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Original Article

The Influence of Serum Leptin Level and Body Mass Index on the Prognosis of Patients with Diffuse Large B Cell Lymphoma

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Abstract

Background: More research is ongoing on obesity as a risk factor for cancer occurrence. Cell of origin (COO), stage and National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI) are frequently used for risk evaluation and treatment tailoring in patients with Diffuse large B-cell lymphoma (DLBCL). Relatively, few studies assessed the prognostic role of obesity and leptin level in patients with DLBCL.

Aim: The aim of this study was to investigate the effect of obesity and leptin level on response and prognosis in DLBCL.

Methods: A single institution prospective study that included patients with DLBCL. For each patient, demographic data, body mass index (BMI), serum leptin level by ELISA, response and survival were determined.

Results: Seventeen (24.3%) out of the 70 patients in our cohort were classified as obese (BMI≥30). They had a higher serum leptin level ($p < 0.001$) and less response to R-CHOP chemotherapy ($P= 0.003$). Forty (57.14%) patients had elevated serum leptin level with B symptoms, Cell of origin and response to chemotherapy were significantly different between the two groups. There was no significant relationship between BMI and survival. On the other hand, higher serum leptin was associated with worse disease-free survival ($p=0.035$).

Conclusion: The results support a relationship between both BMI and serum leptin level and response to treatment in DLBCL patients. Leptin level like other common prognostic factors is related to disease-free survival.

Keywords: Body mass index, Diffuse large B-cell lymphoma, Leptin, Prognosis

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Introduction

Diffuse large b-cell lymphomas (DLBCL) is the commonest adult lymphoid malignancy; representing 30% of non-Hodgkin's lymphomas (NHLs) detected every year [1]. It is an aggressive but highly treatable disorder. Existing 1st line treatment regimen immuno-chemotherapy (rituximab-CHOP) is highly effective with > half of the patients still alive and disease-free at 5 years [2].

Obesity is linked to a considerably increased risk of developing NHL, especially DLBCL. Obesity may cause a mild chronic inflammatory status, which possibly increases the probability of lymphoid neoplasm development [3]. Inflammation caused by obesity results from the production of cytokines and chemokines by adipocytes and macrophages in fatty

tissue. With further gain in weight, the resultant fatty tissue grows, hence increasing the number of adipocytes and macrophages, with consecutive increase in cytokines such as leptin, interleukin-1β (IL-1β), tumor necrosis factor-α, and interleukin-6, in addition to chemokines and acute phase proteins [4].

Leptin (Ob/LEP) is an obesity gene product that is located on chromosome 7. It is a hormone which has a key role in regulating body mass homeostasis, by depressing appetite. There is high leptin level in the serum of obese individuals and has a direct correlation with the overall amount of fatty tissue [5]. Leptin adjusts the intracellular signal pathways that relate to the next molecules: JAK, STAT, PI3K, AKT and MAPK. Leptin is also closely associated with many growth factors such as VEGF, FGF21, and IGF-1 [6].

Leptin stimulates the growth of cancer in the carcinogenesis process by promoting several pathways in the cell which are valuable for tumor proliferation and interim that leads to apoptosis suppression. It was discovered that leptin increases tumor neovascularization, encourages proliferation, immigration, and invasion, and represses apoptosis of malignant cells [7].

The aim of this study was to measure the body mass index (BMI) and serum leptin level in patients with DLBCL to determine the association between the two and the clinical features of DLBCL, and to find their relationship to response to treatment and survival.

Methods

This prospective study recruited 70 patients with recently diagnosed DLBCL from April 2019 to February 2022 at the Departments of Medical Oncology, Clinical Oncology and Internal Medicine (Clinical Hematology Unit), Faculty of Medicine, Zagazig University, Egypt.

Patients

Adult patients (>18 years old) with de novo DLBCL and an Eastern Cooperative Oncology Group (ECOG) performance status of 1-2 and normal liver, renal, and cardiac function tests were enrolled in this study. Previously treated and relapsed DLBCL patients and those with history of other malignancies were excluded from the study.

Measurements

Body mass index

The patients' weights and heights were measured, and the BMI was calculated for each patient based on the formula: BMI = Weight / (Height) ^{2}. The BMI result is expressed in kg/m^2, and the patients were divided into 3 categories, patients with ideal body weight (BMI from 18.5 to 24.9 kg/m^2), overweight (BMI from 25 to 29.9 kg/m^2) and obese patients (BMI of ≥30 kg/m^2) [8].

