Serum Adiponectin As a Predictor of Childhood Non-Hodgkin's Lymphoma: A Nationwide Case-Control Study

Eleni Th. Petridou, Theodoros N. Sergeantanis, Nick Dessypris, Iris T. Vlachantoni, Sofia Tseleni-Balafouta, Apostolos Pourtsidis, Maria Moschovi, Sofia Polychronopoulou, Fani Athanasiadou-Piperopoulou, Maria Kalmanti, and Christos S. Mantzoros

ABSTRACT

Purpose

To our knowledge, this is the first study exploring the association of childhood non-Hodgkin's lymphoma (NHL) with serum adiponectin and leptin levels in a nationwide case-control series. In addition, expression of adiponectin receptors in NHL specimens was assessed, and the association between adipokines and childhood NHL survival and prognosis was examined.

Patients and Methods

We studied 121 incident childhood (0 to 14 years) NHL cases registered in the Nationwide Registry for Childhood Hematological Malignancies (1996 to 2006) and an equal number of matched controls, for whom sociodemographic, lifestyle, prenatal characteristics, and fasting blood serums were collected. Serum adiponectin and leptin levels were determined. Immunohistochemistry for adiponectin receptors expression was performed on commercially available adult NHL specimens ($n = 30$) and in a subset of childhood NHL cases ($n = 6$) that were available. Summary statistics, multiple conditional logistic regression analyses, and survival analysis were performed.

Results

Higher serum adiponectin, but not leptin, levels were independently associated with childhood NHL (odds ratio, 1.82; 95% CI, 1.30 to 2.56), after adjusting for obesity and established risk factors. Higher adiponectin levels at diagnosis were positively associated with relapse and poor survival, but hormone levels did not differ among NHL subtypes. Adiponectin receptors 1 and 2 were present in 90% and 57% of adult samples and in 83% and 100% of childhood NHL samples, respectively.

Conclusion

Elevated serum adiponectin, but not leptin, levels are independently associated with childhood NHL and poor prognosis. Adiponectin receptors are expressed in NHL, suggesting that adiponectin may represent not only a potential clinically significant diagnostic and prognostic marker but also a molecule that may be implicated in NHL pathogenesis.

J Clin Oncol 27:5049-5055. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) currently represents 6% of all cancers in children and adolescents of European descent.^{1,2} Importantly, its incidence in children has increased by 0.9% annually over the past 20 years, according to the Automated Childhood Cancer Information System.³

The etiology and pathogenesis of NHL remain to be fully elucidated both in children and adults.⁴ Previous studies have shown an association with family history, immunosuppression related to rare inherited disorders and transplantation, as well as exposure to infections, namely HIV, human T-cell lymphotropic virus type-1, Epstein-Barr virus, and *Helicobacter pylori* infection.^{1,2} In addition, various

occupational, environmental, and chemical agents have been implicated as risk factors for NHL.⁵

More recently, adiponectin and leptin, two adipocyte-derived hormones, have been studied in several types of malignancies, including endometrial carcinoma, postmenopausal breast cancer, colon cancer, and melanoma.⁶⁻⁸ In addition, a small study of 28 NHL adult cases has reported elevated adiponectin levels both as a risk factor and as a marker of poor prognosis,⁹ but no studies have focused on childhood NHL. Moreover, leptin and leptin receptor polymorphisms have been associated with adult NHL-related immune dysfunction,² but the role of leptin in the pathogenesis of childhood NHL has not been examined to date.

To our knowledge, we evaluate for the first time adiponectin and leptin in childhood NHL, assessing

From the Department of Hygiene, Epidemiology and Medical Statistics, Department of Pathology, and Hematology-Oncology Unit, First Department of Pediatrics, University of Athens Medical School; Department of Pediatric Hematology-Oncology, "Pan. and Agl. Kyriakou" Children's Hospital; Department of Pediatric Hematology-Oncology, "Aghia Sophia" General Children's Hospital, Athens; Second Department of Pediatrics, Aristotelion University of Thessaloniki, AHEPA General Hospital, Thessaloniki; Department of Pediatric Hematology-Oncology, University Hospital of Heraklion, Heraklion, Greece; and Division of Endocrinology, Diabetes and Metabolism, Beth Israel Deaconess Medical Center, Boston, MA.

Submitted August 22, 2008; accepted May 4, 2009; published online ahead of print at www.jco.org on September 8, 2009.

