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Serum Levels of Leptin and Adiponectin in Children with Febrile Seizures: A Case-Control Study

Elsayed Abdelkreem[1]*, Hager A. Mohamed[1], Abdelrahim A. Sadek[1], Abdelhady R. Abdel-Gawad[2], Amr A. Othman[1]

Departments of [1]Pediatrics and [2]Clinical Pathology, Faculty of Medicine, Sohag University, Sohag, Egypt

***Corresponding author:** Elsayed Abdelkreem, **Mobile:** (+20) 01114232126,

ORCID: 0000-0002-8976-2989, **Email:** d.elsayedmohammed@med.sohag.edu.eg,

ABSTRACT

Background: The pathogenesis of febrile seizure (FS), the most prevalent convulsive condition in children under the age of five, has not been fully determined. **Objective:** The aim of the current study is to evaluate serum levels of adiponectin and leptin in children with FS. **Patients and methods**: A case-control study was conducted at the Departments of Pediatrics and Clinical Pathology of Sohag University Hospital,and included 3 groups of 30 children per group: FS, febrile controls (FC), and healthy controls (HC). Serum levels of adiponectin and leptin were measured during the acute phase using human enzyme-linked immunosorbent assay. A multivariate logistic regression analysis was conducted to study independent factors associated with FS. **Results**: Both the FS and FC groups had comparable serum adiponectin (median 43.5 [IQR 40-63] vs. 44 [39-83] µg/L, *p* 0.756) and leptin (86 [56-99] vs. 78.5 [44-111], *p* 0.779) levels, but both groups had significantly higher adiponectin (*p* 0.002, 0.003) and lower leptin (*p* 0.007, 0.002) levels compared with the HC group. The FS group had significantly higher body temperature on admission, WBCs, CRP, and creatinine but lower hemoglobin levels. However, in the multivariate logistic regression model, only higher body temperature on admission retained statistical significance (*p* 0.006). **Conclusion:** Serum adiponectin and leptin levels had no significant associations with FS, but this should be confirmed by larger and more comprehensive studies.

Keywords: Febrile seizure, Febrile convulsion, Adipokines, Adiponectin, Leptin.

INTRODUCTION

A febrile seizure (FS) is a seizure that occurs in children between the ages of 6 months and 5 years old in conjunction with a temperature of at least 38°C and without any signs of a central nervous system (CNS) illness, another known cause of seizures, or a previous afebrile seizure [(1,2)]. This is the most common convulsive disorder among children under 5 years of age with an estimated incidence of 2-10% [(3,4)]. FS is divided into simple and complex categories according to age and seizure type, duration, and recurrence within 24 hours [(2)]. Future recurrence occurs in about 25-50% of children with FS. FS generally has a favorable prognosis, although recent evidence suggests that complex FS may be associated with cognitive deficit in some cases [(4,5)].

The pathogenesis of FS has not been completely understood. The risk of fever's effects on the developing brain, together with underlying genetic predisposition and environmental factors, make up the likely complex etiology of FS [(1)]. Disturbed balance between pro- and anti-inflammatory cytokines has been demonstrated to play an important role in the pathogenesis of FS. Because of recent developments in medical technology, several biomarkers for febrile seizures have been investigated, such as serum lactic acid, copeptin and Von Willebrand factor, proinflammatory cytokines (e.g., interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α]), anti-inflammatory cytokines (e.g., interleukin-4 [IL-4]), and adipocytokines [(6-8)].

Adipocytokines are a group of hormonally active peptides produced by adipose tissue, which include adiponectin, leptin, IL-6, TNF- α, ometin, vaspin, and visfatin [(9)]. Studies on the role of adiponectin and leptin in FS have shown inconsistent results. **Chen *et al.*** [(7)] reported a significant association between higher serum adiponectin levels and having FS, but **Güven *et al.*** [(10)] **and Azab *et al.*** [(6)] described elevated serum adiponectin levels in children with FS as well as febrile controls. Regarding leptin, **Azab *et al.*** [(6)] reported a significant association between lower serum leptin levels and FS. However, **Khoshdel *et al.*** [(11)] showed no significant association, and **Güven *et al.*** [(10)] found significantly higher leptin levels in not only children with FS but also in febrile controls. These inconsistencies may be attributed to differences in study populations, measurement techniques, and potential confounders.

The aim of this study was to evaluate serum levels of adipocytokines, specifically adiponectin and leptin, in children with FS using controls of feverish, as well as healthy children.