Quantitative assay of serum Leptin

The kit uses a double-antibody sandwich ELISA to analyse the level of Human Leptin (LEP). Leptin was added to monoclonal antibody enzyme well which is pre-coated with human LEP monoclonal antibody and incubated. The LEP-labelled antibodies (labelled with biotin) were then added and combined with Streptavidin-HRP to form an immune complex, then incubated and washed once more to remove the uncombined enzyme. Chromogen solution A and B were added which results in changing the colour of the liquid into blue, and with the influence of acid, into yellow. The concentration of the human substance LEP of leptin sample and the chroma of colour were positively associated.

Assessment

The patients' demographic and clinical data and disease characteristics were recorded. Biochemical laboratory evaluation consisted of complete blood picture, liver and kidney function tests, uric acid level, lactate dehydrogenase (LDH), electrolytes, coagulation profile and viral markers (HBs Ag, HBc ab, HCV ab, HIV ab). Serum leptin level was measured for every patient at presentation before starting treatment and was expressed in ng/mL with a normal value range of 10-42 ng/mL in females and 7-23 ng/mL in males. Biopsy was obtained from lesions and examined histopathologically to ascertain the diagnosis of DLBCL and to define the cell of origin, in addition to immunohistochemistry studies were done. Imaging studies were carried out, including echocardiogram, positron emission tomography – computerized tomography (PET/CT) and/or CT scans of the neck, chest, abdomen, and pelvis with contrast. Bone marrow biopsy and aspirate were done if indicated. Pregnancy was tested for in women in the childbearing age.

According to National Comprehensive Cancer Network (NCCN) guidelines, all patients received the standard treatment protocol R-CHOP (rituximab plus CHOP) for 6 cycles with interim restaging after 3-4 cycles. After completing six-cycle chemotherapy regimens, evaluation was performed by PET/CT scan

and/or CT scans of neck, chest, abdomen and pelvis with contrast. The response to chemotherapy was classified into responding (complete or partial response), stationary, and progressive based on the Lugano Response Criteria for NHL [9].

Statistical Analysis

Data management and analysis were performed using SPSS vs. 23 (Armonk, NY: IMB Corp.). Numerical data were summarized using means and standard deviations or medians (ranges), as appropriate. Numbers and percentages were used to represent categorical sets of data. Using the Shapiro-Wilk and the Kolmogrov-Smirnov tests, numerical data were examined for normality. Independent sample t-test was used for comparison between two groups of normally distributed numerical data. For abnormally distributed numeric variables, comparisons between two groups were done using the Mann-Whitney test while for more than two groups comparisons were done using the Kruskal-Wallis test. Chi square or Fisher's tests were used (as appropriate) to compare between groups with respect to categorical data. The Kaplan-Meier method was used to estimate survival functions (time to first response, disease-free and overall survivals). Predictor and prognostic variables were related to survival using log rank test. Cox regression analysis was done to evaluate independent prognostic variables affecting disease free survival. All tests were two-sided. P-values <0.05 were considered significant.

Results

Seventy patients with histopathologically proven de novo DLBCL were included in this study. The patient characteristics are shown in Table 1.

Seventeen (24.3%) patients were obese (BMI >30). Table 2 sums up the comparison of the clinico-laboratory features between the weight groups. Statistically significant difference was found between weight groups in relation to gender, serum leptin level and response to R-CHOP. There is near significant difference between groups in respect to extranodal disease and cell of origin.

Regarding the serum leptin level at presentation, we divided the patients into two groups: those with normal and those with high serum leptin levels. The comparison between the two groups in relation to clinical and laboratory features as shown in Table 3. We found that patients without B-symptoms were significantly more likely to have a high leptin level. A highly significant difference was noted between the 2 groups as regards weight and BMI.