Supported in part by the University of Athens Medical School; the American Institute for Cancer Research; Grants No. DK58785, DK79929, and DK58845 from the National Institutes of Health; and a discretionary grant from Beth Israel Deaconess Medical Center (C.S.M.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Eleni Th. Petridou, MD, MPH, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, 75 Mikras Asias Str, Athens 115 27, Greece; e-mail: epetrid@med.uoa.gr.

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

© 2009 by American Society of Clinical Oncology

0732-183X/09/2730-5049/\$20.00

DOI: 10.1200/JCO.2008.19.7525

whether these adipokines represent risk factors for the disease and whether they are associated with its prognosis and survival. For this purpose, a nationwide case-control series spanning an 11 year-period has been evaluated. We also study the expression of adiponectin receptors in specimens from both childhood and adult NHL.

PATIENTS AND METHODS

NHL Childhood Case-Control Study

From 1996 to 2006, 182 children (0 to 14 years) of Greek origin were diagnosed with histologically confirmed NHL in Greece (incident cases) and recorded in the Nationwide Registry for Childhood Hematological Malignancies.¹⁰ The latter comprises all six Childhood Hematology-Oncology Units across the country. These cases represent the totality of diagnosed NHL cases of children of Greek origin for the study period. Forty-nine of these cases were not included in the study due to administrative or technical reasons (ie, mainly unavailable or inadequate laboratory samples). Given that no systematic factors were responsible for nonparticipation, it is not likely that any significant bias has been introduced. During the same period of time a suitable control was matched for every child with lymphoma, for age ($\pm$ 6 months) and sex. Controls were recruited among children hospitalized in the same hospital for minor pediatric ailments or surgery, such as hernias.¹¹ The study protocol was approved by the ethics committee of the Athens University Medical School. The guardians of all eligible children, both patients and controls, were appropriately informed of the study objectives and informed consent was requested.

An in-person interview was then conducted with the guardians of both patients and controls using a structured questionnaire covering sociodemographic, lifestyle, and prenatal characteristics. Information on the type of NHL was abstracted from the medical records and confirmed by the treating physicians. Blood samples were collected for hormone determinations during routine

clinical procedures on diagnosis for patients and on admission to the clinic for controls no later than 9 AM and before the initiation of any therapy. Adequate serum blood quantities for hormone determinations were eventually available for 121 incident cases and an equal number of controls. All samples were coded, centrifuged, and then stored at -70°C . Although adiponectin and leptin levels are not altered by storage time,¹² the preservation time for patients and controls was on average similar. The samples, coded and blinded as to case-control status, were air shipped with dry ice in one batch to Beth Israel Deaconess Medical Center, Boston, MA. Serum adiponectin and leptin levels were measured utilizing a commercially available radioimmunoassay procedure with sensitivity of 2 ng/mL and of 0.5 ng/mL respectively, as previously described.¹³

Immunohistochemical Study

The histologic samples of the childhood NHL cases are kept at the respective pathology departments for future use, in case the disease relapses. Material was available at the Pathology Department of the University of Athens from only six childhood NHL cases. We also used commercially available tissue samples from adult NHL to study the expression of adiponectin receptors in the malignant tissue. A total of 30 samples, mostly of extranodal location, have been included in the study, consisting of three archival paraffin-embedded blocks and mounted to standard silanized tissue array slides (Imgenex, San Diego, CA; TM 302,328 and TM367).

Immunohistochemical staining for adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2) was performed as previously described.¹⁴ Slides treated with the primary antibody being replaced by buffer solution without admixture of any antibody did not exhibit any positive reaction and served as negative controls. Slides from normal tissues with specific positive reaction for the receptors (normal and striated muscle for AdipoR1 and normal liver for AdipoR2), treated in the same manner as the neoplastic tissue, served as positive controls. The immunostaining of tumor cells was scored semiquantitatively according to its extent and intensity as:

Table 1. Mean Values and SD of Adiponectin and Leptin Levels by Histologic Type, Stage, and Survival Status Among Childhood Non-Hodgkin's Lymphoma Cases (n = 121)

