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B-cell Chronic Lymphocytic Leukemia risk in association with serum leptin and adiponectin levels: a case-control study in Greece

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Abstract

Aim—Leptin and adiponectin are two well studied adipokines in relation to malignancies. In this study, we examined the association between leptin/adiponectin and risk of B-cell chronic lymphocytic leukemia (B-CLL), as well as the relationships between adipokines and several established prognostic factors of B-CLL.

Methods—Ninety-five patients with incident B-CLL and 95 hospital controls matched on age and gender were studied between 2001 and 2007, and blood samples were collected. Leptin, total and high molecular weight adiponectin and prognostic markers of B-CLL were determined.

Results—Cases had a higher body mass index (BMI) than controls (p=0.01) and lower levels of leptin (p<0.01). Significantly more cases than controls presented a family history of lymphohematopoietic cancer (LHC) (p=0.01). Higher serum leptin levels were associated with lower risk of B-CLL adjusting for age, gender, family history of LHC, BMI and serum adiponectin; the multivariate odds ratio comparing highest to lowest tertile was 0.05 (95% CI 0.01–0.29, p trend <0.001); Adiponectin was not significantly different between cases and controls.

Conclusion—Leptin was found to be inversely associated with risk of CLL but in contrast to prior studies of CLL and hematologic malignancies, this study found no significant association between CLL and adiponectin.

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Conflict of interest statement
There is no conflict of interest related to this research.

Keywords

Adiponectin; Leptin; Adipokine; Chronic Lymphocytic Leukemia; Obesity

Introduction

B-cell chronic lymphocytic leukemia (B-CLL) is a malignancy of accumulating well-differentiated monoclonal CD5+ B-lymphocytes and represents the most frequent adult form of leukemia in Western countries, accounting for approximately 30% of all cases[1]. B-CLL is more common in the elderly as well as among white males[1–2]. Although genetic susceptibility plays an important role[1], environmental risk factors such as exposure to chemicals, sunlight, ionizing radiation, viruses and diet do not seem to be associated with the etiology of B-CLL[1–3]. Importantly, recent evidence suggests a contributing role for obesity to the etiology of B-CLL[2,4].

Obesity is considered to increase the risk of many types of cancer, including breast, prostate, endometrial, colon, and other, including certain hematologic malignancies such as childhood AML[5–9]. Hormones whose levels are altered in the obese state, such as the adipokines adiponectin and leptin, may underlie this association. Case-control studies have reported lower levels of the adipokine adiponectin in cancer patients when compared to controls in all of the above cancers[5, 8–10]. Leptin has been proposed to have stimulatory effects on hematopoietic cells, as well as antiapoptotic properties, and its role in leukemic processes has previously been investigated[11–15]. Adiponectin functions as an insulin sensitizing hormone, but also possesses anti-inflammatory, anti-proliferative, and pro-apoptotic properties which make this hormone a possible mediator of the obesity-cancer relationship[8,16–18]. Adiponectin, which is composed of a globular head attached to a collagen-like stalk, circulates in several isoforms, including a low molecular weight adiponectin (LMW) isoform comprising trimers and hexamers, and a high molecular weight (HMW) isoform comprised of multimers of 12–18 units. Globular adiponectin, the product of proteolytic cleavage separating the globular domain from the collagenous domain, has also been studied in relation to malignancies[19–21]. Adiponectin signals mainly through two receptors, AdipoR1 and AdipoR2, but it has also been shown to inhibit tumor growth *in vitro* without receptor interactions by oligomerization-dependent binding of growth factors[19,22–23]. Studies where HMW adiponectin is measured along with total adiponectin have demonstrated that its association with risk for malignancy parallels that of total adiponectin[24].

With regard to hematologic malignancies, we have shown previously that low serum adiponectin levels are associated with myelodysplastic syndrome (MDS), multiple myeloma, childhood acute myelogenous leukemia (AML) but not acute lymphoblastic leukemia (ALL)[9, 25–27]. Avcu and colleagues reported an association between adiponectin and B-CLL in a small study with 19 B-CLL cases and 36 controls[28]. In addition, leptin has also been proposed to have a role in hematopoiesis and has been reported to be positively associated with B-CLL in a previous study with small number of cases[11, 14]. No prior large studies have confirmed these findings and no previous studies have explored simultaneously the role of total and HMW adiponectin, and leptin in the etiology of B-CLL[14, 28–29].

