Serum Leptin Levels in Children with Acute Viral Hepatitis A

I Caner[1], MA Selimoglu[2], H Yazgi[3], V Ertekin[2]

ABSTRACT

Objectives: *In acute viral hepatitis A (AVH-A), involvement of the liver is through cytotoxic cells and cytokine levels are increased. Immune response of the host determines the severity of the disease. Leptin stimulates cytokines, therefore, the authors hypothesized that the relationship between leptin and cellular immunity might cause different clinical presentations of the disease.*

Methods: *Twenty-eight children with AVH-A and 10 healthy children formed the basis of the study. Serum leptin, C-reactive protein (CRP) and alpha-1-antitrypsin (A1AT) levels were determined.*

Results: *There was significant positive correlation between body mass index (BMI) and leptin levels both in patients and controls ($p = 0.003$ and $p = 0.001$ respectively). No significant difference in serum leptin, CRP or A1AT levels between patients and controls was detected ($p > 0.05$). Presence of icterus or fulminant hepatic failure (FHF) did not affect serum leptin level ($p > 0.05$). Mean A1AT level was significantly higher in children with FHF ($p < 0.05$). On the 30th day of admission, mean BMI, weight and leptin levels increased ($p < 0.01$, $p < 0.01$ and $p < 0.05$ respectively) and mean A1AT level decreased ($p < 0.01$).*

Conclusion: *Leptin levels are not altered in children with AVH-A. In the convalescence period, leptin increased parallel to BMI. It is suggested that expected increment in leptin due to inflammation might be balanced with the decrease due to loss of appetite during acute illness or it might be entirely due to loss of production.*

Niveles de Leptina en Plasma en Niños con Hepatitis Viral A Aguda

I Caner[1], MA Selimoglu[2], H Yazgi[3], V Ertekin[2]

RESUMEN

Objetivos. *En la hepatitis viral aguda de tipo A (HVA-A), el comprometimiento del hígado se produce a través de las células citotóxicas y los niveles de citoquina aumentan. La respuesta inmune del huésped determina cuán severa es la enfermedad. La leptina estimula las citoquinas. Por lo tanto, los autores plantearon la hipótesis de que la relación entre la leptina y la inmunidad celular podría dar lugar a diferentes manifestaciones clínicas de la enfermedad.*

Métodos. *Veintiocho niños con HVA-A y 10 niños saludables, constituyeron la base del estudio. Se determinaron los niveles de leptina en plasma, proteína reactiva C (PRC), y alfa-1-antitripsina (A1AT).*

Resultados. *Hubo correlaciones positivas significativas entre el índice de masa corporal (IMC) y los niveles de leptina, tanto en los pacientes como en los controles ($p = 0.003$ y $p = 0.001$ respectivamente). No se detectó diferencia significativa en los niveles de leptina en plasma, PRC y A1AT entre los pacientes y los controles ($p > 0.05$). La presencia de íctero o fallo hepático fulminante (FHF) no afectó el nivel de leptina en plasma ($p > 0.05$). El nivel medio de A1AT fue significativamente más alto en los niños con FHF ($p < 0.05$). El trigésimo (30mo) día, en hospital, los niveles medios de la IMC, el peso y la leptina aumentaron ($p < 0.01$, $p < 0.01$ y $p < 0.05$ respectivamente), y el nivel medio de A1AT disminuyó ($p < 0.01$).*

Conclusión. *Los niveles de leptina no se alteran en los niños con HVA-A. En el período de convalecencia, la leptina aumentó paralelamente con el IMC. Se sugiere que el incremento esperado*

From: Departments of Paediatrics, Division of Paediatric Gastroenterology, Hepatology and Nutrition[1], and Microbiology[3], Faculty of Medicine, Atatürk University, Erzurum, Turkey and Department of Paediatrics, Division of Paediatric Gastroenterology, Hepatology and Nutrition[2], Faculty of Medicine, Inonu University, Malatya, Turkey.

Correspondence: Dr MA Selimoglu, Inonu Universitesi, Tip Fakultesi, Cocuk Sagligi ve Hastaliklari AD, 44280, Malatya, Turkey. E-mail: mayse@atauni.edu.tr. Fax: 00 90 422 3410128.

en la leptina a causa de la inflamación podría ser compensado con la disminución debida a la pérdida de apetito durante la enfermedad aguda o podría deberse enteramente a la pérdida de producción.

