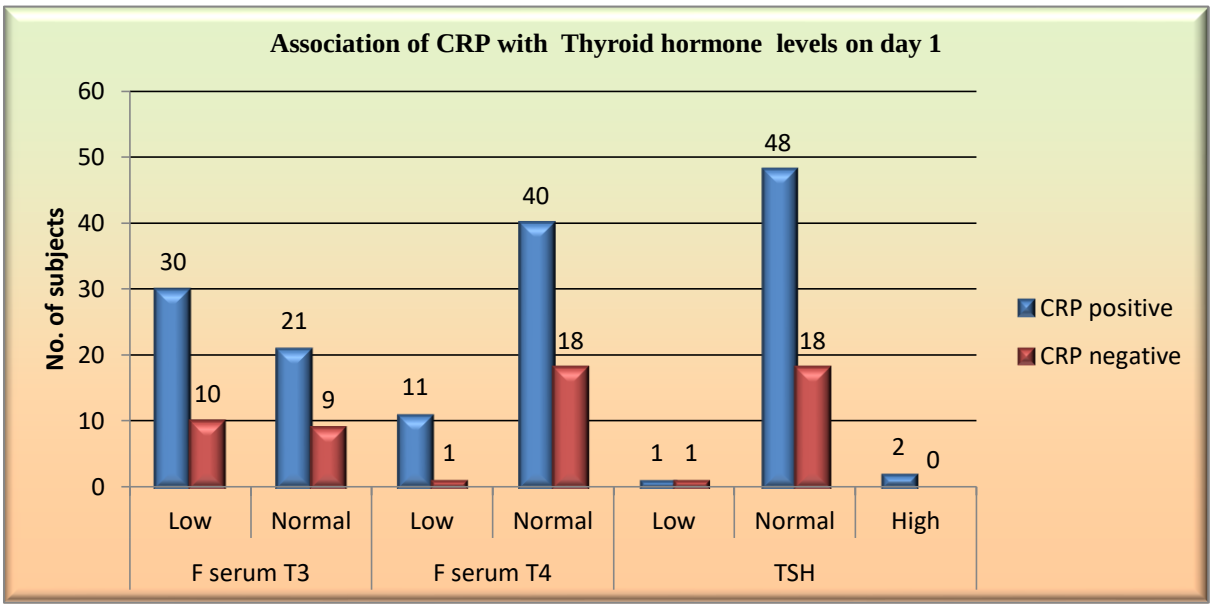
**Table_5: Association of CRP with Thyroid hormone levels on day 1**

| Thyroid Hormones | Levels | CRP | | Total | P Value |
|---|---|---|---|---|---|
| | | Positive (%) | Negative (%) | | |
| **Serum FT3** | **Low** | **30(75.0)** | **10(25.0)** | **40** | **0.642(NS)** |
| | **Normal** | **21(70.0)** | **9(30.0)** | **30** | |
| **Serum FT4** | **Low** | **11 (91.7)** | **1 (8.3)** | **12** | **0.159(NS)** |
| | **Normal** | **40 (69)** | **18 (31)** | **58** | |
| **TSH** | **Low** | **1 (50)** | **1 (50)** | **2** | **0.727(NS)** |
| | **Normal** | **48 (72.7)** | **18 (27.3)** | **66** | |
| | **High** | **2 (100)** | **0 (0)** | **2** | |

**Table_6: Association of CRP with Thyroid hormone levels on follow up**

| Thyroid Hormones | Levels | CRP | | Total | P Value |
|---|---|---|---|---|---|
| | | Positive (%) | Negative (%) | | |
| Serum FT3 | Low | 23 (74.2) | 8 (25.8) | 31 | 1.000(NS) |
| | Normal | 28 (71.8) | 11 (28.2) | 39 | |
| Serum FT4 | Low | 5 (100) | 0 (0) | 5 | 0.313(NS) |
| | Normal | 46 (70.8) | 19 (29.2) | 65 | |
| TSH | Low | 0 (0) | 1 (100) | 1 | 0.472(NS) |
| | Normal | 50 (73.5) | 18 (26.5) | 68 | |
| | High | 1 (100) | 0 (0) | 1 | |

**Figures: Association of CRP with thyroid hormone levels on day 1**




# DISCUSSION

CRP one of the best biomarker to rule out sepsis, On the other hand CRP-guided duration of antibiotic therapy showed a decreased duration of therapy for the neonatal population. Sepsis is the most common cause of mortality in infants and children. Sepsis and septic shock incidences were found to be increasing in the last 30 to 40 years. Sepsis might cause hemodynamic and cardiovascular disorders and hormonal imbalance. In sepsis, thyroid hormones disorder observed to occur in the form of euthyroid sick syndrome (ESS) or nonthyroidal illness syndrome (NTIS) [6], further changes in thyroid hormone will later result in disruption of oxygen consumption, cardiovascular, sympathetic nerves, respiration, digestive, and hematopoiesis which in turn will lead to organ system failure and ended in death.