In this case-control study of 95 cases and 95 age-, gender-, and date-matched hospital controls, we attempted to investigate the contribution of adiponectin, HMW adiponectin and leptin separately and jointly to the pathogenesis of B-CLL, taking also into account potential confounders including the family history of lymphohematopoietic cancer (LHC) and body

mass index (BMI). We also assessed whether a relationship between prognostic markers and levels of these hormones exists among patients diagnosed with B-CLL.

Patients and Methods

In this study, cases and controls were recruited from patients hospitalized at the Veterans' Administration General Hospital of Athens (NIMTS). This hospital is the only Veteran's Hospital in the Athens Metropolitan area and in Southern Greece. The study covered 95 cases and 95 controls under 86 years old from the same study base, who were all of Greek nationality and permanent residents of Greece. Medical records were reviewed and interviews were carried out to obtain information on demographic characteristics, medical history as well as weight and height. Family history of LHC was collected for first-degree relatives (parents and siblings) and for second-degree relatives (grandparents, uncles and aunts).

Selection of cases

Eligible cases included newly diagnosed patients with B-CLL, under age 86, consecutively admitted to the Internal Medicine Department-Hematology Section of the Veterans' Hospital between January 22, 2001 and October 21, 2007. Cases with previous cancer were excluded from the study. A total of 99 cases were identified, and of those 95 cases (66 males and 29 females), aged 51 to 82 years (median age, 63) consented to participate and were interviewed. The main reasons for nonparticipation were severity of the patient's medical condition and/or refusal on the part of the subject or his/hers relatives. Responders and non-responders did not differ on the basis of demographic variables, notably age, gender and time of diagnosis.

Selection of controls

Controls were patients, under age 86, admitted for non-neoplastic and non-infectious conditions to the Orthopedic or Ophthalmologic Department of the same hospital and matched to cases on age (± 5 years), gender, and year/month of diagnosis (±1 month). No control developed B-CLL. The main causes of admission to the hospital in the control group were: scheduled senile cataract operation (27.4 %), scheduled hip (16.8 %) or knee joint replacement (15.8 %) due to idiopathic (primary) osteoarthritis and injuries, in particular fractures not secondary to a disease (40 %). For every eligible case, an attempt was made to randomly identify a control admitted to the Veterans' Administration General Hospital as closely as possible in time to the admission of the corresponding case (±1 month). A total of 102 potential controls were identified and of those 95 consented to participate and were interviewed. Among the latter, 66 were males and 29 females, aged 50 to 86 years (median age, 66). As with cases, the main reasons for non participation were severity of the patient's medical condition and/or refusal on the part of the subject or his/her relatives, but responders and non-responders did not differ on demographic variables, notably age, gender and time of diagnosis.

All cases and controls who participated in our investigation were fully informed of the aim of the study and gave written consent for their participation and their agreement that the results of this study may well be presented or published, solely in the interests of science, provided that their anonymity is maintained. The study was approved by the Scientific and Ethical Committee of the hospital.

Diagnostic procedure, specimen collection and laboratory analysis

The B-CLL diagnosis and staging were based upon standard clinical, morphologic and immunophenotypic criteria proposed by National Cancer Institute using the automated blood

cell counter XE-2100, Sysmex Corporation, Japan and the flow cytometry analyzer Epics XL-MCL Coulter, Miami Florida, USA[30–31]. Biopsy or aspiration of the bone marrow was performed if the patient presented with anemia or thrombocytopenia or as a baseline before treatment. B-CLL patients were also classified in three prognostic stages using the Binet system, a clinical staging system on the basis of the presence of lymphadenopathy, splenomegaly or hepatomegaly, anemia (hemoglobin <100g/L) and thrombocytopenia (platelet number $<100 \times 10^9$/L)[32]. Based on the above staging system, at the time of B-CLL diagnosis, 62 patients had stage A (65.3 %), 23 patients had stage B (24.2 %) and 10 patients presented stage C (10.5 %).