Variable	International Classification of Diseases O3 Code	No.	Adiponectin		Leptin	
			Mean	SD	Mean	SD
Histologic type						
Burkitt, Burkitt like	9687	57	15.3	6.28	5.1	5.80
Precursor B-cell lymphoblastic	9728	5	12.1	5.30	4.4	2.44
Large cell, B diffuse	9680	10	19.5	12.60	5.4	4.23
Other B-cell type lymphoma	9690	1	10.4	—	1.2	—
Precursor T cell	9729	22	15.6	8.05	7.7	8.68
Peripheral mature T cell	9702	6	18.3	7.80	7.9	7.32
Anaplastic large cell lymphoma						
T cell and null cell type	9714	19	15.9	6.46	7.2	6.01
Other or unspecified	9591	1	10.7	—	9.6	—
Stage						
I		14	12.9	5.51	4.1	4.16
II		36	16.0	7.24	6.7	6.61
III		40	17.3	7.75	5.2	5.62
IV		31	14.5	7.40	7.3	7.42
Relapse						
Yes		17	18.8	8.32	6.2	5.60
No		104	15.2	7.11	6.0	6.45
Survival status						
Dead		16	17.7	7.63	6.8	6.65
Alive		105	15.4	7.31	5.9	6.29
Either unfavorable outcome						
Relapse or death		28	18.5	7.92	6.0	5.43
Nothing		93	14.9	7.02	6.0	6.58

Abbreviation: SD, standard deviation.

absent (weak staining in less than 5% extent of the tumor tissue), mild staining (weak staining or limited positivity to an extent of less than 50% of the tumor tissue), and moderate to strong (moderate to strong intensity and extensive positivity in more than 50% of the tumor tissue).

Statistical Analyses

Adiponectin and leptin levels among the NHL cases by disease characteristics were initially compared using analysis of variation and logistic regression analysis; subsequently the frequency distributions of the study variables among childhood NHL and controls were generated using SAS (SAS Institute, Cary, NC) and compared using *t* test or χ^2 . To assess possible correlation of the two hormones with anthropometric variables and age, Pearson correlation coefficients were used among controls. Subsequently, the data were modeled through multiple conditional logistic regression, using the case-control status as the outcome variable and adiponectin and/or leptin (in increments of 1 standard deviation of the hormone among controls), as well as a series of possible confounders, as predictor variables. Potential confounders considered in the study were body mass index (BMI) and alternatively, body weight and height, birth weight, breast feeding history, place of residence and reported movements, crowding index, maternal education, maternal smoking, sun protection history, and annually spent days at seaside resorts.¹¹ Kaplan-Meier survival curves were calculated to determine the overall survival by levels of adiponectin. Finally, analysis concerning the time to relapse or death or either unfavorable outcome (relapse or death) of NHL was conducted, by modeling the data through Cox's proportional-hazards regression. Follow-up was active with a median time of 74.3 months; September 30, 2008, was the censoring date. No further analysis was performed, however, concerning the subtypes of the B and T cell types as the numbers were rather small to generate any reliable estimates.

RESULTS

Table 1 presents descriptive statistics of serum adiponectin and leptin levels by NHL subtype. No statistically significant heterogeneity in adiponectin and leptin levels was evident in both unadjusted and adjusted for age and sex pair-wise comparisons among the different subtypes or the stage of the disease.

Table 2 presents the distribution of anthropometric, lifestyle, sociodemographic, and hormone characteristics among NHL patients in comparison to their matched controls. The mean age of studied NHL patients was 8.8 years, and the vast majority (76%) were male. In line with previous studies, birth weight was positively related to NHL, whereas there was no difference with respect to other somatometric variables. As previously reported, days spent annually at seaside resorts seemed to play a protective role,¹¹ whereas there was some suggestion that NHL patients reside more frequently in less densely populated areas of the country.

Serum adiponectin levels were significantly higher in NHL patients compared with controls, whereas no significant difference was observed for leptin levels. These bivariate data serve mostly descriptive purposes, however, and they are not directly interpretable due to potential mutual confounding. As expected, adiponectin was inversely associated with age, height, weight, and BMI, whereas leptin was positively correlated with weight and BMI (data not shown).

Results of successive univariate and multivariate conditional logistic regression models are displayed in Table 3. A significantly positive association of higher adiponectin levels with NHL was present and remained robust in all models. The adjusted OR for adiponectin was 1.82 (95% CI, 1.30 to 2.56; *P* < .001), whereas leptin was not associated with this malignancy (OR, 1.05; 95% CI, 0.72 to 1.54; *P* = .80).

