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Changes in peroxisome proliferator-activated receptor-gamma activity in children with septic shock

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Abstract *Purpose:* To assess changes in peroxisome proliferator-activated receptor-γ (PPARγ) in peripheral blood mononuclear cells (PBMC) from critically ill children with sepsis. Additionally, to investigate the effects of sepsis on the endogenous activator of PPARγ, 15-deoxy-$\Delta^{12,14}$-PGJ$_2$ (15d-PGJ$_2$), and the downstream targets of PPARγ activity, adiponectin and resistin. *Methods:* Single-center, prospective case–control study in critically ill children with systemic inflammatory response syndrome, sepsis or septic shock. *Results:* PPARγ nuclear protein expression was decreased but PPARγ activity was increased in PBMC from children with septic shock compared with controls. PPARγ activity on day 1 was significantly higher in patients with higher pediatric risk of mortality (PRISM) score compared with controls [mean 0.22 optical density (OD) ± standard error of the mean (SEM) 0.03 versus 0.12 OD ± 0.02; $p < 0.001$]. Patients with resolved sepsis had increased levels of the endogenous PPARγ ligand, 15d-PGJ$_2$, compared with patients with systemic inflammatory response syndrome (SIRS) and septic shock (77.7 ± 21.7 versus 58 ± 16.5 pg/ml; $p = 0.03$). Plasma high-molecular-weight adiponectin (HMWA) and resistin levels were increased in patients with septic shock on day 1 and were significantly higher in patients with higher PRISM scores. Nonsurvivors from sepsis had higher resistin levels on the first day of hospitalization compared with survivors from septic shock [660 ng/ml, interquartile range (IQR) 585–833 ng/ml versus 143 ng/ml, IQR 66–342 ng/ml; $p < 0.05$]. *Conclusions:* Sepsis is associated with altered PPARγ expression and activity in PBMC. Plasma adipokines correlate with risk of mortality scores in sepsis and may be useful biomarkers. Further studies are needed to understand the mechanisms underlying changes in PPARγ in sepsis.

Keywords Sepsis · Resistin · Adiponectin · 15-Deoxy-$\Delta^{12,14}$-PGJ$_2$ · PPARγ · Cytokines

Introduction

Peroxisome proliferator-activated receptor-γ (PPARγ) is a ligand-binding nuclear receptor, and activation of PPARγ controls the inflammatory response [1, 2]. The synthetic insulin-sensitizing drugs, thiazolidinediones (TZDs), and the natural cyclopentenone prostaglandins are specific PPARγ ligands [3, 4]. 15-Deoxy-$\Delta^{12,14}$-PGJ$_2$ (15d-PGJ$_2$) inhibited phorbol myristyl acetate-induced tumor necrosis factor-alpha (TNFα) production in human monocytes [2]. The mechanism of cytokine inhibition in activated monocytes/macrophages occurs, in part, through

repression of several inflammatory response genes, including *activator protein-1 and nuclear factor-κB (NF-κB)* [1]. 15d-PGJ_2 exerts beneficial anti-inflammatory effects, in part, through inhibition of NF-κB activation [5, 6]. The inhibition of the inflammatory response correlates with improved survival in clinically relevant models of septic shock [7–9].

The expression, production, and activity of PPARγ are affected in inflammatory conditions. We have previously demonstrated that in the hypodynamic phase of septic shock PPARγ expression was downregulated on the endothelium of thoracic aortas in rats [7]. Furthermore, sepsis-induced reduction in PPARγ expression was reversed by in vivo treatment with PPARγ ligands. In an experimental model of polymicrobial sepsis, Zhou et al. [10] demonstrate that hepatic PPARγ protein and gene expression is preserved in the early stages of sepsis and decreased in the late stages of sepsis. These findings suggest that there are kinetic differences in PPARγ expression after an inflammatory response.

