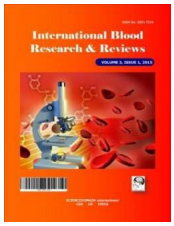

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Serum Leptin and Adiponectin Levels in de Novo Acute Myeloid Leukemia Patients: Correlation with Clinical Characteristics

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Authors' contributions

This work was carried out in collaboration between all authors. Author NABA designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author NABA performed lab analysis at NCI and managed the literature searches analyses of the study. Author MMK managed the experimental process, wrote the protocol and revised the manuscript. Authors MG and OS collected the patient data and revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim of the Study: Acute myeloid leukemia (AML) is a heterogeneous clonal stem cell malignancy characterized by proliferation of immature hematopoietic cells. Adipokines in particular leptin and adiponectin are highly active molecules that attracted considerable interest due to their potential role in the development of cancer as a risk factor. We aimed to measure the body mass index, serum levels of leptin and adiponectin in AML patients, correlating these levels with standard prognostic markers of the disease.

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Study Design: A total of 60 newly diagnosed AML patients and twenty healthy controls age and sex matched were enrolled.
Methodology: All cases had complete blood counts. Patients had bone marrow aspiration/biopsy specimens, EDTA peripheral blood or bone marrow aspirate specimens for flow cytometry analysis, and heparinised sample for cytogenetic study. Body mass index (BMI) was calculated by dividing body weight (kg) by square height (m^2). Serum leptin and adiponectin were assayed by enzyme linked immune assays.
Results: Out of all AML patients; 33 patients (55%) presented with hepatomegaly; 29 patients (49%) presented with splenomegaly and 11 (18.3%) presented with lymphadenopathy. None of our patients showed extramedullary involvement. Serum leptin were determined at a level of 10.9±9.5 ng/ml in the patient group which is significantly lower than the controls 60.2±165.6 ng/ml (*P*= .05). Serum adiponectin showed highly significant lower levels in the studied group compared to controls 1.5±0.9 and 4.6±2.9 respectively (*P*<.001). No significant correlation was detected between serum adipokines and other clinical or laboratory parameters except a negative significant correlation was detected between serum adiponectin and bone marrow blast. Regarding cytogenetic analysis, no significant correlation was detected between cytogenetic and serum leptin and adiponectin levels (*P*= .98, .38), respectively.
Conclusion: The current study addressed the reduction of adipocytokines levels in AML together with negative correlation between bone marrow blasts and adiponectin levels suggesting the implication of adipocytokines in pathogenesis of AML, however these findings necessitate additional studies on large scale of cases.

Keywords: Adipokines; leptin; adiponectin; acute myeloid leukemia; cytogenetic; body mass index; obesity.

1. INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous clonal stem cell malignancy characterized by proliferation of immature hematopoietic cells and accumulation in bone marrow, peripheral blood, and other tissues. This process is associated with manifestations of bone marrow failure (neutropenia, anemia, and thrombocytopenia) [1].

AML accounts for up to 90% of all acute leukemias in adults. It is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths from leukemias [2].

Despite recent advances in diagnosis and treatment of AML, the overall survival in adults remains poor. The 5-year survival reaches <50% in patients <45 years of age and <5% in patients >65 years of age at diagnosis [1].

The prognostic factors affecting outcome of adult AML patients may be subdivided into those related to patient characteristics which include age, performance status, comorbidities and general health condition and those related to characteristics particular to the AML clone such as white blood count (WBC), existence of prior MDS, previous cytotoxic therapy for another disorder, and cytogenetic and molecular genetic changes in the leukemic cells at diagnosis [3].

The host-related factors usually predict treatment-related mortality (TRM) and become more important as patient age increases while the disease-related factors predict resistance to, at least, conventional therapy [3].

Obesity or body mass index (BMI) is considered important host factor as many studies have noted an association between it and higher incidence of various hematologic malignancies, including AML [4,5].

However, data regarding the prognosis of obesity on AML are conflicting. Pediatric leukemia patients with unhealthy BMI showed poor prognosis [6], but other studies showed that obesity did not affect the prognosis of adults with AML [7,8].