Table 4 presents the survival analysis on NHL patients, including the effect of adiponectin levels at diagnosis on the time to relapse

Table 2. Distribution of Childhood Non-Hodgkin's Lymphoma Patients and Their Age- and Sex-Matched Controls by Anthropometric, Lifestyle, Sociodemographic, and Hormone Variables (n = 121)

Variable	Patients		Controls		P
	No.	%	No.	%	
Continuous, mean					
Age, years	8.8		8.8		
SD	3.52		3.44		
Height, cm	135.7		135.2		.87*
SD	21.88		20.99		
Weight, kg	35.3		34.5		.70*
SD	17.74		15.89		
BMI, kg/m ²	17.9		17.9		.95*
SD	4.47		4.08		
Adiponectin, μg/mL	15.7		12.6		.0003*
SD	7.36		5.94		
Leptin, ng/mL	6.0		5.9		.91*
SD	6.31		7.38		
Categorical/ordinal					
Sex					
Male	92	76.0	92	76.0	
Female	29	24.0	29	24.0	
Place of residence by population					.29†
< 100,000	78	64.5	70	57.9	
100,000+	43	35.5	51	42.1	
Change of residence					.12†
No	63	52.1	75	62.0	
Yes	58	47.9	46	38.0	
Crowding index, rooms/person					.50†
< 0.50	24	19.8	24	19.8	
0.50	43	35.5	50	41.3	
0.50-0.74	25	20.7	22	18.2	
0.75+	29	24.0	25	20.7	
Maternal education, years					.74†
≤ 6	24	19.8	19	15.7	
7-9	21	17.4	26	21.5	
10-12	50	41.3	60	49.6	
13+	26	21.5	16	13.2	
Maternal smoking					.24†
No	66	54.5	75	62.0	
Yes	55	45.5	46	38.0	
Birth weight, g					.004†
< 3,000	20	16.5	30	24.8	
3,000-3,459	44	36.4	55	45.5	
3,500-3,999	40	33.1	29	23.9	
4,000+	17	14.0	7	5.8	
Breast fed, months					.95†
0	33	27.3	37	30.6	
1-3	53	43.8	47	38.8	
4-6	21	17.3	22	18.2	
7+	14	11.6	15	12.4	
Eye color					.24†
Dark (brown, black)	109	90.1	103	85.1	
Light (green, blue, gray)	12	9.9	18	14.9	
Reported sun protection					.75†
No	26	21.5	24	19.8	
Yes	95	78.5	97	80.2	
Days spent/year at seaside resorts					.04†
0	48	39.6	30	24.8	
1-14	19	15.7	24	19.8	
15-29	33	27.3	42	34.7	
30+	21	17.4	25	20.7	

Abbreviations: SD, standard deviation; BMI, body mass index.

*Student's test matched variable.

† χ^2 for trend/contrast matched variable.

Table 3. Multiple Conditional Logistic Regression Derived OR and 95% CI for Childhood Non-Hodgkin's Lymphoma in Relation to Adiponectin and Leptin

Model	OR	95% CI	P
1: Adiponectin, univariate Adiponectin	1.59	1.21 to 2.09	.001
2: Leptin, univariate Leptin	1.02	0.77 to 1.36	.91
3: Adiponectin and leptin, mutually adjusted Adiponectin	1.59	1.21 to 2.09	.001
Leptin	1.02	0.76 to 1.38	.89
4: Adiponectin, leptin, and BMI, mutually adjusted Adiponectin	1.60	1.21 to 2.10	.001
Leptin	0.98	0.72 to 1.35	.92
5: Adiponectin, adjusted also for leptin, height, BMI, residence, change of residence, crowding index, maternal education, maternal smoking during child's life, birth weight, breast feeding, eye color, sun protection, days at seaside resorts Adiponectin	1.82	1.30 to 2.56	.001
Leptin	1.05	0.72 to 1.52	.82
6: As model 5, plus weight, instead of BMI Adiponectin	1.82	1.30 to 2.56	.001
Leptin	1.05	0.72 to 1.54	.80

NOTE. OR for an increment of one standard deviation among controls for adiponectin or leptin.
Abbreviations: OR, odds ratio; BMI, body mass index.

occurrence, time to death, or any unfavorable outcome. Lymphomas of B-cell type did not show any significant difference in the outcome in comparison to T-cell NHL, although a considerable heterogeneity seemed to exist within the subtypes (data not shown). Stage appeared to unfavorably affect survival, the overall unfavorable outcome (rate ratio [RR], 2.58; 95% CI, 1.23 to 5.41; $P = .01$; RR, 2.41; 95% CI, 1.35 to 4.28; $P = .003$, respectively) and marginally the relapse occurrence (RR, 2.00; 95% CI, 0.90 to 4.48; $P = .09$, data not shown).

