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Original Article

Serum adiponectin levels in children with nonspecific infections

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Abstract

Aim: Adiponectin, which is mainly produced by adipocytes, has antidiabetic, antiatherosclerotic and anti-inflammatory activities. We analyzed serum adiponectin levels and their relationship with metabolic parameters, fever and acute phase reactants in children with nonspecific infections and tried to analyze whether adiponectin has a role in the processes of inflammation and fever during infections.

Materials and Methods: In this study, we studied serum adiponectin levels in 42 prepubertal children admitted with fever≥38°C and symptoms of nonspecific infections. The children's ideal body weights for their heights were within 100% and 110%. The venous blood samples were collected both in the first admission with fever and three days after the fever dropped (control visit) for the analysis of serum adiponectin levels, complete blood count, erythrocyte sedimentation rate, C reactive protein, High-sensitive CRP, fibrinogen, ferritin, glucose, and insulin levels. The glucose/insulin rate and Homeostasis model assessment of insulin resistance and body mass index were calculated.

Results: The serum adiponectin levels of the children in the first admission were lower than those in the control visit (8.80±1.71µg/ml vs 12.04±2.38µg/ml)(p=0.000). The serum adiponectin levels were not correlated with the body temperature, body weight, ideal body weight for height, body mass index, Homeostasis model assessment of insulin resistance, and all other parameters analyzed in the study (p>0.05) in both admissions except the glucose/insulin ratio and leukocyte counts of the children in the first admission. The serum adiponectin levels were positively correlated with the glucose/insulin ratio and leukocyte counts in the first admission (r=0.338,p=0.029; r=0.304,p=0.05 respectively).

Conclusion: It is not known why the serum adiponectin levels of the children were different in the admission with fever than those in the control visit during the recovery phase. The change in adiponectin levels during the acute infection have raised some questions regarding whether serum adiponectin levels may be an acute phase reactant and if it might be involved in the processes of inflammation and fever.

Keywords: Adiponectin; inflammation; infection

INTRODUCTION

Adiponectin (AN), which is mainly produced by adipocytes (1), increases the insulin sensitivity and it is inversely related with the insulin resistance (2,3). In animal models, administration of AN is accompanied by weight loss and decreased plasma glucose, free fat acids and triglyceride levels (4). Moreover, the reduced AN levels are found in insulin resistance states, such as obesity and type 2 diabetes (5,6,11,12). In contrast, the AN levels increase with weight loss (7).

It has been reported that besides its anti-diabetic effects, AN has anti- inflammatory and anti-atherogenic characteristics (8-11).

It has been shown that AN regulates the expressions of several pro-inflammatory and anti-inflammatory cytokines (12). It inhibits the synthesis of tumor necrotizing factor (TNF)-α and interferon (IFN)-γ, and stimulates production of interleukin (IL)-10 and IL-1 receptor antagonist (13, 14). Maeda et al. (11) found out that the conditions, where the production of cytokines such as IL-6 and TNF-α increased, the secretion of AN from the adipocytes was inhibited, whereas the TNF-α mRNA levels were found to be increased in mice with the reduced AN levels and these levels decreased with AN injection. Similarly, Uji et al. (15) found out that the plasma TNF- α and IL-6 levels were significantly higher in adiponectin-knockout mice with polymicrobial sepsis than the wild-type mice.

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It was also reported that AN has pro-inflammatory effects (16). Saijo et al. (17) suggested that AN facilitated the IL-8 translation in the human macrophages in the presence of lipopolysaccaride (LPS) and also induced the IL-6 secretion from the human monocytes. The authors have concluded that these contrary effects of AN resulted from different types of AN that had different molecular weights and that AN with low-molecular weight had the anti-inflammatory effects, whereas the AN with the high-molecular weight had proinflammatory effects.

Adiponectin accumulates specifically in the veins and inhibits proliferation of the smooth muscle cells, as well as the expressions of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin in the endothelial cells, resulting in the decreased vascular inflammatory response and inhibited macrophage functions (13). Therefore, as Matsuzawa et al. (8) suggested AN may prevent atherosclerosis.