Human data suggest that nuclear receptors are altered in inflammatory disease states. PPARγ is altered in the inflammatory diseases sarcoidosis, colitis, and multiple sclerosis [11–13]. In children with sepsis, glucocorticoid receptor messenger RNA (mRNA) expression was decreased in neutrophils on the first day of hospitalization but expression normalized as children recovered from their illness [14]. In adults with sepsis, PPARγ mRNA expression is increased in T lymphocytes and neutrophils when compared with control subjects [15, 16].

In the current study, we assessed the protein expression and activity of PPARγ in peripheral blood mononuclear cells from a cohort of critically ill children with sepsis. In addition, we investigated the effects of sepsis on the endogenous activator of PPARγ, 15d-PGJ_2, and the downstream targets of PPARγ activity, high-molecular-weight adiponectin (HMWA) and resistin.

Materials and methods

Patients and study design

The study was reviewed and approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board. Patients admitted to the pediatric intensive care unit (PICU) with systemic inflammatory response syndrome (SIRS), sepsis or septic shock as defined according to the International Pediatric Sepsis Consensus Conference were considered eligible for the study [17]. Patients who recovered from their illness with sepsis and remained hospitalized but did not meet the physiologic parameters of any category of sepsis anymore were categorized as "resolved." Control patients were obtained from children undergoing cardiac catheterization who exhibited no evidence of systemic inflammation. Patients with leukopenia [white blood cell (WBC) count <1,000 cells/mm^3] or ongoing cardiopulmonary resuscitation were excluded from the study. Control patients with evidence of a recent illness were excluded. Seventy-four patients were enrolled in the study; however, it was not possible to perform all experiments with all of the specimens because of the limited amount of blood obtained from each patient.

Blood samples

After obtaining informed consent 5 mL blood was obtained within the first 24 h of admission to the PICU and processed as described below. Subsequent blood samples were obtained from each patient on days 3 and 7. However, not all patients provided a blood sample on day 7 because of death, lack of vascular access, or discharge from the hospital. One 5-ml sample was obtained from each control patient.

Clinical data

Clinical data were collected prospectively throughout the study period. Severity of illness at study entry was calculated using the pediatric risk of mortality (PRISM) II score [18].

Isolation of plasma and peripheral blood mononuclear cells (PBMC)

Fresh blood samples were collected in sodium citrate tubes and transported to the Critical Care Medicine laboratories on ice. Samples were centrifuged at 1,500 rpm for 5 min and plasma was obtained and stored at −80°C. The remaining blood was carefully layered onto a Percoll gradient (Amersham Biosciences, Piscataway, NJ) and samples centrifuged at 1,500 rpm for 30 min. After centrifugation the buffy coat was removed, washed in Hanks bovine serum albumin (BSA), and stored at −80°C until protein extraction.

Isolation of PBMC confirmed by flow cytometry

To confirm our experimental technique of isolating PBMC using a Percoll gradient, cells were analyzed by flow cytometry. Whole blood obtained from healthy volunteers (3.5 ml) was carefully layered onto a Percoll gradient and PBMC were isolated as described above. Phosphate-buffered saline (PBS)-diluted whole blood (100 µl) was blocked with rat serum for 20 min on ice. After centrifugation to obtain a pellet, cells were incubated with saturating amounts of fluorescein

isothiocyanate (FITC)-conjugated anti-CD66b murine monoclonal antibody, allophycocyanin (APC)-conjugated anti-CD14 murine monoclonal antibody or isotype control (BD Biosciences, San Jose, CA). Samples were washed and resuspended in phosphate-buffered saline with 2% bovine serum albumin (BSA). Flow cytometric analysis was performed and confirmed that the Percoll layer included monocytes and lymphocytes and excluded neutrophils (data not shown).