Leptin was not found to be a prognostic factor for time to relapse or survival; on the contrary, higher adiponectin levels at diagnosis were associated with time to relapse, survival and time of any unfavorable outcome (RR, 1.56; 95% CI, 1.09 to 2.25; $P = .02$; RR, 1.46; 95% CI, 1.03 to 2.08; $P = .03$; RR, 1.51; 95% CI, 1.16 to 1.97; $P = .002$, respectively). Addition to the survival model (model 2) of relapse occurrence did not practically alter the results concerning adiponectin (RR, 1.44; 95% CI, 1.00 to 2.06; $P = .04$) or the remaining covariates. Kaplan-Meier survival curves showed that overall survival was 95% for children with lower adiponectin levels, whereas the corresponding survival decreased to 79% for children with high adiponectin levels (Fig 1).

In the immunohistochemical study of adult NHL patients (mean age, 53 years; 77% male), the lymphoid neoplastic cells exhibited mainly cytoplasmic staining that was diffuse, with a variable degree of

intensity (Fig 2) for both AdipoR1, which was expressed in 90% of the samples (27 of 30 cases; 19 cases with mild staining and eight cases with moderate to strong staining) and AdipoR2, which was expressed in 57% of samples (17 of 30 cases, 16 cases with mild staining and one case with moderate to strong staining). In childhood NHL cases, AdipoR1 was expressed in 83% of samples (five of six cases with mild staining), whereas AdipoR2 was expressed in 100% of samples (four cases with mild staining and two cases with moderate to strong staining). Overall, it can be reported that NHL expressed both adiponectin receptors in a more diffuse pattern than that seen in other malignancies and that their expression is not restricted to a cytoplasmic distribution.

DISCUSSION

The principal finding of this study, based on a nationwide childhood NHL case-control registry over an 11-year period, is the statistically significant, positive association of serum adiponectin with childhood NHL and the null association in relation to leptin levels, both of which are independent of obesity-related indices. The observed association may pertain to NHL of both B-cell and T-cell origin, as the two subtypes did not exhibit considerable variability in terms of serum

Table 4. RRs and 95% CIs Derived From Proportional Hazards Modeling

Adiponectin Model*	Category or Increment	RR	95% CI	P
1: Time to relapse	1 standard deviation among controls	1.56	1.09 to 2.25	.02
2: Time to death	1 standard deviation among controls	1.46	1.03 to 2.08	.03
3: Time to either unfavorable outcome	1 standard deviation among controls	1.51	1.16 to 1.97	.002

Abbreviation: RR, rate ratio.

*Also controlling for age, sex, body mass index, height, center, histologic type, stage, and leptin.

Fig 1. Kaplan-Meier survival curves of childhood non-Hodgkin's lymphoma cases by adiponectin levels at the time of diagnosis.

adiponectin levels. Furthermore, in the immunochemistry substudy we demonstrate that AdipoR1 and AdipoR2 were expressed in both adult and childhood NHL tissue.

Thorough review of the literature revealed only one relatively small case-control study in adults,⁹ which suggested that adiponectin is positively associated not only with NHL risk per se, but also with poor prognosis. Our results are in accordance with these data by Pamuk et al⁹ reported in adults. However, the adult NHL study included a more limited number of cases ($n = 28$), defined poor prognosis on the basis of shorter median survival of NHL patients, and reported principally an indirect correlation between adiponectin levels and prognosis. To our knowledge, no prior studies have focused on children; this study is the first to demonstrate that elevated serum adiponectin is not only a risk factor, but also an indicator of poor prognosis (in terms of time to relapse and survival) in childhood NHL.