Laboratory Methods

All blood specimens were collected prior to the initiation of any therapeutic approach for the cases (chemotherapy, corticosteroids, monoclonal antibodies, biologic response modifiers, bone marrow transplantation, radiotherapy, splenectomy, etc) and prior to any therapeutic intervention, including surgery, for the control group. Also blood was drawn immediately after diagnosis and prior to patient's information about the disease. Peripheral blood samples were centrifuged in the laboratory. Serum was separated and stored at −80°C. Samples from cases and controls were handled in a similar way concerning the amount of time between collection, processing, and initial storage as well as the amount of time in storage prior to hormones assays performance. Assays were run blindly and the laboratory technician was not aware of the study hypothesis and the case/control status of the patients. Serum leptin and adiponectin levels were measured employing methods previously reported, using a human adiponectin radioimmunoassay (Sensitivity 1.0 ng/mL, 6.9–9.25% Interassay CV, 1.78–6.21 Intraassay %CV, Millipore Co.) and human leptin radioimmunoassay (Sensitivity 0.5-ng/mL, 3.0–6.2 Interassay %CV, 3.4–8.3 Intraassay %CV, Millipore Co.) kits[9,25–26].

Serum lactate dehydrogenase (LDH) and β_2-microglobulin (BMG) were determined using immunonephelometry (Dade-Behring GmbH, Marburg, Germany). Two observers (AL and MT) analyzed lymphocyte morphology on all blood smears stained with May-Grünwald-Giemsa. The presence of atypical morphology was defined as more than 10% cells prolymphocytes or more than 15% cells with cleaved nuclei and/or lymphoplasmacytoid cells[33]. The surface expression of CD38 in >30% of B-CLL lymphocytes was also assessed using the flow cytometry analyzer Epics XL-MCL Coulter.

Statistical analysis

In characteristic description, adiponectin, leptin, and high molecular weight adiponectin were analyzed as continuous variables along with age, and BMI and were presented as mean values with standard deviation. Cases and controls were compared using t-tests for continuous variables and chi-square tests for categorical variables. Correlations between age, weight, BMI, and adiponectin, HMW adiponectin, and leptin as continuous variables were determined using nonparametric Spearman correlation coefficients for the control and the case groups. Correlations between leptin/adiponectin and prognostic variables including BMG and LDH as continuous variables, and CD38 and atypical morphology as categorical variables were determined using Spearman coefficients for the case population. Subjects were divided into control-defined tertiles or quartiles of leptin and adiponectin for analysis. Crude and multivariate models adjusting for age, gender, BMI, family history of LHC, and leptin or total adiponectin (as continuous variables, or in tertiles or quartiles) were obtained using unconditional logistic regression analysis. Total and HMW adiponectin, and leptin were analyzed both in tertiles and as continuous variables, and odds ratios were determined for each 1 unit increase in each hormone. A two-sided p-value of <0.05 was considered as significant.

Results

Cases and controls were matched on age (within five years), gender, and date of diagnosis (within one month). There were no significant differences between matching factors aside from controls being slightly older (66.0 vs. 63.8 years; p=0.05; Table 1). Patients in the case group on average had a higher body mass index as compared with controls (27.8 vs. 26.7 kg/m^2; p=0.01). Significantly more cases than controls presented with a family history of LHC (13 vs. 3 patients; p=0.01). Leptin was significantly lower in cases as compared with controls (10.03 vs. 13.89 ng/ml; p<0.01). Among controls, BMI was positively correlated with leptin levels (p=0.04; Table 2a). Total adiponectin was positively associated with HMW adiponectin (p<0.01) among all study subjects (Tables 2a and 2b).

In unadjusted analysis, adiponectin tended to be lower in cases than controls, though there was no significant difference between the two groups. (p=0.08, Table 1). Table 3 displays the odds ratios and 95% Confidence Intervals (CI) for B-CLL risk by tertiles. Adjusting for age, gender, family history of LHC, BMI, and serum leptin did not alter the reported associations and significance levels for adiponectin. With respect to HMW adiponectin, the highest tertile was associated with an Odds Ratio (OR) of 2.0 (95% CI = 1.01–3.96), compared with the lowest tertile, though this did not persist after adjusting for the above variables. Similar results were observed when quartiles of adiponectin were studied and/or when adiponectin was studied as a continuous variable. In contrast to adiponectin, higher leptin levels were associated with a decrease in B-CLL risk in unadjusted analyses (comparing highest to lowest tertiles of leptin; OR=0.42, 95% CI=0.21–0.87) as well as after controlling for age, gender, family history of LHC, BMI, and serum adiponectin (comparing highest to lowest tertiles of leptin; OR=0.05, 95% CI=0.01–0.29). Similar results were observed when quartiles of leptin were studied and/or when leptin was studied as a continuous variable. No significantly different associations were observed in adiponectin, HMW adiponectin and leptin levels between different stages of B-CLL according to the Binet classification (data not shown).