Data analysis

Not all blood samples were tested for all analytes. Values in the figures and text are expressed as mean and standard error of the mean for parametric data and as median and interquartile range for nonparametric data. The number of subjects per group is referred to as n. For comparison of two groups, Student's t tests were used. For nonparametric data the Mann–Whitney rank-sum test (MWRST) was used. When more than two groups were compared for nonparametric data the Kruskal–Wallis analysis of variance with the Dunn post hoc test was used. A two-tailed $p < 0.05$ was considered significant.

Results

Patient characteristics and plasma cytokine levels

There was no difference in age or body mass index (BMI) between the control group (children undergoing cardiac catheterization without signs of systemic inflammation), SIRS/sepsis, or septic shock groups on admission (Table 1). Patients in the septic shock group had significantly higher PRISM score and number of organ failures compared with the SIRS/septic group. Patients with septic shock had higher plasma levels of TNFα, interleukin (IL)-6, and IL-8 compared with the control group.

PPARγ nuclear protein expression is decreased in PBMC from children with septic shock

To determine the effect of sepsis on PPARγ expression, PBMC were collected from patients with various categories of sepsis on day 1, 3 or 7 of their illness and protein expression evaluated by Western blot analysis. Patients were grouped according to their sepsis category. Therefore multiple samples were obtained from the same patient if they fulfilled the requirement for the diagnostic category on day 1, 3 or 7 of their illness. A representative Western blot demonstrates a decrease in PPARγ protein expression in SIRS and septic shock patients compared with controls (Fig. 1a). Quantitative analysis demonstrates that PPARγ levels were significantly decreased in patients with septic shock when compared with control patients [median 66.5 absolute intensity, interquartile range (IQR) 60–78 absolute intensity versus median 113.5 absolute intensity, IQR 108–133; $p < 0.05$] (Fig. 1b). Patients with resolved sepsis who recovered from their illness with sepsis and remained hospitalized but did not meet the physiologic parameters of any category of sepsis anymore we categorized as "resolved." Although not statistically significant, patients with resolved sepsis had an increase in PPARγ protein levels compared with septic shock. These levels were similar to levels demonstrated in control patients.

PPARγ activity is increased in PBMC from children with septic shock

Nuclear PPARγ activity in PBMC from children with septic shock was determined by use of a PPARγ

Table 1 Clinical characteristics and plasma cytokine levels of the study cohort

Day 1 median (IQR)	Control ($n = 27$)	SIRS/sepsis ($n = 22$)	Septic shock ($n = 25$)
Age (years)	6 (3.4–9.5)	7.3 (4–10.7)	6.1 (2.1–14.3)
BMI (kg/m^2)	17.4 (16.4–20.5)	17.7 (16.1–19.6)	17.3 (16–21.4)
PRISM	NA	6.5 (3–11)	11 (7.8–18.3)[b]
Number of organ failures	NA	0 (0–0.5)	2 (1–2)[c]
PICU LOS	NA	4 (2–11)	6 (3–12)
TNFα (pg/ml)	3.7 (2.6–6) ($n = 24$)	6.3 (3.3–22.1)[a] ($n = 21$)	17 (7.8–28)[ab] ($n = 24$)
IL-6 (pg/ml)	3.8 (2–11.6) ($n = 24$)	38.1 (19.4–96.8)[a] ($n = 21$)	571 (86.6–3100)[ab] ($n = 24$)
IL-8 (pg/ml)	1.2 (1–2.4) ($n = 24$)	10.6 (6.3–33.9)[a] ($n = 21$)	30.7 (11.4–88.7)[ab] ($n = 24$)

[a] $p < 0.05$ versus control by Kruskal–Wallis ANOVA with Dunn post hoc test
[b] $p < 0.05$ versus SIRS/sepsis by t test
[c] $p = 0.001$ versus SIRS/sepsis by MWRST

