# Leptin and C-reactive Protein Levels Correlate during Minor Infection in Children

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## Abstract

**Background:** Leptin, a pleiotropic hormone, has been suggested to be part of an acute-phase response during an inflammatory stimulus. Its correlation with other acute-phase reactants during minor infection in children has not been investigated.

**Objectives:** To study the correlation between levels of serum leptin and those of C-reactive protein, a well-documented acute-phase reactant, in a series of pediatric patients with acute minor infections.

**Methods:** Leptin and CRP levels were measured in 62 blood samples of pediatric patients presenting with mild febrile illness who were admitted to Dana Children's Hospital in Israel. All children were finally diagnosed as having minor infection based on the negative blood/urine cultures and favorable outcome.

**Results:** Serum leptin level was positively correlated with CRP ($r^2$ = 0.5), total white blood cells ($r^2$ = 0.33) and absolute neutrophil count ($r^2$ = 0.31). The regression coefficient was the highest between leptin and CRP.

**Conclusions:** Circulating leptin concentrations are positively correlated with CRP levels during acute minor infection in children visiting the emergency room for febrile illnesses. Our observation suggests that leptin is indeed a part of acute-phase proteins. The wide scattering showed that it is not a better marker in minor infections than CRP, but it may contribute to weight loss and anorexia seen in a minority of patients during mild infections.

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Bacterial infections, trauma, surgery, burns, tissue infarction and advanced cancer may lead to substantial changes in the plasma concentrations of acute-phase proteins that may result in behavioral, physiologic, biochemical and nutritional changes. Either increasing or decreasing concentrations of new acute-phase proteins during those conditions have been documented [1]. One of these proteins is leptin, a pleiotropic hormone that usually controls food intake and body weight via specific receptors in the hypothalamus [2]. Evaluation of leptin levels in response to experimental models of inflammation in rats revealed elevated plasma concentrations [3]. Leptin was also shown to be involved in the early (< 24 hour) acute-phase response after moderately severe surgical trauma [4], and to play a role in acute sepsis [5]. Its significant correlation with other acute-phase proteins indicates that leptin could be a participant in acute-phase protein synthesis regulation during a systemic inflammatory response [6]. To the best of our knowledge its role during mild inflammatory response has never been investigated, nor its correlation with other known acute-phase reaction during minor infection.

The production of acute-phase proteins may help to differentiate severe bacterial infection and sepsis from viral infection, and to predict outcome [7]. Accordingly, C-reactive protein, a well-described and useful acute-phase reactant that was found to increase to as much as 1000-fold during inflammation, was correlated with mortality and organ failure in critically ill patients [8]. Similarly, the clinical outcome of invasive pneumococcal infection in children was associated with CRP levels [9]. Furthermore, quantitative CRP concentration is a valuable adjunctive laboratory test in the evaluation of febrile young children who are at risk for occult bacteremia [10]. CRP is also known to increase in some viral infections associated with an inflammatory response. For example, high CRP values were reported in patients with adenoviral respiratory infection [11], and values of > 40 mg/L were measured in 12% of children with influenza virus infection without bacterial complication [12].

A comparison between the levels of CRP and other acute-phase proteins could lead to a better understanding of the kinetics of the acute-phase response, and possibly shed light on the pathways involved in host defense. Indeed, a recent comparative study demonstrated that procalcitonin, a new and useful acute-phase reactant, was a better marker of sepsis than CRP [13]. The purpose of the current study was to describe the correlation between the known acute-phase reactant CRP, to leptin, in a group of children with fever (> 38°C) who were diagnosed as having minor infections with no evidence of serious bacterial infection.

## Patients and Methods

Blood samples from 62 children (aged 5–15 years) who presented with respiratory symptoms to Dana Children's Hospital, of the Tel Aviv Sourasky Medical Center, during the 1999 winter season were prospectively collected. Children were suspected of having minor infection based on the absence of clinical signs suggestive of serious bacterial infection, negative blood/urine cultures and normal chest X-ray. Although no viral confirmatory assay was used, we were able to follow the patients to confirm that their

CRP = C-reactive protein

clinical status had not changed and that they did not require treatment for a bacterial infection.

