**Impact of body mass index and leptin on response of non-Hodgkin's lymphomas to chemotherapy**

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**Abstract**:

Obesity is a positive chronic imbalance between energy intake and expenditure mediated through leptin (LEP) signaling pathway; its incidence has increased dramatically throughout the last decades. Obesity is linked to a general increase in the incidence and mortality of cancer, including non-Hodgkin's lymphoma (NHL). Also, associations between polymorphisms in LEP and LEP receptor (LEPR) genes and non-Hodgkin's lymphomas have been reported. But, whether obesity and leptin level can change the response of NHL to chemotherapy is less well-studied. Thus, this study was conducted aiming at evaluating the impact of body mass index (BMI) and serum leptin level on the response of Egyptian NHL patients to chemotherapy. **Patients and methods**: 100 adult patients with recently-diagnosed NHLs were included. For each patient, thorough medical history was obtained and complete physical examination was performed. Body mass index (BMI) was determined based on patient's height and weight. The following investigations were performed: laboratory investigations including complete blood count (CBC), serum levels of lactate dehydrogenase (LDH), liver enzymes, bilirubin, albumin, creatinine, uric acid, and lipid profiles, and serum leptin level; imaging studies including pelvi-abdominal ultrasonography, computerized tomography (CT) scans and positron-emission tomography (PET); and pathologic examination of biopsy samples obtained from the affected lesions. Based on the pathologic NHL subtypes, appropriate chemotherapy regimens were given, including R-CHOP, CHOP, CVP, or FC regimen, for 6 cycles. Then, the patients were re-assessed by pan CT scans to determine the response to chemotherapy. **Results**: Significant positive correlation was observed between the values of BMI and the serum levels of leptin. The BMI and serum leptin levels were significantly higher in female NHL patients compared to male patients. Serum leptin level was significantly higher in NHL patients presented with B symptoms compared to those without B symptoms. Both BMI and serum leptin levels were significantly higher in patients with stage-4 disease compared to those with stage-1. Serum leptin level was significantly higher in patients with DLBCL (diffuse large B-cell lymphoma) and mantel cell lymphoma. Patients who showed regressive response had significantly lower BMI and leptin level compared to patients who did not respond and showed progressive disease. **Conclusion and recommendation**: Obesity, increased BMI and elevated serum leptin level had a worse impact on response of NHL patients to chemotherapy. Further studies are recommended to evaluate whether the response of various NHL pathologic subtypes could be affected by BMI and leptin levels.

**Key words**: body mass index, leptin, non-Hodgkin's lymphoma, chemotherapy.

**Introduction**

Obesity is a positive chronic imbalance between energy intake and expenditure mediated through leptin (LEP) signaling pathway [1]. Incidence of obesity has increased dramatically throughout the last decades, and it represents a prominent risk factor in multiple disease conditions as well as for global mortality [2]. Obesity is linked to a general increase in incidence and mortality of cancer, and studies suggest that obesity might be associated with an increased risk of non-Hodgkin's lymphoma (NHL) [3]. The incidence of the most common lymphoma type, diffuse large B-cell lymphoma (DLBCL), is increased in patients with higher body mass index (BMI) [4].

Obesity results in a pathologic state of chronic low-level inflammation and altered immune responses that may influence B- and T-lymphocyte function and, thus, the development of NHL [5]. Obesity can also cause changes in the metabolism of endogenous hormones, which could distort the normal balance between cell proliferation, differentiation and apoptosis; thus, obesity may be a risk factor for non-Hodgkin's lymphoma [6]. Weight loss greater than 10% is regarded as one of the B-symptoms (fever, night sweats, weight loss) that may present in lymphoma patients at diagnosis, which has been shown to be associated with worse prognosis and shortened survival [7].

Adipocytes secrete highly-active biological molecules like leptin, resistin, and adiponectin [1]. Adipocyte-derived adipokines may act as mediators in the NHL pathogenesis [5]. Leptin is a 16-kD (kilo-Dalton) polypeptide which has a role in nutrient intake and in regulation of metabolism. It has been demonstrated that leptin receptor (LEPR) were expressed on CD34+ hematopoietic stem cells and that leptin had influence on maturation and proliferation of normal hematopoietic cells [1]. Leptin participates in the inflammation response and enhances B-cell survival [5].

Associations between polymorphisms in LEP and LEP receptor (LEPR) genes and non-Hodgkin's lymphoma have been reported [8]. Skibola et al. [9] reported that the LEP A19G allele was associated with NHL risk. Willett et al. [10] found that LEPR Q223R genotype was associated with increased risk of follicular lymphoma (FL) among women [10]. Fewer studies reported association between LEP and LEPR and NHL risk in Chinese population, though some previous studies in developed countries concluded that obesity was a risk factor in NHLs [8].