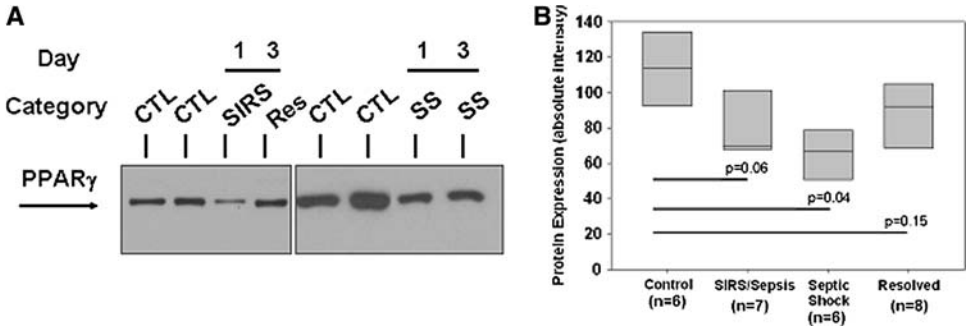

Fig. 1 Nuclear PPARγ protein expression is decreased in PBMC in septic shock. **a** Representative Western blot of nuclear PPARγ protein expression in PBMC from two patients with various categories of sepsis on day 1 or 3 and in four control patients. **b** Box and whisker plot of PPARγ nuclear protein levels from PBMC by Western blot analysis based on densitometric analysis of the absolute intensity. Patients were grouped according to their sepsis category and therefore multiple samples were obtained from the same patient if they fulfilled the requirement for the diagnostic category on day 1, 3 or 7 of their illness. The vertical box represents the 25th percentile (*bottom line*), median (*middle line*), and 75th percentile (*top line*) values

transcription factor assay kit. Interestingly, contrary to PPARγ expression findings, median PPARγ activity levels were higher in patients with SIRS and septic shock when compared with control patients (Fig. 2). Patients with resolved sepsis had median PPARγ activity levels similar to control patients. The PPARγ activity level within the first day of hospitalization was significantly higher in patients with PRISM score >10 compared with control patients (mean 0.22 OD $\pm$ SEM 0.03 versus 0.12 OD $\pm$ 0.02; $p < 0.001$). Thus, our data suggest that, while PPARγ protein expression is decreased in septic shock, the activity of PPARγ is increased, suggesting that additional mediators result in PPARγ activation during septic shock.

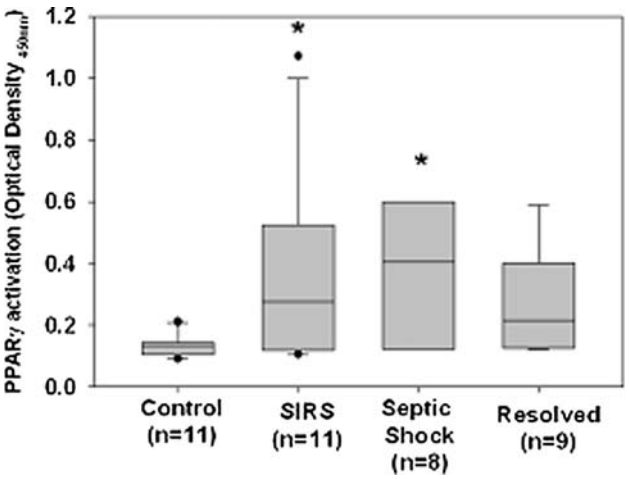

Fig. 2 Nuclear PPARγ activity is increased in PBMC in septic shock. Box and whisker plot of nuclear PPARγ activity levels from PBMC. Patients were grouped according to their sepsis category. The *vertical box* represents the 25th percentile (*bottom line*), median (*middle line*), and 75th percentile (*top line*) values, while the error bars represent the 10th and 90th percentile values. The *dots* represent values outside the 10th and 90th percentile. *$p < 0.05$ versus control

The effect of sepsis on plasma 15d-PGJ_2 levels in children with systemic inflammation from sepsis

Since downregulation of protein expression did not correlate with PPARγ activity in PBMC, we determined whether sepsis is associated with changes in levels of the endogenous activator of PPARγ. Plasma levels of 15d-PGJ_2 were unchanged in patients with SIRS and septic shock when compared with controls. However, patients with resolved sepsis had elevated levels of 15d-PGJ_2 compared with patients with SIRS and septic shock (77.7 $\pm$ 21.7 versus 58 $\pm$ 16.5 pg/ml; $p = 0.03$). Thus, our data suggest that sepsis increases the endogenous ligand for PPARγ and may be one factor increasing PPARγ activity levels despite lower protein levels.

