Obesity Medicine 16 (2019) 100154

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: www.elsevier.com/locate/obmed

Original research

Serum adipokine levels, bodyweight and functional status in children with cerebral palsy

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ARTICLE INFO

Keywords:
Adiponectin
Leptin
Metabolic syndrome
Pediatric obesity
Resistin

ABSTRACT

Objective: The incidence of obesity is increasing, including children with cerebral palsy (CCP). Purposes were to determine the association of serum adipokine levels, anthropometrics and biomarkers measurements with bodyweight and functional status in CCP.

Methods: Seventy-two CCP (age 8.7 ± 1.9 years) were enrolled. They were classified by body mass index (BMI) into thinness, normal and overweight and were characterized by the Gross Motor Function Classification System (GMFCS). Serum levels of adipokines (leptin, adiponectin and resistin) were analyzed. A multivariate regression model was used to examine variables associated with BMI and GMFCS. Correlations between serum adipokines, BMI and GMFCS classifications were evaluated.

Results: The CCP with overweight had the prevalence of 24% and had remarkably higher levels of serum leptin ($p < 0.05$). Strong relationships were observed between BMI and age, leptin, triceps skinfold thickness and hemoglobin ($p < 0.05$). Serum leptin levels were positively correlated ($p < 0.001$) with BMI. A negative association between BMI and serum adiponectin levels was observed ($p = 0.03$). In contrast, serum resistin levels did not associate with BMI. Serum adipokine concentrations did not correlate with the GMFCS classification.

Conclusions: The treatment for CCP should aim to control weight in order to balance adipokine and functional levels and reduce risks of subsequent metabolic disorders.

1. Introduction

Overweight and obesity are conditions when an excessive amount of body fat is accumulated, and potentially leads to serious health problems (World Health Organization, 2019; Wang, 2013). Severities of both are categorized by a disproportion of body weight related to body height as defined by body mass index (BMI) of more than 25 kg/m^2 (Lahti-Koski et al., 2004). An imbalance of nutritional intake and physical activity or adequate exercise is the major contributing factor (Rogozinski et al., 2007; Davids et al., 2015). The incidence of overweight and obesity has increased in population worldwide, particularly among children in developing countries (World Health Organization, 2019; Trivedi et al., 2014; Albataineh et al., 2019; Atay and Bereket, 2016). Cerebral palsy (CP) is a group of movement disorders caused by a permanently damaged brain from many etiologies since prenatal period (Sheung-Tung, 2012). Children with CP (CCP) can also become overweight in relation to a decrease in their physical movements (Sandstrom et al., 2004).

Adipokines, a diverse group of proteins synthesized by adipocytes, are responsible for controlling considerable ranges of body functions, predominantly body energy metabolism (Albataineh et al., 2019; Trayhurn and Wood, 2004; Musiol et al., 2014). Their blood levels, therefore, depend on the composition of body fat, which consequently vary among individual's body weight. An alteration of adipokine levels has been linked to various metabolic issues such as dyslipidemia and insulin resistance (Chen et al., 2013; Pyrzak et al., 2010; Nappo et al., 2017; Moreno et al., 2002; de Castro Ferreira Vicente et al., 2017). Overweight and obesity can create health problems to CCP and adults

Abbreviations: BMI, body mass index; CP, cerebral palsy; CCP, children with cerebral palsy; GMFCS, gross motor function classification system; TST, triceps skinfold thickness

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https://doi.org/10.1016/j.obmed.2019.100154
Received 12 September 2019; Received in revised form 27 October 2019; Accepted 27 October 2019

Table 1
Demographics and biochemical data of children with cerebral palsy grouped by body mass index.