PATIENTS AND METHODS

Study design and setting: A case-control study was conducted between July 2021 and October 2022 at the Departments of Pediatrics and Clinical Pathology of Sohag University Hospital (Southern Egypt).

Participants: The study included 3 groups of 30 children: FS, febrile control (FC), and healthy control (HC). The FS group included children between 6 months and 5 years of age, presented with seizure and fever (temperature ≥38°C) and fulfilled the American Academy of Pediatrics (AAP) diagnostic criteria of FS [(2)]. FC group included age-matched children presented with fever of at least ≥38°C due to acute infection with no seizures, while the HC group included otherwise

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healthy age-matched children presented for routine medical check-up.

Exclusion criteria included having a CNS infection, epilepsy, prior neurological abnormalities, inborn metabolic disorders, endocrine diseases (such as diabetes mellitus), obesity, dietary disorders, and gastrointestinal conditions (e.g., diarrhea).

Sample size was calculated using STATA/BE 17 (StataCorp, College Station, TX, USA) based on a 37% mean difference in adiponectin or leptin levels between FS and control group at a significance level of 0.05 and power 80% [(7)]. This results in 20 subjects per group, but we increased the number to enroll 30 children per group.

Methods: Enrolled children underwent thorough *history taking* and *clinical assessment*, including sociodemographic data, details of acute febrile illness, features of seizures, body temperature on admission and other vital signs, neurological evaluation, and comprehensive systematic examination. Complete blood count, CRP, blood glucose, serum electrolytes, liver and kidney function tests were among the initial *laboratory evaluations*. Other laboratory studies, such as lumbar puncture or brain imaging, were performed when clinically indicated.

We followed the AAP guidelines, which define FS as a seizure occurring in children between the ages of 6 months and 5 years old with a temperature of at least 38°C but no central nervous system (CNS) illness. There are 2 types of FS: simple and complex. Simple FS is described as widespread convulsions that last less than 15 minutes and don't occur again within 24 hours, whereas complex FS is described as focal, lasting more than 15 minutes, or occurring again within 24 hours [(2)].

For evaluating serum adiponectin and leptin levels, 3-ml venous blood samples were obtained from children with FS (within 3 hours of seizures) and 2 control groups. The blood samples were centrifuged at 3,500 rpm for 5 min at 4°C, and the serum was immediately separated and stored at –70°C till further analysis. Serum adiponectin and leptin were measured using human enzyme-linked immunosorbent assay (ELISA) kits (SinoGeneclon Biotech Co., Ltd, Hangzhou, China) following manufacturer's instructions. In principle, the kits adopt purified human adiponectin or leptin antibody to coat microtiter plates, making solid-phase antibody, followed by adding adiponectin or leptin to wells. An antibody-antigen-enzyme-antibody complex was then formed by combining tagged HRP with adiponectin or leptin antibody. After thorough washing, a blue color was produced by adding TMB substrate solution. After applying a stop solution to end the reaction, the color difference was detected at a wavelength of 450 nm. The O.D. of the samples is then compared to the standard curve to determine the amount of adiponectin or leptin present in the samples. The adiponectin kit has a detection range of 50-1000 μg/L, and the adiponectin kit has a detection range of 36-2000 pg/ml.

Ethical Consideration:

The Medical Research Ethics Committee of the Faculty of Medicine at Sohag University granted approval for this study (Approval Number: Soh-Med-21-07-06). All parents or designated legal guardians of children who participated in the study provided written informed consent. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical Analysis:

STATA/BE 17 was used to analyze the data, which were presented as frequencies and proportions for categorical data, mean (standard deviation: SD) for quantitative data with a normal distribution, and median (Interquartile range: IQR) for quantitative data that did not have a normal distribution. When comparing proportions between research groups, Chi-square/Fisher's exact test was used. One-way analysis of variance (ANOVA; for three groups) and independent sample t-test (for two groups) were used to compare normally distributed quantitative measures, whereas Kruskal-Wallis test (for three groups) and Mann-Whitney U test (for two-groups) were used to evaluate non-normally distributed data. Potential risk factors of febrile seizures were taken into account in a multivariate logistic regression analysis. P value ≤0.05 was considered to be statistically significant.

RESULTS

The present study included 30 children with FS (19 males, median age 29 months, 24 had simple FS) as well as 30 febrile controls and 30 healthy controls. The demographic and clinical features are shown in **Table 1**.

