Nutrition 78 (2020) 110942

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Obesity and cardiovascular risk among Sri Lankan adolescents: Association of adipokines with anthropometric indices of obesity and lipid profile

Thilini Abeyratne Ph.D. [a], Rasika Perera M.B.B.S., Ph.D. [b,*], Sharaine Fernando M.B.B.S., Ph.D. [c]

[a] Department of Nursing and Midwifery, Faculty of Allied Health Sciences, University of Sri Jayewardenepura, Gangodawila, Nugegoda, Sri Lanka
[b] Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura, Gangodawila, Nugegoda, Sri Lanka
[c] Department of Physiology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Gangodawila, Nugegoda, Sri Lanka

ARTICLE INFO

Article History:
Received 10 November 2019
Received in revised form 27 June 2020
Accepted 4 July 2020

Keywords:
Adolescents
Anthropometry
Obesity
Adipokins
Lipid profile

ABSTRACT

Objectives: Obesity and being overweight among adolescents pose a significant problem and are known to cause several physical and biochemical disorders during adulthood. This study was designed to identify the biomarkers of obesity and describe associations with selected metabolic disorders of obesity among Sri Lankan adolescents.

Methods: The present study compared the characteristics of obese (n = 121) and normal weight (n = 263) adolescents, including sociodemographic, anthropometric, and selected biochemical parameters (e.g., lipid profile, serum leptin, adiponectin, and high-sensitivity C-reactive protein [hs-CRP]). An enzyme-linked immunosorbent assay technique and fully automated clinical chemistry analyzer were used to analyze the biochemical parameters among adolescents ages 10 to 16.

Results: The mean age of the sample was 13.1 y [standard deviation (SD): 1.9 y], and the male-to-female ratio 1:1. The mean weight of obese children was 55.70 kg (SD: 14.82 kg), which was significantly higher than that of children of normal weight [41.63 kg (SD: 7.88 kg)]. Total cholesterol, triacylglycerol, and low-density lipoprotein cholesterol levels were significantly higher (P = 0.000) among obese adolescents compared with those of normal weight. High-density lipoprotein cholesterol was significantly lower among obese adolescents. Serum leptin and hs-CRP were higher among obese adolescents, but adiponectin was lower. In the multivariate analysis, owing to confounding effects among the tested adipokines, serum leptin was the only predictor of an abnormal lipid profile.

Conclusions: Serum leptin, adiponectin, and hs-CRP were found to be reliable biomarkers of predicting adiposity related metabolic disorders in adolescents. Obese adolescents showed disorders in the lipid metabolism with abnormal lipid profiles compared with children of normal weight.

Introduction

In the spectrum of malnutrition, being overweight or obese is one extreme. The World Health Organization (WHO) defines overweight and obese as "abnormal or excessive fat accumulation that may impair health." Overweight or obesity in children is a global public health issue and its prevalence, especially in urban settings, is trending upward worldwide regardless of the economic status of the individual country [1].

Besides being a source of energy, adipose tissue is recognized as an endocrine organ and plays an important role in modulating insulin activity, inflammation, and vascular thrombosis [2]. Adipose tissue secretes adipokines, regulated by multiple signaling pathways, and acts on different receptors, which markedly influences lipid and glucose/insulin metabolism, oxidative stress, and cardiovascular integrity [3].

Markers for early identification of comorbidities of childhood obesity are not clearly defined and require new strategies [4]. Although there are identified risk factors related to obesity, such as prothrombotic factors (fibrinogen, plasminogen activator inhibitor-1, homocysteine), proinflammatory factors (C-reactive protein [CRP], interleukin [IL] 6, tumor necrosis factor [TNF] alpha), and some adipocytokines (leptin, adiponectin) [5], they have not yet

This study was funded by the University of Sri Jayewardenepura, Gangodawila, Nugegoda, Sri Lanka (grant number: ASP/01/RE/MED/2017/40).
*Corresponding author. Tel.: +94714402928, Fax. +94 11 2801480.
E-mail address: rasika@sjp.ac.lk (R. Perera).

https://doi.org/10.1016/j.nut.2020.110942
0899-9007/

been fully explained. The impact of increased body weight in children and the risks of developing atherosclerosis and overall cardiometabolic risks have not been clearly defined.

Leptin is associated with control of body weight, and affects insulin sensitivity [6]. In vitro studies show that physiological concentrations of leptin inhibit insulin secretion and insulin mediated function in islet cells and adipocytes [6]. Although clinical surveys show a relationship between leptin and insulin resistance (IR) [7], only a few have been performed in adolescents.

