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The Efficacy of Resistin as a Biomarker of Neonatal Sepsis

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Abstract: ***Background: Sepsis is an important cause of neonatal death and perinatal brain damage, particularly in preterm infants. It is thought that activation of the inflammatory cascade triggered by cytokine may play a role in the pathogenesis of sepsis. Recent evidence supports a role for resistin in inflammation. There are no data in the literature on resistin levels in neonates with sepsis, which can also cause inflammatory response. The objective of this study was to evaluate the role of resistin as an indicator in neonatal sepsis. Materials and methods: Forty neonates considered to have sepsis were included in the study. Forty gestational and postnatal age- and sex-matched neonates without prolonged premature rupture of membrane or sepsis had served as controls. Results: The mean resistin level of the neonates with sepsis were 115 ng/mL, and was higher than those of the control group (41.1 ng/mL). There was statistically significant direct correlations between serum resistin and both TLC and CRP. The sensitivity, specificity, positive, and negative predictive values for resistin were 100%, 93%, 96%, and 100%, respectively. Conclusion: Resistin levels were higher in newborns with sepsis and correlated with TLC and CRP levels, which are indicators of neonatal sepsis. This suggests that resistin may also be used in the diagnosis of neonatal sepsis***

Keywords: C-reactive protein; resistin; neonatal; sepsis; biomarker

1. Introduction

Sepsis is one of the main causes of mortality and morbidity in preterm babies and is responsible for 45% of late deaths in the neonatal intensive care units (NICUs)[1] early diagnosis and management of sepsis are a great challenge facing neonatologists. Clinical diagnosis is difficult due to non specific symptoms and signs while laboratory diagnosis is time consuming.[2]Blood culture is the gold standard diagnostic method of neonatal sepsis. However, technical problems as insufficient blood sample or maternal use of antibiotics can be an obstacle in isolating the responsible pathogens. In recent years, there has been great interest in studying new indicators of infection such as interleukin-6 (IL-6), IL-8, and procalcitonin (PCT) and their value in the diagnosis of sepsis.[2, 3] Resistin is a newly discovered hormone and it has been implicated in adipogenesis and in the development of insulin resistance.[4] In rates, resistin is mainly secreted by adipocytes, whereas in humans, it is expressed and/or secreted by mononuclear cells, neutrophils, and macrophages.[5] Studies in adult patients with sepsis demonstrated that resistin expression and secretion by macrophages and neutrophils are elevated in the presence of acute bacterial infection[6,7,8]. In addition, it has been reported that resistin is an indicator of disease severity and possibly a mediator of the prolonged inflammatory state seen in critically ill patients with infection[8]. The objective of this study was to evaluate the role of resistin as an indicator of neonatal sepsis.

2. Materials and Methods

2.1. Patients

We obtained informed consents from the families of the infants included in the study. Forty neonates (18 male and 22 female) considered to have sepsis were included in the study; forty age and sex matched neonates without premature rupture of membranes (PROM) or sepsis served as controls. Sepsis was diagnosed based on clinical and laboratory findings, and positive culture results. The clinical findings of sepsis included apnea, gastrointestinal problems, increased need for oxygen or ventilatory support, lethargy/hypotonia, poor neonatal reflexes and hypotension. The components of the laboratory investigation are hematological counts and ratios such as total leukocyte count, absolute neutrophils count, thrombocyte count, immature-to-total neutrophils ratio, and serum or plasma concentrations CRP. All included case was proved to have sepsis based on positive blood culture.

2.2 Blood samples

Venous blood samples were drawn to measure whole blood count, CRP, and resistin level on the 1st day of sepsis. The CRP levels were quantitatively estimated using latex agglutination assay using the AVITEX CRP commercial kit.The resistin level (LINCO Research, St. Charles, MO, USA) was determined using enzyme-linked immunosorbent assay kit.

2.3 Statistics

Statistical analysis was done using statistical package for social sciences (SPSS), computer software (version22), IBM software, USA. Data were described in the form of mean ± standard deviation for quantitative data, and frequency and proportions for qualitative data. A p value <0.05 was considered statistically significant. Differences were analyzed between the groups by Student t test as regards normally distributed data; otherwise, Mann–Whitney U test was used. Correlations were analyzed by Spearman correlation coefficient test. The receiver operating characteristics (ROC) curve analysis was performed to identify the optimal cutoff value for resistin distinguishing between the cases with sepsis and the controls

3. Results

Mean gestational age, mean birth weight, and male-to-female ratio of the newborns included in the study are shown in Table 1.

