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Infections in children with simple obesity: The relation to phagocytic function and serum leptin

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ABSTRACT

Introduction: There is a possible association between obesity and infections. We sought to investigate phagocytic functions in obese children and their relation to serum leptin levels.
Methods: A cross sectional, controlled study was conducted, comprising 40 cases with simple visceral-type obesity. Subjects were evaluated for percentage of caloric intake, frequency and type of infections, body mass index (BMI) z score, in addition to complete blood counting, serum leptin assay (ELISA) and Dihydrorhodamine (DHR) flowcytometry.
Results: Cases were 21 males (52.5%) and 19 females (47.5%) with mean age 7.14 years ± 2.73 SD with median duration of obesity 4.2 years (IQR: 2–6). Cases had higher frequency of infections compared with controls ($p < 0.001$). Serum leptin was significantly higher among cases ($t = -12.391$, $p < 0.001$), while DHR results were comparable in the studied groups ($p = 0.067$). Among cases, absolute lymphocytic count (ALC) correlated negatively with percentage of total caloric intake ($p = 0.045$). Leptin levels correlated positively with frequency of infections ($p = 0.019$) but negatively with ALC ($p = 0.043$). DHR results showed weak negative correlations with serum leptin ($p = 0.177$) and with BMI Z score ($p = 0.109$).
Conclusion: Obese children are posed at increased risk of infections and have higher serum leptin levels with possible negative effects of leptin on phagocytic functions.

Introduction

The prevalence of obesity has been increasing dramatically over the past 30 years in children and adolescents [1]. Childhood obesity has both immediate and long-term effects on health and well-being. Obese youth are more likely to have risk factors for cardiovascular diseases, such as high cholesterol or high blood pressure [2].

Leptin protein is synthesized mainly by adipose tissue and was originally identified as the gene defect responsible for the obesity syndrome. The structure of leptin and its receptor suggest that leptin is a member of the cytokine family. The overall increase in leptin during infection and inflammation indicates that leptin is a part of the immune response and host defense mechanisms [3].

Leptin is found to be involved in regulation of fundamental effector functions of mononuclear phagocytes, which express receptors for this hormone. The regulation of mononuclear phagocytes by leptin is associated with activation of the JAK/STAT signaling pathway, resulting in stimulation of phagocytosis, production of oxygen and nitrogen reactive species, leading to increased secretion of pro-inflammatory cytokines [4]. In this study, we sought to evaluate phagocytic functions (respiratory burst assay) in metabolically healthy obese children and their relation to serum leptin levels compared to healthy age- and sex-matched controls.

Subjects and methods

This study was designed to be a cross-sectional study that was carried out in Children's Hospital, Ain-Shams University, in the period from May 2016 to April 2017.

Abbreviations: ALC, Absolute lymphocytic count; ANC, Absolute neutrophil count; BMI, Body mass index; CBC, Complete blood count; DHR, Dihydrorhodamine; *E. coli*, *Echerichia coli*; IFN-gamma, Interferon-gamma; HDL, High density lipoproteins; IL-2, Interleukin-2; LDL, Low density lipoproteins; PMI, Phorbol myristate acetate; SDS, Standard deviation score; TLC, Total leukocytic count; TG, Triglycerides; VLDL, Very low-density lipoproteins.

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Study subjects

The study comprised 2 groups of subjects: Cases' group which comprised 40 children, 21 boys and 19 girls, aged 3–12 years, with simple obesity and having BMI ≥ 95th centile for age and sex, coming for routine medical examination complaints. Children with clinical or laboratory evidence of primary or secondary immunodeficiency, cases with endocrinal, genetic or drug-induced obesity (steroids or anti-epileptics) and those with diabetes mellitus or on steroid therapy were excluded from our study. Forty, age- and sex-matched healthy lean children (BMI between 5th and 85th centile for age and sex) were enrolled as controls. Controls were recruited from the Outpatient Clinic of Children's Hospital, Ain-Shams University and from primary care units. All studied subjects were prepubertal at time of enrollment in the study.