Adiponectin, an antiinflammatory adipokine, appears to have a role in the regulation of energy balance and peripheral tissue lipid metabolism [2]. Most studies on adiponectin and IR have been performed in rodents, nonhuman primates, and adult subjects who are obese and have type 2 diabetes. However, information on circulating levels of adiponectin in children is scarce [3].

CRP is an acute phase reactant and a marker of systemic inflammation, which in turn is a marker of atherosclerosis. In particular, CRP levels measured by a high-sensitivity (hs) assay is recognized as a useful and sensitive predictor of the future risk of myocardial infarction and stroke [8]. Although CRP levels in adults are well known to elevate with age, increasing body mass index (BMI) score, smoking status, and progression of hypertension [9], information on hs-CRP and its clinical significance as a marker of inflammation in children is scarce.

Therefore, we investigated the relationship between serum leptin, adiponectin, hs-CRP, and anthropometry and lipid profile among Sri Lankan adolescents. Furthermore, this knowledge will enable an understanding of the metabolic effects of these cytokines and predict the cardiometabolic outcomes among adolescents.

Methods

Study population

A case control study was conducted between 2017 and 2019 in all Divisional Secretariat (DS) divisions in the Colombo district. The study population was obese (cases) and normal-weight (controls) adolescents, ages 10 to 16 y, who were selected after obtaining informed consent from the adolescents and their guardians. A stratified random sampling method was used. Each DS division was considered as a stratum, and the total sample was divided among the DS division according to the probability proportions depending on the population of adolescents in each DS division. Accordingly, 121 obese and 263 normal-weight adolescents of both sexes were included.

Adolescents ages 10 to 16 y, whose z-score values for BMI-for-age were more than +1 standard deviation (SD) according to the WHO child growth reference of 2007 [10], were considered as cases. A control was an adolescent age 10 to 16 y, whose z-score value for BMI-for-age was between −2 and +1 SD according to the WHO child growth reference of 2007. Adolescents with acute febrile diseases and trauma causing discomfort or interfering with the biochemical parameters (especially hs-CRP) were excluded. Acute febrile diseases were defined as infection or inflammation, along with the use of antipyretic, analgesic, or antibiotic agents within 3 wk of recruitment into the study. In addition, adolescents with dysmorphic pathologies, drug therapy, lesions of the central nervous system, and clinical conditions that could affect the endocrine and metabolic status or normal growth were excluded.

Data collection

Anthropometric measurements

Height and weight were measured using standard techniques [11]. Participants were wearing only their school uniform with no tie, badge, footwear, or other accessories. Body weight was measured to the nearest 0.1 kg using calibrated electronic weighing scales (Seca 770, Digital Scales, Seca Ltd., Birmingham, United Kingdom). Height was measured using a portable Stadiometer (Seca Stadiometer, Seca Ltd., Birmingham, United Kingdom) and recorded to the nearest mm. The z-score values for BMI-for-age were calculated using AnthroPlus software. Overweight (> +1 SD) and obesity (> +2 SD) were defined according to the WHO child growth reference of 2007 [10].

Waist circumference (WC) to the nearest 0.1 cm was measured using a flexible plastic tape placed midway between the last rib and iliac crest. WC measurements were classified according to the British WC percentiles. The 90th percentile was considered obese [12]. Total body fat percentage (BF%) was estimated using a commercially available Karada scan body composition monitor with a scale (body fat analyzer; bioelectrical impedance analysis [BIA]; HBF-362 model; OMRON). The BF% to the nearest 0.1% was recorded. BF% was defined according to the charts published by McCarthy et al. in 2006 [13].

Collection of venous blood samples and biochemical analysis

Venous blood samples were taken after 12 h of fasting. Approximately 5 mL of venous blood was collected under aseptic conditions using sterile needles by an experienced nursing officer from the Colombo South Teaching Hospital. Blood was collected into both plain an ethylenediaminetetraacetic acid bottles (2.5 mL to each). Blood was allowed to clot for 30 to 45 min at room temperature, and serum was separated centrifuging at 3000 rpm for 5 min. Separated serum/plasma was aliquoted and stored between −20°C and −80°C pending batch analysis.

Total cholesterol (TC; cholesterol oxidase phenol 4-amino antipyrene peroxidase method), triacylglycerol (TG; glycerol phosphatase oxidase-phenol 4-amino antipyrene peroxidase method), and high-density lipoprotein cholesterol (HDL-C; cholesterol oxidase phenol 4-amino antipyrene peroxidase method) were determined by using the Konelab 20 XT auto analyzer (Thermo Scientific Co, Finland). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedwald's formula as follows: LDL-C = TC (mg/dL) − HDL-C (mg/dL) − (TG/5) mg/dL.