Table 1: Demographic characteristics of the newborns with sepsis and controls

	Study group (n = 40)	Control group (n = 40)	p
Gestational age (wk)	38.4 ± 1.19	37.9± 1.03	0.2
Birth weight (g)	2740 ± 0.09	3050 ± 0.09	0.41
Gender (M/F)	18/22	19/21	0.82

Data are presented as mean ± standard deviation.

Forty neonates with sepsis were included in the study and a pathogen could be isolated in 90% of them. The isolated microorganisms were as follows: *Staphylococcus aureus* in three cases, *Enterobacter* in eight cases, *Klebsiella* species in eight cases, *Escherichia coli* in six cases, *Pseudomonas aeruginosa* in three cases, Acinetobacter in eight cases.

Table 2 shows CRP and resistin levels in both the study and the control groups. Both resistin and CRP levels substantially decreased on the 7th day of sepsis and positive correlations were observed between them (Figure 1,2).

Table 2: TLC, C - reactive protein and plasma resistin levels in babies with sepsis compared with control

	Study group (n = 40)	Control group (n = 40)	p
TLC(x10^{3}cell/mm^3)	15.23± 0.62	5.51±0.36	0
CRP (ng /mL)	38.8± 5.54	2.32± 0.2	0
Resistin (ng/mL)	115± 2.29	41.1± 1.01	0.001

Data are presented as mean ± standard deviation.
TLC=total leukocytes count
CRP = C-reactive protein.

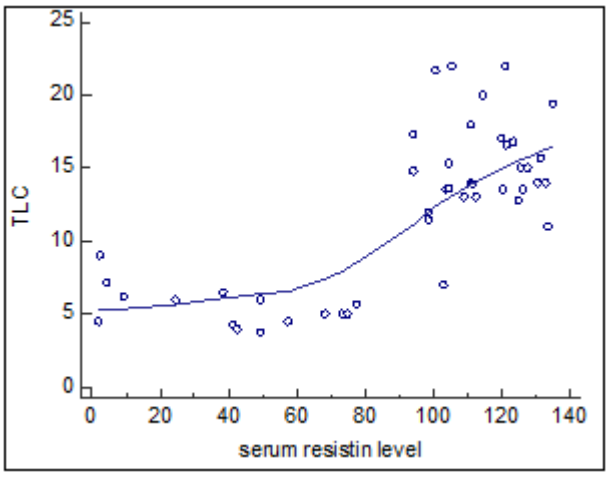
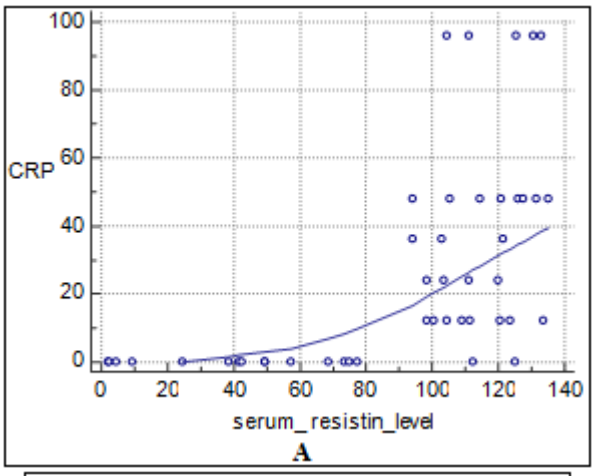


Figure 1: Correlations between plasma resistin and TLC levels in the patients with sepsis (r = 0.73, p = 0.000).