Spearman correlation coefficients were obtained among cases to investigate an association between adiponectin, HMW adiponectin, and leptin with continuous prognostic markers of disease burden or severity (Table 4). A weak but statistically significant positive correlation between LDH and adiponectin, and HMW adiponectin and leptin was observed (r=0.22, 0.24, and 0.22 respectively, p<0.05), and between leptin and BMG (r=0.27 p<0.01). No significant association was noted between the measured adipokines and total lymphocyte count. When partial correlation coefficients were performed controlling for age and BMI, HMW adiponectin was weakly positively correlated with lymphocyte count (r=0.21, p=0.04) and the association between leptin and LDH became nonsignificant (data not shown). Adiponectin, HMW adiponectin, and leptin were also not significantly associated with presence of atypical morphology or CD38 using unpaired t-tests.

Discussion

Adiponectin and leptin are the two main adipocytokines being the focus of scientific investigations aiming at explaining the finding of excess cancer risk among obese individuals[34]. Adiponectin has been shown previously to be inversely related to risk of AML, MDS, myeloproliferative disorders and multiple myeloma[9, 25–28,35]. In this case-control study, mean serum adiponectin levels were not statistically different between cases and controls. It has been previously suggested that adiponectin plays a protective role as a tumor suppressor through an array of mechanisms, including improved insulin resistance, inhibition of growth factors, inhibition of proliferative signaling pathways, and induction of apoptosis. Prior work has shown that adiponectin induces apoptosis, and inhibits

proliferation of myeloid, but not of lymphoid, cell lines[35]. Several metabolic pathways including AMPK, AKT, MAPK, and GSK/Beta Catenin appear to be affected by adiponectin leading to downstream tumor suppressor effects[5,24,47–49]. Cell models of hematopoiesis and cancer have shown that adiponectin is an important inhibitor of cell growth[50–52]. Adiponectin is bioavailable within the bone marrow, and has been shown by Iversen et al to repress hematopoiesis within a hypocellular marrow[51]. Yokota performed similar work to test whether adiponectin could inhibit proliferation of lymphocytes. Yokota et al demonstrated that adiponectin inhibited lymphopoiesis, but in contrast to the effect in AML which took place in a hypocellular marrow fluid, these effects were observed in marrow cultures with stromal cells[35, 52]. Adiponectin has been shown to induce apoptosis and to downregulate *bcl2*, an antiapoptotic gene upregulated in B-CLL, as well as to upregulate other factors such as *Bax* which favor apoptosis in cell models of different solid tumors[18,47–48,53]. Similarly to a smaller study with 19 patients with CLL by Avcu et al, there was no significant association between disease staging and serum adiponectin[28]. Molica and colleagues also observed that adiponectin was not statistically different between cases and controls among a cohort of 69 patients with Binet stage A B-CLL[36]. However, they were able to demonstrate that adiponectin was inversely correlated with CD38-positive CLL cells, absolute peripheral blood lymphocyte count and presence of ZAP-70, all markers of disease severity[36]. HMW adiponectin constitutes a multimeric complex of adiponectin that has been considered to be a more potent activator of AdipoR1, one of two seven transmembrane receptors of adiponectin with ubiquitous expression. Prior studies with HMW in breast cancer demonstrated that HMW adiponectin paralleled the association with total adiponectin, but was not a better predictor than total adiponectin[24]. In this case-control study, total adiponectin did strongly correlate with HMW adiponectin, and likewise there was no significant difference in HMW adiponectin between cases and controls after multivariate adjustments.

In our study, leptin levels were lower in cases than controls. This is in contrast to data from a previous study with 13 B-CLL patients and 25 controls reporting that higher levels of leptin were positively associated with B-CLL, but consistent with findings that serum leptin levels were decreased in patients with AML and ALL[12,14,37–38]. We did not reproduce the findings of Pamuk et al who reported an association between leptin and presence of CD38[14]. However, a weak positive correlation was seen between leptin and β_2-microglobulin as well as between leptin and LDH, though the clinical relevance of these findings remains unknown.