Quantitative measurements of serum leptin, adiponectin, and hs-CRP were done using commercially available enzyme-linked immunosorbent assay kits (DRG International, Inc, Springfield Township, NJ), and absorbance was measured using spectrophotometry at 450 nm (Multiskan FC enzyme-linked immunosorbent assay microplate photometer; Thermo Scientific Co., Finland).

Statistical analysis

Data were coded and entered into the Statistical Package for Social Sciences software, version 20.0. A probability of $P < 0.05$ was considered statistically significant. Anthropometric measurements are presented as means and SD. Continuous variables were tested for normality by using skewness and kurtosis value of distribution, which are relatively reliable in both small and large samples [14]. An acceptable range of skewness and kurtosis between −1 and +1 was used to determine normality [15]. Skewed variables were log transformed. An independent sample *t* test was used to compare anthropometric and biochemical parameters of obese and normal-weight adolescents. Pearson's correlation was used to determine correlates of leptin, adiponectin, and hs-CRP serum levels.

Multiple regression analyses were performed to assess the collective effect of serum leptin, adiponectin, and hs-CRP on identified metabolic disorders among adolescents, including obesity (including both overweight and obese), WC > 90th percentile, high waist:hip ratio (WHR), waist:height ratio (WHtR), and abnormal lipid profiles (high TC, high TG, high LDL-C, and low HDL-C).

Ethical considerations

Participation in the study was strictly voluntary and participants were free to refuse or withdraw from the study at any stage. Informed written consent and assent from participants was obtained after explaining the protocol and the advantages of participation. A serial number was given to each participant to maintain anonymity and confidentiality of the information. The results of the blood tests were provided to the participants/guardians, and adolescents with abnormal findings were referred to relevant specialists. Ethical clearance was obtained from the ethics review committee of the Faculty of Medical Sciences at the University of Sri Jayewardenepura before commencing the study.

Results

Anthropometric and biochemical parameters among obese and normal-weight adolescents

The mean age of the sample is 13.1 y (SD: 1.9 y), and the male-to-female ratio is 1:1. The mean weight of obese adolescents was 55.70 kg (SD: 14.82 kg), which was significantly higher than that of normal-weight children (41.63 kg [SD: 7.88 kg]). The anthropometric and biochemical parameters of obesity and normal weight are shown in Table 1. Anthropometric characteristics, such as weight (t [382] = 12.12; $P = 0.000$), BMI for age z score (t [382] = 21.23; $P = 0.000$), BMI (t [382] = 14.67; $P = 0.000$), WC (t [382] = 18.54; $P = 0.000$), hip circumference (t [382] = 11.20; $P = 0.000$), WHR (t [382] = 6.34; $P = 0.000$), and WHtR (t [382] = 13.9; $P = 0.000$) were higher among obese adolescents. Percentage of body fat derived using a BIA (t [382] = 24.36) was also higher among obese adolescents ($P = 0.000$) compared with those of normal weight.

Table 1
Anthropometric and biochemical parameters of obese and normal-weight adolescents

Characteristic	Obese (n = 121) mean (SD)	Normal weight (n = 263) mean (SD)	*P*-value*
Weight (kg)	55.70 (14.82)	41.63 (7.88)	< **0.001**
Height (cm)	151.73 (10.57)	150.28 (9.77)	0.188
BMI for age z score	1.51 (0.85)	−0.26 (0.52)	< **0.001**
BMI (kg/m^2)	23.81 (4.01)	18.25 (1.65)	< **0.001**
WC (cm)	84.9 (9.10)	69.83 (7.05)	< **0.001**
HC	90.65 (10.41)	79.27 (8.66)	< **0.001**
WHR	0.93 (0.74)	0.83 (0.06)	< **0.001**
WHtR	0.56 (0.06)	0.46 (0.04)	< **0.001**
BF% BIA	30.72 (3.46)	21.64 (3.35)	< **0.001**
TC (mg/dL)	175.87 (22.75)	153.53 (22.71)	< **0.001**
HDL-C (mg/dL)	39.84 (7.52)	48.57 (6.09)	< **0.001**
TG (mg/dL)	111.81 (34.41)	82.79 (31.09)	< **0.001**
LDL-C (mg/dL)	113.81 (22.76)	88.80 (22.09)	< **0.001**
Leptin (ng/mL)	26.33 (10.43)	9.27 (6.23)	< **0.001**
Adiponectin (μg/mL)	2.47 (0.82)	9.79 (5.36)	< **0.001**
hs-CRP (mg/l)	2.36 (0.69)	1.28 (0.63)	< **0.001**

BF% BIA, percentage of body fat mass by bioelectrical impedance analysis; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; TC, total cholesterol; TG, triacylglycerol; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
*Independent sample *t* test.