The effects of obesity may be explained by two different mechanisms, first as a result of the greater mass of fat itself and second as a result of an expansion of the endocrine function of the enlarged and higher numbers of fat cells and the effects of these endocrine changes on target tissues (e.g., increased plasma leptin, insulin, insulin growth-factor [IGF]-1, androgens, estrogens, IL-6, and tumor necrosis factor-α) [9].

Leptin is expressed by adipocyte tissue as a product of the obesity gene (ob gene). It consists of a 16 KD secreted protein [10,11]. Leptin receptors are commonly expressed in newly diagnosed cases of AML, Chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). Leptin receptor expression is higher in CD34 positive immature hematopoietic cells than in mature neutrophils [12].

Leptin is identified as a key hormone in the regulation of energy expenditure by reducing food intake and controlling adipose tissue metabolism, also it can stimulate proliferation and inhibit apoptosis of leukocyte subgroups. Moreover, leptin also stimulates the growth and viability of leukemic cells, suggesting a role for leptin in the pathogenesis of hematologic malignancies [13].

Adiponectin is an adipose-tissue protein and it has insulin-sensitizing, anti-inflammatory, and antiatherogenic activities [14]. Decrease level of adiponectin is associated with malignancies [15].

Adiponectin has been linked to increase the risk of myeloid hematological malignancies, myelodysplastic syndromes (MDS), and myeloproliferative disorders including chronic myelogenous leukemia (CML). These findings may be explained by hypothesis stating that adiponectin induces apoptosis and inhibits predominantly the proliferation of myeloid cell lineage [16].

1.1 Aim of the Study

The aim of current study is to measure the body mass index, serum levels of leptin and adiponectin in AML patients comparing with normal healthy controls, and correlate these levels with standard prognostic markers of the disease.

2. MATERIALS AND METHODS

2.1 Study Design

A total of 60 untreated newly diagnosed acute myeloid leukemia patients presenting to the Clinical Pathology Department of the National Cancer Institute (NCI), Cairo University, Egypt from October 2013 to June 2015 were enrolled. The studied patients included 28 males (46.7%) and 32 females (53.3%) in addition to 20 healthy age and sex matched controls were taken.

Patients with febrile neutropenia, sepsis, any organ failure, with hypertension or diabetes were excluded.

Body mass index (BMI) was calculated by dividing body weight (kg) by square height (m^2). We dichotomized BMI as BMI < 25 (non-overweight and non-obese) and BMI ≥ 25 (overweight and obese). Diagnosis was based on WHO criteria in addition to FAB classification.

Pretreatment evaluation included thorough history and full clinical examination, complete blood count (CBC), bone marrow (BM) aspiration and trephine biopsy for morphology, cytochemistry, EDTA peripheral blood or bone marrow aspirate specimens for flow cytometry analysis [17] and heparinised sample for cytogenetic study [18] were collected from all patients. Serum samples from both patients and controls were taken for serum leptin, adiponectin, liver and kidney functions tests, uric acid level, serum electrolytes and LDH. Radiological examination includes chest radiographs, abdominal ultrasound, ECG and echocardiography.

Enzyme-linked immunosorbent assay (ELISA): Leptin and adiponectin were assayed by quantitative sandwich enzyme linked immune assays according to the manufacturer's instructions. The assays was performed on serum samples collected from both patients and controls using DIA Source Leptin-ELISA kit (Belgium) and Avibion Human Adiponectin (Acrp30) ELISA kit (Finland) respectively. The intensity of color developed is proportional to the concentration of leptin and adiponectin in the samples. The concentration of the samples can be read directly from standard curve.

2.2 Statistical Analysis

Statistical Data were analyzed using IBM SPSS advanced statistics version 20 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation for variables with normal distribution. Qualitative data were expressed as frequency and percentage. The Wilcoxon Rank Sum test was used to compare categorical variables and the independent “t” test or the Mann Whitney test was used to compare numeric variables according to the type of data distribution. For possible association between each two variables Ranked Sperman test was used for non-parametric data. Chi-square test was used for comparison between two

independent groups as regards the categorized data. Probability *p* =.05 was considered significant and highly significant if *P* <.001.

3. RESULTS

The studied patients included 28 males (46.7%) and 32 females (53.3%) with M: F ratio 1:1.4. Their age ranged from 15 to 73 years. Twenty healthy subjects were taken as control. They were 11 males (55%) and 9 females (45%) with male to female ratio 1.2:1. Their age ranged from 26 to 50 years.