Table 1. Characteristics of 70 patients with diffuse large B-cell lymphoma patients

Characteristic	
	Mean (SD)
Age	47 ± 11.6
Weight	76.5 ± 12.1
	Median (range)
Length	168 (147 - 182)
Body mass index	27.6 (20.2 - 39)
Serum leptin	
Male	26.5 (15 - 40)
Female	47.0 (20 - 57)
	***n* (%)**
Gender	
Male	42 (60)
Female	28 (40)
Performance status	
0	16 (22.9)
1	34 (48.6)
2	17 (24.3)
3	3 (4.3)
Diabetes mellitus	
No	32 (457)
Yes	38 (54.3)
B-symptoms	
No	35 (50)
Yes	35 (50)
Lactate dehydrogenase	
No	13 (18.6)
Yes	57 (81.4)
C-reactive protein	
No	30 (42.9)
Yes	40 (57.1)
Extranodal disease	
No	49 (70)
Yes	21 (30)
Stage	
1	2 (2.9)
2	19 (27.1)
3	35 (50)
4	14 (20)
International Prognostic Index	
Low	25 (35.7)
Intermediate	39 (55.7)
High	6 (8.6)
Cell of origin	
Germinal center B-cell-like	55 (78.6)
activated B-cell-like	15 (21.4)
Response to R-CHOP	
Response	60 (85.7)
Stationary	7 (10)
Progression	3 (4.3)

Table 2. Diffuse large B-cell lymphoma patients' characteristics in relation to weight groups (n = 70)

Characteristics		Ideal (n =25)	Overweight (n = 28)	Obese (n=17)	*p* value
		Median (range)			
Age		45 (23 - 70)	46 (33 - 68)	48 (26 - 64)	0.814
Serum leptin		20 (15 - 40)	29 (18 - 52)	48 (30 - 57)	< 0.001
			n (%)		
Gender	Male	15 (35.7)	21 (50)	6 (14.3)	0.031
	Female	10 (35.7)	7 (25)	11 (39.3)	
Performance status	0 – 1	18 (36)	20 (40)	12 (24)	0.995
	2 – 3	7 (35)	8 (40)	5 (25)	
Diabetes mellitus	No	13 (40.6)	10 (31.3)	9 (28.1)	0.390
	Yes	12 (31.6)	18 (47.4)	8 (21.1)	
B-symptoms	No	9 (25.7)	15 (42.9)	11 (31.4)	0.168
	Yes	16 (45.7)	13 (37.1)	6 (17.1)	
Lactate dehydrogenase	No	6 (46.2)	6 (46.2)	1 (7.7)	0.335
	Yes	19 (33.3)	22 (38.6)	16 (28.1)	
C-reactive protein	No	13 (43.3)	12 (40)	5 (16.7)	0.348
	Yes	12 (30)	16 (40)	12 (30)	
Extranodal disease	No	19 (38.8)	22 (44.9)	8 (16.3)	0.059
	Yes	6 (28.6)	6 (28.6)	9 (42.9)	
Stage	1 – 2	8 (38.1)	10 (47.6)	3 (14.3)	0.424
	3 – 4	17 (34.7)	18 (36.7)	14 (28.6)	
International Prognostic Index	Low	10 (40)	12 (48)	3 (12)	0.359
	Intermediate	14 (35.9)	13 (33.3)	12 (30.8)	
	High	1 (16.7)	3 (50)	2 (33.3)	
Cell of origin	GBC	16 (29.1)	25 (45.5)	14 (25.5)	0.074
	ABC	9 (60)	3 (20)	3 (20)	
Response to R-CHOP	Yes	24 (40)	26 (43.3)	10 (16.7)	0.003
	No	1 (10)	2 (20)	7 (70)	

GBC: Germinal center B-cell-like, **ABC:** activated B-cell-like

Patients with high leptin levels had a greater percentage of germinal center B-cell-like (GBC) DLBCL, whereas patients with normal leptin levels had a higher percentage of activated B-cell-like (ABC) DLBCL. The response to R-CHOP differed significantly according to the leptin level as well. Ninety percent of patients who didn't respond to R-CHOP had a high leptin level while only one patient with normal leptin level didn't respond to R-CHOP.

By calculating time to first response (TTR) to standard R-CHOP protocol. TTR calculated as the time from date of diagnosis to date of initial response among responders only. Median time to first response in obese patients was longer than that in non-obese patients (6.4 m_s vs 5.6 m_s respectively) with statistically significant difference (p= 0.005). High leptin level also associated with longer time to response to chemotherapy than those with normal leptin level with near significant difference (p=0.076).

In the overall survival analysis for all 70 patients in the study; the median overall survival was 33 months with no statistical significance relationship to weight, leptin level, stage, IPI or cell of origin.