TC (t [382] = 8.92; *P* = 0.000), TG [t [382] = 8.21; *P* = 0.000), and LDL-C (t [382] = 10.21; *P* = 0.000) were higher among obese adolescents compared with those of normal weight, but HDL-C (t [382] = −11.74; *P* = 0.000) was lower among those who were obese. Serum leptin (t [382] = 14.86; *P* = 0.000) and hs-CRP (t [382] = 9.22; *P* = 0.000) were also higher among obese adolescents, but adiponectin was lower (t [382] = −8.41; *P* = 0.000).

Correlations between adipokines and anthropomorphic indices of obesity and lipid profile

The correlation of serum leptin, adiponectin, and hs-CRP with anthropometric and biochemical parameters are presented in Table 2. All anthropometric parameters assessed, including BMI for age z score (r = 0.690; *P* = 0.000), WC (r = 0.628; *P* = 0.000), WHtR (r = 0.584; *P* = 0.000), and BF% BIA (r = 0.738; *P* = 0.000), showed a strong positive correlation with serum leptin, but serum adiponectin showed a significantly negative correlation with BMI for age z score (r = −0.459; *P* = 0.000), WC (r = −0.358; *P* = 0.000), WHtR (r = −0.377; *P* = 0.000), and BF% BIA (r = −0.453; *P* = 0.000). Similarly, BMI for age z score (r = 0.453; *P* = 0.000), WC (r = 0.380; *P* = 0.000), WHtR (r = 0.387; *P* = 0.000), and BF% BIA (r = 0.509; *P* = 0.000) had a positive correlation with hs-CRP among the adolescents assessed in this study. Serum leptin and hs-CRP positively correlated with TC, TG, and LDL-C, but leptin and hs-CRP negatively correlated with HDL-C. Serum adiponectin negatively correlated with TC, TG, and LDL-C, but positively correlated with HDL-C. As expected, the association between leptin and hs-CRP was strongly positive, but adiponectin showed a negative association with leptin and hs-CRP.

With multiple regression analyses, serum leptin, adiponectin, and hs-CRP levels were found to be reliable biomarkers of predicting BMI for age z score (F [3,380] = 171.50; *P* < 0.001; R^2 = 0.57), body fat percentage (F [3,380] = 175.23; *P* < 0.001; R^2 = 0.58), WHR (F [3,380] = 55.05; *P* < 0.001; R^2 = 0.30), and WHtR (F [3,380] = 138.21; *P* < 0.001; R^2 = 0.52) among adolescents (Table 3). Furthermore, serum leptin is also a reliable biomarker of predicting TC (F [3,380] = 25.49; *P* < 0.001; R^2 = 0.16), HDL-C (F [3,380] = 37.96; *P* < 0.001; R^2 = 0.23), TG (F [3,380] = 25.90; *P* < 0.001; R^2 = 0.17), and LDL-C (F [3,380] = 29.59; *P* < 0.001; R^2 = 0.18) among adolescents. Serum adiponectin can be considered a reliable biomarker of predicting HDL-C but not TC, TG, or LDL-C (Table 4).

Discussion

Obesity is well known to be associated with comorbidities, such as hypertension, dyslipidemia, diabetes mellitus, and subsequently leads to cardiovascular disease. Adipokines secreted from adipose tissue is linked to these comorbidities in obesity. With increased adiposity, leptin (an adipokine with proinflammatory properties) is overproduced, but some adipokines with antiinflammatory or insulin sensitizing properties (e.g., adiponectin) are decreased [16]. In addition, inflammatory markers, such as CRP, IL-6, and TNF-α, are increased in obese individuals compared with those who are lean [17]. This dysregulation in adipokine secretion is thought to promote obesity-linked cardiometabolic disorders. Therefore, serum leptin, adiponectin, and CRP were measured in the present study because they are reliable biomarkers associated with obesity and cardiovascular diseases.

The present study compared the levels of serum leptin (proinflammatory), adiponectin (antiinflammatory), and hs-CRP (marker of inflammation) between obese and normal-weight adolescents. The association between serum leptin, adiponectin, and hs-CRP with anthropometry and lipid profile and IR were also assessed.

