



Diagnostic Value of Serum Leptin Level in Critically Ill Septic Child

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Authors' contributions

This work was carried out in collaboration among all authors. Author AAAEY designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors AIH, AYA and AAAE managed the literature searches and revise the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Diagnosis of sepsis is important to reduce morbidity and mortality. Leptin is an important immunoregulatory hormone that enhances a number of immune responses in sepsis.

Objective: to assess serum leptin in diagnosing sepsis in critically ill pediatric patients.

Subjects and Methods: This study was carried out on 50 children divided into a case group included 40 critically ill patients initially sepsis free and fulfilling 2 of 4 criteria of SIRS admitted to the Pediatric Intensive Care Unit, children hospital, Tanta university and a control group included 10 apparently healthy children. According to the presence or absence of infection, our patients were classified into SIRS group and sepsis group. For all studied patients; serum leptin, CRP and others indicators of sepsis were measured at admission and 72h later, while were measured one time only for control group.

Results: patients who developed sepsis had significantly higher serum leptin levels than those of

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the control group and SIRS (33.9 ± 20.8 vs. 1.9 ± 0.4 , 21.5 ± 10.1 respectively, $p < 0.05$).

Conclusion: Serum leptin may have a role in early diagnosis of sepsis.

Keywords: Diagnostic value; serum leptin; critically ill; septic child.

1. INTRODUCTION

Sepsis is a clinical syndrome resulting from a systemic inflammatory response (SIRS) evoked by severe infection. Physiological changes during SIRS (such as leukocytosis, changes in body temperature and the development of tachycardia) are consequences of pathological immune-dysregulation leading to inflammation, microcirculatory disturbance, abnormal vasodilation or vasoconstriction, increased capillary permeability, and abnormal white blood cell accumulation [1]. However, these classic indicators of systemic inflammation are neither sensitive nor specific for sepsis. They have only moderate sensitivity and specificity and are not early markers due to the time taken to produce a reaction [2].

Leptin is a 16-kDa peptide hormone produced mainly by adipocytes, although other tissues and organs, such as mammary gland, ovary, skeletal muscle, stomach, pituitary gland and lymphoid tissue may produce lower amounts, possibly for local action [3]. Leptin has a dual role as a hormone and a cytokine. As hormone, it influences multiple endocrine functions and bone metabolism, in addition to the key function of modulating energy homeostasis through mechanisms that include thermoregulation. As a cytokine, leptin promotes inflammatory responses [4].

Leptin is involved in the inflammatory process, and may modulate key processes during sepsis development such as cytokine production, immune cell proliferation and endothelial function through interaction with other cytokines and its receptors [5].

The aim of the present study was to assess serum leptin in diagnosing sepsis in critically ill pediatric patients.

2. SUBJECTS AND METHODS

The present study was conducted from February 2019 to February 2020 on 50 children. They were divided into a case group included 40 critically ill patients aged between 1 and 13 years (mean 4.2 ± 3.7), initially sepsis free and fulfilling

2 of 4 criteria of SIRS (SIRS1) from Pediatric Intensive Care Unit, Children Hospital, Tanta University and a control group included 10 apparently healthy children recruited from relatives of the patients in PICU. In enrollment of the study, our patients were classified in two groups according to presence of infection into SIRS group (SIRS2, $n=25$) and sepsis group ($n=15$). For all studied patients; serum leptin, CRP and other indicators of sepsis as body temperature, HR, WBCs, and platelets were measured at admission and 72h later, while were measured one time only for control group. Patients with sepsis, who had received corticosteroids before admission, who had immunosuppressive illness, who had chronic organ failure, who had received massive blood transfusion, or whose anticipated duration of stay was less than 24 hours were excluded from the study.

2.1 Statistical Analysis

Data were analyzed using the IBM® SPSS statistical software, version 21. The level of significance was adopted at $p < 0.05$.

3. RESULTS

There are multiple clinical and laboratory signs that could indicate presence of infections and sepsis such as body temperature changes, leukocytosis and tachycardia. In the present study, clinical indicators other than leptin, such as body temperature and heart rate were evaluated. Higher temperature was in sepsis cases (mean 38.9 ± 0.2) than SIRS1, SIRS2 cases, and control (Mean: 36.8 ± 0.7 , 37.3 ± 0.7 , 36.7 ± 0.25 respectively). Also, heart rate was higher in sepsis cases (mean 128.3 ± 13.8) than SIRS1, SIRS2 cases, and control (Mean: 112.2 ± 15.5 , 114.5 ± 15.5 , 98.0 ± 12.2 respectively). In relation to the laboratory indicators for the presence of sepsis CRP and WBCs level were tested. There was a significant increase in CRP level in sepsis cases (mean 70.4 ± 4.6) than SIRS1, SIRS2 cases, and control (Mean: 10.8 ± 1.2 , 15 ± 2.1 , 4 ± 1.62 respectively) which showed a statistically significant difference (Table 1). There was a statistically-significant difference in relation to WBCs level between sepsis cases

and controls with higher level in sepsis cases (mean 14922 ± 12600) than that in control group (mean 6070 ± 1295).