Table 4 shows the one and two-year disease-free survival rates for the 67 patients who achieved response in relation to different prognostic factors. There were statistically significant relations with stage, IPI and cell of origin. Despite being significantly related to DFS in univariate analysis (Figure 1), leptin level was not an independent prognostic factor for DFS in mutivariate Cox proportional hazard analysis.

Table 3. Diffuse large B-cell lymphoma patients' characteristics in relation to leptin levels (*n* = 70)

Characteristics		Leptin level		*p* value
		Normal (n = 30)	**High** (n = 40)	
		Median (range)		
Age		46.5 (23 - 70)	46.5 (26 - 68)	0.882
Length		169.5 (150 - 180)	166.5 (147 - 182)	0.256
Body mass index		23.6 (20.2 - 27)	29.8 (24.2 - 39)	< 0.001
Weight		69 (49 - 77)	85 (65 - 104)	< 0.001
		***n* (%)**		
Gender	Male	18 (42.9)	24 (57.1)	1.000
	Female	12 (42.9)	16 (57.1)	
Performance status	0 – 1	23 (46.0)	27 (54)	0.401
	2 – 3	7 (35)	13 (65)	
Diabetes mellitus	No	15 (46.9)	17 (53.1)	0.533
	Yes	15 (39.5)	23 (60.5)	
B-symptoms	No	10 (28.6)	25 (71.4)	0.016
	Yes	20 (57.1)	15 (42.9)	
Lactate dehydrogenase	No	8 (61.5)	5 (38.5)	0.131
	Yes	22 (38.6)	35 (61.4)	
C-reactive protein	No	14 (46.7)	16 (53.3)	0.577
	Yes	16 (40)	24 (60)	
Extranodal disease	No	22 (44.9)	27 (55.1)	0.598
	Yes	8 (38.1)	13 (61.9)	
Stage	1 – 2	9 (42.9)	12 (57.1)	1
	3 – 4	21 (42.9)	28 (57.1)	
International Prognostic Index	Low	12 (48)	13 (52)	0.448
	Intermediate	17 (43.6)	22 (56.4)	
	High	1 (16.7)	5 (83.3)	
Cell of origin	GBC	20 (36.4)	35 (63.6)	0.036
	ABC	10 (66.7)	5 (33.3)	
Response to R-CHOP	Yes	29 (48.3)	31 (51.7)	0.023
	No	1 (10)	9 (90)	

GBC: Germinal center B-cell-like, **ABC:** activated B-cell-like

Table 4. Disease free survival of diffuse large B-cell lymphoma patients in relation to different characteristics

Variable		*n*	No. of events	Disease-free Survival			*p value*
				1 year %	**2 years %**	**Median** (months)	
All		67	20	80.6	70.7	30.1	
Weight	Non-obese	51	12	80.4	76.3	*	0.180
	Obese	16	8	81.3	51.1	30.1	
Leptin level	Normal	29	4	86.2	86.2	*	0.035
	High	38	16	76.3	59	30.1	
Stage	1 & 2	21	2	90.5	90.5	*	0.030
	3 & 4	46	18	76.1	61	30.1	
International Prognostic Index	Low	25	3	92	92	30.1	0.003
	Intermediate	37	14	78.4	60.3	*	
	High	5	3	40	NA	6	
Cell of origin	GBC	53	13	84.9	76.4	30.1	0.019
	ABC	14	7	64.3	48.2	18.4	

