

Evaluation of Serum Leptin Level in Children With Acute Leukemia

Iraj Shahramian,¹ Noor Mohammad Noori,^{2,*} Elmira Akhlaghi,³ Mohamad Ali Mashhadi,⁴ Elham Sharafi,⁵ and Alireza Teimouri⁶

¹Department of Pediatrics, Zabol University of Medical Sciences, Zabol, IR Iran

²Department of Pediatrics, Children and Adolescents Health Research Center, Zahedan University of Medical Sciences, Zahedan, IR Iran

³General Physician, Faculty of Medicine, Zabol University of Medical Sciences, Zabol, IR Iran

⁴Department of Internal Medicine, Zahedan University of Medical Sciences, Zahedan, IR Iran

⁵Resident of Ophthalmology, Zahedan University of Medical Sciences, Zahedan, IR Iran

⁶Children and Adolescents Health Research Center, Zahedan University of Medical Sciences, Zahedan, IR Iran

*Corresponding author: Noor Mohammad Noori, Department of Pediatrics, Children and Adolescents Health Research Center, Zahedan University of Medical Sciences, Zahedan, IR Iran. E-mail: dr-noori-cardio@yahoo.com

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Abstract

Background: Leptin is a multifunctional hormone plays an important role in regulating lipid, energy, homeostasis, angiogenesis, inflammation, hematopoiesis and cell cycle. This polypeptide is effective in growth and differentiation of leukemic cells through an Ob-R receptor expressed by them.

Objectives: The purpose of this study was to evaluate serum leptin levels in patients with acute leukemia and compare it in lymphoid and myeloid groups.

Patients and Methods: This analytical case-control study, conducted on 60 children in age ranged from 6 months to 16 years in two case and control groups in Ali ibn Abi Talib hospital, Zahedan. They matched based on age and gender and examined after their parent's satisfaction according to the parental consent forms. None of patients had heart disease, digestive, glandular and metabolic problems, iron deficiency anemia and chronic kidney disease. After collecting the samples, leptin levels of both groups were measured with ELISA kit. Then, the gathered data were analyzed in SPSS-20 software, using independent t-test in considering of 95% confidence interval.

Results: Leptin serum levels in patients with acute leukemia and controls showed significant difference ($P < 0.05$). Leptin serum levels in patients with acute lymphoblastic leukemia and acute myeloblastic leukemia showed significant difference ($P < 0.05$). Leptin serum level in relation to age and gender groups was not statistically significant.

Conclusions: The findings of this study showed that in patients with acute leukemia, leptin serum levels increase independently of age and gender. In addition, leptin serum levels in acute lymphoid leukemia were higher than acute myeloid leukemia in this study.

Keywords: Acute Leukemia, Leptin, Acute Lymphoblastic Leukemia, Acute Myeloblastic Leukemia

1. Background

Leptin is a protein with 146 amino acid and a multifunctional polypeptide hormone which is produced from fat cells and bone marrow cells [1]. Leptin hormone plays an important role in regulating fat, energy, homeostasis, angiogenesis, inflammation, hematopoiesis and cell cycle [1-3]. Membrane proteins are members of cytokine family and gp130 [4-6]. This polypeptide not only differentiates the normal cells, but also is effective in growth and differentiation of leukemic cells through an Ob-R receptor. Thus, it can be involved in hematologic malignancy pathogenesis [7-9]. Angiogenesis plays a key role in stimulation and proliferation of non-solid malignant cells and their extension along with leukemia pathophysiology [10]. On the other hand, environmental factors, including changes in the micro-environment of the bone marrow can have an

impact on leukemia development.