Ethical considerations

- Ethical approval: The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964 as revised in 2008 and the study protocol gained approval from the local Ethical Committee of the Pediatric department, Faculty of Medicine, Ain Shams University.
- Informed consent: Informed consent was obtained from parents/care givers of enrolled children before enrollment, with preservation of patient anonymity using documents and methods approved by the ethical review committee of Faculty of Medicine, Ain-Shams University.

Study methods

All enrolled subjects were clinically evaluated. Detailed medical history was taken including the history of parental consanguinity and age at onset of obesity. The dietetic history was obtained using a 3-days recall of usual dietary intake including meals and snacks. The total caloric intake was calculated using tables of food composition from the National Nutrition Institute, Egypt, 2006. History of infections was thoroughly evaluated (including documented pneumonias, bronchitis, gastroenteritis, physician diagnosed sinusitis, septicemia, deep organ abscesses, skin or mucous membranes infections whether fungal or bacterial and persistent oral thrush). Subjects were evaluated for frequency of infections per year, site, severity, response to treatment, need for hospitalization or parenteral antibiotics therapy, and complications of infections and/or vaccines over the last year before enrollment. All data were confirmed by revising hospital records and were based on physician diagnosis.

Detailed clinical examination was performed for all subjects laying stress on anthropometric measurements; weight and height measurement. Body mass index (BMI) [BMI = Weight (kg)/(Height in m^2)] and standard deviation score (SDS) of BMI for age and sex were calculated [5]; Waist and hip circumferences were measured in centimeters followed by calculation of waist/hip ratio [6]. Blood pressure was measured in seated subjects three times with calculation of the average of readings.

Laboratory assessment

Six cubic centimeters venous blood were withdrawn from each subject (cases and controls) and divided into two portions: The *first portion* 3 mls were collected into plain tubes, left to clot, centrifuged and serum was separated under complete aseptic conditions for serum leptin and fasting levels of serum triglycerides, cholesterol, low density lipoproteins (LDL), very low density lipoproteins (VLDL) and high density lipoproteins (HDL). Serum leptin was assayed by ELISA using DRG, Gmbh, ELISA leptin kit, Germany, while lipid profile was measured using Synchron CX-9 autoanalyzer using Beckman Instruments Inc., Fullerton, California USA.

The *second portion*, 3 mls were added to ethylenediamine tetraacetic acid, dipotassium salt (K2-EDTA) in vacutainer tubes (final concentration of 1.5 mg/mL) for performing complete blood count (CBC) and flow cytometry based oxidative burst assay (Dihydrorhodamine test), within 2 h from sampling. All samples were taken at the same time 10–12 a.m. CBC was done immediately on coulter® LH 750 cell counter (Coulter Corporation, Florida, USA). The blood film was then smeared and stained with Leishman stain and examined for manual differential count. For flow cytometry-based, oxidative burst assay "Dihydrorhodamine test" (DHR 123), reagents were supplied from Sigma-Aldrich, St Louis, MO and from Pharm Lyse, Becton Dickinson, Mountain View, CA. Coulter Epics, XL flow cytometer (Coulter, Electronics, Hialeah, FL, USA) was used. The assessment of the respiratory burst by this method relies upon the change in the fluorescence of resting neutrophils following Phorbol myristate acetate (PMA) stimulation. A control was used for each patient sample. Three tubes are set up for each patient and control: (a) Blood only; (b) Blood + DHR123 (Resting tube); (c) Blood + DHR123 + PMA (Stimulated tube). Results were expressed as a percentage of oxidative response, which is the percentage of the fluorescence noticed in stimulated cells compared to pre-stimulation.

Statistical methods

The results were tabulated, graphically represented and analyzed using standard computer program SPSS for Windows, release 13.0 (SPSS Inc, USA). All numeric values were expressed as mean ± SD. Comparisons between various groups were done using student t test and Mann–Whitney test for normal and non-parametric variables respectively, Chi square (X^2) test was used to compare the frequency of qualitative variables among different groups. For all tests, a probability value (p) less than 0.05 was considered significant. Spearman's correlation test was used for correlating non-parametric variables. The correlation coefficient (Spearman rho) is interpreted as guided by Hinkle et al. 2003 [7].