Table 2
Anthropometric and biochemical correlates of serum leptin adiponectin and hs-CRP

Variable	Leptin		Adiponectin		hs-CRP	
	r*	*P*	r*	*P*	r*	*P*
BMI for age z score	0.690	< 0.001	−0.459	< 0.001	0.453	< 0.001
WC	0.628	< 0.001	−0.358	< 0.001	0.380	< 0.001
WHR	0.159	0.002	−0.257	< 0.001	0.165	0.001
WHtR	0.584	< 0.001	−0.377	< 0.001	0.387	< 0.001
BF% BIA	0.738	< 0.001	−0.453	< 0.001	0.509	< 0.001
TC (mg/dL)	0.268	< 0.001	−0.173	0.001	0.182	< 0.001
HDL-C (mg/dL)	−0.354	< 0.001	0.358	< 0.001	−0.344	< 0.001
TG (mg/dL)	0.194	< 0.001	−0.181	< 0.001	0.233	< 0.001
LDL-C (mg/dL)	0.270	< 0.001	−0.203	< 0.001	0.173	0.001
Leptin (ng/mL)	–	–	−0.402	< 0.001	0.547	< 0.001
Adiponectin (μg/mL)	−0.402	< 0.001	–	–	−0.348	< 0.001
hs-CRP (mg/L)	0.547	< 0.001	−0.348	< 0.001	–	–

BF% BIA, percentage of body fat mass by bioelectrical impedance analysis; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triacylglycerol; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
*Pearson's correlation coefficients.

Table 3
Association between adipokines and anthropomorphic indices of obesity

Dependent variable	Determinant	Standardized Beta coefficient	*P*	95% CI	R^2
BMI for age z score					0.57
	Leptin	0.049	0.000	0.04–0.056	
	Adiponectin	−0.057	0.000	−0.07 to −0.04)	
	hs-CRP	0.152	0.003	0.053–0.250	
BF% BIA					0.58
	Leptin	0.294	0.000	0.26–0.331	
	Adiponectin	−0.139	0.000	−0.21 to −0.07)	
	hs-CRP	1.060	0.000	0.55–1.567	
WC					0.48
	Leptin	0.548	0.000	0.46–0.636	
	Adiponectin	−0.545	0.000	−0.71 to −0.37)	
	hs-CRP	1.035	0.096	−0.186 to 2.256	
WHR					0.30
	Leptin	0.001	0.000	0.00–0.002	
	Adiponectin	−0.006	0.001	−0.008 to −0.005	
	hs-CRP	0.013	0.008	0.004–0.023	
WHtR					0.52
	Leptin	0.003	0.000	0.003–0.004	
	Adiponectin	0.010	0.000	−0.005 to −0.003	
	hs-CRP	−0.004	0.005	0.003–0.018	

BF% BIA, percentage of body fat mass by bioelectrical impedance analysis; BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.

According to our findings, in the obese group, the concentrations of serum leptin (26.33 ng/mL) and hs-CRP (2.36 mg/l) were higher ($P < 0.001$), whereas serum adiponectin (2.47 μg/mL) was lower ($P < 0.001$) compared with those of normal-weight adolescents. A case control study among Portuguese children ages 6 to 17 y also report the relationship between markers of adiposity, inflammation, and adipokines [18]. Serum leptin levels were significantly higher among obese adolescents (29.04 ± 2.13 ng/mL) compared with those of nonobese adolescents (4.76 ± 0.87 ng/mL), but serum adiponectin was significantly lower among obese adolescents (3.23 ± 0.19 μg/mL) compared with those of the controls (4.76 ± 0.87 μg/mL). In 2016, Mantovani et al. [19] also reported similar findings with serum leptin levels and adiponectin among obese adolescents in Brazil. In Greece, a study of obese and nonobese children ages 7 to 16 y showed that hs-CRP in obese children was high (6.1 ± 1.08 mg/l) compared with that of the control group (0.5 ± 0.18 mg/l) [20].

Thus, leptin is an adipokine directly related to adiposity. In the present study too, surrogates of adiposity (i.e., BMI Z score, WC, WHtR, and BF%) had a strong positive correlation with serum leptin concentration. The paradox of raised levels of leptin is explained by the resistance to leptin via an increase in levels of suppressor of cytokine signaling 3, which is an inhibitor of leptin signaling [21]. Thus, in obese adolescents, leptin leads to increased IR, homeostatic imbalances, and vascular inflammation [22].