Adiponectin may act on NHL cells either directly or indirectly. A recent report has revealed that AdipoR mRNA is expressed in human lymphocytes,¹⁵ and we demonstrate herein expression of AdipoR protein, as detected by immunohistochemistry in NHL tissue samples. It remains to be investigated in future studies whether, as demonstrated in other tissues, AdipoRs are capable of direct downstream tumor-promoting signaling in NHL.¹⁶

Apart from any putative direct effects, the association between adiponectin and childhood NHL may also reflect indirect effects of adiponectin through alterations of circulating levels of other cytokines, including upregulation of interleukin 10 (IL-10) and/or down-regulation of tumor necrosis factor (TNF) α , both of which may be playing a central role in adult NHL.⁹ Adiponectin is considered to be a potent anti-inflammatory factor which could alter IL-10 expression in human macrophages,¹⁷ primary monocytes, as well as dendritic cells.¹⁸ In fact, plasma adiponectin and IL-10 concentrations are closely and positively correlated, independently of BMI.¹⁹ Similarly, adiponectin influences the TNF- α system and both TNF- α and IL-10 are pivotal molecules in the pathogenesis of NHL. IL-10 is an established growth factor with antiapoptotic properties in normal B lymphocytes,^{20,21} as well as for B-cell²² and T-cell²³⁻²⁵ NHLs,²⁶ and

Fig 2. Immunostaining for adiponectin receptors in commercially available adult non-Hodgkin's lymphoma (NHL) specimens. (A) NHL femur, strong diffuse immunostaining for adiponectin receptor (AdipoR) 1 ($\times 400$); and (B) NHL femur (previous case), weak immunostaining for AdipoR2 ($\times 400$).

elevated serum IL-10 has been linked to poor prognostic properties for NHL patients.²⁷

Although the nature of the study cannot elucidate underlying mechanisms, the robust association of adiponectin with childhood NHL, after adjustment for potential confounders and obesity indices, adds to the validity of the findings. As reflected on the negative adiponectin-BMI association in this study, decreased adiponectin levels are a hallmark of obesity, not only in adults but also in children.²⁸ Adjustment for BMI and for the other two established covariates of childhood NHL (ie, birth weight and sun exposure)^{11,29} did not alter the adiponectin-related association demonstrated herein.

We also report a lack of association between leptin and childhood NHL. Studies focusing on the serum levels of leptin have been either exploratory in nature³⁰ or have yielded null results with respect to disease prognosis in adults.³¹ Nevertheless, either leptin or leptin signaling deficiency, but not leptin sufficiency or excess, may alter Th1-Th2 balance and circulating levels of cytokines including TNF- α and IL-10 in both humans and animal knockout models.³²⁻³⁹ There is no indication in this study that serum leptin levels are an independent risk factor for childhood NHL.

Although prospective cohort studies are considered superior to case-control investigations given their potential to provide time-sequence criterion for causality, nationwide case-control studies are particularly appropriate in the case of rare diseases, such as childhood NHL. Thus, despite the relatively small size of the current investigation, the data presented herein derive from the ongoing National Registry for Childhood Hematological Malignancies¹⁰ and its case-control derivative study functioning over an 11-year period. Nevertheless, a limitation of this study is the fact that the analysis of AdipoR1 and AdipoR2 has been possible only in a small subset of childhood NHL cases for which material was available. No obvious bias potentially confounding the findings could be discerned in the selection of these samples, however. At any case, the frequent positivity of adiponectin receptors in both adult and childhood NHL cases demonstrated herein suggests that adiponectin may be a molecule with physiological relevance in NHL, independently of age.

In conclusion, this study demonstrates that elevated serum adiponectin, but not leptin, concentrations are an independent risk factor for development of childhood NHL. Moreover, this study highlights the potential prognostic value of measuring serum adiponectin levels in childhood NHL, as the former is associated with poor prognosis and survival. Noticeably, when exploring the underlying physiological relevance of adiponectin, AdipoR were detected in both adult and childhood NHL tissue. Further studies

focusing on underlying mechanisms, evaluating the associated circulating cytokine networks and exploring potential adiponectin signaling pathways in NHL are needed.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Eleni Th. Petridou, Theodoros N. Sergentanis, Nick Dessypris, Christos S. Mantzoros

Provision of study materials or patients: Apostolos Pourtsidis, Maria Moschovi, Sofia Polychronopoulou, Fani Athanasiadou-Piperopoulou, Maria Kalmanti

Collection and assembly of data: Eleni Th. Petridou, Apostolos Pourtsidis, Maria Moschovi, Sofia Polychronopoulou, Fani Athanasiadou-Piperopoulou, Maria Kalmanti

Data analysis and interpretation: Eleni Th. Petridou, Theodoros N. Sergentanis, Nick Dessypris, Iris T. Vlachantoni, Sofia Tseleni-Balafouta, Christos S. Mantzoros