Table (1): Demographic and clinical features of children with febrile seizures and controls

Characteristics	FS group (n= 30)	FC group (n= 30)	HC group (n= 30)	*P*-value (within groups)	*P*-value (FS vs. HC)	*P*-value (FC vs. HC)	*P*-value (FS vs. FC)
Age, months, median (IQR)	29 (12-36)	18 (7-39)	18 (10-48)	0.624*	0.486#	0.710#	0.373#
Gender, no., male/female	19/11	20/10	18/12	0.866$	0.791$	0.592$	0.787$
BMI, Kg/m^2, median (IQR)	16 (15-19)	14.5 (13-19)	17 (15-18)	0.165*	0.988#	0.150#	0.067#

Body temperature on admission, °C, median (IQR)	40 (40-40)	39 (38.5-39)	–	–	–	–	<0.001[#]
Type of infection (bacterial/viral)	27/3	25/5	–	–	–	–	0.706[‡]

Median, IQR: Non-parametric test.
[*] Kruskal-Wallis test; [#] Mann-Whitney U-test; [$] Chi-square test, [‡] Fisher's exact test. BMI, body mass index, FC, febrile controls; FS, febrile seizures; HC, healthy control.

The laboratory findings of the study groups are described in **Table 2**. There were statistically significant differences within groups in hemoglobin, WBCs, CRP, creatinine, adiponectin, and leptin levels. FS group had significantly lower hemoglobin levels than the FC (*P-value* 0.011) and HC (*P-value* 0.006) groups. The WBCs and CRP were significantly higher in the FS group compared with the HC group but not with the FC group. Serum creatinine levels were significantly higher in the FS group than in both the FC (*P-value* 0.001) and HC (*P-value* 0.010) groups. Importantly, both the FS and FC groups had comparable serum adiponectin and leptin levels, but both groups had significantly higher adiponectin and lower leptin levels compared with the HC group (**Figure 1**).

Table (2): Laboratory findings in children with febrile seizures and controls.

Variables[*]	**FS group** (n= 30)	**FC group** (n= 30)	**HC group** (n= 30)	***P*-value (within groups)**[#]	***P*-value (FS and HC)**[$]	***P*-value (FC and HC)**[$]	***P*-value (FS and FC)**[$]
WBCs ($\times 10^9$/L)	14.7 (11.9-18)	12.3 (9.7-14.4)	11.8 (7.7-14.4)	0.014	0.004	0.383	0.052
Hemoglobin (g/dL)	9.9 (1.43)	10.9 (1.39)	10.9 (1.26)	0.008	0.006	0.911	0.011
Platelets ($\times 10^9$/L)	314 (227-378)	343 (275-426)	321 (268-409)	0.298	0.367	0.487	0.128
CRP (mg/dL)	24 (12-24)	12 (6-24)	6 (0-12)	0.016	0.006	0.044	0.384
Glucose (mg/dL)	129 (118-148)	120 (116-150)	126 (118-138)	0.537	0.573	0.323	0.394
Sodium (mmol/L)	136 (133-139.8)	136 (134-137.9)	136.7 (134-139)	0.672	0.500	0.389	0.976
Potassium (mmol/L)	3.95 (3.5-4.3)	3.8 (3.5-4.6)	3.9 (3.5-4.4)	0.897	0.842	0.640	0.795
Calcium (mg/dL)	1.1 (1.02-1.2)	1.1 (1.01-1.18)	1.09 (1.03-1.15)	0.739	0.442	0.778	0.627
ALT (IU/L)	22 (20-25)	24.5 (20-28)	22 (18-28)	0.769	0.835	0.876	0.368
AST (IU/L)	24 (22-26)	26 (22-28)	24.5 (23-28)	0.360	0.420	0.531	0.156
Albumin (g/dL)	3.2 (3.2-3.6)	3.2 (3.1-3.8)	3.7 (3.2-4.1)	0.080	0.033	0.082	0.934
Creatinine (mg/dL)	0.4 (0.4-0.5)	0.3 (0.26-0.4)	0.36 (0.25-0.43)	0.003	0.010	0.468	0.001
Adiponectin (µg/L)	43.5 (40-63)	44 (39-83)	38 (22-45)	0.002	0.002	0.003	0.756
Leptin (pg/ml)	86 (56-99)	78.5 (44-111)	100 (85-321)	0.004	0.007	0.002	0.779

Median, IQR: Non-parametric test.
[*] Reported as median (IQR), except for hemoglobin as mean (SD); [#] Using Kruskal-Wallis test, except for hemoglobin by one-way ANOVA test; [$] Using Mann-Whitney U-test, except for hemoglobin by Student's t-test. ALT, alanine aminotransferase; AST, asparate aminotransferase; CRP, C-reactive protein; FC, febrile control; FS, febrile seizures; HC, healthy controls; WBCs, white blood cells.