Leptin is the product of the *ob* gene and increases with BMI and physiologically exerts an appetite suppressing effect, in addition to other energy expending metabolic changes. Severe deficiency leads to obesity through increased appetite and energy conservation, though most obese humans present high levels of leptin and are thought to have leptin resistance mediated by downregulation of central leptin receptors, changes in signaling, or protein binding[39–40]. Energy deprivation leads to a reduction in serum leptin levels with several metabolic consequences ameliorated by replacement with exogenous leptin[41–42]. Leptin has been investigated in hematopoiesis showing that leptin is highly expressed in the bone marrow. Hematopoietic tissues express the leptin receptor and leptin contribute to multilineage hematopoiesis, likely through an indirect role via regulation of other cytokines[43–45]. Leptin possesses antiapoptotic effects when studied in myelogenous leukemia cell lines[46]. In addition, leptin appears to have a stimulatory effect on myeloid leukemic cells, and its receptors are expressed in these cells, particularly the normally long receptor subtype which is seen in CD 34+ progenitor cells but lost during subsequent differentiation into promyelocytes[13,15,46]. In CML, leptin receptor expression was observed to be even higher in cases with a blast crisis[15]. However, *in vitro* proliferative effects have been observed with only supraphysiologic leptin levels in some studies[37].

The significance of serum levels of leptin in relation to risk for B-CLL is unclear, especially without performing prospective studies. Although case control studies like this one are appropriate for rare diseases, these studies do not incorporate the time sequence criterion for causality. Thus, one potential explanation for our finding that leptin levels are decreased could be that CLL patients have downregulated production of leptin due to other factors relating to their overall condition, and that this is not mediated by BMI but through other cytokines. In one study of patients with ALL, affected patients had a 2.8 fold lower levels of leptin at diagnosis compared to levels at remission after 33 days of chemotherapy, despite a tendency to have a lower BMI after undergoing treatment[12].Whether or not elevated leptin levels are simply a marker of risk versus an etiologic factor for developing B-CLL remains unclear.

Despite its modest size, this case-control study was bigger than prior studies on adiponectin/leptin in B-CLL and, in addition, was adequately large to generate statistically significant associations[14,28–29,36]. However, the observational nature of the study limits the ability to prove causality. This is the first study exploring simultaneously the role of adiponectin, HMW adiponectin and leptin in a reasonable number of subjects with B-CLL and appropriate controls. We have included hospital controls with admission diagnoses not known to be related with the principal exposure variables i.e. adiponectin, leptin and/or obesity. Neither the study subjects nor laboratory personnel were aware of the study hypotheses, a fact that eliminates bias from these sources. Assays were run blindly minimizing error from that source too. The rarity of B-CLL in the general population makes the case-control study design more appropriate for studying adipokines in the pathogenesis of this rather rare disease entity, than a cohort study design. Future cohort and, if feasible, interventional studies are needed to confirm the data of this hypothesis generating study. Our study may be limited by measuring serum adipokines when the microenvironment in the bone marrow may be of more significance. Two studies in very small numbers of patients have reported discordance between serum and marrow adiponectin levels, and this aspect of adiponectin biology needs to be better understood[51]. It has been shown that osteoblasts also possess the ability to express adiponectin mRNA, which may be locally important, but this remains to be fully elucidated too[51,54].

In conclusion, our results suggest that circulating leptin, but not adiponectin, levels are altered in patients with B-CLL. Further work and larger, ideally prospective studies, as well as mechanistic studies will be needed to understand better the role of adipokines in this disease state.

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Table 1

Descriptive Characteristics of B-CLL cases (n=95) and control subjects (n=95).