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INTRODUCTION

Leptin, a recently isolated protein encoded by the *ob* gene, is a peptide hormone that mainly regulates food intake and energy expenditure of the human body. A positive correlation between serum leptin level and the percentage of body fat stores is well known (1). Leptin receptors are from the class I cytokine receptor family and are similar to other cytokines with regard to receptor structure (2). It is known that cytokine and leptin levels are affected by each other; it has been demonstrated that leptin stimulates cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-2 (IL-2) and interleukin-6 (IL-6) (3, 4).

In acute viral hepatitis A (AVH-A), involvement of the liver is through cytotoxic cells and increase in cytokine levels was shown in previous studies (5, 6). Immune response of the host determines the severity of the disease. It was hypothesized therefore, that this relationship between leptin and cellular immunity might cause different clinical presentations of the disease.

There is no reported study investigating serum leptin level in AVH-A. In this study, serum leptin level and its relationship with the clinical presentation of AVH-A were investigated.

SUBJECTS AND METHODS

Twenty-eight children (14 males and 14 females) with AVH-A were included in the study. Their sex and age-matched controls (ten healthy children) were randomly selected. Diagnosis of AVH-A was established by clinical features, abnormal liver function tests and positive anti-hepatitis A virus antibodies IgM and IgG. Patients were excluded if they had hepatitis B, C or HIV infection. In addition to the routine laboratory investigations such as full blood count, serum transaminases, total protein, albumin, electrolytes, prothrombin time, INR (international normalized ratio) and ammonia, factors 2, 5 and 7, leptin, C-reactive protein (CRP) and alpha-1-antitrypsin (A1AT) were studied. Serum samples were obtained after 12-hour fasting, and were stored at -80°C until the procedure. Biosource leptin EASIA commercial kit (KAP2281, BioSource Europe SA rue de I'Industrie 8B-1400 Nivelles Belgium) was used for leptin measurement.

Weight, height and body mass index (BMI) of all patients were recorded. BMI was calculated as weight (kg)/height (m^2). Except for one patient who died on the 8th day, patients were re-evaluated as outpatients on the 30th day of the first assessment.

For statistical analysis, Mann-Whitney U and Pearson's correlation tests were used. Parents of the patients were required to give written informed consent before entering the study. The Ethics Committee of Ataturk University Medical Faculty approved the study.

RESULTS

Mean age was 8.2 ± 2.7 years (1–13 years). In the study group, there was no statistical difference in mean age between girls and boys (8.1 ± 2.1 years and 8.3 ± 3.1 years in girls and boys respectively, $p > 0.05$).

Mean BMI, height and weight of the patients and controls were not statistically different (Table 1).

Table 1: Body mass index (BMI), height and weight of the patients on admission and on the 30th day of admission, and of healthy children

Parameters	Healthy children (n = 10)	Patients on admission (n = 28)	Patients on 30th day (n = 27)	p*
Weight (kg)	24.4 ± 8.9	24.1 ± 7.5	25.9 ± 8.4	< 0.01
Height (cm)	121.0 ± 23.4	124.0 ± 16.9	124.1 ± 17.1	> 0.05
BMI (kg/m^2)	15.9 ± 0.3	15.4 ± 1.8	16.5 ± 1.9	< 0.01

*Statistical difference between the values obtained on admission and on 30th day. No statistical difference was detected between the values obtained from healthy children and patients on admission

A statistically significant positive correlation between BMI and serum leptin levels was detected in both patients and healthy children ($p = 0.003$ and $p = 0.001$, respectively). The regression curve of leptin and BMI in children with AVH-A is shown in Fig.1.

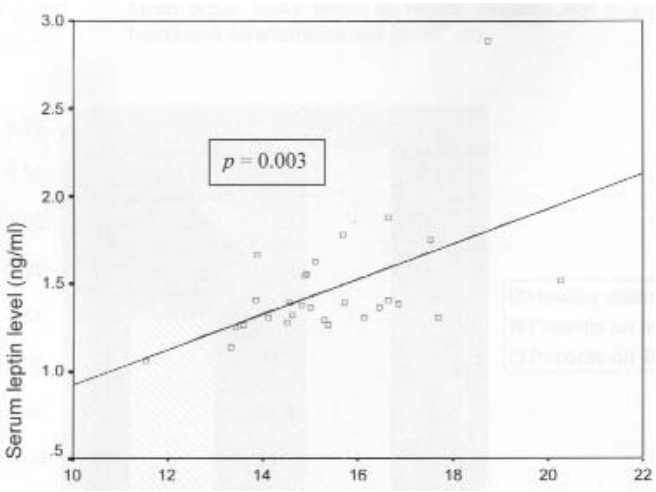

Fig. 1: Relationship between BMI and serum leptin levels in children with acute viral hepatitis A.

