

Procalcitonin Correlates with C-Reactive Protein as an Acute-Phase Reactant in Pediatric Patients

Raz Somech MD¹, Vera Zakuth MSc^{1,2}, Ayala Assia MD¹, Uri Jurgenson MD¹ and Zvi Spirer MD¹

¹Department of Pediatrics and ²Pediatric Immunology Laboratory, Dana Children's Hospital, Tel Aviv Sourasky Medical Center, and Sackler Faculty of Medicine, Tel Aviv University, Israel

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Abstract

Background: Previous reports on the behavior of procalcitonin blood levels in diverse clinical conditions suggest that it is part of the activation of cellular immunity and is another acute-phase reactant.

Objective: To compare procalcitonin with C-reactive protein, a well-known acute-phase reactant, in a series of acutely febrile pediatric patients and to review recent literature on procalcitonin.

Methods: Procalcitonin and CRP levels were evaluated in 38 blood samples of pediatric patients who were admitted to the Dana Children's Hospital for evaluation of unexplained fever or for sepsis work-up.

Results: The parallelism between procalcitonin and CRP was found to be highly significant ($P < 0.01$).

Conclusion: The rise of procalcitonin blood levels in febrile pediatric patients suggests that it is part of the acute-phase reaction, parallel with the CRP reaction.

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Procalcitonin, the precursor molecule of calcitonin, has been found to increase in serum of patients with diverse clinical condition such as sepsis, severe invasive bacterial infections and systemic inflammatory response syndrome. Procalcitonin blood levels are low or undetectable in the serum of healthy subjects [1]. Inflammatory processes other than infection appear to cause secretion of procalcitonin [2]. The types of cells producing procalcitonin during the inflammatory processes are not known. The pattern of procalcitonin production seems to be similar to that of some markers of the activation of cellular immunity, suggesting that it is another acute-phase reactant during infection [1]. Moreover, the increase in procalcitonin associated with septicemia may be mediated through the effect of the endotoxin [3].

In order to assess the reliability of procalcitonin as an early acute-phase reactant in acutely febrile pediatric patients, we compared it to C-reactive protein, a proven and useful acute-phase reactant in pediatric patients.

Patients and Methods

Blood samples from 38 patients (ages 4 month to 11 years) who were admitted to the Dana Children's Hospital of the Tel Aviv Sourasky Medical Center for evaluation of unexplained fever or for sepsis work-up were evaluated. Both the procalcitonin and CRP levels were measured from the same blood sample of each patient at admission. We could not separate those patients into groups according to different etiologies of their illness because we suspected they had infections — based mainly on clinical signs, blood count, urine examination, or chest X-ray — although there was no clear evidence of bacterial infection.

Procalcitonin was detected with a radioimmunoassay kit (Peninsula Laboratories, USA) with a range of 1–128 pg/ml. The assay is based upon the competition of labeled ¹²⁵I-peptide and unlabeled peptide binding to the limited quantity of antibodies specific for the standard peptide in each reaction mixture. CRP was detected with an immunochemistry method by rate nephelometry (Beckman Instruments, USA), the normal level being less than 0.6 mg/dl.

Statistical analyses were performed using the two-sample *t* and Fisher exact tests. Data are expressed as mean±SD. $P < 0.05$ was considered statistically significant.

Results

Seventeen patients with CRP values above the normal range (mean 13.37 ± 9.7 mg/dl) also had high levels of procalcitonin (mean 99.72 ± 52.6 pg/dl) ($P < 0.01$). Fourteen patients with the highest level of procalcitonin (128 pg/ml) also had high CRP values (mean 16.27 ± 9.2 mg/dl) ($P < 0.01$). Patients with CRP levels below the normal range (mean 0.56 ± 0.45 mg/dl) also had low procalcitonin levels (mean 12.44 ± 8.2 pg/d) ($P < 0.01$). One patient who had a high procalcitonin level in serum (128 pg/ml) showed no correlation with the CRP level (0.1 mg/dl).