Categorical Variables	Cases		Controls		p-value
Gender, n (%)					
Male	66 (69.5)		66 (69.5)		-
Female	29 (30.5)		29 (30.5)		-
Age in years (mean, SD)	63.83	(7.82)	65.99	(7.43)	0.05
Weight in kg (mean, SD)	81.01	(9.66)	79.36	(9.24)	0.23
Height in m (mean, SD)	1.71	(0.08)	1.73	(0.09)	0.17
BMI in kg/m^2 (mean, SD)	27.78	(2.88)	26.69	(2.67)	0.01
Binet Stage, n (%)					-
A	62 (65.3%)		.		
B	23 (24.2%)		.		
C	10 (10.5%)		.		
Family History of LHC, n (%)					0.01
Yes	13 (13.7)		3 (3.1)		
No	82 (86.3)		92 (96.8)		
Adiponectin (mean, SD) (μg/ml)	12.78	(5.84)	14.60	(8.53)	0.08
HMW Adiponectin (mean,SD) (μg/ml)	7.18	(4.34)	6.43	(5.13)	0.28
Leptin (mean,SD) (ng/ml)	10.03	(7.91)	13.89	(10.33)	<0.01

Abbreviations: SD, Standard Deviation; HMW, high molecular weight; LHC, lymphohematopoietic cancer

Table 2

Table 2a. Spearman correlation coefficients of study variables among controls (n=95)

	Weight	BMI	Adiponectin	HMW Adiponectin	Leptin
Age	0.09	0.02	0.09	0.07	−0.09
Weight		0.54**	0.09	0.05	0.12
BMI			0.06	0.05	0.21*
Adiponectin				0.96**	−0.13
HMW Adiponectin					−0.18

Table 2b. Spearman correlation coefficients of study variables among B-CLL cases (n=95)

	Weight	BMI	Adiponectin	HMW Adiponectin	Leptin
Age	−0.13	−0.23	0.04	0.06	−0.09
Weight		0.53**	0.03	0.04	0.06
BMI			0.06	0.13	0.09
Adiponectin				0.93**	0.01
HMW Adiponectin					−0.02

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

Table 3

Odd ratios and 95% confidence intervals for B-CLL risk in relation to total adiponectin, HWM adiponectin, and leptin in 95 cases and 95 controls.

	Tertile 1		Tertile 2		Tertile 3		
	OR	95% CI	OR	95% CI	OR	95% CI	P trend
Total Adiponectin							
Unadjusted	1.00	(ref)	1.16	0.59–2.23	1.12	0.57–2.18	0.74
Model 1	1.00	(ref)	0.96	0.36–2.54	1.29	0.50–3.33	0.61
Model 2	1.00	(ref)	0.88	0.31–2.46	1.44	0.53–3.93	0.48
Model 3	1.00	(ref)	0.43	0.11–1.69	0.99	0.31–3.15	1.00
HWM Adiponectin							
Unadjusted	1.00	(ref)	1.59	0.77–3.30	2.00	1.01–3.96	0.05
Model 1	1.00	(ref)	2.89	0.96–7.86	2.80	0.99–7.86	0.06
Model 2	1.00	(ref)	2.98	0.96–9.30	3.16	1.06–9.43	0.05
Model 3	1.00	(ref)	2.08	0.61–7.10	2.21	0.64–7.61	0.22
Leptin							
Unadjusted	1.00	(ref)	1.13	0.54–2.37	0.42	0.21–0.87	0.01
Model 1	1.00	(ref)	0.58	0.18–1.89	0.05	0.01–0.28	<0.001
Model 2	1.00	(ref)	0.70	0.20–2.44	0.05	0.10–0.30	<0.001
Model 3	1.00	(ref)	0.77	0.22–2.71	0.05	0.01–0.29	<0.001

Model 1: Age, Gender, BMI adjusted

Model 2: Age, Gender, Family History of LHC, and BMI adjusted

Model 3: Age, Gender, Family History of LHC, BMI, and Total adiponectin or Leptin adjusted.

Table 4

Nonparametric correlation coefficients between prognostic markers and adipokines in 95 B-CLL cases

Variables	Adiponectin	HMW	BMG	Lymphocyte count	LDH	Atypical morphology	CD38 presence
Leptin	0.01	−0.02	0.27**	0.19	0.22*	0.13	0.13
Adiponectin		0.93**	0.14	0.16	0.22*	0.09	0.1
HMW			0.12	0.14	0.24*	0.07	0.09
BMG				0.82**	0.75**	0.56**	0.67**
Lymphocyte count					0.79**	0.57**	0.59**
LDH						0.49**	0.56**
Atypical morphology							0.74**

LDH: lactate dehydrogenase ; BMG: β_2-microglobulin; HMW: high molecular weight adiponectin

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).