Manuscript writing: Eleni Th. Petridou, Theodoros N. Sergentanis, Nick Dessypris, Iris T. Vlachantoni, Sofia Tseleni-Balafouta, Christos S. Mantzoros

Final approval of manuscript: Eleni Th. Petridou, Christos S. Mantzoros

REFERENCES

- Melbye M, Ekström Smedby K, Trichopoulos D: Non-Hodgkin Lymphoma, in: Adami HO, Hunter D, Trichopoulos D (eds): Textbook of Cancer Epidemiology (ed 2). New York, NY, Oxford University Press, 2008, pp 669-693
- Skibola CF, Holly EA, Forrest MS, et al: Body mass index, leptin and leptin receptor polymorphisms, and non-hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev* 13:779-786, 2004
- Izarzugaza MI, Steliarova-Foucher E, Martos MC, et al: Non-Hodgkin's lymphoma incidence and survival in European children and adolescents (1978-1997): Report from the Automated Childhood Cancer Information System project. *Eur J Cancer* 42:2050-2063, 2006
- Hardell L, Lindstrom G, Van Bavel B, et al: Some aspects of the etiology of non-Hodgkin's lymphoma. *Environ Health Perspect* 106:S679-S681, 1998 (suppl 2)
- Müller A, Ihorst G, Mertelsmann R, et al: Epidemiology of non-Hodgkin's lymphoma (NHL): Trends, geographic distribution, and etiology. *Ann Hematol* 84:1-12, 2005
- Petridou E, Mantzoros C, Dessypris N, et al: Plasma adiponectin concentrations in relation to endometrial cancer: A case-control study in Greece. *J Clin Endocrinol Metab* 88:993-997, 2003
- Barb D, Williams CJ, Neuwerth AK, et al: Adiponectin in relation to malignancies: A review of existing basic research and clinical evidence. *Am J Clin Nutr* 86:S858-S866, 2007 (suppl 3)
- Mantzoros CS, Trakatelli M, Gogas H, et al: Circulating adiponectin levels in relation to melanoma: A case-control study. *Eur J Cancer* 43:1430-1436, 2007
- Pamuk GE, Turgut B, Demir M, et al: Increased adiponectin level in non-Hodgkin lymphoma and its relationship with interleukin-10: Correlation

with clinical features and outcome. *J Exp Clin Cancer Res* 25:537-541, 2006

10. Petridou E, Pourtsidis A, Dessypris N, et al: Childhood leukaemias and lymphomas in Greece (1996-2006): A nationwide registration study. *Arch Dis Child* 93:1027-1032, 2008

11. Petridou ET, Dikaliti SK, Skalkidou A, et al: Sun exposure, birth weight, and childhood lymphomas: A case control study in Greece. *Cancer Causes Control* 18:1031-1037, 2007

12. Wei EK, Giovannucci E, Fuchs CS, et al: Low plasma adiponectin levels and risk of colorectal cancer in men: A prospective study. *J Natl Cancer Inst* 97:1688-1694, 2005

13. Petridou E, Mantzoros CS, Belehri M, et al: Neonatal leptin levels are strongly associated with female gender, birth length, IGF-I levels and formula feeding. *Clin Endocrinol (Oxf)* 62:366-371, 2005

14. Michalakis K, Williams CJ, Mitsiades N, et al: Serum adiponectin concentrations and tissue expression of adiponectin receptors are reduced in patients with prostate cancer: A case control study. *Cancer Epidemiol Biomarkers Prev* 16:308-313, 2007

15. Alberti L, Gilardini L, Girola A, et al: Adiponectin receptors gene expression in lymphocytes of obese and anorexic patients. *Diabetes Obes Metab* 9:344-349, 2007

16. Williams C, Mitsiades N, Sozopoulos E, et al: Adiponectin receptor expression is elevated in colorectal carcinomas but not in gastrointestinal stromal tumors. *Endocr Relat Cancer* 15:289-299, 2008

17. Kumada M, Kihara S, Ouchi N, et al: Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. *Circulation* 109:2046-2049, 2004

18. Wolf AM, Wolf D, Rumpold H, et al: Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochem Biophys Res Commun* 323:630-635, 2004

19. Manigrasso MR, Ferroni P, Santilli F, et al: Association between circulating adiponectin and interleukin-10 levels in android obesity: Effects of weight loss. *J Clin Endocrinol Metab* 90:5876-5879, 2005