The correlation between procalcitonin and CRP detected by the Fisher exact test was highly significant ($P < 0.01$).

CRP = C-reactive protein

Discussion

Procalcitonin is a 116 amino acid peptide that undergoes proteolysis into the mature hormone, calcitonin, which is composed of 32 amino acids. Procalcitonin is known to be elevated in several systemic conditions, while it is low or undetectable in the serum of healthy subjects [1]. The types of cells producing procalcitonin during inflammatory processes are not known. The transformation of procalcitonin into calcitonin occurs in thyroid C cells, but the thyroid is not the sole tissue involved in the secretion. Indeed, one burn victim who had undergone thyroidectomy reportedly had high procalcitonin values but no secretion of mature calcitonin [2]. Assicot et al. [3] demonstrated that the liver or lungs can serve as the site for production of procalcitonin during inflammatory processes [2]. *In vitro* studies using various cells, including endothelial cells, monocytes, macrophages, and polymorphonuclear cells stimulated with endotoxin, failed to reveal procalcitonin secretion [3].

The pattern of procalcitonin production seems to be similar to that of some components of the cytokine cascade, and markers of the activation of cellular immunity suggest that it is an acute-phase reactant [1]. The procalcitonin level in serum was found to be closely related to severe invasive bacterial infection and SIRS. When the infection is loco-regional or confined to a single organ in the absence of systemic response of the inflammatory reaction, the procalcitonin is low or moderately increased. It also remains low in viral infection [4]. It is likely that inflammatory processes other than infection lead to secretion of procalcitonin, but its place in the cytokine cascade that occurs in sepsis and other inflammatory processes is not known [2].

A trial administration of a supraphysiologic amount of procalcitonin exacerbated mortality in experimental sepsis in an animal model, while prophylactic and therapeutic immune blockade of procalcitonin with multiregion-specific goat antiserum reactive to procalcitonin increased survival [5]. Dandona et al. [3] investigated the effect of endotoxin, a product of gram-negative bacteria, on procalcitonin concentration in normal human volunteers. After endotoxin injection, procalcitonin levels increased at 3–4 hours in the blood of the volunteers and then rose rapidly to a plateau at 6 hours, remaining elevated for at least 24 hours. The authors concluded that the increase in procalcitonin associated with septicemia in patients may be mediated through the effect of the endotoxin.

Measurement of plasma procalcitonin might be of value in the differential diagnosis of meningitis of either bacterial or viral origin. In a study by Gendrel et al. [6], 18 children with acute bacterial meningitis had elevated procalcitonin levels and 41 children with viral meningitis had low levels of procalcitonin. No traces of procalcitonin were found in the cerebrospinal fluid, and the plasma levels de-

creased rapidly during antibiotic therapy. Serum procalcitonin levels were increased in children with febrile urinary tract infection when renal parenchymal involvement was present, and enabled the prediction of patients at risk of severe renal lesion [7]. Serum concentration of procalcitonin correlated well with the severity of *Pseudomonas pseudomallei* infection (melioidosis) [1] and *Plasmodium falciparum* malaria infection [8], and seemed to be a specific marker of bacterial sepsis in HIV-infected patients [9]. No increase in other secondary infections including *Pneumocystis carinii*, cerebral toxoplasmosis, viral infections, mycobacterial infections, fungal infections and localized bacterial infection, could be detected in HIV patients [9].

Procalcitonin is a good marker for detecting sepsis in neonates. Increased levels were found in all neonates with bacterial sepsis, while neonates with viral infection, bacterial colonization, or neonatal distress had normal or only slightly increased levels [10]. For detecting early-onset sepsis, procalcitonin levels yielded a sensitivity of 92.6% and specificity of 97.5% [11].