There are also a few studies examining the relationship between AN and fever and inflammation secondary to infection (18-20).

In this study we aimed to determine whether there is a change in the serum AN levels of children who are admitted to our pediatric outpatient clinic with an acute infection and fever, and whether the serum AN levels are related to fever, and other metabolic and inflammatory parameters.

MATERIALS and METHODS

We included forty-two prepubertal children (18 boys, 24 girls) in this study who are admitted to our pediatric emergency unit and policlinics with fever ≥38°C. The children, whose ideal body weights (BW) for their heights (IBW) were within the margin between 100% and 110%, were included in the study. The children with gastroenteritis, chronic diseases, malnutrition, growth retardation, history of any drug use other than antipyretics, and obese children were not included in the study.

The study protocol was approved by the Board of Ethics of Eskisehir Osmangazi University and the informed consent was obtained from the children's parents.

The children who were admitted to the hospital with fever were initially examined physically. Children received treatment or advice in accordance to their diagnoses. They were asked to come back to the hospital for re-evaluation three days after the fever dropped. Their physical examinations were repeated in the second admission. Their body weights and heights were measured and the body mass index (BW/height^2) and IBW values were calculated. The body temperatures were measured by a glass mercury thermometer.

The venous blood samples were collected during both admissions. The blood samples were used for the analyses of the serum AN levels, hematological and biochemical parameters and erythrocyte sedimentation rate (ESR).

The hematological, and biochemical parameters and ESR were studied with the standard methods of our Hematology and Biochemistry Laboratories.

The glucose/insulin ratio and Homeostasis model assessment of insulin resistance (HOMA-IR) [glucose level (mg/dl) x insulin level (µu/ml)/405] were calculated.

The serum AN levels were analyzed by a commercially available ELISA kit (Phoenix Pharmaceuticals, Inc). The venous blood samples were taken from each patient at the time of fever and three days after fever subsided, for serum AN levels, in centrifuge tubes without anticoagulants. The samples were centrifuged at +4°C and, 3000 rpm for 15 minutes and the obtained serum samples were stored at -80°C. The samples that were taken for the serum AN levels were studied by the ELISA method (Phoenix Pharmaceuticals, Inc.). The AN molecule determined in the study was the whole molecule AN. All of the samples were brought to the room temperature (20-23ºC) before starting the process and the samples were placed in metal wells. 100 µl of Human AN Standard was added to each well. It was incubated at room temperature (20-230C) for two hours. The immunoplasts were washed four times with 300-350 µl 1x assay buffer. Then, 100 µl of Biotinylated anti Human AN Detection Antibody was added to each well. It was incubated at room temperature (20-230C) for two hours. Immunoplasts were washed four times with 300-350 µl 1x assay buffer. 100 µl of the Streptavidin-Horseradish Peroxidase solution was added to each well. It was incubated at room temperature (20-230C) for 30 minutes. The immunoplasts were washed four times with 300-350 µl 1x assay buffer. 100 µl substrate solution (TMB) was added to each well. It was incubated for 20-30 minutes at room temperature (20-230C). The reaction was terminated by adding 100 µl of stop solution to each well. The results were read as ng/ml at 450 nm absorbance and converted to µg/ml.

Statistical Analysis

SPSS Patch 15 Program (SPSS Inc., Chicago, IL) was preferred for the statistical analysis of the data. The Kolmogorov- Smirnov test was applied to assess the distribution of the variables. The Mean±SD for parametric variables and the median (minimum-maximum) values were reported for summarizing data. The Paired samples t test and the Mann Whitney U test were used for the comparisons. The correlations were performed by the Pearson and Spearman correlation tests. The data were accepted as statistically significant $p<0.05$.

RESULTS

A total of 42 prepubertal patients were included in the study. 18 (42.9%) of the patients were male and 24 (57.1%) of them were female. The clinical features and diagnosis of the patients are summarized in Table 1 and Table 2, respectively. The mean time interval between the first and second admission was 4.9 ± 1 day.

The mean body temperature was significantly different between the first and second admissions ($p=0.000$). The mean BW, BMI and IBW values were not different between both admissions ($p>0.05$).