Regarding serum leptin level, the current study revealed a statistically significant difference in its level in sepsis cases compared to SIRS1, SIRS2 cases, and control. The highest level was in sepsis cases (mean 33.9 ± 20.8), then SIRS1 and SIRS2 cases (Mean: 20.3 ± 7.1, 21.5± 10.1, respectively) while the control group recorded the lowest values of serum leptin (mean 1.9 ± 0.4) (Table 2).

The correlation between serum leptin levels and other indicators of sepsis were evaluated among the studied patients, the data revealed the levels of serum leptin in sepsis, were positively correlated with CRP, body temperature, heart rate, and WBCS. While were negatively correlated with platelets.

It was found that serum leptin was reliable in the detection of SIRS (P 0.02), the cut off value was > 3.4 ng/ml with 100% sensitivity &

92%specificity, while CRP was also reliable in detection of SIRS (p 0.18) but with a lower sensitivity (77%) and specificity (70%) with cut off value was > 8.2 mg/dl (Table 3, Fig. 1)

It was found that the serum leptin sensitivity in diagnosis of sepsis at the cutoff point > 5.9 ng/ml was 98% & specificity was 97%, while CRP sensitivity in diagnosis of sepsis at the cutoff point >10.5 mg/dl was 85% & specificity was 80% (Table 4, Fig. 2).

4. DISCUSSION

Sepsis is a one of the major causes of mortality and morbidity among children. Early identification of sepsis and prompt initiation of its therapy is the most important measure in reducing mortality from sepsis. Early identification of sepsis is difficult in children for many reasons, the clinical signs in children are very variable at the start of the infection; microbiological culture results are expected only after 48-72 hours; and false negative results are common [6].

Table 1. Level of CRP at admission and three days after among the studied groups

CRP	Cases (n = 40)	Control (n = 10)	t test (p value)
At admission (SIRS)	SIRS ₁ (n=40)		
Min.-Max.	4-25		
Mean ± SD	10.8 ± 1.2		
Median	5.5		
3 days after admission	SIRS ₂ (n=25)	Sepsis(n=15)	7.5 (0.001)*
Min.-Max.	5- 30	6-176	P1,p2, P3
Mean ± SD	15 ± 2.1	70.4 ± 4.6	<0.05*
Median	7	53	
t test (P value)	3.98(0.84)	-9.1 (0.01*)	

P1: comparing between SIRS₂ and Sepsis; P2: comparing between SIRS₂ and Control; P3: comparing between Sepsis and Control

Table 2. Serum leptin level at admission and three days after among the studied groups

Serum leptin	Cases (n = 40)	Control (n = 10)	t test (p value)
At admission (SIRS)	SIRS ₁ (n=40)		
Min.-Max.	3.5 – 55		
Mean ± SD	20.3 ± 7.1		
Median	13		
3 days after admission	SIRS ₂ (n=25)	Sepsis(n=15)	-2.2 (0.01)*
Min.-Max.	3.8-65	1.3-99.6	P 1 ,
Mean ± SD	21.5± 10.1	33.9 ± 20.8	P2, P3
Median	16	28	<0.05*
t test (P value)	1.94(0.25)	2.65 (0.01)*	

P1: comparing between SIRS₂ and Sepsis; P2: comparing between SIRS₂ and Control; P3: comparing between Sepsis and Control

Table 3. Sensitivity and specificity of CRP and serum leptin among controls and cases at admission (SIRS1)

	Area under the curve	P	Cut off point	Sensitivity	Specificity
Serum leptin	0.78	0.02*	> 3.4	100%	92%
CRP	0.59	0.18	> 8.2	77%	70%