**Aim of study**:

Whether obesity and leptin level could change the response of NHL to chemotherapy is less well-studied. Thus, the aim of this study was to evaluate the impact of obesity, body mass index (BMI) and serum leptin level on response of Egyptian non-Hodgkin's lymphoma patients to chemotherapy.

**Patients and methods**:

This prospective multi-centers study was conducted at Internal Medicine Department, Benha University Hospital, Benha University, and Medical Oncology Department, National Cancer Institute, Egypt, during the period from March 2018 to October 2019, including 100 adult patients with non-Hodgkin's lymphomas. After approval of ethics committee of both Benha University Hospital and National Cancer Institute, the patients were informed about the nature of study and a written consent as obtained from each patient. Patients with recently-diagnosed NHL, aged 18 years or older, either males or females, and with various body mass indices were included in this study. Exclusion criteria included patients with relapsed NHL, patients with newly-diagnosed NHL who already started their treatment regimens, patients with history of previously receiving NHL therapies, and patients with past or present history of other malignancies. The included patients were subjected to full medical history and thorough physical examination. The patients' heights and weights were measured and their body mass indices were determined according to the following equation: BMI = Wt / Ht2, where BMI is body mass index, Wt is weight in kilograms, and Ht2 is square of height in meters. The BMI is expressed in kg/m2, and the patients were categorized into patients with normal body weight (BMI of 18.5-24.9 kg/m2), overweight (BMI of 25-29.9 kg/m2), stage-I obesity (BMI of 30-34.9 kg/m2), stage-II obesity (BMI of 35-39.9 kg/m2), and stage-III obesity (BMI of ≥ 40 kg/m2) [11].

From each patient, venous blood sample (5mL) was obtained from the antecubital vein under complete aseptic conditions, and centrifuged at 1000xg for 10 minutes; the serum was separated and stored at -10 oC or lower for later determination of various serum parameters [12]. For each patient, the following laboratory investigations were evaluated: complete blood count (CBC), serum levels of lactate dehydrogenase (LDH), alanine transaminase (ALT), aspartate transaminase (AST), bilirubin (total, direct, and indirect), albumin, and other routine laboratory investigations (including creatinine, lipid profiles, and uric acid). Serum leptin levels were evaluated for all patients at their presentation before staring treatment regimens using enzyme immunoassay (EIA) method [13]. Serum leptin level was expressed in nanogram "ng" per milliliter "mL" (ng/mL), with expected average normal value in females of 7.4 ng/mL (range, 3.7-11.1 ng/mL) and in males of 3.8 ng/mL (range 2.-5.6 ng/mL) [14]. Biopsy samples were obtained from the affected NHL lesions for histopathological examination to confirm the diagnosis of NHLs and determine its pathological subtypes. Flow cytometry and immunohistochemistry were done for all biopsy samples [15]. Full imaging studies were carried out for patients including pelvi-abdominal ultrasonography, chest X-ray, computed tomography "CT" scans on neck, chest, abdomen, and pelvis, and positron emission tomography (PET) scan.

Appropriate chemotherapy regimen was given for each patient according to his NHL pathologic subtype for 6 cycles. Four chemotherapy regimens were used, which are: CHOP (cyclophosphamide, doxorubicin "hydroxydaunorubicin", vincristine "oncovin", prednisone) regimen given to patients with Burkitt Lymphoma and follicular lymphoma; R-CHOP (rituximab plus CHOP) regimen given to patients with DLBCL; CVP (cyclophosphamide, vincristine "oncovin", prednisone) regimen given to patients with mantel cell lymphoma and MALT lymphoma; and FC (fludarabine, cyclophosphamide ) regimen given for patients with T-cell lymphoma and patients with CLL [16]. After finishing their 6-cycle chemotherapy regimens, the patients were re-assessed by pan CT scans with contrast, and their response to chemotherapy were categorized according to Cheson et al. [17] into regressive (respond to chemotherapy), stationary, and progressive, as follows:

i-regressive: characterized by;

-lymph nodes and extra-lymphatic sites: target nodes/nodal mass regress to 1.5cm in longest transverse diameter and no extra-lymphatic sites of disease.

-non-measured lesion: no applicable.

-organ enlargement: should regress to normal.