There was no significant difference in serum leptin, CRP and A1AT levels between patients and healthy children ($p > 0.05$). Mean serum levels of those parameters are shown in Table 2. No significant correlation was detected between serum leptin levels and liver function tests, haematological or lipid parameters.

Table 2: Mean serum leptin, C-reactive protein (CRP) and alpha-1-antitrypsin (A1AT) levels in patients and healthy children

Parameters	Healthy children (n = 10)	Patients on admission (n = 28)	Patients on 30th day (n = 27)	p*
Leptin (ng/ml)	1.55 ± 0.25	1.50 ± 0.39	1.73 ± 0.68	< 0.05
CRP (mg/dl)	0.75 ± 0.76	2.4 ± 9.5	0.43 ± 0.85	> 0.05
A1AT (mg/dl)	246.9 ± 77.3	273.5 ± 90.1	194.6 ± 64.3	< 0.01

*Statistical difference between the values obtained on admission and on the 30th day. No statistical difference was detected between the values obtained from healthy children and patients on admission.

When the patients were evaluated in respect to the presence of icterus, it was found that serum leptin levels were not different ($p > 0.05$; Table 3). On admission, three children had fulminant hepatic failure (FHF). Serum leptin levels and CRP were not different in patients with or without FHF. In contrast, mean A1AT level was significantly higher in children with FHF compared to others ($p < 0.05$; Table 3).

Evaluation of the patients on the 30th day after the first assessment revealed that mean BMI, weight, and serum leptin level increased significantly ($p < 0.01$, $p < 0.01$, $p < 0.05$, respectively) (Tables 1, 2). In contrast, mean A1AT level was significantly lower and mean CRP level was not different ($p < 0.01$ and $p > 0.05$, respectively) (Table 2). Figure 2 shows graphical presentation of serum leptin levels in healthy children and patients with AVH-A on admission and on the 30th day. Serum leptin levels were comparable in previously icteric and anicteric patients on the 30th day ($p > 0.05$). While mean serum leptin and CRP levels were also similar in children who were admitted with or without FHF ($p > 0.05$), mean A1AT level was significantly higher in children with FHF on the 30th day ($p < 0.05$; Table 4).

Table 3: Mean serum leptin, C-reactive protein (CRP) and alpha-1-antitrypsin (A1AT) levels in children with or without fulminant hepatic failure (FHF).

Parameters	Icteric (n = 24)	Anicteric (n = 4)	p	With FHF (n = 3)	Without FHF (n = 25)	p
Leptin (ng/ml)	1.53 ± 0.42	1.32 ± 0.07	> 0.05	1.33 ± 0.25	1.52 ± 0.4	> 0.05
CRP (mg/dl)	2.58 ± 9.86	0.37 ± 0.27	> 0.05	17.4 ± 28.9	0.6 ± 0.4	> 0.05
A1AT (mg/dl)	276.65 ± 92.84	233.50 ± 21.92	> 0.05	438.3 ± 209.6	253.8 ± 40.9	< 0.05

Table 4: Mean serum leptin, C-reactive protein (CRP) and alpha-1-antitrypsin (A1AT) levels on the 30th day of admission in children with different presentations

Parameters	Icteric (n = 23)	Anicteric (n = 4)	p	With FHF (n = 2)	Without FHF (n = 25)	p
Leptin (ng/ml)	1.75 ± 0.72	1.64 ± 0.46	> 0.05	1.81 ± 1.04	1.72 ± 0.6	> 0.05
CRP (mg/dl)	3.02 ± 11.08	0.27 ± 0.12	> 0.05	2.10 ± 2.11	0.25 ± 0.24	> 0.05
A1AT (mg/dl)	196.07 ± 66.49	175.0 ± 12.72	> 0.05	334.6 ± 129.9	177.8 ± 22.2	< 0.05

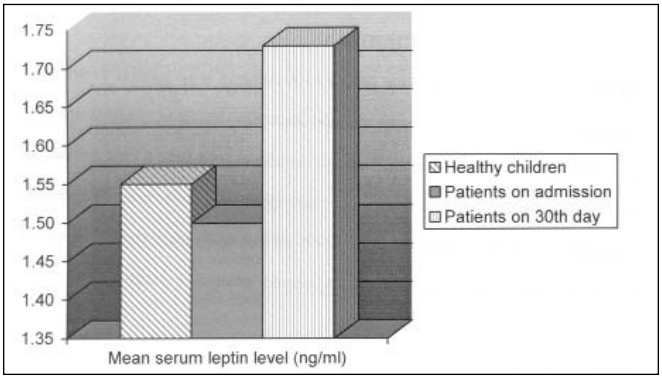

Fig. 2: Mean serum leptin levels in healthy children and inpatients with acute viral hepatitis A on admission and on the 30th day.