In patients with lymphoma the increase of serum leptin levels likely will be used to predict response to treatment or progressive disease in patients with lymphoma [11]. Concentration of adipocytokins is effective in diagnosis and treatment and remission malignancies in adults. Leptin proved, serum levels and resisting levels increase in the children with malignancy in duration of diagnosis and chemotherapy, but the adiponectin has low level. However, it seems that the adipocytokines can be used as new biomarkers in relation with a stage of disease and a reaction to chemotherapy and a target in ALL treatment in futures. Therefore, for its accomplishment, this subject requires more studies on malignancy, especially on pediatric leukemia patients [12]. There was not association between Hodgkin lymphoma and serum leptin levels, but

there was correlation between increase serum adiponectin and Hodgkin lymphoma in childhood [13]. Among survived children from leukemia, high levels of leptin along with anthropomorphic and metabolic changes were observed in the years of follow up even in improved patients [14]. Moreover, this multifunctional hormone probably has some antiapoptotic activities that lead to inhibition of apoptosis in leukemia progenitor cells; on the other hand, it enhances the survival of leukemic cells created in the body [15-17]. Adiponectin levels have an inverse relationship with myeloid leukemia, just unlike other childhood leukemia [13].

Adipose tissue is the main source of leptin secretion; however, normal and malignant breast tissue has been reported to also secrete leptin. Interestingly, high leptin and low adiponectin have been reported in children with ALL compared to age, sex and BMI matched healthy controls [18]. Krysiak reported the increase in adiponectin levels in leukemia [19].

Occurring mutations in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) lead to a polymorphism of leptin receptor gene [20]. Relationship among leptin genotype and the etiology of acute leukemia is not clear but likely there is a correlation between serum leptin levels and properties of high-dose methylprednisolone in patients with acute leukemia [21].

Several studies show that, there is a significant correlation between serum leptin levels and every anthropometric parameter in patients with acute lymphoblastic leukemia after diagnosis and chemotherapy during in the follow up. Also, these studies demonstrated that there is significant relationship between serum leptin in patients treated with cranial irradiation compared with the non-cranial-irradiated patients [22, 23].

2. Objectives

According to the above and the possible role of leptin in leukemia this study designed with aim of evaluating the leptin serum levels in children with acute leukemia.

3. Patients and Methods

In this case-control study, 60 children admitted to the pediatric ward of Ali ibn Abi Talib hospital and were divided into two groups, 30 children as the case group (children with acute leukemia in two groups of 15 patients with AML and 15 with ALL) and 30 children as the control group (healthy children referred to the pediatric clinic for check-ups). Age range of all patients was from 6 months to 16 years. Every patient was newly diagnosed and no treatment had been performed and the control group had no

malignancy. Exclusive criteria were heart disease, gastrointestinal, endocrine, metabolic disorders, anemia, iron deficiency and chronic kidney disease. They were enrolled after their parents signed the consent forms. Two milliliter blood was drawn from these children in fasting at 8:00 am. Samples were centrifuged for 10 minutes at 5°C with 3000 g. The separated serum was held in a -70°C fridge till measuring leptin. Finally, they were transferred to the laboratory of biochemistry, Zahedan University of Medical Sciences. Then, using 250 microns of the isolated serum of these samples, the leptin serum levels were measured by ELISA kit. Data were collected and analyzed in SPSS-20, non-parametric Mann Whitney U statistical and Pearson correlation tests used for the analysis. The level of significant $P < 0.05$ was considered for the 95% confidence interval.

4. Results

From all patients 65% were males. The mean of age was 3.44 ± 5.95 year. Mean of leptin serum levels in the case and control groups were 3.06 ± 3.42 and 0.73 ± 0.98 Pg/mL respectively.

A comparison between the mean leptin serum level in the control (0.98 ± 0.73 Pg/mL) and case (3.06 ± 3.42 Pg/mL) groups showed a significant difference ($P = 0.014$). Comparison of leptin serum levels in the case group between ALL and AML showed a significant difference ($P = 0.014$). Comparison of leptin serum levels in sex groups did not show any significant differences (Table 1). The correlation of leptin serum levels with case and control groups was not significant.