Table 1. Clinical features of patients

	First Admission	Control Visit	
	Mean ± SD	Mean ± SD	p
Age (month)	73 ± 39		
BW (kg)	22.2 ± 9.7	22.2 ± 9.7	>0.05
Height (cm)	114.7 ± 22.1	114.7 ± 22.1	>0.05
BMI (kg/m²)	16.6 ± 1.7	16.6 ± 1.7	>0.05
IBW (%)	101.9 ± 3.3	101.9 ± 3.3	>0.05
Body temp.(°C)	38.5 ± 0.4	36.4 ± 0.2	**0.000**

Table 2. Diagnosis of Patients

	n
Tonsillitis	22
Urine tract infection	7
Acute sinusitis	6
Mumps	3
Acute otitis media	2
Pneumonia	1
Periorbital cellulites	1

The mean serum AN levels were different between the first and second admission (p=0.000) (Table 3 and Figure 1). The mean AN level was lower in the first admission than that of at the control visit. The relationship of the serum AN levels with the body temperature is shown in Figure 2. There were no differences in the serum AN levels between the both sexes (p=0.456).

Table 3. Clinical features of patients

	At First Admission	At Control Visit	p
AN (µg/ml)	8.8 ± 1.7	12.04 ± 2.38	**0.000**
	8.6 (5.7-13)	12.5 (6.6-16.1)	

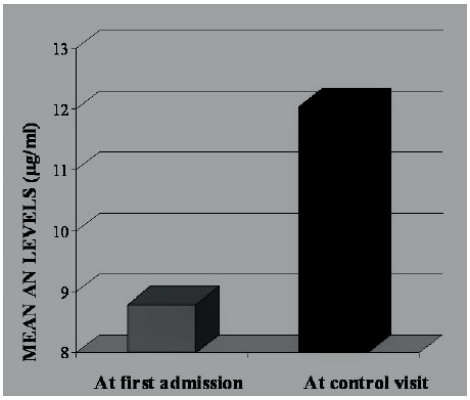

Figure 1. Serum AN levels at the both admissions

Table 4. Hematological and biochemical parameters at admission and control

	First Admission	Control Visit	
	Mean ± Sd - Median (Min.- Max.)	Mean ± Sd - Median (Min.- Max.)	p
Leukocyte (/mm³)**	14066 ± 6007	8059 ± 3315	**0.000**
	12150 (6200-27500)	7400 (3500-17000)	
Neutrophil (%)*	73 ± 15.8	52.5 ± 16.3	**0.000**
	76 (24-96)	56 (20-80)	
Lymphocyte (%)*	26.9 ± 15.9	47.4 ± 16.3	**0.000**
	24 (4-76)	44 (20-80)	
Fibrinogen (mg/dl)*	389 ± 107	366 ± 90	0.105
	374 (89.1-620)	352 (220-613)	
Ferritin (ng/ml)**	86.3 ± 78.3	74.3 ± 52.4	0.274
	61.1 (16.5-45.6)	65.3 (16.7-254.6)	
ESR (mm/h)**	32.8 ± 19.6	33.5 ± 21.8	0.782
	27 (4-90)	35 (5-116)	
CRP (mg/dl)**	5.57 ± 8.5	1.7 ± 2.2	**0.005**
	1.95 (0.100-45.1)	0.87 (0.100-9.56)	
HsCRP (mg/dl)**	50.6 ± 88.1	19.8 ± 31.6	0.077
	19.6 (0.100-474)	6.2 (0.100-119)	
Glucose (mg/dl)*	96 ± 21.6	84.2 ± 11.8	**0.002**
	95 (57-173)	83 (63-107)	
Insulin (µu/ml)**	8.8 ± 10.6	11.4 ± 15.1	0.242
	5 (2-60.9)	6.2 (2-88.2)	
Glucose/insulin**	21.8 ± 14.2	16 ± 12.2	**0.044**
	19.6 (1.8-57)	12.9 (1-43.5)	
HOMA-IR**	2.7 ± 3.9	2.5 ± 3.6	0.778
	1.18 (0.28-17.4)	1.2 (0.32-20.6)	