-new lesions: none.

ii-stationary: characterized by;

-lymph nodes and extra-lymphatic sites: target nodes/nodal masses show < 50% decrease in baseline and extra-lymphatic sites without criteria for progression.

-non-measured lesions: no increase consistent with progression.

-organ enlargement: no increase consistent with progression.

-new lesions: none.

iii-progressive: characterized by;

-lymph nodes and extra-lymphatic sites: target nodes/nodal masses > 1.5cm in longest transverse diameter) or show > 50% increase in baseline and new or recurrent splenomegaly.

-non-measured lesions: re-growth of previously resolved lesions.

-organ enlargement: new or re-growth.

-new lesions: new or recurrent involvement.

**Statistical methods**:

Statistical analyses were done using SPSS (Statistical Package of Social Science) version 20. Quantitative data were expressed in numbers, range, mean, and standard deviation (SD). Qualitative data were expressed in frequencies and percentage. Student t-test was used for comparison of mean values of two groups of quantitative data. ANOVA test (F value) was used for relationships between variables using Pearson correlation test for parametric data and Spearman correlation test for non-parametric data. P value of less than 0.05 (P < 0.05) was considered statistically significant; P value >0.01 was considered highly-significant in all analyses [18].

**Results**:

This prospective multi-centers study included 100 NHL patients, 70 males (70%) and 30 females (30%), with a mean age ± SD of 50.2±16.8 years (range, 22-83 years). The frequencies and percentages of studied patients regarding various parameters are shown in table 1. Significant positive correlation was observed in this work between BMI and serum leptin levels, where the higher the BMI values the higher the serum leptin levels, and the reverse was true (figure 1). Mean serum leptin level in female patients with NHLs (26.1±16.4 ng/mL) was significantly higher than its level in male patients (15.5±8.4 ng/mL) (t = 4.29; p = 0.001) (table 3). Mean serum leptin level in NHL patients presented with B symptoms (fever, sweating, weight loss) was 22.9±15.2 mg/mL and its mean level in patients without B symptoms was 14.4±6.2 ng/mL; mean serum leptin level was significantly higher in patients presented with B symptoms compared to those without B symptoms (t = 3.64; p = 0.001) (table 3).

The BMI values showed significant differences among patients with various disease stages, where the mean BMI±SD in patients with stage-1 disease was 22.5±2.1 kg/m2, in patients with stage-2 disease was 25.5±3.9 kg/m2, in patients with stage-3 disease was 22.5±4.1 kg/m2, and in patients with stage-4 disease was 26.1±5.1 kg/m2 (F = 4.19; P = 0.002) (table 2). Also, the results revealed that NHL patients with stage-1 disease had mean serum leptin level of 11.6±2.5 ng/mL, while its mean level in patients with stage-2 disease was 18.4±9.2 ng/mL, in patients with stage-3 disease was 13.1±6.6 ng/mL, and in patients with stage-4 disease was 21.7±13.9 ng/mL; the mean serum leptin level was higher in patients with stage-2 and stage-4 disease compared to patients with stage-1 and stage-3 disease (F = 2.97; P = 0.015) (table 2).

Table 3 showed that mean serum leptin level ± SD in patients with Burkitt lymphoma was 14.3±5.8 ng/mL, in patients with CLL (chronic lymphatic leukemia) was 12.9±5.3 ng/mL, in patients with DLBCL (diffuse large B-cell lymphoma) was 22.4±12.1 ng/mL, in patients with follicular lymphoma was 14.1±2.6 ng/mL, in patients with MALT lymphoma was 13.8±1.2 ng/mL, in patients with mantel cell lymphoma was 26.3±8.1 ng/mL, and in patients with T-cell lymphoma was 15.1±2.3 ng/mL; the mean serum level was significantly higher in patients with DLBCL lymphoma and patients with mantel cell lymphoma (F = 2.61; P = 0.022) (table 3).

Significant correlation between BMI and response to chemotherapy was revealed in this study, where patients who showed regressive response had mean BMI±SD of 21.6±2.2 kg/m2, patients who showed stationary lesions had mean BMI±SD of 23.4±3.4 kg/m2, patients who showed progressive disease had mean BMI±SD of 28.6±5.4 kg/m2, and patients who died during course of therapy had mean BMI±SD of 25.8±1.6 kg/m2 (F = 17.57; P = 0.001) (table 4; figure 2). Similar to BMI, significant correlation was also observed between mean serum leptin level and response to chemotherapy, where mean serum leptin level ±SD in patients who responded to chemotherapy and showed regressive response was 10.5±4.1 mg/mL, in patients who showed stationary lesions was 14.8±7.9 ng/mL, in patients who showed progressive disease was 27.6±15.5 ng/mL, and in those who died during course of therapy was 19.2±2.7 ng/mL. Mean serum leptin level was significantly higher in patients who showed progressive disease (i.e., not respond to chemotherapy) compared to those who showed regressive response (F = 14.45; P = 0.001) (table 4; figure 3).