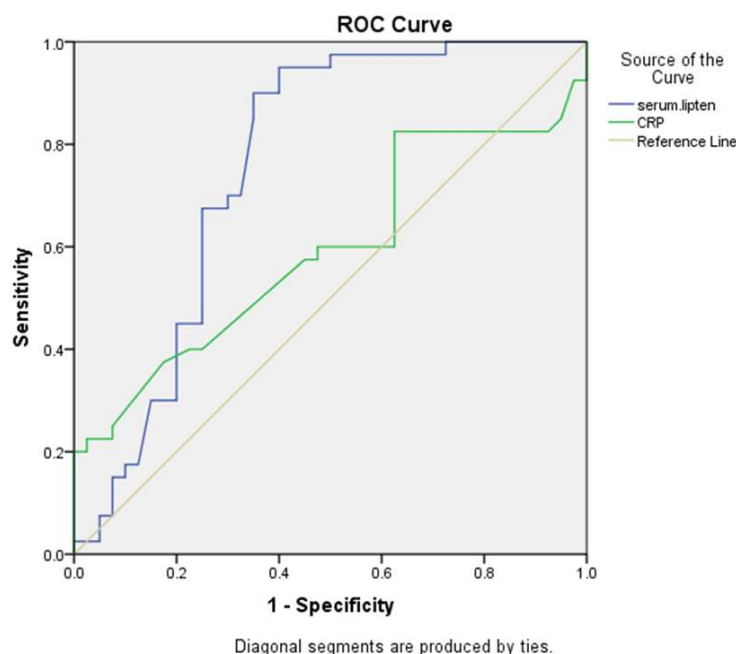


Fig. 1. ROC curve for serum leptin and CRP in diagnosis of SIRS

In the current study, we found that Serum leptin concentrations were higher in septic patients than controls. This is in line with multiple previous researches as Saker M et al. [7] whose study showed highly significant increase in serum leptin between septic and controlled neonates (p 0.001) and Karampela R et al. [8] who found that free leptin index (FLI) was significantly higher in patients compared to controls while it significantly decreased one week after in all patients in the prospective case-control study in which, FLI was measured at sepsis onset and one week after.

Similar results have been found also El-Mashad G et al. [9] and Orbak et al. [10]. They found that serum leptin levels in newborns with septicemia were significantly higher than those of the control group in in both studies. On the other hand, there are multiple previous studies documented different leptin levels in septic patient in relation

to control as Koc et al. [10] who demonstrated that there was no significant difference in serum leptin level between septic patient and controls. This difference may be due to exposure of controls to some conditions that increase serum leptin as maternal corticosteroids usage during pregnancy, in addition to their breast feeding in contrast with parental nutrition in septic neonates. Also, Quiro's A et al. [11] in a study conducted on 55 children admitted to the pediatric intensive care unit because of severe sepsis, found leptin not increased in children with sepsis and the control group had leptin level similar to patients. Explanation of this differences may be that sepsis did not start acutely and therefore leptin was not measured at the onset of the disease. moreover, the patients in his study did not received oral feeding during the time of the study, only intravenous fluids were given therefore they were in a state of clear under nutrition. So, serum leptin was not increased.

Table 4. Sensitivity and specificity of CRP and serum leptin among cases 3 days after admission (sepsis) and controls

	Area under the curve	P	Cut off point	Sensitivity	Specificity
Serum leptin	0.88	0.001*	> 5.9	98%	97%
CRP	0.62	0.06	> 10.5	85%	80%

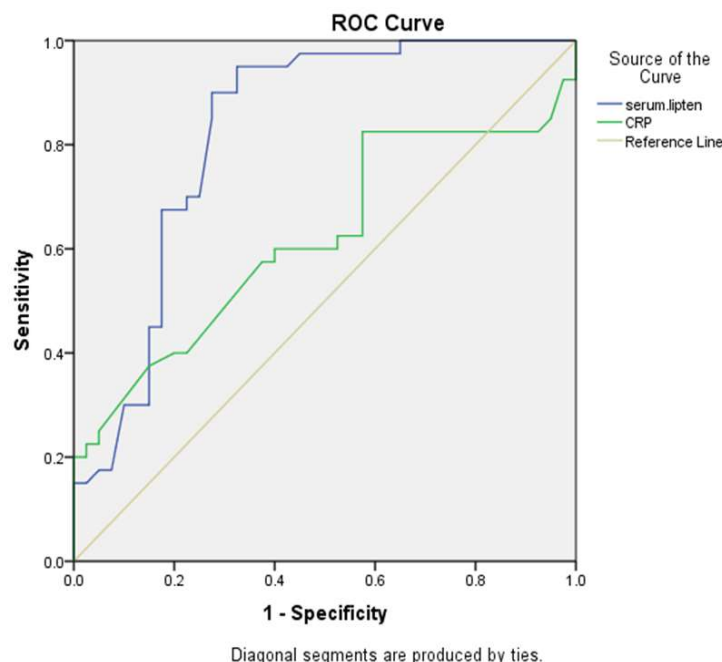


Fig. 2. ROC Curve for serum leptin & CRP In diagnosis of sepsis

In the present study, at the third day of admission the serum Leptin level was significantly higher in the sepsis group compared to the SIRS group and controls. This comes in agreement with the result of Farag N et al. [12] who found that on Day 2 the serum Leptin level was significantly higher in the sepsis group compared to the SIRS group with no significant difference on admission and on day4. Also, Yousef et al. [13] found significant elevation in serum leptin on the 2nd day of admission among SIRS& Sepsis groups with higher level in sepsis group than SIRS and non-SIRS.