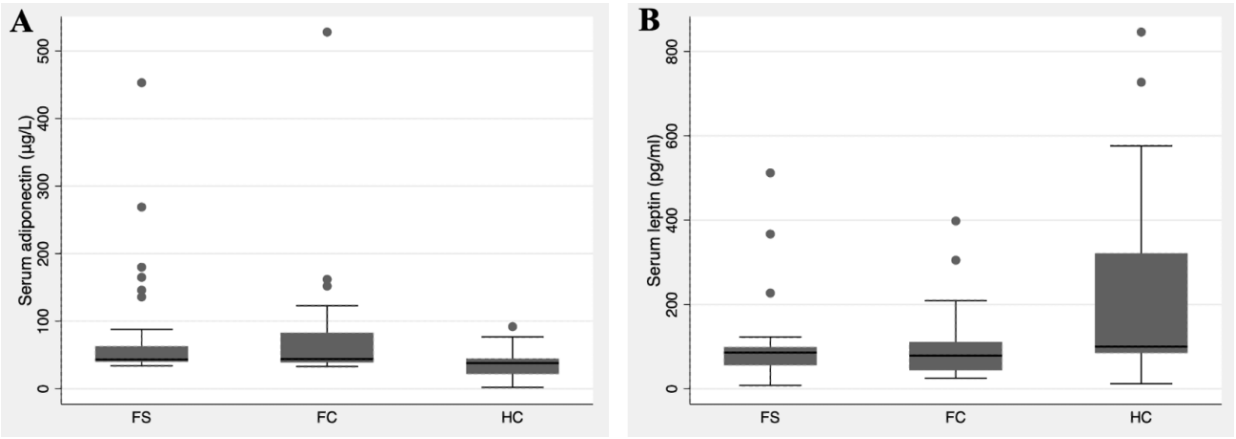

Figure 1: Serum adiponectin and leptin levels in children with febrile seizures and controls. **(A)** Children with febrile seizures (FS) and febrile controls (FC) have significantly higher serum adiponectin levels than healthy controls (HC), but adiponectin levels are not significantly different between FS and FC groups. **(B)** FS and FC groups have significantly lower serum leptin levels than the HC group, but leptin levels are not significantly different between FS and FC groups.

Table 3 shows the results of the multivariate logistic regression model that included age, gender, and BMI, as well as factors that had a *P*-value <0.05 in bivariate analysis. In the adjusted model, only higher body temperature at admission retained statistical significance (*P-value* 0.006). Hemoglobin, WBCs, CRP, creatinine, adiponectin, and leptin had no statistically significant association with FS in the adjusted model. The overall model had great discrimination for FS with an area under the curve of 0.9767 (**Figure 2**).

Table (3): Multivariate logistic regression of factors associated with febrile seizures.

Variables	aOR	95%CI	P-value
Age	0.969	0.885-1.062	0.502
Male gender	0.952	0.052-17.522	0.974
BMI	1.035	0.707-1.514	0.861
Body temperature on admission	1085	7.729-152382	0.006
WBCs	0.840	0.600-1.175	0.308
Hemoglobin	0.402	0.119-1.363	0.143
CRP	0.977	0.925-1.032	0.405
Creatinine	63455	0.047-867000	0.125
Adiponectin	0.998	0.988-1.008	0.708
Leptin	0.994	0.978-1.010	0.466

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; aOR, adjusted Odds ratio; WBCs, white blood cells.