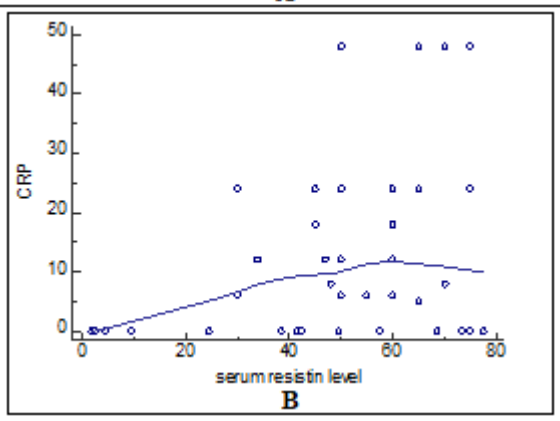


Figure 2: Correlations between plasma resistin and CRP levels in the patients with sepsis. A. in the first day of sepsis (r = 0.58, p = 0.000).B. in the 7th day of sepsis *(r =0.032, p =0.02)*

The cutoff value for resistin that can be used to distinguish the babies with sepsis from healthy ones was found to be 76 ng/mL The area under the curve value for resistin was 1.00 (95% confidence interval = 0.92–1.00; p < 0.001). The sensitivity, specificity, positive, and negative predictive values for this cutoff value were 100%, 93%, 96%, and 100%, respectively (figure 3).

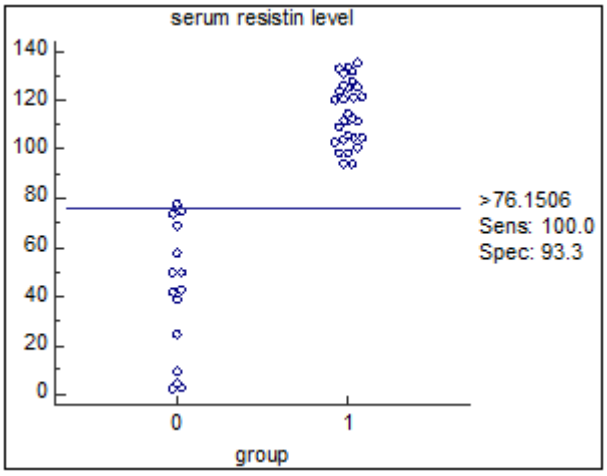


Figure 3: ROC curve for serum resistin level

4. Discussion

In this study, we showed that mean resistin levels of the neonates with sepsis were significantly higher than those are

without sepsis, and there were significant direct correlations between resistin and both CRP and TLC levels in neonates with sepsis. It has been thought that activation of the inflammatory surge triggered by cytokines may play a role in the pathogenesis of sepsis.[9,10]. The first step of the inflammatory response is largely characterized by the influx of neutrophils.[11] and the release of IL6 [12] IL-6 is a well-known biomarker of inflammation that alters the expression of other inflammatory proteins.[13]. Besides its direct proinflammatory effects, IL-6 also increases the CRP production by the liver and resistin messenger RNA expression in human peripheral blood mononuclear cells.[14]. As mentioned before, resistin, originally described as an adipokine, has emerged as a potent proinflammatory protein, and its role in both acute and chronic inflammation has been described.[15, 16]. In inflammatory bowel disease, it was shown that circulating resistin levels were elevated and correlated with WBC, CRP levels and disease activity [17]. Increased circulating resistin levels were also observed in patients with chronic pancreatitis, which might suggest its impact on the development of pancreatic fibrosis. [18] There are limited data on resistin levels in neonates with sepsis. Recently, Cekmez et al[19] studied resistin as a biomarker of neonatal sepsis and they showed that resistin could be used in the diagnosis of neonatal sepsis with a similar efficacy as other markers such as CRP, IL-6, and PCT. The diagnosis of neonatal sepsis is hard due to vague clinical symptoms and signs. Therefore, reliable biomarkers of sepsis would be helpful in an accurate diagnosis, resulting in a decrease in the unnecessary use of antibiotics. In this study, we investigated the use of resistin in the diagnosis of neonatal sepsis and compared it with CRP as a known marker of sepsis. The cutoff value for resistin that can be used to discriminate the babies with sepsis from healthy babies was found to be 75 ng/mL The sensitivity, specificity, positive, and negative predictive values for this cutoff value were found to be 100%, 493%, 76%, and 100%, respectively. The area under the curve was 1.00 for resistin.

In conclusion, plasma-resistin levels were significantly increased in neonates with sepsis. Increased levels of resistin and correlations found with the CRP and TLC levels suggest that resistin may be used as an indicator of neonatal sepsis

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