Table 1: Frequencies and percentages of studied patients regarding various parameters

Total number = 100 patients

|  |  |  |
| --- | --- | --- |
| **parameters** | **Number of patients** | **Percentages****(%)** |
| Sex  | Males  | 70 | 70% |
| Females  | 30 | 30% |
| Obesity  | Obese  | 48 | 48% |
| Non-obese  | 52 | 52% |
| B symptoms | Yes  | 60 | 60% |
| No  | 40 | 40% |
| Pathological Types | Burkitt lymphoma | 10 | 10% |
| CLL | 12 | 12% |
| DLBCL  | 44 | 44% |
| Follicular lymphoma | 14 | 14% |
| MALT lymphoma | 4 | 4% |
| Mantel cell lymphoma | 8 | 8% |
| T-cell lymphoma  | 8 | 8% |
| Stages  | Stage-1 | 16 | 16% |
| Stage-2  | 16 | 16% |
| Stage-3 | 8 | 8% |
| Stage-4 | 60 | 60% |
| ChemotherapyRegimens | R-CHOP | 26 | 26% |
| CHOP | 48 | 48% |
| CVP | 18 | 18% |
| FC | 8 | 8% |
| Response to chemotherapy  | Regressive  | 22 | 22% |
| Stationary  | 34 | 34% |
| Progressive  | 34 | 34% |
| Dead  | 10 | 10% |

Table 2: BMI and serum leptin levels in various NHL disease stages

Total number = 100 patients

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Disease stages**  | **BMI (kg/m2) (mean±SD)** | **Statistical test** | **Serum leptin level** **(ng/mL) (mean±SD)** | **Statistical test** |
| Stage 1 (n = 16) | 22.5±2.1 | F = 4.19P = 0.002 | 11.6±2.5 | F = 2.97P = 0.015 |
| Stage 2 (n = 16) | 25.5±3.9 | 18.4±9.2 |
| Stage 3 (n = 8) | 22.5±4.1 | 13.1±6.6 |
| Stage 4 (n = 60) | 26.1±5.1 | 21.7±13.9 |

Table 3: Serum leptin level and various parameters

Total number = 100 patients

|  |  |  |
| --- | --- | --- |
| **Parameters** | **Serum leptin level (ng/mL) (mean±SD)** | **Statistical test &****P value** |
| Sex  | Males (n = 70) | 15.5±8.4 | t = 4.29P = 0.001 |
| Females (n = 30) | 26.1±16.4 |
| B symptoms | Yes  | 22.9±15.2 | t = 3.64P = 0.001 |
| No  | 14.4±6.2 |
| Pathological subtypes | Burkitt lymphoma (n = 10) | 14.3±5.8 | F = 2.61P = 0.022 |
| CLL (n = 12) | 12.9±5.3 |
| DLBCL (n = 44) | 22.4±12.1 |
| Follicular lymphoma (n = 14) | 14.1±2.6 |
| MALT lymphoma (n = 4) | 13.8±1.2 |
| Mantel cell lymphoma (n =8) | 26.3±8.1 |
| T-cell lymphoma (n = 8) | 15.1±2.3 |

Table 4: Response to chemotherapy according to BMI and serum leptin level

Total number = 100 patients

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Response to chemotherapy** | **BMI (kg/m2) (mean±SD)** | **Statistical test** | **Serum leptin level** **(ng/mL) (mean±SD)** | **Statistical test** |
| Regressive (n = 22) | 21.6±2.2 | F = 17.57P = 0.001 | 10.5±4.1 | F = 14.45P = 0.001 |
| Stationary course (n = 34 | 23.4±3.4 | 14.8±7.9 |
| Progressive (n = 34) | 28.6±5.4 | 27.6±15.5 |
| Dead (n = 10) | 25.8±1.6 | 19.2±2.7 |