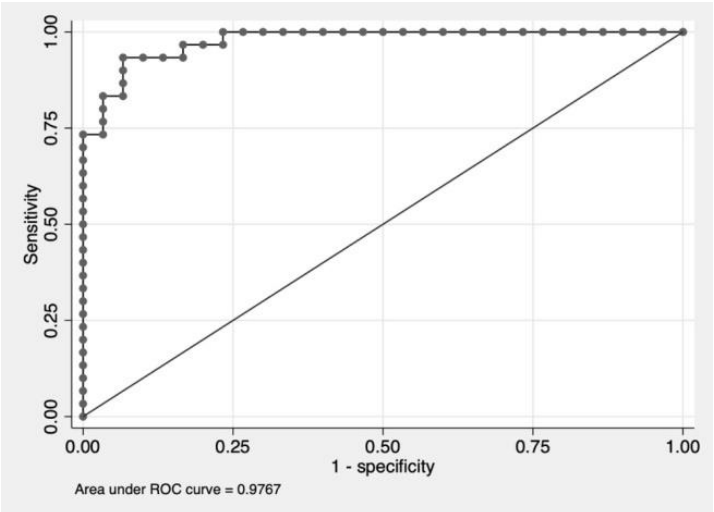

Figure (2): Receiver operating characteristic (ROC) curve for febrile seizure model prediction. The model is based on a multivariate logistic regression including age, gender, body mass index, body temperature on admission, hemoglobin level, white blood cells, CRP, serum creatinine, adiponectin, and leptin.

DISCUSSION

FS is a common pediatric convulsive disorder whose exact etiology has not been completely delineated. In this case-control study, we evaluated serum levels of adiponectin and leptin in children with FS as well as febrile (FC) and healthy (HC) controls. In unadjusted analysis, we found that blood levels of adiponectin and leptin in the FS and FC groups are comparable, but both groups had significantly higher adiponectin and lower leptin levels compared with the HC group. However, in the adjusted regression model, only higher body temperature on admission was significantly associated with having FS. This indicates that changes in adiponectin and leptin levels may be related to febrile illness rather than the pathogenesis of febrile seizures.

Children with FS in our study had a significantly higher body temperature at admission than the FC group, which is consistent with previous studies [12,13]. Moreover, higher body temperature on admission was the only statistically significant factor associated with FS in a regression model adjusted for age, gender, BMI, hemoglobin, WBCs, CRP, creatinine, adiponectin, and leptin. This indicates the important role of higher body temperature in the pathogenesis of FS [1,3,14]. **Berg *et al.*** [15] reported that each one-degree increase of body temperature above 101°F approximately doubles the risk of developing febrile FS. Interestingly, among children with the first episode of febrile FS, having a lower body temperature, specifically less than 39.2°C, has been shown to be significantly associated with recurrent seizures during the same febrile illness [16].

Children with FS in the current study exhibited considerably lower hemoglobin levels than the FC and HC groups. This agrees with research by **Chen *et al.*** [7] and **Güven *et al.*** [10]**.** In addition, iron deficiency anemia is substantially related to 98% greater odds of having FS, according to a systematic review and meta-analysis of 17 studies that included 2416 children with FS and 2387 controls [17]. Iron impacts several enzymatic pathways important for the metabolism of DNA and RNA, which are involved in nerve development and myelination, as well as the synthesis and function of neurotransmitters, which may enhance brain excitability and susceptibility to seizures [7,17]. Furthermore, iron deficiency adversely affects nutrition, growth, immunity, and general health of children, all of which may play a role in predisposition to FS [18].

WBCs and CRP in the current study were considerably greater in the FS group when compared to the HC group, but not when compared to the FC group. Our results are in agreement with those of a few earlier research [10,19]. Nevertheless, **Marol *et al.*** [20] reported that children with FS have significantly higher CRP levels than the FC group. In contrast, **Gontko-Romanowska *et al.*** [12] described significantly lower CRP levels among children with FS compared with the FC group. The differences among studies could be attributed to several potential confounders, such as trauma, bleeding, vomiting, and dehydration, all of which can impact WBCs and CRP levels. Of note, the raised creatinine level in the FS group suggests dehydration. Furthermore, WBCs and CRP levels are affected by the nature of infection as well as the time of sampling since CRP levels peak at 24-48 hours after the onset of inflammatory response. Last, the duration and severity of the seizures themselves may have an important contribution [19].

Adiponectin and leptin belong to a group of hormonally active peptides produced by adipose tissue called adipocytokines, which also include IL-6, TNF- α, ometin, vaspin, and visfatin [9]. In the present study, serum adiponectin and leptin levels were comparable between the FS and FC groups, but both groups had significantly higher adiponectin and lower leptin levels compared with the HC group. However, no significant association was observed in the multivariate regression model. This indicates that changes in adiponectin and leptin levels may be related to febrile illness rather than the pathogenesis of febrile seizures.

Azab *et al.* [6] and **Güven *et al.*** [10] found that children with FS and FC had considerably greater adiponectin levels than the HC group but not in-between, which is consistent with our study results. However, **Chen *et al.*** [7] demonstrated that children with FS have considerably greater adiponectin levels than both the FC and HC groups.