Table 1. Comparison of Leptin Serum Levels in Acute Leukemia Group and Controls, ALL and AML and Sex Groups^a

Variables	Leptin, Pg/mL	P Value
Leukemia		0.025
ALL	4.24 ± 3.71	
AML	1.88 ± 2.73	
Gender		0.232
Male	0.507 ± 0.438	
Female	2.081 ± 3.005	

^aValues are expressed as mean \pm SD.

5. Discussion

According the result of this study, leptin serum levels were higher in children with leukemia than in healthy children whereas leptin serum levels in children with ALL were

higher than those with AML. There was not any relationship between leptin serum levels and age and sex in children with leukemia.

Several authors [4, 8, 9, 15] shown the increase of leptin serum levels in children who suffering from leukemia. Same results of the present study demonstrated the fact of increasing leptin serum levels in patients with acute leukemia. In our patients with acute leukemia the leptin serum level increased but was higher in ALL compared to ALM.

Krysiak analyzed the receptor of leptin in leukemic patients and reported an increase in adiponectin levels in leukemia [19]. However, mutations that are occurring in ALL and AML lead to a polymorphism of leptin receptor gene and subsequently the leptin increases in patients [3, 20] Therefore, not leptin only affects normal cells, but it also plays an important role in growth and differentiation of leukemia cells. The receptor of this hormone is expressed by B cells, T cells and CD34 of promyelocytes and explanation of CD34 receptor by stem cells leads to its effects on colonial differentiation of granulocyte-macrophage colony stimulating factor (G-MCSF) and granulocyte-colony stimulating factor (G-CSF) [7-9]. On the other hand, the most effective factor in the survival and proliferation of tumor cells is angiogenesis. The strongest factor in stimulating angiogenesis in vascular endothelial growth factor (VEGF) endothelial cell is the driving factor of the growth of colonies in granulocytes, which stimulates the G-MCSF production from human strap tough cells. It also stimulates the G-CSF, macrophage-colony stimulating factor (M-CSF), IL-6 production of stem cell factor and endothelial cell. Leptin's synergistic effect on VEGF stimulates angiogenesis [10]. Tavil et al. showed that there was no relationship among leptin genotype and the etiology of acute leukemia in childhood but a likely correlation between serum leptin levels and properties of high-dose methylprednisolone in patients with acute leukemia [21] and this is dissimilar with the results of our study. In our study the leptin serum levels was higher in patients with acute leukemia in compared to controls which is agree with the results of Tavil's study.

Several authors conducted various studies and resulted significant correlation between serum leptin levels and every anthropometric parameters in patients with ALL after diagnosis and chemotherapy during follow up [22, 23]. In our research we also concluded that in patients with ALL the leptin serum levels were increased in similarity. Also, these studies demonstrated that there was significant relationship between serum leptin in patients treated with cranial irradiation compared with their counterparts [22, 23]. Their results are partially consisting by the results of the present research.

In another study conducted by Gorska et al. the leptin serum levels were different in children with acute myeloid and lymphocytic leukemia, they were higher in patients with ALL than AML [24]. We received to a conclusion of higher leptin serum levels in patients with ALL compared to AML in which consists with the later study.

A study by Mariani et al. on patients with CML resulted that, leptin serum level is higher than the reference ranges and in comparison of our results a similarity was found when we measured the leptin serum level in patients with acute leukaemia in terms of ALL and AML [25].

Findings of a study by Tonorezos et al. suggested that among survivors of childhood leukemia, higher leptin levels were associated with measures of body fat and also anthropomorphic and metabolic changes many years after ALL treatment, and it remains a major health problem facing by survivors and may be related to central leptin resistance [14]. We measured the leptin serum level in patients with acute leukaemia in terms of ALL and AML and concluded similar results with Tonorezos et al. [14] study.

The findings of this study showed strong evidence that in patients with acute leukemia, leptin serum levels increase independently of age and gender. In addition, leptin serum levels in acute lymphoblastic leukemia were higher than acute myeloid leukemia.