Results

Forty children with simple obesity were evaluated in the study. They were 21 boys (52.5%) and 19 girls (47.5%). Their age ranged from 3 to 12 years with a mean (SD) of 7.14 (2.73) years. The controls were 21 boys (52.5%) and 19 girls (47.5%), with age ranging 3–12 years with mean age 6.85 (2.68) years. The mean BMI of cases was significantly higher being 30.14 (6.64) kg/m^2 in comparison to controls (15.52 (1.11) kg/m^2) ($p < 0.001$). The mean BMI percentile, waist circumference, waist centiles, hip circumference and waist/hip ratio were all significantly higher in cases than controls ($p < 0.001$).

The mean BMI z-score in obese subjects was 2.94 (0.882) which was higher than that of controls [−0.215 (0.869) with $p < 0.001$]. Among cases, the mean age of onset of obesity was 3.55 (2.31) years, with a median duration of obesity 4.2 years (IQR: 2–6 years). Systolic blood pressure readings (in mmHg) were comparable between cases and controls (mean ± SD: 111.25 ± 7.91 and 113.5 ± 4.89 respectively, p = 0.129). Diastolic blood pressure readings were higher among cases compared to controls (mean ± SD: 73.50 ± 5.33 and 70.0 ± 7.5 respectively, p = 0.019).

Concerning their metabolic status, lipid profile of cases and controls are demonstrated in Table 1, with significant difference between the two groups.

Obese children had 2–10 physician documented infections per year, in the year preceding enrollment with median (IQR) 4 (3–6.7). However, in control group, the frequency of infections ranged from

Table 1
Lipid profile results among cases and controls.

	Cases	Control	T-test	p-Value
LDL (mg/dl)				
Range	55–154.60	71–118	5.33	<0.001
Mean ± SD	108.88 ± 31.25	81.78 ± 7.87		
VLDL (mg/dl)				
Range	11.40–120	12.6–17.8	9.483	<0.001
Mean ± SD	73.20 ± 38.82	16.34 ± 1.04		
Cholesterol (mg/dl)				
Range	110–187	127–146	1.78	0.07
Mean ± SD	121.44 ± 52.92	136.1 ± 4.95		
HDL (mg/dl)				
Range	15–89	44–67	4.667	<0.001
Mean ± SD	43.36 ± 9.75	51.18 ± 6.3		
TG (mg/dl)				
Range	44–179	63–89	5.488	<0.001
Mean ± SD	118.76 ± 42.30	79.65 ± 16.79		

LDL = Low density lipoprotein, VLDL = Very low-density lipoprotein, HDL = High density lipoprotein, TG = triglycerides.

1 to 5 times per year with median (IQR) of 2 (2–3), with a significant difference between cases and controls. Among cases, 21 (52.5%) had 4 or less infections per year (versus 39 children (975%) in the control group), while 19 cases (47.5%) had more than 4 infections per year (versus one child (2.5%) in the control group), with significant difference between cases and controls (Table 2).

There was no history of hospitalization or a serious infection that necessitated prolonged (≥2 months) or parenteral antibiotic therapy among enrolled subjects. Bronchitis and gastroenteritis were the most common form of infections among the studied groups, with higher frequency among cases, albeit the difference between cases and controls did not reach statistical significance. Although values are limited by the small sample size, yet, cases appeared to have a higher incidence of sinusitis ($p = 0.03$) (Table 3).

Blood picture parameters of cases and controls were comparable; while, serum leptin was significantly higher among cases ($t = -12.391$, $p < 0.001$). DHR results seemed to be slightly lower in cases compared to controls, yet the difference did not reach statistical significance ($p = 0.067$) (Table 4).

