Enteric parasites can disturb leptin and adiponectin levels in children

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Abstract

Introduction: Infection by intestinal parasites in childhood may be the main cause of many health-related problems in developed countries such as anemia, anorexia, loss of appetite, retarded growth and development. The aim of the present study was to assess the effect of different intestinal parasites on white adipose tissue hormones.
Material and methods: Eighty-one children infected by different parasites and 35 apparently healthy children were enrolled in this study. All patients and controls were subjected to clinical examination, measurement of body mass index (BMI) and laboratory examination.
Results: For BMI percentiles, there was a significant increase in serum leptin level (p = 0.042) and a significant decrease in serum adiponectin level (p = 0.039) in uninfected children, whereas there were no significant changes in the infected group (p = 0.068 and 0.082 respectively). A significant increase in leptin and decrease in adiponectin levels were observed for *E. histolytica*, *Strongyloides* and *E. histolytica* and *Giardia* infections compared to the control group (p = 0.047, 0.035 and 0.019 for leptin, and p = 0.025, 0.038 and 0.041 for adiponectin, respectively).
Conclusions: The infection by some intestinal parasites may deregulate the secretion of leptin and adiponectin and also affect the absorption of some nutrients which can disturb the BMI and cause anorexia.

Key words: leptin, adiponectin, *Entamoeba histolytica*, *Strongyloides stercoralis*, anorexia, body mass index.

Introduction

Parasitosis has an enormous impact all over the world since helminth infections affect about a billion people [1]. Schistosomiasis affects 200 million people, while 400 million schoolchildren harbor other intestinal parasites [2]. Intestinal parasites are associated with anorexia, malabsorption, weight loss, malnutrition and anemia. The potential impact of diarrhea on nutritional status is well known, and there exists a syner-

gistic relationship between diarrhea and malnutrition [3].

Intestinal mucosal infection by parasites activates mesenteric lymph nodes which are adjacent to adipose tissue. So once the lymph nodes are activated, the adipocytes respond by releasing the so-called adipocytokines to supply energy for the functioning of the lymph nodes [4].

The fecal-oral transmission of *Entamoeba histolytica* usually involves contaminated food or water [5]. The factors that can lead to tissue invasion by *E. histolytica* are poorly understood [6]. Virulent *E. histolytica* strains can infect intact intestinal mucosa. This infection does not require pre-existing mucosal damage.

Leptin and adiponectin are included among adipocytokines [7]. Leptin is a 16 kDa protein encoded by the ob gene [8]. Leptin is a pleiotropic cytokine-like hormone affecting immunologic reactions and hormone axis regulation [9]. In fact, leptin acts at the hypothalamus level and plays an important role in regulating energy production and expenditure, appetite and hunger, metabolism, and behavior [10]. It is one of the most important hormones that is produced by the adipose tissue [11]. Leptin functions by binding to the leptin receptor. Leptin is released locally within the intestinal mucosa and is implicated in interactions with pro-inflammatory cytokines to control local inflammations [12].

Adiponectin is a 30 kDa protein product of the adipose most abundant gene transcript 1 (apM1) gene with high structural similarity to collagen VIII, X, and complement C1q [13]. Adiponectin has a role in the regulation of energy homeostasis [14]. Adiponectin modulates glucose regulation and fatty acid oxidation [15]. It is secreted from the adipose tissue into the bloodstream and is abundant in the plasma [16]. Levels of adiponectin are inversely related to body fat percentage in adults [17]. The association in infants and young children is less clear.

Infection of some types of intestinal parasites (*Entamoeba histolytica* and *Strongyloides*) can deregulate the secretion of leptin and adiponectin levels and also affect the absorption of some nutrients, which can disturb the body mass index (BMI) and cause anorexia. Parasite-induced anorexia is an acute phase response to infection [18] which is also mediated via cytokine induction of leptin synthesis [19]. This case control study employed 81 pediatric subjects with different parasitic infections and 35 control subjects to elucidate the relation of leptin and adiponectin in children with parasite-induced malnutrition.

Material and methods

The procedures followed in this case control study on pediatric subjects were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Biometric data

Eighty-one children with parasitic infections, selected from Mansoura University Children Hospital, were enrolled in this study. There were 46 (39.7%) males and 17 (60.3%) females with ages ranging from one to 15 years. Thirty-five apparently healthy volunteers – 15 males (43%) and 20 (57%) females, aged from 5 to 12 years – were taken as controls. Written consent was obtained from parents of children. Height and weight were measured using a portable free-standing stadiometer and an electronic weighing scale (BS-8001). In measurement of weight, each participant was made to stand still in an upright position on the scale. Weight was recorded to the nearest 0.1 kg, whilst height was recorded to the nearest 0.5 cm. Body mass index was calculated as weight (kg) divided by the square of height (m). Based on the Centers for Disease Control and Prevention (U.S.A.) growth charts, BMI was defined at the following levels: normal weight (10^{th} percentile ≤ BMI ≤ 90^{th} percentile), underweight (BMI < 10^{th} percentile), overweight and obese (BMI > 90^{th} percentile).