***** Median not reached. **GBC:** Germinal center B-cell-like, **ABC:** activated B-cell-like.

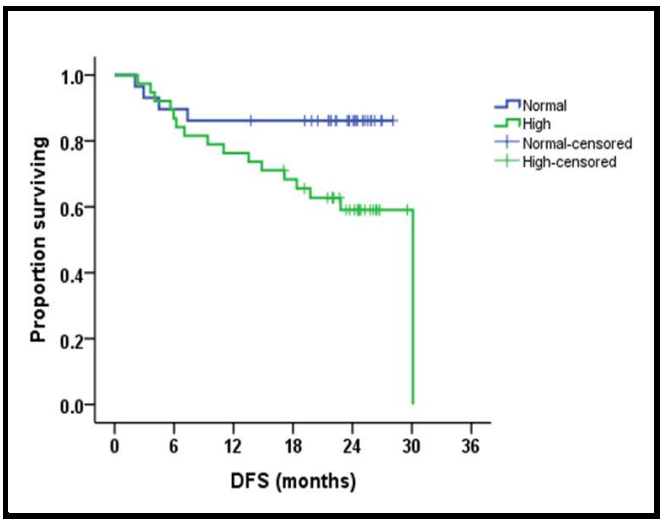

Figure 1. Relation between disease free survival and leptin level

Discussion

In 2014, more than 2.1 billion (30%) people worldwide, were classified as overweight or obese with 5% of all deaths attributable to obesity. Therefore, obesity represents both a national and global threat with resultant extra health care costs. In addition, it is an economic burden on the individuals and their families with about 2.8% of the worldwide overall gross domestic product (2.0 trillion US dollars) [10]. Obesity also hinders productivity and progress due to lost workdays, less productivity at work, death and long-lasting disability [11, 12].

In this study, NCCN-IPI, cell of Origin, and the serum leptin level were integrated to highlight the significant data on the clinical characteristics and prognosis in obese patients with DLBCL. Higher BMI and henceforth obesity were significantly correlated with elevated serum leptin level in our study. Leptin level in adults is linked to obesity and increased BMI [13].

Obesity rate was higher in females than males in our study; while in other study, obesity was higher among male patients. The response rate (complete response plus partial response) was significantly less in obese patients after immunochemotherapy when compared to non-obese patients confirming the findings of Wu et al [14].

Leptin level was negatively correlated with presence of B symptoms. In contrast, serum leptin level in the study of Ali et al was significantly higher in patients who had B symptoms at presentation than those free of B symptoms [13].

The distribution of cell of origin (GCB versus Non-GCB) was noticeably different between patients with higher leptin level and those with normal leptin level as GBC percentage was higher in patients with elevated serum leptin level (63.6%), while ABC percentage was higher in patients with normal leptin level (66.7%) (p=0.036). In another study, leptin receptor overexpression did not show significant association with the cell of origin status [15].

Like BMI, a strong correlation was observed between serum leptin levels and chemotherapy response, where the serum leptin level was significantly higher in patients who did not respond to chemotherapy in agreement with another study [13].

Traditionally, NCCN-IPI, cell of origin, and stage have all been correlated with the treatment consequence in patients with DLBCL. Moreover, we assessed the effects of other variables on DFS outcome as leptin level and BMI.

Non-obese patients showed better outcome; however, DFS did not differ significantly between the weight groups. On the other hand, Wu et al found that obese patients had a worse PFS in comparison to non-obese (p=0.022) [14].

Diffuse large B-cell lymphoma with elevated serum leptin level had a significantly worse 2-year DFS rate of 59% compared to 86.2% in DLBCL cases with normal leptin level. Non-significant difference was found in another study [15].

Patients with high NCCN-IPI risk category and advanced stage disease showed worse DFS in comparison to their corresponding counterparts on univariate analyses as shown in previous studies [16, 17].

For the cell of origin comparison, ABC type had inferior DFS compared to GBC type. This confirms the findings of Yoon et al who found that the 5-year DFS rate was significantly worse in the ABC type when compared to the GCB type (5-year DFS rate of 79.2% for ABC vs. 96.6% for GBC, p=0.01) [18].

Marked weight loss more than 10 percent is considered as one of the B-symptoms associated with lymphoma, which is related to poor prognosis and short survival. This is the justification that the present study evaluated the effect of obesity on response to chemotherapy and prognosis of DLBCL and did not include underweight patients to avoid bias that may alter the results.

Conclusion

Obesity is significantly related to outcome with inferior treatment response in DLBCL without influencing survival. Increased serum leptin level, as well, showed inferiority on both response to chemotherapy and DFS.

Various environmental factors may establish different phenotypes in obese DLBCL patients. New studies with further patient stratification are needed to better allocate and understand these subgroups.

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Authors' contribution

Conception & Design: FMA & AAM; Acquisition, analysis, or interpretation of data: EAM, RB, RMA & AIK; Drafting / revising the manuscript: AAM, EAM, RB & FMA; Approval of the final version of the manuscript: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical considerations

The Institutional Review Board of the Faculty of Medicine - Zagazig University approved the study (Reference #: ZU-IRB #9091\28-9-2022), All participating subjects signed a written informed consent before enrolment.

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Not applicable.

Study registration

Not applicable.

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