Both high-molecular-weight adiponectin (HMWA) and resistin are increased early in septic shock and remain elevated in children with resolving sepsis

Because of the importance of PPARγ in adipocyte proliferation we sought to measure the effects of sepsis on adipocyte proteins. We utilized HMWA plasma levels as an easily obtainable mechanism to measure an endpoint of PPARγ activity for two reasons. First, HMWA has a PPAR response element in its promoter region. Second, levels of high-molecular-weight adiponectin correlate with synthetic PPARγ agonist treatment [19]. We found that HMWA levels are increased in patients with septic shock on day 1 compared with controls (8.0 µg/ml, IQR 4.8–12.3 versus 3.3 µg/ml, IQR 2.4–9.4; $p < 0.05$) (Fig. 3). The plasma levels of HMWA correlate with risk of mortality scores. HMWA levels were higher in patients with PRISM score >21 (13.7 $\pm$ 4.3 µg/ml) when compared with patients with low PRISM score ($\leq$10)

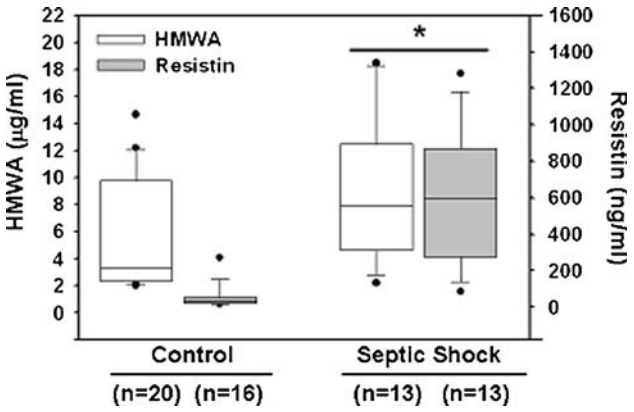

Fig. 3 Plasma high-molecular-weight adiponectin (HMWA) and resistin levels are increased in sepsis on the first day of hospitalization. Box and whisker plot of day 1 plasma resistin levels grouped by sepsis category. The *vertical box* represents the 25th percentile (*bottom line*), median (*middle line*), and 75th percentile (*top line*) values, while the error bars represent the 10th and 90th percentile values. The *dots* represent values outside the 10th and 90th percentile. $*p < 0.05$ versus control

(7 ± 1 µg/ml; $p < 0.05$) (Fig. 4). Patients with resolved sepsis also have higher levels of HMWA (10.3 µg/ml, IQR 5.4–12.7 µg/ml) when compared with controls (4.3 µg/ml, IQR 2.6–9.8 µg/ml; $p < 0.05$).

We demonstrate that plasma resistin levels are increased in patients with septic shock on the first day of hospitalization compared with controls (Fig. 3). Furthermore, patients with septic shock had significantly higher resistin levels on the first day of hospitalization compared with patients with SIRS/sepsis (597 ng/ml, IQR 273–851 ng/ml versus 78 ng/ml, IQR 60–325; $p < 0.01$). Resistin levels also correlate with risk of mortality scores and outcomes. We demonstrate that plasma levels of resistin on the first day of hospitalization from sepsis were significantly higher in patients with PRISM score >21 when compared with patients with PRISM score ≤10 (Fig. 4) (682.4 ± 171.6 versus 237.4 ± 62.5 ng/ml; $p < 0.05$). As evidence that resistin may be a useful biomarker, nonsurvivors from sepsis had significantly higher resistin levels on the first day of hospitalization compared with survivors from septic shock (660 ng/ml, IQR 585–833 ng/ml versus 143 ng/ml, IQR 66–342 ng/ml; $p < 0.05$).