Gender variation among cases did not show to have significant impact on frequency or duration of infection, TLC, ALC, ANC, serum leptin levels or DHR results with p values: 0.967, 0.309, 0.935, 0.255, 0.284, 0.776 and 0.096 respectively.

Total leukocytic count (TLC) showed significant negative correlation with the duration of obesity ($r = -0.334$, $p = 0.035$). Also, absolute lymphocytic count (ALC) among cases correlated negatively with the percentage of total caloric intake ($r = -0.318$, $p = 0.045$). On the other hand, serum leptin levels correlated positively with the frequency of infections ($r = 0.369$, $p = 0.019$) and negatively with ALC ($r = -0.321$, $p = 0.043$). DHR results showed weak negative correlations with serum leptin levels ($r = -0.218$, $p = 0.177$) and with BMI Z score ($r = -0.257$, $p = 0.109$) (Table 5).

In the control group, serum leptin levels showed moderate positive correlation with ALC and mild positive correlation with each of TLC and absolute neutrophil count (ANC) (Table 6).

Table 3
Infection history among cases and controls.

Type of infection	Cases (n = 40)		Controls (n = 40)		Comparison	
	No.	%	No.	%	X^2	*p* Value
Gastroenteritis	17	42.5	13	32.5	1.056	0.304
Bronchitis	10	25	8	20	0.355	0.551
Common cold	8	20	4	10	1.94	0.163
Acute sinusitis	4	10	0	0	4.67	**0.03**[a]
Asthma	2	5	0	0	2.538	0.111
Skin boils	8	20	7	17.5	0.102	0.750

Bold value denotes statistical significance.
[a] Significant results at *p* value <0.05.

Discussion

Emerging data indicate an association between obesity and infectious diseases. Obesity may influence either the risk of getting an infection or the outcome of an infection once it is established. Obesity-related immune system dysregulation decreased innate and/or adaptive immune responses, dysregulated cytokine production, obesity-related comorbidities and respiratory dysfunction have all been proposed as possible mechanisms [8].

Circulating leptin levels directly reflect the amount of energy stored in the adipose tissue and are proportional to the body adipose mass both in mice and in humans. Thus, obese individuals typically produce higher leptin than leaner individuals [9,10]. In our study, we had the same observation with significantly higher leptin levels among obese children compared to controls.

In our series, infections were more common among cases in comparison to their matched controls. All forms of observed infections, including bronchitis, sinusitis, common cold, gastroenteritis and skin infections were more frequent among obese children although the difference did not reach statistical significance except in sinusitis. However, none of our children had life-threatening infection. In a recent retrospective study by Okubo et al. [11], pediatric obesity was found to be an independent risk factor for severity and morbidity among pediatric cases with lower respiratory tract infections and was associated with increased risk for mechanical ventilation, septicemia and prolonged hospital stay. Small sample size, relatively short duration of obesity (median 4.2 years (IQR: 2–6 years) and enrollment of metabolically healthy children might explain the absence of significant difference between the 2 groups.

Blood picture parameters including TLC, ANC, and ALC were all comparable between cases and controls. However, among the obese subjects, TLC showed significant negative correlation with the duration of obesity, albeit none of the obese children had leukopenia. This could be related to the normal white blood cell count variation with age. Worth to note that, white blood cell counts have been previously reported to be significantly elevated together with CRP in obese children in comparison to lean controls, indicating a pro-inflammatory state in the obese group. However, this observation is more distinguishable among obese individuals with the cardiometabolic syndrome and subcutaneous rather than

Table 2
Frequency of infections among obese subjects and controls.

Parameter		Cases	Control	Comparison	*p*- Value
Frequency of infections/year	Median (IQR)	4 (3–6.75)	2 (2–3)	$z = -5.91$	<0.001[b]
	Range	2–10	1–5		
	≤4 [n (%)]	21 (52.5%)	39 (97.5%)	$X^2 = 21.600$[c]	<0.001[a]
	>4 [n (%)]	19 (47.5%)	1 (2.5%)		

[a] Chi square test.
[b] Mann–Whitney U test.
[c] Significant results at *p* value <0.05.