20. Rousset F, Garcia E, Defrance T, et al: Interleukin 10 is a potent growth and differentiation factor for activated human B lymphocytes. *Proc Natl Acad Sci U S A* 89:1890-1893, 1992

21. Levy Y, Brouet JC: Interleukin-10 prevents spontaneous death of germinal center B cells by induction of the bcl-2 protein. *J Clin Invest* 93:424-428, 1994

22. Benjamin D, Knobloch TJ, Dayton MA: Human B-cell interleukin-10: B-cell lines derived from patients with acquired immunodeficiency syndrome and Burkitt's lymphoma constitutively secrete large quantities of interleukin-10. *Blood* 80:1289-1298, 1992

23. Ho JW, Liang RH, Srivastava G: Differential cytokine expression in EBV positive peripheral T cell lymphomas. *Mol Pathol* 52:269-274, 1999

24. Boulland ML, Meignin V, Leroy-Viard K, et al: Human interleukin-10 expression in T/natural killer-cell lymphomas: Association with anaplastic large cell lymphomas and nasal natural killer-cell lymphomas. *Am J Pathol* 153:1229-1237, 1998

25. Cohen SB, Parry SL, Feldmann M, et al: Autocrine and paracrine regulation of human T cell IL-10 production. *J Immunol* 158:5596-5602, 1997

26. Voorzanger N, Touitou R, Garcia E, et al: Interleukin (IL)-10 and IL-6 are produced in vivo by non-Hodgkin's lymphoma cells and act as cooperative growth factors. *Cancer Res* 56:5499-5505, 1996

27. Blay JY, Burdin N, Rousset F, et al: Serum interleukin-10 in non-Hodgkin's lymphoma: A prognostic factor. *Blood* 82:2169-2174, 1993

28. Cambuli VM, Musiu MC, Incani M, et al: Assessment of adiponectin and leptin as biomarkers

of positive metabolic outcomes after lifestyle intervention in overweight and obese children. *J Clin Endocrinol Metab* 2008 93:3051-3057, 2008

29. Kricker A, Armstrong BK, Hughes AM, et al: Personal sun exposure and risk of non hodgkin lymphoma: A pooled analysis from the Interlymph Consortium. *Int J Cancer* 122:144-154, 2008

30. Willett EV, Skibola CF, Adamson P, et al: Non-hodgkin's lymphoma, obesity and energy homeostasis polymorphisms. *Br J Cancer* 93:811-816, 2005

31. Pamuk GE, Demir M, Harmandar Yesil Y, et al: Leptin and resistin levels in serum of patients with hematologic malignancies: Correlation with clinical characteristics. *Exp Oncol* 28:241-244, 2006

32. Bertolini F, Paolucci M, Peccatori F, et al: Angiogenic growth factors and endostatin in non-hodgkin's lymphoma. *Br J Haematol* 106:504-509, 1999

33. Faggioni R, Fantuzzi G, Gabay C, et al: Leptin deficiency enhances sensitivity to endotoxin-induced lethality. *Am J Physiol* 276:136-142, 1999

34. Busso N, So A, Chobaz-Péclat V, et al: Leptin signaling deficiency impairs humoral and cellular immune responses and attenuates experimental arthritis. *J Immunol* 168:875-882, 2002

35. Matarese G, Mantzoros C, La Cava A: Leptin and adipocytokines: Bridging the gap between immunity and atherosclerosis. *Current Pharmaceutical Design* 13:3676-3680, 2007

36. Chan JL, Moschos SJ, Bullen J, et al: Recombinant methionyl human leptin administration activates signal transducer and activator of transcription 3 signaling in peripheral blood mononuclear cells in vivo and regulates soluble tumor necrosis factor- α receptor levels in humans with relative leptin

deficiency. *J Clin Endocrinol Metab* 90:1625-1631, 2005

37. Chan JL, Bullen J, Stoyneva V, et al: Recombinant methionyl human leptin administration to achieve high physiologic or pharmacologic leptin levels does not alter circulating inflammatory marker levels in humans with leptin sufficiency or excess. *J Clin Endocrinol Metab* 90:1618-1624, 2005

38. Chan JL, Matarese G, Shetty GK, et al: Differential regulation of metabolic, neuroendocrine, and immune function by leptin in humans. *Proc Natl Acad Sci U S A* 103:8481-8486, 2006

39. Farooqi IS, Matarese G, Lord GM, et al: Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* 110:1093-1103, 2002