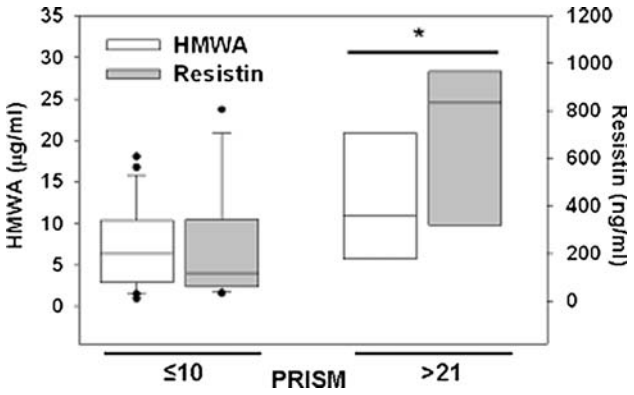

Fig. 4 Plasma HMWA and resistin levels are increased in children with increased pediatric risk of mortality score (PRISM). Box and whisker plots showing levels of plasma HMWA and resistin categorized by severity using the admission PRISM score. The *vertical box* represents the 25th percentile (*bottom line*), median (*middle line*), and 75th percentile (*top line*) values, while the *error bars* represent the 10th and 90th percentile values. The dots represent values outside the 10th and 90th percentile. $*p < 0.05$ versus PRISM ≤10

Discussion

Our results demonstrate that sepsis is associated with altered PPARγ expression and activation in PBMC. First, in children with septic shock, PPARγ nuclear protein expression is decreased; however, PPARγ activity is increased. This occurs most likely as a result of an increase in production of the endogenous ligand, 15d-PGJ_2. Second, PPARγ activity in early sepsis correlates with risk of mortality. Third, the adipokines resistin and high-molecular-weight adiponectin correlate with PPARγ activity in sepsis and can be useful biomarkers in sepsis. Furthermore, these adipokines are elevated in the resolution of sepsis and may play a role in the compensatory anti-inflammatory response syndrome.

Our findings are consistent with previous animal studies which demonstrate that sepsis alters PPARγ expression [7, 20]. The current study is the first to demonstrate alterations in PPARγ in children with sepsis. We found that PPARγ protein expression in PBMC was decreased in children with septic shock. This is consistent with findings in PBMC from patients with multiple sclerosis, a disease with significant inflammation. Multiple sclerosis patients had ~65% reduction in PPARγ protein expression in PBMC compared with healthy donors [13]. Although beyond the scope of this current study, a possible explanation for the decrease in PPARγ protein expression demonstrated in the current study may occur through posttranslational modifications of PPARγ [21]. The activation function-1 domain of PPARγ contains a consensus mitogen-activated protein kinase site, and serine phosphorylation leads to inhibition of PPARγ transactivation [22, 23]. Once phosphorylated, PPARγ becomes degraded by the ubiquitin–proteasome system [24]. These mechanistic changes may provide an explanation for our current findings and will need to be explored in further studies.

Contrary to our data, studies in adults with sepsis demonstrate an increase in PPARγ mRNA expression in T cells and neutrophils [15, 16]. Differences in PPARγ

detected in the current study and previously published data may occur through cell type differences in PPARγ. PBMC includes a mixed population of monocytes and lymphocytes while other studies demonstrate changes in isolated neutrophils and T lymphocytes [15, 16]. Further studies are needed to confirm our findings in specific cell populations.