Out of all AML patients; 33 patients (55%) presented with hepatomegaly; 29 patients (49%) presented with splenomegaly and 11 (18.3%) presented with lymphadenopathy. None of our patients showed extramedullary involvement.

Serum leptin were determined at a level of 10.9±9.5 ng/ml in the patient group which is significantly lower than the controls 60.2±165.5 ng/ml (*P*= .05). Furthermore serum adiponectin showed highly significant lower levels in the studied group compared to controls 1.5±0.9 and 4.6±2.9 respectively *P* = .001 (Table 1).

Forty eight patients (80%) were non-overweight and non-obese BMI <25 Kg/m^2. 11 of the control group (55%) were non-overweight and non-obese BMI <25 Kg/m^2. Statically significant difference exists regarding BMI between acute myeloid leukemia patients when compared with normal controls (*P*= .05) (Table 2).

According to cytogenetic analysis, the patient group was divided into two risky subgroups: favorable (n=20), both intermediate and unfavorable (n=40) were joined together due to low numbers of unfavorable. There was no significant correlation between cytogenetic abnormalities and both serum leptin and adiponectin levels (*P*= .98, .38), respectively (Table 3).

Correlation between leptin and other laboratory data showed no significant difference for parameters including white blood cell count, hemoglobin level, platelet count, percentage (%) of peripheral or bone marrow blasts infiltration, serum lactate dehydrogenase (LDH) level, *P* > .05 (Table 4).

Correlation between adiponectin and the previously mentioned laboratory data revealed significant negative correlation with BM blast % (r 0,326 & *P*=.05). However no significant difference with other parameters including white blood cell count, hemoglobin level, platelet count, percentage (%) of peripheral blasts , serum lactate dehydrogenase level *P* >.05 Table 5.

Table 1. Serum leptin and adiponectin levels in acute myeloid leukemia patients versus controls

Item	AML cases n=60	Normal controls n=20	*P*- value
Leptin (ng/ml)			
Mean±SD	10.9±9.5	60.2±165.5	.02*
(Median)	9.0	20.0	
Adiponectin (ng/ml)			
Mean±SD	1.5±0.9	4.6±2.9	<.001**
(Median)	1.2	3.6	

*** Highly significant; *Significant*

Table 2. Comparison between patients and controls with regard to BMI

Item		Patients n= 60		Control n= 20		*P*- value
		No.	%	No.	%	
BMI (kg/m^2)	<25	48	80%	11	55%	
	≥25	12	20%	9	45%	0.02*

**Significant*

Table 3. Serum adipocytokine levels (mean ±SD) in different cytogenetically classified acute myeloid leukemia patients

AML cases n= 60	Favorable n= 20	Intermediate+ Unfavorable n= 40	*P*-value
Leptin (ng/ml)	10.94±9.9	10.87±9.4	.980
Adiponectin (ng/ml)	1.3±0.8	1.6±1.1	.386

Table 4. Correlation between serum leptin level and, WBCs, HB, PLT count, blast % (Blood & bone marrow), LDH in acute myeloid leukemia patients

Leptin (ng/ml)	WBC (blood)	HB (blood)	PLT (blood)	Blast % (blood)	Blast % (bone marrow)	LDH Iu/L
R	-0.09	0.03	-0.03	-0.11	0.09	0.014
P- value	0.470	0.846	0.821	0.389	0.484	0.914

Table 5. Correlation between serum adiponectin level and WBCs, HB, PLT count, blast % (blood & bone marrow), LDH in acute myeloid leukemia patients

Adiponectin (ng/ml)	WBC (blood)	HB (blood)	PLT (blood)	Blast% (blood)	Blast % (bone marrow)	LDH Iu/L
R	0.05	-0.10	-0.13	-0.07	-0.326	-0.02
P- value	0.692	0.446	0.329	0.573	0.04*	0.859

** Significant*

4. DISCUSSION

Acute Myeloid Leukemias (AML) are heterogeneous group of blood malignancies, characterized by a block at various stages of hematopoietic differentiation, leading to the accumulation of immature myeloid cells in bone marrow and peripheral blood [19]. The more carefully AML is studied; the clearer appears the heterogeneity between cases regarding morphology, immunological phenotype, and associated molecular genetic abnormalities [20]. Serum leptin levels are affected by many factors including energy imbalance, fasting, acute infection, inflammation, hormones and many cytokines [21,22].