SIRS is initiated by pro-inflammatory cytokines. As one of those cytokines, procalcitonin can serve as a marker to predict outcome [12], identifying patients who may benefit from pro- or anti-inflammatory therapies, and monitoring the immune status of the patients [13]. Patients with septic shock had high concentration of procalcitonin and nitrite/nitrate, while other pro-inflammatory cytokines, including tumor necrosis factor and interleukin-6, resulted from inflammation, not shock [14]. Al-Nawas and Shah [15] investigated whether the rise of procalcitonin in septic patients is related to their immune status. Patients with sepsis and immunodeficiency had high values on days 0 to 2, similar to patients with no immunodeficiency, but showed significantly lower levels in the following 3 days.

Procalcitonin was found to be a sensitive, specific and predictive indicator of infections in heart transplantation [16], and of invasive bacterial infection or partial graft necrosis in 57 kidney graft recipients [17].

An early and transient release of procalcitonin into the circulation was observed after severe trauma, and the amount of circulating procalcitonin seemed proportional to the severity of tissue injury and hypovolemia. It exhibited an early and transient increase in serum levels similar to a more delayed change of CRP levels. Peak levels of both procalcitonin and CRP were related to the injury severity score, the extent of tissue damage, and hypovolemia [18].

In addition, procalcitonin seems to be an early predictive marker of infective complications after elective colorectal or aortal surgery [19]. Patients who undergo intestinal surgery and other major operations more often demonstrate an increase in procalcitonin values, whereas they are normal in the majority of patients after minor and primarily aseptic surgery [20].

SIRS = systemic inflammatory response syndrome

Measurement of procalcitonin is helpful for differentiating infection from active autoimmune diseases. It is an important marker because patients with autoimmune diseases are prone to infection, particularly under conditions of immunosuppression [21]. Interpretation of the values must be supplemented by clinical and laboratory findings, since procalcitonin levels can be elevated in rare cases of highly active Wegener's granulomatosis without infection [22].

Procalcitonin levels did not exceed the normal range as do other cytokines, such as interleukin-10 and -6, in patients with acute pancreatitis following endoscopic retrograde cholangiopancreatography [23], but it was found in high concentrations in infected necrosis and associated systemic complications in patients with acute pancreatitis. [24].

The serum concentration of procalcitonin in burn victims was closely related to infectious complications and acute septic episodes [2]. In contrast, Carsin et al. [25] found that procalcitonin and interleukin-6 levels correlated well with the severity of skin burn injury although no proven infection was found in those patients. Procalcitonin was not associated with smoke inhalation [25].

A Saudi Arabian study, addressing the correlation of serum procalcitonin with the course of classic (non-exertional) heatstroke, revealed that heatstroke was associated with increased concentration of serum procalcitonin, particularly among survivors [26].

We chose to compare procalcitonin with CRP because the latter is a well-known acute-phase protein that is sensitive and a rapidly reacting index in bacteremic infection [27]. We did not check the value of procalcitonin as a marker for severe invasive bacterial infections because cultures were either not available or were sterile in most of the study patients, although we suspected those patients to have infections, based mainly on clinical signs, blood count, urine examination or chest X-ray. We found a good correlation between both proteins, suggesting that procalcitonin is another sensitive acute-phase reactant. Monneret et al. [28] also found a good correlation between procalcitonin and CRP in infected newborn infants. They showed that the procalcitonin levels increased and returned to the normal range more quickly than CRP.

It emerged from the present work that procalcitonin paralleled the CRP reaction, and that the rise in procalcitonin blood levels occurs earlier in acutely febrile pediatric patients. The recent literature on this subject indicates that procalcitonin is a promising marker for the diagnosis of invasive bacterial infection, and enables a differential diagnosis between bacterial and nonbacterial etiologies of acute situations. The serum concentration of procalcitonin correlates well with the severity of other systemic conditions and is also a very useful marker for SIRS.

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Correspondence: Dr. Z. Spirer, Chairman, Dana Children's Hospital, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel. Tel: (972-3) 697 4271; Fax: (972-3) 697 4533; email: spirer@post.tau.ac.il.