Multiple previous studies showed higher level of serum leptin in sepsis group than non-sepsis group as Chen et al. [2] in a study evaluate diagnostic value of serum leptin in critically ill septic patients admitted to ICU and El-Mashad G et al. [9] who found leptin levels were significantly higher in patients before antimicrobial therapy than after antimicrobial therapy and higher in patients with a positive blood culture compared

with those with a negative blood culture. Similarly, Malek et al. [14] found significant increase in Leptin among culture positive cases compared with negative cases in a study conducted on 34 neonates. And, Saleh et al. [15] found a highly significant increase in serum leptin levels on comparing the studied cases before and after treatment. Also, a study of Militsi H et al. [16] that found Leptin levels increased in all patients independently of their BMI, at diagnosis of the infection and returned to normal levels after treatment in study conducted on children with bacterial infections mainly respiratory and urinary tract.

This reported rise in serum Leptin concentration following acute infection suggests that it may actively participate in the immune response and host defense. Leptin and its receptors have structural similarities with cytokine family that includes IL-6 and IL-12, so it should not be surprising that it acts as a pro-inflammatory cytokine [12].

In contrast, Carlson et al. [17] showed that sepsis was not associated with significant change in serum Leptin concentration. The population of this study was however not comparable with ours as patients were enrolled in the study after about 14 days of sepsis diagnosis. This delay in time of enrollment relative to sepsis onset could explain these differences.

Also, Langouche et al. [18] found low serum Leptin levels in critically ill patients on admission to the ICU, with lowest values in patients with sepsis in a study planned to evaluate the effect of conventional and intense insulin therapy on serum Leptin. He explained acute lowering of leptin with stress by reduced synthesis or increased removal, or both, either by extravasation or by increased metabolic clearance and also, explained the lower values in patients with sepsis, as this condition is characterized by capillary leakage, which could have removed the leptin to the interstitial compartment or a consequence of the inactivity and malnourished status of the medical intensive care patients on admission to the ICU.

Our study found that serum leptin was reliable in the detection of SIRS with 100% sensitivity & 92% specificity, this is compatible with that found by Yousef et al. [13] who stated that the serum leptin had a sensitivity of 100% and specificity of 100% in distinguishing non-SIRS patients from SIRS and septic patients.

In the present study, serum leptin at third day of admission was found having 98% sensitivity & 97% specificity in diagnosis of sepsis, this comes with agreement with Farag N et al. [12] who found a serum Leptin level on second day of admission had a sensitivity of 93% and a specificity of 100% to diagnose sepsis in patients initially admitted with SIRS.

Thus, leptin may be utilized as a potential diagnostic marker of sepsis. Concentrations of CRP have been monitored in septic patients, but these concentrations fail to allow immediate diagnosis and prognosis due to the time taken for the body to produce a reaction and the duration of the increased serum concentration [19,20]. However, leptin is involved in the network of inflammatory mediators and during SIRS its plasma concentration is increased by the action of these inflammatory mediators [21].

A useful sepsis marker is required to not only facilitate the identification of sepsis, but may also

be used to guide therapy. The possible role of leptin in the prognosis of sepsis requires further study.

5. CONCLUSION

This study revealed that serum leptin level significantly increased early in sepsis cases and it may have a role in early diagnosis of sepsis at cut off point > 5.9 ng/ml with a sensitivity of 98% and a specificity of 97% which was more than the sensitivity and specificity of CRP (85%, 80% respectively) suggesting that leptin is not only an adipostatic hormone but also a sepsis-related hormone and, it seems to be more reliable marker of pediatric early sepsis diagnosis.

6. RECOMMENDATIONS

Based on the results of this study, we recommend measurement of serum leptin level early on suspicion of sepsis which may aid in confirming the sepsis diagnosis and addition of serum leptin in sepsis diagnostic panel. However, prospective multi-center studies should be done to confirm the association between early high serum leptin level and pediatric sepsis.

7. STUDY LIMITATIONS

Limitations of this study included the limited number of samples of the biomarkers (only two samples) that may have missed higher levels. Some other studies screened Leptin at admission, 2nd day and 4th day; however we aimed at evaluating the patients at early onset of sepsis. Another limitation was the limited number of patients included in the study; further studies are needed to confirm our results. Finally, Antibiotics had to be given early in some patients with SIRS with no obvious infection, for the possibility of hidden infection, which may have had an impact on the markers. In other patients in which infection appeared later could have had an occult infection that aggravated rather than a superadded infection and may not have been appropriately assigned.

CONSENT AND ETHICAL APPROVAL

The present study was conducted on 50 children after the approval of the ethical committee, and consent from all studied groups.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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