In our study we found that on day one serum FT3 level was low in 40 (57.2%) subjects and was normal in 30 (42.8%) subjects. Serum FT4 level was low in 12 (17.2%) subjects and was normal in most 58 (82.8%) subjects. TSH was normal in most66 (94.2%) subjects, low in 2(2.9%) subjects and high in 2(2.9%) subjects. At follow up investigation, Serum FT3 level was low in 31 (44.3%) subjects and was normal in 39 (55.7%) subjects. Serum FT4 level was low in 5 (7.2%) subjects and was normal in most 65(92.8%) subjects. TSH was normal in most 68(97.2%) subjects, low in only 1 (1.4%) subject and high in only 1 (1.4%) subject.

Similar results of low T3 and T4 in sepsis was reported by other authors. **Sikha s et al** (2014)[13] found that The FT3 and FT4 hormones levels were significantly decreased ($P < 0.001$) in neonates with sepsis as compared to controls without sepsis. No significant difference was observed in TSH levels between the groups. **Agung G et al** (2014)[14] found that the free T3, free T4, and TSH levels were decreased in 97%, 50% and 40% of the neonates with sepsis. **Bhat K et al** (2014)[15] found that Low FT3 level was the most common abnormality found in these patients. High TSH and low FT4 levels were the other common abnormalities.

**Pikala Tarakeswara Rao et al** (2019)[16] observed that Serum T3, T4, Free T3 and Free T4 levels were significantly lower among cases of neonatal sepsis as compared to gestational age matched control. **Yanni G N et al** (2019)[17] observed that Level of T3 and T4 were decreased on day 1 in pediatric sepsis. Of 80 subjects, 57 (71.2%) with low level T3 and 41 (51.2%) with low T4 were found. The relationship between T3 and T4 level on day 1 with the length of stay were not found (P = 0.500; P = 0.987). There were a significant relationship between level of T3 and T4 with outcome (P = 0.0001; OR 24.706; P = 0.014; OR 3.086).**Den Brinker M et al** (2005)[18] were also observed that children had decreased total T3 (TT3)/rT3 ratios without elevated TSH.

In our study among 10 expired patients the CRP was positive in 9(90%) simultaneously culture was also positive in 7(70%).These evidence support our diagnosis of sepsis in these cases. In our study there was positive correlation in CRP and culture positivity with negative outcome (Death). CRP positivity was more in patient with low FT3 (75%) and FT4 (91.7%) as compared those with normal FT3 (70%) and FT4 (69%) and same result in follow up also.

**Wang F et al** (2012)[19] found that CRP level (standardized β = 0.367, P = 0.030) could independently predict primary outcome. **Sikha s et al** (2014)[13] observed a significant negative correlation between CRP and FT3 level in non-survivor group (r = -0.60; P = 0.02) and septic shock survivor group (r = -0.78; P = 0.006).

There was a significant negative correlation between CRP and FT3 levels in the septic shock survivors and non-survivor groups. **Dilli D et al** (2012)[20] observed that CRP levels significantly correlated with T3 levels at the 4th week of life.

CRP is an acute phase protein produced in the liver under the influence of cytokines like IL-1,IL-6, TNF-α etc. The 5'-deiodinase which mediates the conversion of T4 to T3 is also found in rich quantities in the liver. It is possible that cytokines especially IL-6 play an important role in stimulating the production of CRP and simultaneously inhibit the activity of 5'-deiodinase.[21]

# CONCLUSION

This study concludes that abnormalities of thyroid hormones are common in children with sepsis. Low level of FT3 was the most common abnormality seen in more than half of the cases of children with sepsis. There was positive correlation in CRP and culture positivity with negative outcome. CRP positivity was more in patient with low FT3 and FT4 as compared those with normal FT3 and FT4. In our study we found that there is an inverse relationship of thyroid hormones with CRP levels this supports the interplay between thyroid hormones and the immune system.

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