Both leptin and CRP levels were measured from the same blood sample at presentation. Age, weight, and prior days of illness were recorded. Leptin was detected with the Immunoradiometric Assay kit (Diagnostic Systems Laboratories, Inc. Webster, TX, USA), which has a range of 0.25–120 ng/ml. The assay is based on the reversible and non-covalent binding of protein by a specific antibody labeled with a radioactive nuclide as a tracer. CRP was detected with an immunochemistry method by rate nephelometry (Beckman Instruments, Inc., Brea, CA), with the normal level being less than 5 mg/dl.

#### Statistical analysis

Statistical analyses were performed using the two-sample *t*-test. The Fisher exact probability test, Student's *t*-test or linear regression models were applied to calculate significance. Data are expressed in mean ± SD. *P* values ≤ 0.05 were considered statistically significant.

## Results

Sixty-two patients (mean age 4.9 ± 4.7 years) were enrolled in this study. The mean leptin value was 3.8 ± 4.1 ng/ml and the mean CRP value 5.9 ± 8.6 mg/dl [Table 1]. Comparison of leptin and CRP values revealed a high positive correlation ($r^2$ = 0.5, P < 0.01) [Figure 1]. A positive correlation was also observed when the leptin and CRP values were compared to those of total white blood counts ($r^2$ = 0.33 and $r^2$ = 0.39, respectively, $P < 0.05$) and absolute neutrophil counts ($r^2$ = 0.31 and $r^2$ = 0.45, respectively, $P < 0.01$). No correlation was noted between leptin values and the patient's weight.

As seen in Figure 2, a high positive correlation was noted when leptin levels were compared to groups with normal CRP (< 5 mg/dl, 39 patients, mean CRP 0.9 ± 1.2 mg/dl) and above normal CRP (> 5 mg/dl, 23 patients, mean CRP 14.5 ± 9.2 mg/dl). The mean leptin values in these groups ranged from 6.1 ± 5.7 ng/ml in the high CRP patients to 2.5 ± 1.7 ng/ml in the lower CRP group [Figure 2]. The two subgroups were similar in terms of days of illness before hospitalization, days of hospitalization, and hemoglobin levels. As expected, the children with high CRP values had higher white blood cell counts compared to those with lower CRP values (15.9 ± 9.4 ×$10^9$ cells/L and 11.8 ± 6.1 × $10^9$ cells/L × $10^9$ cells/L, respectively).

**Table 1.** Clinical and laboratory parameters of the 62 study children after subdividing them according to CRP protein blood levels

| | Low CRP (39 children, < 5 mg/dl) | High CRP (23 children, ≥ 5 mg/dl) | Whole cohort |
|---|---|---|---|
| Age (yrs) | 3.9 ± 4.1 | 6.6 ± 5.2 | 4.9 ± 4.7 |
| Weight (kg) | 17.7 ± 12.2 | 22.9 ± 14.2 | 19.6 ± 13.1 |
| Days of illness before admission | 1.1 ± 0.7 | 1.2 ± 0.8 | 1.1 ± 0.7 |
| Days of hospitalization | 2.1 ± 1.1 | 3 ± 2.1 | 2.4 ± 1.6 |
| CRP (mg/L) | 0.9 ± 1.2 | 14.5 ± 9.2 | 5.9 ± 8.6 |
| Leptin (ng/L) | 2.5 ± 1.7 | 6.1 ± 5.7 | 3.8 ± 4.1 |
| White blood cells (× 109 cells/L) | 11.8 ± 6.1 | 15.9 ± 9 | 13.3 ± 7.7 |
| Neutrophil count (%) | 54.8 ± 16.3 | 67.1 ± 20.3 | 59.4 ± 18.8 |
| Hemoglobin (mg/dl) | 11.6 ± 1.2 | 11.5 ± 1.3 | 11.6 ± 1.3 |
| Platelets (× 109 cells/L) | 380.9 ± 121.8 | 349.9 ± 127.6 | 369.4 ± 123.9 |