In present study, adiponectin has a negative correlation with obesity and fat mass. The possible mechanism could be that synthesis of adiponectin is inhibited in situations of cellular hypoxia and oxidative stress, as well as by IL-6 and TNF-α, which are increased with obesity [23]. Adiponectin production appears to be regulated by insulin and inhibited in an IR state, which is also common with obesity [18,24]. Another mechanism for the downregulation of adiponectin in obese individuals could be a 30% decline in the expression of adiponectin receptors, AdipoR1 and AdipoR2, in the skeletal muscles and liver [25].

Increased CRP in obese individuals is related to an increase in adipokine, such as leptin, TNF-α, IL-1β, IL-6, and IL-8, which induces the proinflammatory status and decreases in adiponectin and leads to reduced antiinflammatory activity in the body [23]. This imbalance in pro- and antiinflammatory status of the body induces the

Table 4
Association between adipokines and lipid profile

Dependent variable	Determinant	Standardized Beta coefficient	*P*	95% CI	R^2
TC					0.16
	Leptin	0.74	0.000	0.50–0.98	
	Adiponectin	−0.24	0.298	−0.69 to 0.21	
	hs-CRP	2.98	0.077	−0.32 to 6.28	
HDL-C					0.23
	Leptin	−0.22	0.000	−0.29 to −0.15	
	Adiponectin	0.29	0.000	0.15–0.42	
	hs-CRP	−0.65	0.190	−1.62 to 0.32	
TG					0.16
	Leptin	1.02	0.000	0.69–1.35	
	Adiponectin	−0.42	0.192	−1.05 to 0.21	
	hs-CRP	4.08	0.082	−0.51 to 8.67	
LDL-C					0.18
	Leptin	0.76	0.000	0.52–0.99	
	Adiponectin	−0.44	0.054	−0.89 to 0.008	
	hs-CRP	2.81	0.092	−0.46 to 6.08	

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triacylglycerol.

synthesis of CRP in the liver. In the present study, the associations of each of the markers of obesity (i.e., leptin, adiponectin and hs-CRP) was assessed with parameters related to cardiometabolic consequences of obesity, including anthropometry (BMI for age Z score, WC, WHtR, and BF %) and lipid profile (TC, TG, LDL-C, and HDL-C).

Serum leptin correlated positively with BMI Z score, WC, WHtR, and BF%, which are indices of the extent of adiposity. The reverse was found with serum adiponectin concentration, showing a negative correlation with BMI Z score, WC, WHtR, and BF%. Coutinho et al. [26] also described the association between indicators of adiposity and reported similar findings with leptin correlating positively with BMI, WC, and BF%, and adiponectin correlating negatively with BMI but not with central adiposity indices. These findings also confirm the bidirectional association of body fat with leptin and adiponectin.

In the present study, serum leptin correlated positively with TC, TG, and LDL-C, but serum adiponectin had a negative correlation with TC, TG, and LDL-C. The reverse was observed for HDL-C with a positive correlation with serum adiponectin and a negative correlation with serum leptin. These findings are comparable with those of other studies conducted elsewhere. A study of obese and nonobese children ages 6 to 9 y in Spain found that serum leptin positively correlated with TG and negatively with HDL-C, but adiponectin correlated negatively with TG [27]. Mantovani et al. [19] has also reported that plasma levels of adiponectin negatively correlated with TG, and leptin concentrations positively correlated with TG. However, in the present study, TC showed only a weak correlation with serum leptin and adiponectin.

Serum TC, LDL-C, HDL-C, and TG are traditionally used to assess cardiovascular risks in obese individuals [19]. The abnormalities observed in our study are warnings of the risk of developing cardiometabolic disorders among children. The association between serum leptin, adiponectin, and CRP with an abnormal lipid profile is explained by an proinflammatory state and impairment of endothelial function [28,29]. The associations of leptin with proatherogenic blood lipids can be explained by its role in IR, as well as endothelial dysfunction and proinflammatory activity, which triggers cardiovascular diseases [30]. In addition, preclinical and clinical experiments show that obese rodents and humans displayed leptin resistance that may directly contribute to the reduction of lipid oxidation in insulin-sensitive organs, leading to the accumulation of lipids and IR [31,32]. Furthermore, the bioavailability of nitric oxide is compromised by increased levels of leptin and reduces the vasodilatory capacity of the vessel. Endothelial dysfunction is considered the earliest step in the atherosclerotic process and precedes any morphologic changes in the vessel wall. If the inflammatory milieu is maintained, the arterial wall phenotype undergoes progressive changes that culminate in the formation of an atheromatous plaque [33]. Studies have shown that atherosclerotic disease begins in childhood, mostly in children with cardiovascular risk factors [34]. Thus, childhood obesity is an important predictor of morbidity and mortality in adulthood [35].