Adiponectin has been known to play an important role in improving insulin sensitivity and fat oxidation. In addition, evidence from recent studies indicates that adiponectin has a role in metabolism and function in the brain and may have neuroprotective effects in epilepsy. In fact, the brain has many adiponectin receptors, yet the CSF only contains small amounts of adiponectin [9]. Animal studies demonstrated that a low adiponectin level is associated with more severe seizures and hippocampal damage. This may be explained by the importance of adiponectin for retaining the integrity of the blood-brain barrier, thereby mitigating seizure-related neuronal injury [21,22]. In addition, adiponectin may have anti-inflammatory effects. In line with that, adiponectin has been found to inhibit the synthesis of TNF- α in macrophages [23]. Furthermore, both adiponectin and IL-6 were found to be closely linked in children with epilepsy. FS may be associated with high IL-6 levels, and the increased adiponectin levels in such cases may play an anti-inflammatory role by reducing IL-6-mediated inflammatory brain damage. The modulatory effects on inflammatory pathways and vascular endothelial function may also mediate the observed associations of low adiponectin levels with several neurological disorders, including higher mortality after ischemic stroke [24]. Notably, animal research found that peroxisome proliferator-activated receptor agonists, which hasten the expression of adiponectin, might safeguard against seizure-caused neuronal damage [25].

In agreement with our study findings, **Chen *et al.*** [7] reported that children with FS and FC have significantly lower leptin levels than the HC group but

not in-between. **Azab *et al.*** [6] also described lower leptin levels in children with FS compared with both FC and HC, but the FC group had significantly higher leptin levels than the HC group. Yet, **Khoshdel *et al.*** [11] showed no significant difference in serum leptin levels among FS, FC, and HC groups. On the other side, **Güven *et al.*** [10] found that FS and FC children had significantly higher leptin levels compared with HC but no significant difference between them.

Leptin is known to regulate lipogenesis and fatty acid oxidation, inhibit food intake, and maintain energy balance [9]. Researchers have also demonstrated that leptin regulates immune response under normal and pathologic states; it acts as an acute phase reactant, similar to proinflammatory cytokines, contributing to febrile response in systemic inflammation [26]. Circulating leptin can cross the blood-brain barrier, where it regulates neural plasticity and cognitive function [9,27]. Moreover, previous studies have reported that leptin exerts both pro-seizure and antiseizure effects [28,29]. In a rodent model, intranasal leptin administration increased both serum and CSF leptin levels, which was associated with a delay in the onset of pentylenetetrazole-induced convulsive seizures, and leptin was demonstrated to suppress glutamate transmission in the hippocampus, which could lower seizure threshold and propagation [30]. On the other hand, **Lynch *et al.*** [31] demonstrated that leptin exerts dose-related proconvulsant effects in mice models of seizures. Similarly, the administration of leptin has been shown to enhance penicillin-induced epileptiform activity in a rat model [32].

The inconsistent results among studies on the association between serum levels of adiponectin and leptin with FS may be attributed to several factors. *First*, there are differences in study populations, including age and race, and kits used for measuring adiponectin and leptin levels, which may contribute to differences in results. *Second*, the time interval between seizures and obtaining blood samples varies within and in between studies, which could affect the measured levels of leptin and adiponectin. *Third*, many possible confounders were not measured or adjusted for in most studies, such as socioeconomic level, nutritional status, primary etiology of fever, duration of fever, type of febrile seizures, used medications (e.g., antipyretics), genetic background, and socioeconomic factors. For instance, FS has been found to be more common among children with low socioeconomic levels [14]. In addition, some genetic epilepsy syndromes typically present with febrile seizures [33]. Moreover, nutrition may have an important role since adiponectin level has been shown to increase in children on a ketogenic diet [34]. Furthermore, most studies didn't specify the antipyretics, but animal studies have shown that ibuprofen could decrease serum levels of leptin and IL-6 [35]. Last, the type and duration of seizures may play an important role. While **Chen *et al.*** [7] reported no differences in serum leptin and adiponectin among children with simple and complex febrile seizures, **Azab *et al.*** [6] reported that serum and CSF leptin, but not adiponectin, levels are significantly lower in children with complex subtype. The fact that blood samples are obtained after FS raises the possibility that FS itself might contribute to the observed changes in leptin and adiponectin levels. All the above factors have to be considered for proper interpretation of adiponectin and leptin levels in association with FS; among previous studies, only **Azab *et al.*** [6] conducted multivariate analysis, which revealed that adiponectin and leptin levels were no longer significantly associated with FS.