Serum testing

Serum level of glucose and lipid profile were measured using a fully automated clinical analyzer (Biolis 24i Premium, Tokyo, Boeki Machinery, Japan). Serum level of leptin was measured using the DRG leptin Sandwich enzyme-linked immunosorbent assay kit [20] (DRG Diagnostics, GmbH, Germany) and serum level of adiponectin using the Ray Bio R Human Adiponectin/Acrp30 ELISA kit [21] (Ray Biotech, Inc. USA). For stool examination, direct smear, the formol-ether concentration method [22] and acid fast stain were used for Coccidea [23]. Gomori's trichrome stain [24] and Weber's trichrome stain for Microsporidia [25] and agar plate culture for *Strongyloides stercoralis* [26] were used.

Stool testing

The presence of *E. histolytica*/*E. dispar* trophozoites in stool samples was demonstrated by enzyme-linked immunosorbent assay (ELISA) (E histolytica Test TechLab, Blacksburg, VA, USA). Only fresh samples, obtained no more than 48 h prior to testing, were used. No specimens treated with formalin or any other preservative (SAF or PVA) were included [27].

Statistical analysis

Exclusion criteria for the study included patients receiving drugs with known anti-hyperlip-

Table I. Serum leptin and adiponectin levels in infected children and controls according to BMI percentiles

Group	BMI	*N*	Leptin	*P*-value	Adiponectin	*P*-value
Controls	Under weight	10	1.38 ±0.87	0.042	8.99 ±2.45	0.039
	Normal weight	15	2.15 ±1.68		7.97 ±0.34	
	Over weight	10	3.25 ±0.78		6.70 ±0.68	
Patients	Under weight	27	2.30 ±1.37	0.068	8.10 ±2.80	0.082
	Normal weight	36	2.51 ±1.37		6.05 ±3.02	
	Over weight	18	3.43 ±2.10		5.60 ±2.89	

idemic effect, patients exhibiting thyroid function disorder, patients suffering from diabetes mellitus (DM) and cardiovascular disease. The data was analyzed using the SPSS program, standard version 16. Quantitative data is presented as mean ± standard deviation. Student's *t*-test and ANOVA were used to compare the means. Correlations between variables were evaluated by Pearson's correlation study and a p-value ≤ 0.05 was considered to be statistically significant.

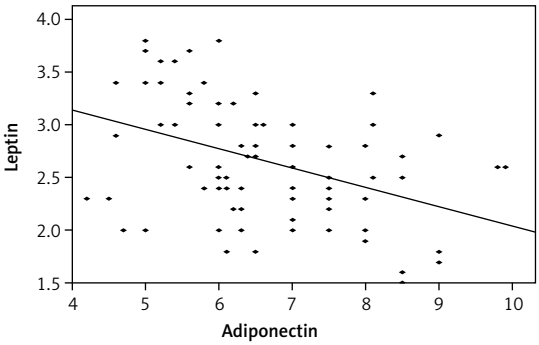

Figure 1. Correlation between leptin and adeponectin levels in patient group

Results

Table I shows a significant increase in serum leptin level (p = 0.042) and a significant decrease in serum adiponectin level (p = 0.039) concerning the BMI percentile in uninfected children but no significant change was found in the group of infected children (p = 0.068 and 0.082 respectively). Figure 1 shows a negative correlation between leptin and adiponectin levels in the patient group (r = –0.415, p = 0.001). A significant increase of leptin level and a significant decrease of adiponectin level (Table II) were observed in *E. histolytica*, *Strongyloides* and both *E. histolytica* and *Giardia* infections compared to the control group (p = 0.047, 0.035 and 0.019 for leptin and p = 0.025, 0.038 and 0.041 for adiponectin respectively).