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Footnotes

Authors' Contribution: Iraj Shahramian and Noor Mohammad Noori provided conception and design of the study and revised the article. Mohamad Ali Mashhadi, Elmira Akhlaghi and Elham Sharafi participated in data collection and drafting the manuscript, also the data analysis and interpretation performed by Alireza Teimouri.

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References

1. Ziyilan YZ, Baltaci AK, Mogulkoc R. Leptin transport in the central nervous system. *Cell Biochem Funct.* 2009;27(2):63-70. doi: [10.1002/cbf.1538](https://doi.org/10.1002/cbf.1538). [PubMed: 19205004].

2. Shahramian I, Noori NM, Hashemi M, Sharafi E, Baghbanian A. A study of serum levels of leptin, ghrelin and tumour necrosis factor-alpha in child patients with cyanotic and acyanotic, congenital heart disease. *J Pak Med Assoc.* 2013;**63**(11):1332-7. [PubMed: [24392513](#)].
3. Kim JY, Park HK, Yoon JS, Kim SJ, Kim ES, Song SH, et al. Molecular mechanisms of cellular proliferation in acute myelogenous leukemia by leptin. *Oncol Rep.* 2010;**23**(5):1369-74. [PubMed: [20372853](#)].
4. Alizadeh S, Bohloli S, Abedi A, Mousavi SH, Jafazadeh B, Hamrang N, et al. Evaluation of leptin, LIF and IL-6 serum levels in lymphoid leukemia patients [in Persian]. *J Ardabil Univ Med Sci.* 2010;**10**(4):340-51.
5. Wasik M, Gorska E, Popko K, Pawelec K, Matysiak M, Demkow U. The Gln223Arg polymorphism of the leptin receptor gene and peripheral blood/bone marrow leptin level in leukemic children. *J Physiol Pharmacol.* 2006;**57** Suppl 4:375-83. [PubMed: [17072067](#)].
6. Gainsford T, Alexander WS. A role for leptin in hemopoieses?. *Mol Biotechnol.* 1999;**11**(2):149-58. [PubMed: [10464769](#)].
7. Haluzik M, Markova M, Jiskra J, Svobodova J. [Is leptin physiologically important in the regulation of hematopoiesis?]. *Cas Lek Cesk.* 2000;**139**(9):259-62. [PubMed: [10953422](#)].
8. Iversen PO, Drevon CA, Reseland JE. Prevention of leptin binding to its receptor suppresses rat leukemic cell growth by inhibiting angiogenesis. *Blood.* 2002;**100**(12):4123-8. doi: [10.1182/blood-2001-11-0134](#). [PubMed: [12393625](#)].
9. Bruserud O, Huang TS, Glenjen N, Gjertsen BT, Foss B. Leptin in human acute myelogenous leukemia: studies of in vivo levels and in vitro effects on native functional leukemia blasts. *Haematologica.* 2002;**87**(6):584-95. [PubMed: [12031914](#)].
10. Hussong JW, Rodgers GM, Shami PJ. Evidence of increased angiogenesis in patients with acute myeloid leukemia. *Blood.* 2000;**95**(1):309-13. [PubMed: [10607717](#)].
11. Beaulieu A, Poncin G, Belaid-Choucair Z, Humblet C, Bogdanovic G, Lognay G, et al. Leptin reverts pro-apoptotic and antiproliferative effects of alpha-linolenic acids in BCR-ABL positive leukemic cells: involvement of PI3K pathway. *PLoS One.* 2011;**6**(10):e25651. doi: [10.1371/journal.pone.0025651](#). [PubMed: [21991326](#)].
12. Moschovi M, Trimis G, Vounatsou M, Katsibardi K, Margeli A, Damianos A, et al. Serial plasma concentrations of adiponectin, leptin, and resistin during therapy in children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol.* 2010;**32**(1):e8-13. doi: [10.1097/MPH.0b013e3181b8a50c](#). [PubMed: [20051777](#)].