*: Paired samples t; **: Mann Whitney U test

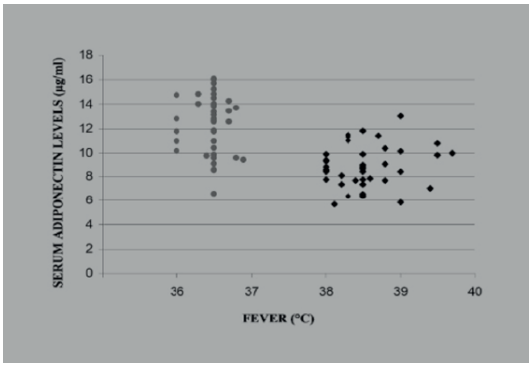

Figure 2. The relation of serum AN levels with body temperature

The hematological and biochemical parameters analyzed in the study are shown in Table 4. The higher leukocyte and neutrophil counts (p=0.000 for both) and serum CRP levels (p=0.005) and lower lymphocyte count (p=0.000) were found at in the first admission when compared to those at in the second admission. There were no differences fibrinogen, and ferritin levels and ESR between the of both admissions (p>0.05). Although the mean HsCRP level of the children in the first admission was higher than at that of the children in the second admission, it was not statistically different (p>0.05).

The glucose levels and the glucose/insulin ratio were higher in the first admission than those in the second admission (p=0.002, and 0.044, respectively). The serum insulin levels and HOMA-IR were not different between both admissions (p>0.05).

In the first admission, the serum AN levels were positively correlated with glucose/insulin ratio and leukocyte counts (r=0.338, p=0.029; r=0.304, p=0.05, respectively). In the second admission, the serum AN levels were negatively correlated with only IBW (r=-0.326, p=0.035). The serum AN levels were not correlated with body temperature, BW, BMI, HOMA-IR, and other hematological and biochemical parameters analyzed in the study at the in both admissions (p>0.05).

DISCUSSION

We found out that the serum AN levels of the samples collected from the children with fever in the first admission were significantly different than those collected three days after the fever of the children with acute nonspecific infections dropped. It is not known why the serum AN levels were lower at in the first admission than those in the second admission. But these changes in the AN levels might may be caused by the decreased synthesis, increased synthesis or catabolism, or increased use of AN in the different stages of the infection.

Adiponectin is produced mainly by the adipose tissue. But its levels decreased in obesity and correlates inversely with the percentage of the fat tissue, BW, waist/hip ratio, BMI, and skin fold thickness (21-23). In our study, the AN levels were not correlated with the BW, IBW, and BMI. This finding may be related to our inclusion criteria in the study, because we only included the children into the study, whose IBWs were between 100% and110%.

Behre et al. (7) reported that the AN levels increased with weight loss in the obese subjects. Although the children could have lost weight during the infection, we did not find any differences in the BWs of the children 4-7 days after the first admission in our study.

There are several studies indicating that AN increases insulin sensitivity and correlates negatively with the parameters of insulin resistance (2,3) and increased AN levels are found in the insulin resistance conditions, such as obesity, type 2 diabetes and metabolic syndrome (5,6). Moreover, Lindsay et al. (24) reported that AN treatment reverses insulin resistance in mice (24). It is well-known that there is a peripheral insulin resistance during infections (25-27). In a study comparing adipocytokine profiles of septic patients and morbidly obese patients, Hillenbrand et al. (28) concluded that as in MO patients, the increased levels of proinflammatory cytokines and altered levels of adipokines may contribute to the development of insulin resistance in critically ill patients. However, the serum AN levels were not correlated with the serum glucose, insulin levels and HOMA-IR in both admissions in our study. On the other hand, the lower AN levels together with the higher glucose levels and higher glucose/insulin ratio, and the positive correlation between AN and the glucose/insulin ratio in the first admission suggest that AN may have a role in providing increased energy requirements during acute infections with fever. But it must be noted that the changes in the AN levels may also be related with unknown factors related to acute inflammation and fever during infections.