One of the children with FHF died on the eighth day of admission. Serum leptin, CRP and A1AT levels of that patient were 1.05 ng/ml, 50.9 mg/dl and 675 mg/ml respectively.

DISCUSSION

It is well known that there is a positive correlation between serum leptin levels and BMI in healthy adults and children, and in some hepatic diseases such as nonalcoholic steatohepatitis and chronic hepatitis B and C (3, 7–13). Sarraf *et al* (14) demonstrated that cytokines increase serum leptin levels in acute inflammation in rats. Such increase was also demonstrated by Maruna *et al* (15) in septic patients and by Orbak *et al* (16) in neonatal sepsis. Maruna *et al* (15) found a posi-

tive correlation between serum leptin levels and several cytokines and acute phase proteins such as TNF-alpha, interleukin-6, CRP and A1AT. Orbak *et al* (16) showed a correlation between serum leptin and CRP levels. IL-6 plays a crucial role in induction of acute phase protein production in the liver (17, 18). Budarina *et al* (5) reported that children with AVH-A had elevated levels of TNF-α, IL-1 beta and IL-4 in the icteric period. In another study, it was found that IL-6 and CRP were higher and A1AT was lower in cases of FHF compared to controls (19). In the present study, mean serum CRP levels of children with or without FHF were 17.4 ± 28.4 mg/dL and 0.6 ± 0.4 mg/dL respectively. The statistical non-significance was entirely due to the lack of patients with FHF. Atono *et al* (20) found that CRP levels were higher in acute illness compared to the convalescence period. Mean CRP levels of patients in the present study, on admission and on the 30th day, were 2.4 ± 9.5 mg/dL and 0.43 ± 0.85 mg/dL respectively. It was not statistically significant; however, it was noticeable that the initial value was out of the normal range. CRP and other acute phase reactants are not sensitive parameters in viral infections (21).

Cytokine levels were not investigated in this study; however, there were no significantly positive correlations between serum leptin levels and either CRP or A1AT. Moreover, no increase was detected in leptin levels of children with AVH-A compared to that of healthy children. In contrast, serum leptin levels were higher in the convalescence period compared to active disease ($p < 0.05$). The authors attributed that increase to the increased appetite during the convalescence period because increase in weight and BMI accompanied the leptin increase. It is known that leptin regulates food intake and energy expenditure of the human body (1). The reason for not recording a difference in leptin levels in hepatitis A infection may be because of a shift in balance in the active phase of the disease or entirely due to a loss of appetite and weight. Because there was no correlation between serum leptin level and parameters that show the synthetic function of the liver *ie* albumin, cholesterol, prothrombin time and factor levels, the authors suggested that serum leptin level was not a good indicator of the synthetic functions of the liver and could not be used as a parameter for prognosis. High transaminase levels are good indicators of hepatic cell destruction (necrosis). Since no correlation between leptin and transaminase levels could be shown, it is suggested that leptin could not be used as a parameter for hepatocellular necrosis in AVH-A. In the study of Crespo *et al* (22), performed in adults with chronic hepatitis C, it was demonstrated that serum leptin level was not correlated with serum levels of albumin, bilirubin, alkaline phosphatase (ALP), gamma globulin, gamma glutamyl transpeptidase (GGT) and transaminases. No correlation was found between serum leptin and parameters of cholestasis, such as ALP, GGT, and bilirubin; thus, from this study the authors suggest that serum leptin level is not affected by cholestasis.

Recent studies have shown that leptin might play a role in haematopoesis. Leptin contributes to an increase in erythroid cells and erythropoietin (23, 24). However, some authors found a negative correlation between leptin and haemoglobin level (25). Wilson *et al* (26) showed a positive correlation between leptin level and white blood cell count. Contrary to this, some other investigators did not determine such correlations between serum leptin levels and haematological parameters such as haemoglobin, leukocyte and platelet count (16, 27). In this study, no correlation between leptin and haematologic parameters either in acute illness or the convalescence period was found.

In conclusion, no significant difference in leptin levels was detected between children with AVH-A and controls. In the convalescence period, leptin increased parallel to BMI, compared to levels in acute illness. It is therefore suggested that the expected increase in leptin levels due to acute inflammation might be balanced with the decrease resulting from loss of appetite during acute illness, or leptin is not affected by hepatic inflammation at all.

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