Table 4
Laboratory parameters of cases and control groups.

Parameter		Cases	Controls	Independent t-test	
				t	*p* Value
HB (g/dl)	Mean (SD)	11.59 (0.93)	11.47 (0.97)	−0.577	0.566
	Range	9.5–14.1	9.5–14.1		
PLT (x10^3/ul)	Mean (SD)	309.8 (67.01)	331.0 (66.36)	1.422	0.159
	Range	160–415	160–423		
TLC (x10^3/ul)	Mean (SD)	7.45 (1.11)	7.85 (1.41)	1.401	0.165
	Range	5.1–11.3	5.4–11.4		
ALC (x10^3/ul)	Mean (SD)	2.83 (0.92)	3.09 (1.04)	1.202	0.233
	Range	1.39–6.22	1.37–6.27		
AEC (x10^3/ul)	Mean (SD)	0.17 (0.06)	0.15 (0.06)	−0.813	0.419
	Range	0.077–0.36	0.77–0.339		
ANC (x10^3/ul)	Mean (SD)	4.09 (0.73)	4.02 (0.85)	−0.364	0.717
	Range	2.24–5.2	2.4–5.6		
Serum Leptin	Mean (SD)	24.67 (10.90)	2.99 (1.91)	−12.391	<0.001[a]
	Range	12.5–58	0.5–6.9		
DHR	Mean (SD)	95.15 (2.54)	96.09 (1.95)	1.857	0.0671
	Range	89.2–99.4	91.2–99.2		

Key: AEC = Absolute eosinophilic count, ALC = Absolute lymphocytic count, ANC = Absolute neutrophilic count, DHR = Dihydrorhodamine test, HB = hemoglobin, PLT = platelets, TLC = total leucocytic count.
[a] Significant results at *p* value <0.05.

Table 5
Correlation between the obesity measures and immunological parameters among cases.

Parameter	Obesity duration		Waist/hip ratio		BMI Z score		% percentage of caloric intake[b]		Serum leptin level	
	r	*p*	r	*p*	R	*p*	r	*p*	r	*p*
Frequency of infection/yr	0.014	0.929	−0.072	0.658	0.157	0.334	−0.058	0.721	0.369	0.019[a]
TLC	−0.334	0.035[a]	0.113	0.489	0.131	0.419	−0.296	0.064	−0.013	0.935
ALC	−0.084	0.607	0.082	0.615	−0.036	0.827	−0.318	0.045[a]	−0.321	0.043[a]
ANC	−0.196	0.226	0.027	0.867	0.062	0.704	0.144	0.374	0.086	0.598
DHR	0.286	0.073	0.236	0.142	−0.257	0.109	0.044	0.788	−0.218	0.177

ALC = Absolute lymphocytic count, ANC = Absolute neutrophilic count, BMI: Body mass index, DHR = Dihydrorhodamine test, TLC = total leucocytic count.
[a] Significant results at *p* value < 0.05.
[b] percentage of total caloric intake from normal average caloric intake according to age.

Table 6
Correlation between serum leptin levels and other numerical variables among controls.

Parameter	Serum leptin level (in controls)	
	R	*P*
Frequency of infection/year	0.198	0.221
TLC	0.125	0.443
ALC	0.106	0.517
ANC	0.118	0.467
DHR	0.174	0.283

ALC = Absolute lymphocytic count, ANC = Absolute neutrophilic count, DHR = Dihydrorhodamine test, TLC = total leucocytic count.

visceral adiposity [12–14], while our enrolled obese children were in general metabolically healthy with visceral type of obesity.