13. Petridou ET, Dessypris N, Panagopoulou P, Sergentanis TN, Mentis AF, Pourtsidis A, et al. Adipocytokines in relation to Hodgkin lymphoma in children. *Pediatr Blood Cancer.* 2010;**54**(2):311-5. doi: [10.1002/pbc.22294](#). [PubMed: [19856392](#)].
14. Tonorezos ES, Vega GL, Sklar CA, Chou JF, Moskowitz CS, Mo Q, et al. Adipokines, body fatness, and insulin resistance among survivors of childhood leukemia. *Pediatr Blood Cancer.* 2012;**58**(1):31-6. doi: [10.1002/pbc.22964](#). [PubMed: [21254377](#)].
15. Hamed NA, Sharaki OA, Zeidan MM. Leptin in acute leukaemias: relationship to interleukin-6 and vascular endothelial growth factor. *Egypt J Immunol.* 2003;**10**(1):57-66. [PubMed: [15719623](#)].
16. Petridou E, Mantzoros CS, Dessypris N, Dikalioti SK, Trichopoulos D. Adiponectin in relation to childhood myeloblastic leukaemia. *Br J Cancer.* 2006;**94**(1):156-60. doi: [10.1038/sj.bjc.6602896](#). [PubMed: [16404369](#)].
17. Dalamaga M, Crotty BH, Fargnoli J, Papadavid E, Lekka A, Triantafylli M, et al. B-cell chronic lymphocytic leukemia risk in association with serum leptin and adiponectin: a case-control study in Greece. *Cancer Causes Control.* 2010;**21**(9):1451-9. doi: [10.1007/s10552-010-9573-y](#). [PubMed: [20454844](#)].
18. Sheng X, Mittelman SD. The role of adipose tissue and obesity in causing treatment resistance of acute lymphoblastic leukemia. *Front Pediatr.* 2014;**2**:53. doi: [10.3389/fped.2014.00053](#). [PubMed: [24926474](#)].
19. Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. *Eur J Nutr.* 2012;**51**(5):513-28. doi: [10.1007/s00394-012-0370-0](#). [PubMed: [22584415](#)].
20. Skoczen S, Tomasiak PJ, Bik-Multanowski M, Surmiak M, Balwierz W, Pietrzyk JJ, et al. Plasma levels of leptin and soluble leptin receptor and polymorphisms of leptin gene -18G > A and leptin receptor genes K109R and Q223R, in survivors of childhood acute lymphoblastic leukemia. *J Exp Clin Cancer Res.* 2011;**30**:64. doi: [10.1186/1756-9966-30-64](#). [PubMed: [21631924](#)].
21. Tavit B, Balta G, Ergun EL, Ozkasap S, Tuncer M, Tunc B, et al. Leptin promoter G-2548A genotypes and associated serum leptin levels in childhood acute leukemia at diagnosis and under high-dose steroid therapy. *Leuk Lymphoma.* 2012;**53**(4):648-53. doi: [10.3109/10428194.2011.626881](#). [PubMed: [21955253](#)].
22. Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. *Ital J Pediatr.* 2012;**38**:4. doi: [10.1186/1824-7288-38-4](#). [PubMed: [22284631](#)].
23. Siviero-Miachon AA, Spinola-Castro AM, Guerra-Junior G. Adiposity in childhood cancer survivors: insights into obesity physiopathology. *Arq Bras Endocrinol Metabol.* 2009;**53**(2):190-200. [PubMed: [19466212](#)].
24. Gorska E, Popko K, Wasik M. Leptin receptor in childhood acute leukemias. *Adv Exp Med Biol.* 2013;**756**:155-61. doi: [10.1007/978-94-007-4549-0_20](#). [PubMed: [22836631](#)].
25. Mariani S, Basciani S, Giona F, Lubrano C, Ulisse S, Gnessi L. Leptin modification in chronic myeloid leukemia patients treated with imatinib: An emerging effect of targeted therapy. *Leuk Res Rep.* 2013;**2**(2):58-60. doi: [10.1016/j.lrr.2013.07.001](#). [PubMed: [24371782](#)].