Figure 1: Correlation between BMI and serum leptin level

Figure 2: Response to chemotherapy regarding BMI

Figure 3: Response to chemotherapy regarding serum leptin levels

**Discussion**:

In this study, higher BMI and hence obesity was associated with increased serum leptin level. It was reported that leptin level in adults was associated with obesity and body mass index [19]. Similarly, Tilg and Moschen [20] reported that obesity is related to increased leptin levels and decreased adiponectin and resistin levels [20]. In current study, obesity is reported in 48% of the NHL patients. In a study of Susanna and Alicja, [21] the risk of non-Hodgkin's lymphoma increased with obesity and this may be related to changes in circulating levels of Adipocytokines, including adiponectin, resistin and leptin; besides their role in insulin resistance, these adipocyte-derived hormones are involved in immunity and inflammation. Several autoimmune and chronic inflammatory conditions have been associated with increased risk of non-Hodgkin's lymphoma [22]. Obesity also gives rise to insulin resistance and compensatory hyperinsulinemia. Insulin may mediate tumorigenic effects directly through insulin receptors in pre-neoplastic target cells, or indirectly through alterations in endogenous hormone metabolism [23]. For instance, elevated insulin levels lead to an increase in bioavailable insulin-like growth factor-I (IGF-I); both insulin and IGF-I act as growth factors that promote cell proliferation and inhibit apoptosis [24].

In this study, both BMI and serum leptin levels were significantly higher in female NHL patients compared to male patients. The serum leptin level in this study was significantly higher in patients presented with B symptoms than those without B symptoms. In contrast, in a study conducted by Pamuk et al., [1] serum leptin level has negative correlations with parameters of poor prognosis like IPI (international prognostic index) in non-Hodgkin's lymphomas. In present study, mean serum leptin level was significantly higher in patients with DLBCL lymphoma and patients with mantel cell lymphoma. Hai-Yan et al., [8] reported that leptin A19G polymorphism was significantly associated with decreased follicular lymphoma risk but not for DLBCL. Concurrently, Susanna and Alicja [21] reported that overweight and obesity may be associated with an elevated risk of non-Hodgkin's lymphomas, particularly of DLBCL.

In this study, patients with stage-4 NHL disease had significantly higher BMI compared to those with stage-1 disease. Serum leptin level, which is positively-correlated with BMI and obesity, was also significantly higher in NHL patients with stage-4 disease compared to those with stage-1 disease. As the response to chemotherapy is related to the disease stages, and the response is bad with advanced stages, thus increased BMI and elevated serum leptin levels could affect the response of NHL patients to chemotherapy. Consistently, in 2019, Scheich et al. [25] reported that obesity was associated with impaired overall survival and increased rates of relapse in lymphoma patients undergoing high-dose chemotherapy (HDT) followed by autologous hematopoietic stem cell transplantation (auto-SHCT).

The results of current study revealed significant correlation between BMI and response to chemotherapy, where patients who showed regressive response had significantly lower BMI compared to those who showed progressive disease. Also, increased serum leptin, which is associated with obesity, had significant correlation with response to chemotherapy, where the serum leptin level was significantly higher in patients who did not respond to chemotherapy and showed progressive disease compared to those who showed regressive response. Consistent with our results, Scheich et al. [25] reported association between obesity and inferior outcomes in cancer patients; in addition, obesity is associated with impaired overall survival due to a higher incidence of relapse in lymphoma patients treated with HDT and concomitant auto-HSCT [25]. In contrast, Han et al. [26] found that being underweight or obese at baseline and weight loss before or after diagnosis was associated with reduced overall survival of NHL, and their findings highlight the importance of maintaining a healthy body weight before and after developing NHL and avoiding weight fluctuations near the time of treatment. In a study by Han et al., [27] weight loss greater than 10% is regarded as one of the B-symptoms, which has been shown to be associated with worse prognosis and shortened survival. The contrast between our results and that of Han et al. [26] could be explained by that Han et al. [26] studied the impact of body weight changes before and after developing NHL on the patients' survival, but the current study evaluate the impact of obesity on response to chemotherapy. Also, in contrast to our results, Stanisavljevic and Marisavljevic [28] reported that weight gain during treatment was associated with better survival among NHL patients using chemotherapy. This contrast could be explained by that Stanisavljevic and Marisavljevic [28] studied the correlation between weight gain during treatment with survival but the present study evaluate the impact of obesity at patient's presentation, not the body weight changes with treatment, on the response to chemotherapy.

***Conclusion and recommendations***:

In conclusion, both obesity, increased BMI and elevated serum leptin level had a worse impact on response of NHL patients to chemotherapy, regardless of pathologic subtypes. The impact of BMI and leptin level on response of various NHL subtypes to chemotherapy was not evaluated in this study and this was limited by the small number of included patients. Further studies are recommended to evaluate the impact of BMI and serum leptin level on response of different NHL pathologic subtypes to chemotherapy.

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