The strengths of our study include the consistent measurement of adipocytokines using the same method and at the same time, the use of both healthy and febrile control children, and conducting multivariate regression analysis. However, we acknowledge that our study has some limitations. First, the sample size was relatively small, which might have reduced the study power to detect some statically significant associations. Second, we measured adipocytokines levels in only the serum but not in the CSF. Third, we did not follow up cases to study the recurrence of FS. Last, our study didn't investigate certain factors that may affect FS development or serum adiponectin and leptin levels, such as genetic abnormalities, detailed nutrition, and other cytokines levels.

CONCLUSION

Our study found no significant associations of serum adiponectin and leptin levels with FS, but this should be confirmed by larger and more comprehensive studies.

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Author contributions: Elsayed Abdelkreem and Abdelrahim A. Sadek initiated the research idea. All authors shared in the study design and planning. Elsayed Abdelkreem, Hager A. Mohamed, Abdelrahim A. Sadek, and Amr A. Othman shared in collection of patients' data. Abdelhady R. Abdel-Gawad evaluated serum levels of leptin and adiponectin. Elsayed Abdelkreem, Hager A. Mohamed, and Amr A. Othman performed data analysis. Elsayed Abdelkreem, Hager A. Mohamed wrote the first draft of manuscript. All authors revised the manuscript. Abdelrahim A. Sadek supervised the whole study. Each author has agreed to be accountable for the full manuscript's content and has given their approval for submission.

Conflict of interest: None.

REFERENCES

1. **Leung A, Hon K, Leung T (2018):** Febrile seizures: an overview. Drugs Context, 7:212536. doi: 10.7573/dic.212536
2. **Subcommittee on Febrile Seizures (2011):** Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child With a Simple Febrile Seizure. Pediatrics, 127(2):389-94.