In obese subjects, ALC showed significant negative correlation with the percentage of caloric intake and with serum leptin as well. On the other hand, serum leptin levels correlated negatively with ALC and to less extent with TLC and ANC among controls. Physiologic leptin levels are reported to enhance the activation and proliferation of human T lymphocytes and enhance T cell cytokine production [15,16]. Leptin deficient mice or those with leptin receptor deficiency/abnormality were found to have impaired in-vitro T cell mediated immunity, with low IL-2 and IFN-gamma (IFN-ɣ) production and decreased delayed type hypersensitivity responses in vivo, as compared to normal controls [15–17]. Thus, serum leptin might have a paradoxical effect on cells of the immune system with physiological levels enhancing the immune function and abnormally high levels showing inhibitory effects. Wider scale studies might elucidate the variable impact of serum leptin on the immune status and can help investigating the actual relation between ALC, serum leptin levels and/or leptin receptor abnormalities.

In our study, DHR test results were comparable between obese subjects and healthy controls. In obese subjects, DHR results also showed negative although negligible correlations with BMI z score and with serum leptin but correlated positively, yet, insignificantly with obesity duration. Also, among controls, DHR results had positive, although, negligible correlations with serum leptin. Studies investigating phagocytic functions in relation to serum leptin have shown contradictory results. Several studies have reported that leptin can stimulate the oxidative burst in control monocytes and that leptin up-regulates phagocytic function via phospholipase activation as well as the expression of adhesion molecules and proinflammatory cytokine secretion. Also, leptin was reported to promote neutrophils chemotaxis and the secretion of oxygen radicals, through direct and indirect mechanisms. Phenotypic abnormalities in macrophages from obese mice with deficient or dysfunctional leptin or leptin receptor abnormalities have also been found [18–22]. On the other hand, studies of Mariano et al. [23], Cohen et al. [24], have found that leptin did not change the basal oxidative burst in human neutrophils stimulated by *Echerichia Coli* (*E.Coli*) or by PMA. The results of a study by El Solh et al. 2009 [25], indicated that the ex vivo anti-inflammatory and antimicrobial responses of alveolar macrophages in obese and morbidly obese cases are preserved when compared to age and gender matched non-obese individuals. Mariano et al. demonstrated that the stimulation of oxidative burst was significantly attenuated when the concentration of recombinant leptin was increased from 10 to 500 ng/mL [23]. Thus, abnormally elevated levels of serum leptin

might exert an inhibitory effect on the phagocytic functions, an issue that needs further investigation.

In our study, we observed a significant positive correlation between serum leptin levels and the frequency of infection per year among the obese subjects ($r = 0.369$, $p = 0.019$) which supports the reported proinflammatory role of leptin. This in agreement with Somech et al., who found that circulating leptin concentrations correlated positively with CRP levels during acute minor infection in children visiting the emergency room for febrile illnesses. Their observation suggests that leptin is indeed a part of acute-phase proteins [26].

Conclusion

In conclusion, obese children have higher frequency of infections compared to healthy controls. Serum leptin in obese children seems to have negative effects on lymphocyte counts and possibly total leukocyte and neutrophil counts and phagocytic functions, an effect that differs from the possible positive effect of leptin on immune function in non-obese individuals. Results of our study are limited by the small sample size and the relatively short duration of obesity. Also, we did not include obese children with metabolic syndrome. Further wider scale studies are warranted to investigate the upper limit of serum leptin with enhancing effect on immune system and the relation between serum leptin, leptin receptor abnormalities and predisposition to infection. In-vitro studies can help to detect and clarify the molecular events associated with exposure of immune cells to different standardized concentrations of leptin. As immune system changes with age, assessment of various aspects of innate and adaptive immune system in obese individuals with different age groups could be worthwhile.

Authors contributions

- Nadin Nabil Toaima: put down the study design, supervised the clinical part and data interpretation and drafted the manuscript.
- Rasha Hassan El-Owaidy: put down the study design, supervised the clinical work and data interpretation and refined the manuscript writing.
- Dina Leksan Zaki: Collected subjects' data and performed the statistical analysis.
- Lerine Bahy Eldin: Suggested the study idea, contributed to design, supervised the data analysis and approved the final manuscript.
- All authors discussed the results and contributed to the final manuscript.

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Competing interests

None declared.

Ethical approval

Not required.

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