Serum adiponectin correlated negatively with serum TC, TG, and LDL-C concentrations and positively with HDL-C. These findings are consistent with those of previous studies reporting that serum levels of TG and LDL-C were significantly increased but HDL-C was decreased with decreasing adiponectin levels [18,26]. This could be due to the antiatherogenic activity of adiponectin by increasing fatty acid uptake and oxidation through the activation of AMP-activated protein kinase, p38-mitogenactivated protein kinase, and peroxisome proliferator-activated receptor gamma pathways [36,37].

Furthermore, hs-CRP shows a positive correlation with indicators of obesity and a positive but weak correlation with TC, TG, and LDL-C. Also, hs-CRP negatively correlated with HDL-C. Similar to the present study, Pires et al. [18] reported that hs-CRP positively correlated with BMI (r = 0.198; P = 0.031), WC (r = 0.236; P = 0.031), and BF% (r = 0.230; P = 0.021). In addition, Valle et al. [27] found that hs-CRP was positively correlated with TG and negatively correlated with HDL-C.

In addition, hs-CRP is associated with the development of cardiovascular diseases by mechanisms including altered sensitivity to insulin induced by the proinflammatory status of adiposity, increased liberation of adhesion molecules by endothelium, increase in hepatic production of fibrinogen, and platelet coagulation factors [38]. In conformity with the evidence in the literature, the present study also found that hyperleptinaemia, hypoadiponectinaemia, and high CRP levels in obese adolescents correlated positively with the main variables of metabolic syndrome, namely dyslipidemia, impaired glucose metabolism, abdominal obesity, and proinflammatory state.

With the multivariate analysis, serum leptin, adiponectin, and hs-CRP were found to be reliable biomarkers to predict adiposity. Due to the confounding effects among these adipokines, serum leptin was identified as the only predictor of an abnormal lipid profile (TC, TG, LDL-C, and HDL-C). However, adiponectin, which was low among obese individuals, was positively associated with HDL-C and is a cardioprotective factor. Inflammation and adipokines associated with adiposity seem to play an important role in the pathogenesis of cardiometabolic disorders among obese children. Measuring serum concentrations of leptin, adiponectin, and hs-CRP in children may provide important prognostic information in terms of future cardiovascular risk.

Conclusions

In the present study, serum leptin, adiponectin, and hs-CRP were found to be reliable biomarkers of predicting adiposity-related metabolic disorders in adolescents. Serum leptin was identified as the only predictor of an abnormal lipid profile (TC, TG, LDL-C, and HDL-C) on regression analysis. Adiponectin was positively associated with HDL-C, which is a cardioprotective factor.

Conflict of interest

The authors declare that they have no competing interests.

References

[1] World Health Organization. Childhood overweight and obesity. Available at: https://www.who.int/dietphysicalactivity/childhood/en/>Accessed March 15, 2017.
[2] Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol 2003;148:293–300.
[3] Stefan N, Stumvoll M. Adiponectin-its role in metabolism and beyond. Horm Metab Res 2002;34:469–74.
[4] Sypniewska G. Laboratory assessment of cardiometabolic risk in overweight and obese children. Clin Biochem 2015;48:370–6.
[5] McMurray RG, Ondrak KS. Cardiometabolic risk factors in children: The importance of physical activity. Am J Lifestyle Med 2013;7:292–303.
[6] Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: A review of its peripheral actions and interactions. Int J Obes 2002;26:1407.
[7] Huang JS, Barlow SE, Quiros-Tejeira RE, Scheimann A, Skelton J, Suskind D, et al. Childhood obesity for pediatric gastroenterologists. J Pediatr Gastroenterol Nutr 2013;56:99.
[8] Guijarro C. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001;104:e127.
[9] Chenillot O, Henny J, Steinmetz J, Herbeth B, Wagner C, Siest G. High sensitivity C-reactive protein: Biological variations and reference limits. Clin Chem Lab Med 2000;38:1003–11.