3. **Eilbert W, Chan C (2022):** Febrile seizures: A review. J Am Coll Emerg Physicians Open, 3(4):e12769. doi: 10.1002/emp2.12769
4. **Mewasingh L, Chin R, Scott R (2020):** Current understanding of febrile seizures and their long-term outcomes. Dev Med Child Neurol., 62(11):1245-9.
5. **Kloc M, Marchand D, Holmes G *et al.* (2022):** Cognitive impairment following experimental febrile seizures is determined by sex and seizure duration. Epilepsy Behav., 126:108430. doi: 10.1016/j.yebeh.2021.108430
6. **Azab S, Abdalhady M, Almalky M *et al.* (2016):** Serum and CSF adiponectin, leptin, and interleukin 6 levels as adipocytokines in Egyptian children with febrile seizures: a cross-sectional study. Ital J Pediatr., 42(1):38. doi: 10.1186/s13052-016-0250-y
7. **Chen J, Jin M, Tang L *et al.* (2020):** Acute Phase Serum Leptin, Adiponectin, Interleukin-6, and Visfatin Are Altered in Chinese Children With Febrile Seizures: A Cross-Sectional Study. Front Endocrinol., 11:531. doi: 10.3389/fendo.2020.00531
8. **Chen R, Li S, Wang X *et al.* (2020):** Analysis of cytokines and trace elements in children with febrile seizures. Transl Pediatr., 9(6):809-17.
9. **Lee T, Cheng K, Hoo R *et al.* (2019):** The Novel Perspectives of Adipokines on Brain Health. Int J Mol Sci., 20(22):5638. doi: 10.3390/ijms20225638
10. **Güven A, Icagasioglu F, Duksal F *et al.* (2015):** Serum adiponectin, leptin, and interleukin 6 levels as adipocytokines in children with febrile seizures: The role of adipose tissue in febrile seizures. Hum Exp Toxicol., 34(9):878-83.
11. **Khoshdel A, Parvin N, Abbasi M (2013):** Selenium and leptin levels in febrile seizure: a case-control study in children. Korean J Pediatr., 56(2):80-5.
12. **Gontko - Romanowska K, Żaba Z, Panieński P *et al.* (2017):** The assessment of laboratory parameters in children with fever and febrile seizures. Brain Behav., 7(7):e00720. doi: 10.1002/brb3.720
13. **Sharawat I (2022):** Evaluation of Risk Factors Associated with First Episode Febrile Seizure. J Clin Diagn Res., 10(5):SC10-13.
14. **Canpolat M, Per H, Gumus H *et al.* (2018):** Investigating the prevalence of febrile convulsion in Kayseri, Turkey: An assessment of the risk factors for recurrence of febrile convulsion and for development of epilepsy. Seizure, 55:36-47.
15. **Berg A, Shinnar S, Shapiro E *et al.* (1995):** Risk factors for a first febrile seizure: a matched case-control study. Epilepsia, 36(4):334-41.
16. **Kubota J, Higurashi N, Hirano D *et al.* (2021):** Body temperature predicts recurrent febrile seizures in the same febrile illness. Brain Dev., 43(7):768-74.
17. **Kwak B, Kim K, Kim S *et al.* (2017):** Relationship between iron deficiency anemia and febrile seizures in children: A systematic review and meta-analysis. Seizure, 52:27-34.
18. **Ekiz C, Agaoglu L, Karakas Z *et al.* (2005):** The effect of iron deficiency anemia on the function of the immune system. Hematol J., 5(7):579-83.
19. **Bakhtiari E, Heydarian F, Kiani M *et al.* (2020):** Febrile children with or without seizure: a Comparison between CBC, ESR and CRP. Rev Clin Med., 7(3):100-3.
20. **Marol R, Marol R, Matti S *et al.* (2020):** Can we predict occurrence of febrile convulsions in children with fever by increased neutrophil-to-lymphocyte ratio and C-reactive protein? Indian J Child Health, 7(11):450-3.
21. **Jeon B, Shin H, Kim J *et al.* (2009):** Adiponectin protects hippocampal neurons against kainic acid-induced excitotoxicity. Brain Res Rev., 61(2):81-8.
22. **Lee E, Warmann G, Dhir R *et al.* (2011):** Metabolic Dysfunction Associated with Adiponectin Deficiency Enhances Kainic Acid-Induced Seizure Severity. J Neurosci., 31(40):14361-6.
23. **Diez J, Iglesias P (2003):** The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol., 148(3):293-300.
24. **Chen B, Liao W, Xu N *et al.* (2009):** Adiponectin protects against cerebral ischemia–reperfusion injury through anti-inflammatory action. Brain Res., 1273:129-37.
25. **Abdallah D (2010):** Anticonvulsant potential of the peroxisome proliferator-activated receptor gamma agonist pioglitazone in pentylenetetrazole-induced acute seizures and kindling in mice. Brain Res., 1351:246-53.
26. **Francisco V, Pino J, Campos-Cabaleiro V *et al.* (2018):** Obesity, Fat Mass and Immune System: Role for Leptin. Front Physiol., 9:640. doi: 10.3389/fphys.2018.00640
27. **Van Doorn C, Macht V, Grillo C *et al.* (2017):** Leptin resistance and hippocampal behavioral deficits. Physiol Behav., 176:207-13.
28. **Lambrechts D, Brandt-Wouters E, Verschuure P *et al.* (2016):** A prospective study on changes in blood levels of cholecystokinin-8 and leptin in patients with refractory epilepsy treated with the ketogenic diet. Epilepsy Res., 127:87-92.
29. **Li L, Li Y, Zhao D *et al.* (2018):** Leptin-regulated autophagy plays a role in long-term neurobehavioral injury after neonatal seizures and the regulation of zinc/cPLA2 and CaMK II signaling in cerebral cortex. Epilepsy Res., 146:103-11.
30. **Xu L, Rensing N, Yang X *et al.* (2008):** Leptin inhibits 4-aminopyridine– and pentylenetetrazole-induced seizures and AMPAR-mediated synaptic transmission in rodents. J Clin Invest., 118(1):272-80.
31. **Lynch J, Shek E, Castagné V *et al.* (2010):** The proconvulsant effects of leptin on glutamate receptor-mediated seizures in mice. Brain Res Bull., 82(1–2):99-103.
32. **Ashrafi M, Shams S, Nouri M *et al.* (2007):** A Probable Causative Factor for an Old Problem: Selenium and Glutathione Peroxidase Appear to Play Important Roles in Epilepsy Pathogenesis. Epilepsia, 48(9):1750-5.
33. **Møller R, Wuttke T, Helbig I *et al.* (2017):** Mutations in GABRB3: From febrile seizures to epileptic encephalopathies. Neurology, 88(5):483-92.
34. **Chyra M, Roczniak W, Świętochowska E *et al.* (2022):** The Effect of the Ketogenic Diet on Adiponectin, Omentin and Vaspin in Children with Drug-Resistant Epilepsy. Nutrients, 14(3):479. doi: 10.3390/nu14030479
35. **Zivna H, Zivny P, Palicka V (2002):** Serum leptin concentrations after surgery in young rats. Nutrition, 18(7–8):643-6.