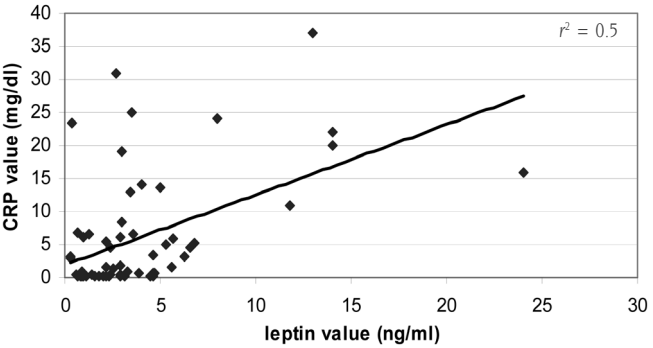


**Figure 1.** Positive correlation between blood levels of leptin and CRP. ($r^2$ = 0.5, $P < 0.01$)

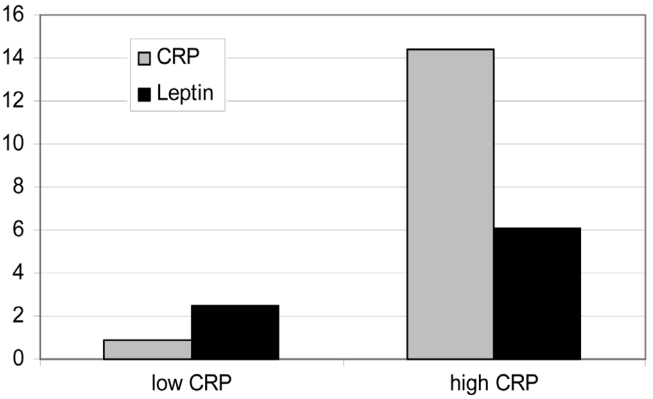


**Figure 2.** Correlation between CRP and leptin values in children with low CRP (less than the normal range) and high CRP (higher than the normal range).

## Discussion

The results of the present study provided a unique investigation of leptin as an acute-phase reactant. We selected a group of children with minor infection since the role of leptin during minor infection has not been studied to date. Our results showed the correlation between CRP, which has been studied extensively, and leptin values during minor infection.

Acute-phase reactants have been used in acute-care pediatrics in order to help predict patients who are more likely to have serious illnesses. Leptin (*leptos* in Greek, meaning thin), a product of the anti-obesity gene, is a 16 kDa protein that is considered a major player in the regulation of body fat and has a lipo-atrophic effect [14,15]. It also functions in immunity, inflammation and hematopoiesis, and exerts proliferative and anti-apoptotic activities in a variety of cell types. Its production is acutely increased during infection and inflammation [16,17] and it seems to be influenced by pro-inflammatory cytokines [18] and cortisol [19]. Additionally, leptin is a factor of the inflammatory mediator network, probably essential for an adequate course of the inflammatory defense reaction. Both leptin and its receptor share structural and functional similarities with the interleukin-6 family of cytokines [20,21]. Cachexia (anorexia, weight loss,

and hypermetabolism) could be partly mediated by inappropriately high plasma levels of leptin in patients with cancer and an ongoing inflammatory response [18]. Papathanassoglou et al. [22] studied 35 critically ill patients with systemic inflammatory response-multiple organ dysfunction and revealed that cytokines, such as tumor necrosis factor-alpha and interleukin-6, and cortisol up-regulate leptin levels, a process that may contribute to the development of the hypercatabolism, wasting and immune dysfunction. Arnalich and co-authors [23] reported that patients with sepsis or septic shock who exhibit significant inflammation process, changes in plasma concentrations of acute-phase proteins as well as nutritional changes had greater leptin concentrations than the control group. A minority of children with non-specific viral infection may also be prone to exhibit an inflammatory process.

In the present study, we compared leptin levels with CRP levels in children who had a minor infection. Our results showed a correlation between CRP and leptin levels: the children with an increased CRP level also had a high leptin level. As expected, a high level of both proteins was correlated with increased white blood cell and absolute neutrophil counts. Our results emphasize the sensitivity of leptin as an acute-phase reactant during minor infection. Like Maruna et al. [6], we failed to show any correlation between serum leptin levels and body mass index in ill patients. One can argue that the overproduction of leptin during an infection might interfere with the balance between leptin and a child's weight, but the lack of any correlation between leptin and weight – even among children in the low CRP group – negates this argument.

This study has a number of limitations, mainly the relatively small number of children studied and the inability to confirm viral infections. In addition, unmeasured confounders may have influenced our presumption that a change in leptin level explained the anorexia observed in the minority of children with mild infections.

Mild inflammation, weight loss and anorexia, probably secondary to cytokines and glucocorticoids release or endotoxin exposure, may apparently be expected in the minority of patients during a mild infection, as expressed by high levels of both CRP and leptin. The possible interactions between the endocrine, immune and adipose systems through leptin, that occur mainly during severe infection or inflammation, may also occur during mild infection.

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