Children with resolved sepsis have elevated 15d-PGJ_2 levels similar to levels found in the synovial fluid of rheumatoid and osteoarthritis patients [25]. This finding confirms previous suggestions that an endogenous activator of PPARγ is present in septic blood. 15d-PGJ_2 was found in blood from septic rats, and sera from septic patients were able to activate PPARγ [16, 26]. It is not surprising that 15d-PGJ_2 is activated during the inflammatory response to sepsis. 15d-PGJ_2 is produced from arachidonic acid via cyclooxygenases (COX), enzymes known to be induced after lipopolysaccharide (LPS) stimulation [27]. Therefore, 15d-PGJ_2 levels may be increased in sepsis as a compensatory mechanism and contribute to the increase in PPARγ activity. As a result, despite a decrease in PPARγ protein expression, it is plausible to hypothesize that PBMC of septic patients has a sufficient receptor reserve, which can still be recruited by endogenous ligands.

Our data are consistent with published data demonstrating that resistin levels are increased in patients with septic shock on the first day of hospitalization [28]. We demonstrate for the first time that day-1 resistin levels correlate with survival outcomes and disease severity. Nonsurvivors from sepsis have significantly higher resistin levels on the first day of their illness compared with survivors. These findings are in agreement with data that demonstrate that resistin levels correlate with inflammatory markers [29]. Resistin levels from human PBMC are increased after treatment with LPS [28]. As part of a feedback loop, PBMC and synovial leukocytes respond to resistin by producing pro-inflammatory cytokines [30]. Unlike adiponectin, both upregulation and downregulation of resistin gene expression occurs after TZD treatment [31, 32].

Adiponectin has anti-inflammatory effects and is affected by PPARγ agonists. Expression of the adiponectin gene is induced by PPARγ ligands via direct binding to the peroxisome proliferator response element in the adiponectin promoter [33]. Multiple studies have demonstrated that treatment with thiazolidinediones increase adiponectin mRNA levels in adipocytes and adipose tissues [34, 35]. Few studies have evaluated the effects of sepsis on plasma adipokines. Adiponectin levels were lower in polymicrobial sepsis and adiponectin knockout mice had higher inflammatory cytokine production and higher mortality after polymicrobial sepsis compared with wild-type mice [36, 37]. However, human studies have failed to detect alterations in plasma adiponectin levels after endotoxin injection [38, 39]. One explanation for the lack of difference in adiponectin levels after endotoxin is that those subjects were not severely ill. Second, total adiponectin may not accurately correlate with inflammation. The high-molecular-weight form of adiponectin has been proposed as the most potent form mediating the metabolic actions of adiponectin and the form preferentially increased by TZDs [19].

We acknowledge that our study has many limitations. The major limitation of this study is the lack of power due to the small sample size. This may contribute to the small PPARγ differences in patients with sepsis. Another limitation is the absence of information on prehospital administration of antipyretic medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), which may affect PPARγ activity and are often used in children. NSAIDs have anti-inflammatory effects through inhibition of cyclooxygenase activity. High concentrations of NSAIDs can activate PPARγ similarly to the natural ligand 15d-PGJ_2 [40]. Although our current study did not include data on NSAID use, it is possible that PPARγ activity could be affected by prehospital administration of this drug. Another limitation of this study is the small amount of blood volume obtained from each patient and that not all blood samples were tested for all analytes. We recognize that this study is descriptive and not mechanistic. Although animal studies have demonstrated alterations in PPARγ in sepsis no other studies demonstrate changes in PPARγ in children with sepsis. Furthermore, the results of this study provide the foundation for future studies to investigate the mechanism involved in the PPARγ response to sepsis.

Conclusions

Sepsis is associated with altered PPARγ expression and activity in PBMC. PPARγ activity in sepsis correlates with plasma adipokines and risk of mortality score. However, taken together with our previously published in vivo studies, these findings suggest that an increase in PPARγ activity may represent a counter-regulatory mechanism in the inflammatory response. Further studies are needed to understand the mechanistic changes altering PPARγ expression and activity in sepsis.

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