Leptin alone and in combination with other cytokines has a stimulatory effect on leukemia hematopoiesis and has anti –apoptotic effect [23,24]. We could speculate that lower levels of leptin could represents a stimulating factor for uncontrolled proliferation. This effect could be explained by the expression of leptin by bone marrow stromal cells and the detection of leptin receptors on normal and leukemic hematopoietic cells [25,26,27].

Serum leptin levels have been examined in different malignancies including leukemia. Significant lower levels of serum leptin in the studied AML group was detected than the control group (*P* =.05). This is in agreement with (Aref et al. [28], (Bruserud et al. [29]). Both detected significant lower levels of serum leptin in their AML patients. This reduction in serum level of leptin is not altered during chemotherapy – induced cytopenia and complicating febrile neutropenia [29].

In addition studies on gastrointestinal cancers revelaed lower circulating leptin concentration, which were not altered by the presence of an inflammatory response and is not a determined factor in weight loss in those patients [30,31].

However in contrary to our results in a small study done by Hamed NA and his colleague a significantly elevated level of leptin was detected. This elevation was unrelated to the presence of extramedullay infiltaration or repose to chemotherapy [32].

Adiponectin, an adipocyte-derived secretory protein, is a 30-kDa complement C1q- related protein. Adiponectin circulates as several multimericspecies, including a high molecular weight form thought to be the most clinically relevant. Serum levels of adiponectin are markedly decreased in individuals with visceral obesity and states of insulin resistance, such as type 2 diabetes mellitus and atherosclerosis [33].

In the present work, adiponectin levels were significantly lower in AML patients as compared to healthy controls. This reduction might be due to decrease in the bone marrow fat mass due to overcrowding of the BM by blast cells; this is confirmed by the significant negative correlation between the BM blast cell counts and adiponectin levels detected in our AML patients. This finding is keeping with that reported in several types of cancers including leukemia [14,15,28].

In an *in vitro* study done by Yokota et al. [34] in 2000 they have investigated the functions of adiponectin in haematopoiesis and found that adiponectin predominantly inhibits proliferation of myeloid cell lines, and induces apoptosis in myelomonocytic leukemia lines, but did not suppress proliferation of erythroid or lymphoid cell lines. This hormone has also been inversely

associated with adult forms of cancer that have been epidemiologically investigated, namely breast cancer [35,36], endometrial cancer [37], acute leukemia [38,39].

Regarding correlation studies a negative significant correlation was detected between serum adiponectin and bone marrow blast cell percentage (P = .05), which is in line with different other studies [28,40]. On the other hand no significant correlation was detected between serum adipocytokines (leptin and adiponectin) and different hematologiocal parameters (WBCs, Hb, platelet count), serum LDH level and, peripheral blood blasts. These finding were demonstrated by Yilmaz et al. [12] and Hamed et al. [32], who reported a none significant correlation with peripheral blood and bone marrow blasts.

Leptin and adiponectin levels did not show a significant correlation with the two cytogenetic groups, contrary to Aref et al. [28] and Molica et al. [40], who demonstrated a significant correlation between adipocytokines and different cytogenetic groups. In their study higher levels of leptin and adiponectin were estimated in unfavourable and favourable cytogentic groups respectively. Their results point out for the prognostic value of serum leptin and adiponectin levels in acute myeloid leukemia patients.

In a series of recent papers researches described leptin and adiponectin levels during diagnosis and treatment of different hematological diseases demonstrating the changes in adipose tissue and metabolism in their disease states [22,38,41,42].

5. CONCLUSION

The current study addressed the reduction of adipocytokines levels in association with de novo AML together with negative correlation between bone marrow blasts and adiponectin .These finding suggest the implication of both leptin and adiponectin in AML pathogenesis which might be useful as prognostic markers of AML , however These findings necessitate additional studies of leptin and adiponectin in AML patients and to be related to other risk factors as severe illness, altered energy balance and disease complications on large scale of cases.

CONSENT

Written informed consent was obtained from all participants involved in the study.

ETHICAL APPROVAL

The study was approved by the Regional Research and Ethics Committee at the National Cancer Institute (NCI), Cairo University.

DISCLAIMER

This manuscript was presented in the conference.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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