[10] de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660–7.
[11] World Health Organization. Physical status: The use of and interpretation of anthropometry, Report of a WHO Expert Committee. 1995.
[12] McCarthy HD, Jarrett KV, Crawley HF. The development of waist circumference percentiles in British children aged 5.0–16.9 y. Eur J Clin Nutr 2001;55:902.
[13] McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obes 2006;30:598.
[14] Kim HY. Statistical notes for clinical researchers: Assessing normal distribution (2) using skewness and kurtosis. Restor Dent Endod 2013;38:52–4.
[15] Chan YH. Biostatistics 102: Quantitative data–parametric & non-parametric tests. Singapore Med J 2003;44:391–6.
[16] Maury E, Brichard SM. Adipokine dysregulation, adipose tissue inflammation and metabolic syndrome. Mol Cell Endocrinol 2010;314:1–16.
[17] Apovian CM, Bigornia S, Mott M, Meyers MR, Ulloor J, Gagua M, et al. Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. Arterioscler Thromb Vasc Biol 2008;28:1654–9.
[18] Pires A, Martins P, Pereira AM, Marinho J, Silva PV, Marques M, et al. Pro-inflammatory triggers in childhood obesity: Correlation between leptin, adiponectin and high-sensitivity C-reactive protein in a group of obese Portuguese children. Rev Port Cardiol 2014;33:691–7.
[19] Mantovani RM, Rocha NP, Magalhães DM, Barbosa IG, Teixeira AL, Simões AC. Early changes in adipokines from overweight to obesity in children and adolescents. J Pediatr (Rio J) 2016;92:624–30.
[20] Kitsios K, Papadopoulou M, Kosta K, Kadoglou N, Papagianni M, Tsiroukidou K. High-sensitivity C-reactive protein levels and metabolic disorders in obese and overweight children and adolescents. J Clin Res Pediatr Endocrinol 2013;5:44.
[21] Enriori PJ, Evans AE, Sinnayah P, Cowley MA. Leptin resistance and obesity. Obesity 2006;14:254S–8.
[22] Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. Annu Rev Physiol 2008;70:537–56.
[23] Aprahamian TR, Sam F. Adiponectin in cardiovascular inflammation and obesity. Int J Inflam 2011;2011:376909.
[24] Balsan GA, da Costa Vieira JL, Marcadenti de Oliveira A, Portal VL. Relationship between adiponectin, obesity and insulin resistance. Rev Assoc Med Bras (1992) 2015;61:72–80.
[25] Cohen SS, Gammon MD, North KE, Millikan RC, Lange EM, Williams SM, et al. ADIPOQ, ADIPOR1, and ADIPOR2 polymorphisms in relation to serum adiponectin levels and BMI in black and white women. Obesity 2011;19:2053–62.
[26] Coutinho PR, Leite N, Lopes WA, Rosa da Silva L, Consentino CM, Araújo CT, et al. Association between adiposity indicators, metabolic parameters and inflammatory markers in a sample of female adolescents. Arch Endocrinol Metab 2015;59:325–34.
[27] Valle M, Martos R, Gascon F, Canete R, Zafra MA, Morales R. Low-grade systemic inflammation, hypoadiponectinemia and a high concentration of leptin are present in very young obese children, and correlate with metabolic syndrome. Diabet Metab 2005;31:55–62.
[28] Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. J Clin Invest 1996;97:2601–10.
[29] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135–43.
[30] Li ZY, Wang P, Miao CY. Adipokines in inflammation, insulin resistance and cardiovascular disease. Clin Exp Pharmacol Physiol 2011;38:888–96.
[31] Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;116:1784–92.
[32] Rajkovic N, Zamaklar M, Lalic K, Jotic A, Lukic L, Milicic T, et al. Relationship between obesity, adipocytokines and inflammatory markers in type 2 diabetes: Relevance for cardiovascular risk prevention. Int J Environ Res Public Health 2014;11:4049–65.
[33] Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, et al. Endothelial cells in physiology and in the pathophysiology of vascular disorders. Blood 1998;91:3527–61.
[34] Li J, Li F, Zhao A. Inflammation and leptin. Drug Discov Today Disease Mech 2006;3:387–93.
[35] Berenson GS, Srinivasan SR, Bao W, Newman WP, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med 1998;338:1650–6.
[36] Yoon MJ, Lee GY, Chung JJ, Ahn YH, Hong SH, Kim JB. Adiponectin increases fatty acid oxidation in skeletal muscle cells by sequential activation of AMP-activated protein kinase, p38 mitogen-activated protein kinase, and peroxisome proliferator–activated receptor α. Diabetes 2006;55:2562–70.
[37] Goldstein BJ, Scalia RG, Ma XL. Protective vascular and myocardial effects of adiponectin. Nature Rev Cardiol 2009;6:27.
[38] Namburi RP, Ponnala AR, Karthik TS, Rani PR, Maheshwari R. A study on metabolic variables and its association with high sensitive C-reactive protein in obese children and adolescents. Indian J Endocrinol Metab 2013;17:S360.