The study found a positive correlation between leptin and fasting blood glucose in both patients (r = 0.564, p = 0.045) and controls (r = 0.783, p = 0.016) and a negative correlation between adiponectin and fasting blood glucose in both patients (r = –0.690, p = 0.037) and controls (r = –0.574, p = 0.021) (Table III). Also, plasma leptin concentration had a positive correlation with cholesterol, triglyceride and low-density lipoprotein cholesterol (LDL-C) but a negative correlation with high-density lipoprotein cholesterol (HDL-C) in both the patient group (r = 0.693, p = 0.043; r = 0.784, p = 0.005; r = 0.563, p = 0.021; r = –0.583, p = 0.003 respectively) and controls (r = 0.654, p = 0.014; r = 0.654, p = 0.038; r = 0.429, p = 0.000; r = –0.660, p = 0.050 respectively). On the other hand, plasma adiponectin concentration had a negative correlation with cholesterol, triglyceride and LDL-C but a positive correlation with HDL-C in both the patient

Table II. Serum leptin and adiponectin concentrations in different parasitic infections

Parameter	*N*	Leptin [ng/ml]	*P*-value	Adiponectin [µg/ml]	*P*-value
Controls	35	2.35 ±1.03		7.81 ±1.96	
Entamoeba histolytica	41	2.84 ±1.27	0.047	5.43 ±2.60	0.025
Giardia lamblia	8	2.15 ±0.10	0.088	7.43±2.60	0.091
Strongyloides stercoralis	6	3.09 ±2.30	0.035	5.92 ±0.48	0.038
Hymenolepis nana	6	2.25 ±0.35	0.125	6.92 ±1.48	0.080
Oxyuris	10	2.51 ±0.09	0.069	7.97 ±3.16	0.103
Entamoeba histolytica and *Giardia*	10	3.85 ±0.05	0.019	5.94 ±2.81	0.041

Table III. Correlation between leptin and adiponectin with percentile BMI, fasting blood glucose level, cholesterol level, TG level, HDL-C level and LDL-C level

Variable	Leptin		Adiponectin	
	Patients	Control	Patients	Control
BMI percentile	$r = 0.086$ $p = 0.987$	$r = 0.786$ $p = 0.001$	$r = -0.035$ $p = 0.159$	$r = -0.532$ $p = 0.032$
Fasting blood glucose	$r = 0.564$ $p = 0.045$	$r = 0.783$ $p = 0.016$	$r = -0.690$ $p = 0.037$	$r = -0.574$ $p = 0.021$
Cholesterol	$r = 0.693$ $p = 0.043$	$r = 0.654$ $p = 0.014$	$r = -0.531$ $p = 0.001$	$r = -0.664$ $p = 0.041$
Triglyceride (TG)	$r = 0.784$ $p = 0.005$	$r = 0.654$ $p = 0.038$	$r = -0.765$ $p = 0.030$	$r = -0.951$ $p = 0.021$
HDL-C	$r = -0.583$ $p = 0.003$	$r = -0.660$ $p = 0.050$	$r = 0.559$ $p = 0.002$	$r = 0.631$ $p = 0.044$
LDL-C	$r = 0.563$ $p = 0.021$	$r = 0.429$ $p < 0.001$	$r = -0.884$ $p = 0.008$	$r = -0.894$ $p = 0.021$

group ($r = -0.531$, $p = 0.01$; $r = -0.765$, $p = 0.030$; $r = -0.884$, $p = 0.008$; $r = 0.559$, $p = 0.002$ respectively) and controls ($r = -0.664$, $p = 0.041$; $r = -0.951$, $p = 0.021$; $r = -0.894$, $p = 0.021$; $r = 0.631$, $p = 0.044$).

Discussion

Leptin and its receptor are present in the human gastric mucosa. In the human stomach, leptin is produced by the pepsinogen-secreting chief cells of the fundic mucosa. In terms of physiological function, gastric leptin may be involved in the short-term control of satiety, acting in synergy with cholecystokinin (CCK) via vagal afferent fibers in rats [28]. Leptin is secreted into the gastric juice and has a biological effect on food digestion and absorption [29].

The results show that there is a direct relationship between infection and malnutrition (indicated by a low BMI percentile). Indeed, the prevalence of underweight is increasing in the world. This might be due to greater concern about body image among children and adolescents, consuming foods with low nutritional value and also infection [30]. Infection leads to reduced dietary intake and intestinal absorption, while malnutrition leads to infection by inducing alterations in host immune function [2]. Adipose tissue has an active role in regulating energy homeostasis, lipid and glucose metabolism as well as autoimmunity and inflammatory processes [31]. The adipocytokines adiponectin and leptin have emerged as the most abundant adipocyte products that link nutrition to immunity [12, 32].