The second serum samples were collected from the children three days after the fever dropped. Because, the patients may have recovered and their metabolic situation would be more stable at that time, and therefore the effects of the acute inflammatory changes on the serum AN levels during infection may be better observed. The decreased CRP levels in the second admission also support our statement about the recovery time of the patients.

It has been shown that the serum AN levels were correlated negatively with acute phase reactants (29). As well, lower serum AN levels and higher ESR were found in obese children when compared to the healthy children (30) and there was a negative correlation between the serum AN levels and CRP, IL-6, phospholypase A2 and soluble E-selectine levels in PIMA Indians (31). Another study reported decreased AN levels in women with metabolic syndrome and higher HsCRP levels in women with metabolic syndrome and normal HsCRP levels (32). But there are no reports regarding the relationship between the serum AN levels with acute phase reactants during infections and fever. Although the serum AN levels were not correlated with any acute phase reactants in our study, the changes observed in the AN levels during infection have raised the question whether the serum AN levels by themselves may be an acute phase reactant.

Various infectious agents and toxins stimulate the production of endogenous pyrogens including cytokines IL-1, IL-6, TNF-α and interferon (33). These cytokines reset the thermostat in the hypothalamus and raise the body temperature, resulting in fever. At the same time, they induce synthesis of CRP in the liver (34). In our study, we found out increased CRP levels and HsCRP in the first admission. This finding and the presence of fever suggest indirectly that the pyrogenic cytokine levels increased during the infection. As reported previously, the pyrogenic cytokines, TNF-α and IL-6, inhibit or regulate the AN synthesis (11,35).

In our study, the AN levels were lower in the first admission with fever when compared to the levels three days after the fever dropped. So, decreased serum AN levels during acute infection may lead to the dysregulation of inhibition of synthesis and expression of pro-inflammatory cytokines as described previously (11,35). On the other hand, because of its anti-inflammatory properties, the higher serum AN levels, which were found after the fever dropped in our study, may contribute to the recovery phase of the infection. But we did not determine any cytokine levels in this study, therefore these are indirect suggestions and should be proved with further detailed clinical studies.

There are a limited number of publications in the literature on how the serum AN levels change in febrile illness. In a study made by Tang et al. (36), it was found out that the plasma AN levels increased at different degrees from the onset of fever and remained high at the convalescent phase compared to the healthy control group in adult patients with hemorrhagic fever with renal syndrome. In their studies, Ozgen et al. (37) found out that the children with acute rheumatic fever had higher serum AN levels in the recovery period in comparison to the acute period, particularly in the carditis group. Keskin et al. (38) found out that the serum AN levels were higher in patients with both active and inactive FMF compared to the healthy control group in their studies with the FMF patients. In contrast, Gerdan et al. (39) reported that the patients with FMF had lower serum AN levels during the acute attack compared to the healthy individuals, suggesting that AN production may be suppressed during acute attack in patients with the FMF, or lower AN levels may be caused by the subclinical inflammation in those patients. Takesthita et al. (40) reported that the children with fever and Kawasaki disease had lower AN levels (6.8 ± 2.9 µg/ml) than the healthy children (8.8 ± 1.7 µg/ml) and the children with acute febrile viral infections (8.6 ± 1.3 µg/ml). In that study, these latter two groups were not statistically compared, but they had similar serum AN levels. We found out that there was a change in the AN levels during infection. But, contrary to our study, Takesthita et al. (40) did not reanalyze serum AN levels in children with the febrile viral infection after recovery. On the other hand, in that children with Kawasaki Disease, increased serum AN levels to the levels of healthy control group after treatment is similar to our result.

CONCLUSION

In conclusion, we found out a change in the serum AN levels of children with acute febrile infections. The serum AN levels were lower in the first admission where children had fever than those in the second admission where the fever dropped three days later.. This finding suggests that AN may have a role in the processes of inflammation and fever during infections and should be investigated further in other studies.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: The approval for the study was granted by the Board of Ethics of Eskisehir Osmangazi University (Date of decision date: 27/12/2007, number: 2).

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