In the present study, there was a significant positive correlation between leptin and BMI percentile in uninfected children, but this significant correlation disappeared in the group of infected children. This agreed with Lõhmus *et al.* [33], who claimed a possible effect of parasites on leptin secretion. On the other hand, many experimental studies have shown that leptin levels increase during parasitic infection [34]. This contradictory result may be due to, in children, serum leptin levels being low in many forms of malnutrition; and then those children are susceptible to opportunistic infection [35].

A significant negative correlation between adiponectin and BMI percentile is also observed in uninfected children, but this is not observed in infected children. Matsubara *et al.* [36] also observed that serum adiponectin levels are reduced in obesity and plasma adiponectin concentration was inversely correlated with leptin concentrations in nondiabetic normal weight and obese women. Fantuzzi [37] found reduced adiponectin levels in chronic low grade inflammation associated with visceral obesity, or metabolic syndrome, or type II DM, while there is an elevated adiponectin level in most chronic inflammatory and autoimmune diseases. In those (latter) patients the increased adiponectin level is independent of BMI.

A significant increase of leptin and decrease in adiponectin in *E. histolytica*, *Strongyloides* and simultaneous *E. histolytica* and *Giardia* infections has been observed. This can be attributed to the fact that those intestinal parasites may cause damage of intestinal mucosa such as ulceration, shortening of intestinal villi and dilation of crypts which can activate mesenteric lymph nodes then activate adjacent adipose tissues to secrete leptin [4]. Leptin is important in immunity to the enteric pathogens such as *E. histolytica* [38]. In addition to the pro-inflammatory effects on the immune system, leptin may also promote regeneration and inhibition of apoptosis of intestinal epithelium [39] as well as stimulating mucin secretion [40] and maintaining intestinal morphology [41]. Also, leptin has a role as an eosinophil survival factor in humans [42]. Eosinophil has a very significant

role in host defense against parasitic infection. The level of eosinophilia is relative to the extent of pathology due to tissue invasion by parasites [43]. This may explain the significant increase of leptin in *E. histolytica* and *Strongyloides*, which have marked tissue invasion and pathology, and the absence of this significant increase in *Giardia*, *Hymenolepis nana*, and *Oxyuris*, which has no or minimal tissue invasion, and reappearance of a significant increase in both *E. histolytica* and *Giardia* infection because of tissue invasion by *E. histolytica*.

The study found a negative correlation between leptin and adiponectin in the patient group. Matsubara *et al.* [36] observed hypoadiponectinemia and hyperleptinemia in non-diabetic obese women, and a significant inverse relationship between plasma adiponectin and leptin concentrations that was independent of age, BUN, blood pressure, body composition, lipid and insulin resistance. Smith *et al.* [44] found a strong relationship between leptin, adiponectin, and abdominal obesity with increased cardiovascular disease (CVD) risk.

Many authors have reported a positive correlation between leptin and glucose in healthy nondiabetic subjects [45]. Eizadi *et al.* [46] also reported that serum adiponectin level is negatively correlated with fasting blood glucose and positively with insulin and β-cell function. This similarity may be due to the choice of healthy children and exclusion criteria used in this study. Also, it is known that leptin and adiponectin control blood glucose level. Decreased adipose tissue glucose metabolism leads to decreased leptin and increased adiponectin, whereas increased adipose tissue glucose metabolism after refeeding leads to the reverse [46].

In this study, plasma leptin concentration showed a positive correlation with cholesterol, triglycerides (TG) and LDL-C but a negative correlation with HDL-C in both the patient group and controls. In contrast, plasma adiponectin concentration showed a negative correlation with cholesterol, TG and LDL-C but a positive correlation with HDL-C. This agreed with Wu *et al.* [47], who found that leptin was significantly correlated with TG, LDL-C, and Apo-B but negatively correlated with HDL-C and apoprotein A_1 (Apo-A_1). However, Banerji *et al.* [48] found no correlation between leptin and plasma lipids. These contradictory results may be due to different methodologies used. Cnop *et al.* [49] noted that adiponectin was negatively correlated with plasma TG and positively correlated with HDL-C. This may be attributed to the fact that adiponectin increases fat oxidation, leading to reduced levels of fatty acids and tissue triglycerides [50].

In conclusion, both leptin and adiponectin play a role in enteric parasitosis by modulating body immunity, food intake and blood chemistry. Infection of some types of intestinal parasites (*Entamoeba histolytica* and *Strongyloides*) may deregulate the secretion of leptin and adiponectin levels and also affect the absorption of some nutrients which can disturb the BMI and cause anorexia. Further studies are needed to identify their exact role in enteric parasitosis.

Conflict of interest

The authors declare no conflict of interest.

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