		Total	Group by standardized BMI for age and gender[a]			P-value
			Thinness (< 18.5 kg/m^2)	normal weight (18.5– < 25 kg/m^2)	Overweight (≥25 kg/m^2)	
N		72	19	36	17	
GMFCS	2	9	2	6	1	0.29
	3	30	11	13	6	
	4	24	3	12	9	
	5	9	3	5	1	
age (years)		8.7 ± 1.9 (4.6–11.8)	9.9 ± 1.6[b] (4.9–11.8)	8.6 ± 1.7 (4.6–11.4)	7.6 ± 1.8 (4.6–10.9)	< 0.001
TST (mm)		8.6 ± 3.9 (4.0–24.3)	8.1 ± 2.9 (4.3–13.7)	7.6 ± 2.9 (4.0–16.0)	11.4 ± 5.2[c] (4.2–24.3)	0.002
leptin (ng/mL)		5.0 ± 5.9 (2.0–31.0)	3.4 ± 1.7 (2.1–7.7)	4.4 ± 5.4 (2.0–27.7)	8.3 ± 8.7[c] (2.0–31.0)	0.03
adiponectin (μg/mL)		10.3 ± 4.2 (2.4–20.8)	11.4 ± 4.3 (3.8–19.4)	10.3 ± 4.1 (2.4–20.8)	9.2 ± 4.2 (3.5–18.9)	0.28
resistin (ng/mL)		10.6 ± 8.4 (0.9–60.5)	12.6 ± 13.5 (0.9–60.5)	10.1 ± 6.5 (3.4–36.4)	9.5 ± 2.8 (3.2–15.1)	0.47
albumin (g/L)		45.9 ± 2.2 (40–51)	46.3 ± 2.2 (43–51)	45.8 ± 2.4 (40–51)	45.9 ± 1.8 (43–51)	0.78
hemoglobin (g/L)		128.8 ± 10.1 (106–151)	128.4 ± 11.4 (110–151)	127.8 ± 9.4 (106–149)	131.7 ± 9.6 (116–151)	0.40
leucocyte (x10^3/μL)		8.6 ± 2.6 (5.2–21.8)	9.0 ± 2.8 (5.2–14.3)	8.6 ± 2.9 (5.5–21.8)	8.1 ± 1.5 (6.3–10.7)	0.61
platelets (x10^9/L)		340.8 ± 79.4 (174–568)	336.4 ± 91.4 (174–568)	342.4 ± 80.5 (213–528)	342.2 ± 66.4 (207–457)	0.96

Data were presented as number or mean ± standard deviation (range) as appropriate. Statistical analysis was performed utilizing a chi-square or one-way ANOVA with Bonferroni adjustment tests when appropriate.
BMI; body mass index, GMFCS; gross motor function classification system, TST; triceps skinfold thickness.
[a] Standardized BMI for age and gender were derived utilizing the cutoff value recommended by International Obesity Task Force.
[b] Data of the thinness group was significantly higher than the normal weight and overweight groups.
[c] Data of the overweight group was significantly higher than the thinness group.

with CP either short or long term, similarly to the general population. On the other hand, the conditions would economically impact on societies by a remarkable increase in healthcare costs (World Health Organization, 2019; Atay and Bereket, 2016; Peterson et al., 2013). The serum adipokine levels could represent a biomarker for such conditions.

The objectives of the present study were, firstly, to evaluate the serum levels of the metabolism-associated three different adipokines (leptin, adiponectin and resistin) and anthropometrics and other biomarkers in CCP comparing among different BMI categories and, secondly, to examine the correlation of the adipokine levels and the ambulatory status determined by Gross Motor Function Classification System (GMFCS) in CCP.

2. Materials and methods

A cross-sectional study was conducted during January to June 2017. All CCP who attended the rehabilitation program at our department during the study period were enrolled. Anthropometric data including: age, gender, body weight, knee height and triceps skinfold thickness (TST) were recorded. Body weight in kilogram (kg) was obtained and the height was calculated using Stevenson's formula from the knee height; BMI (kg/m^2) was then derived from body weight and the calculated height (Stevenson, 1995). The knee height (cm) in sitting position and TST (mm) were measured using a measurement tape and a handheld caliper (Marathon (Thailand) Co., Ltd, Bangkok, Thailand) respectively. All measurements were done by experienced physiotherapists; in addition, knee height and TST were repeated three times for the accuracy and reliability. Lastly, GMFCS, a tool to determine a child's current motor function, was evaluated and recorded for individual's ambulatory status. CCP with a feeding problem, gastrostomy feeding and the children who previously had osteotomy of the lower extremities or had conditions affected growth were excluded.

2.1. Biochemical marker assays

Venipunctured blood samples were drawn after overnight fasting. Serum was extracted from the sample by centrifugation and stored in a refrigerator at −80°c until analysis. The serum leptin, adiponectin and resistin were analyzed using the Human Leptin Duoset (R&D Systems Inc., Minneapolis, MN, USA), the Human Adiponectin Duoset (R&D Systems Inc., Minneapolis, MN, USA), and the Human Resistin Quantikine ELISA kits (R&D Systems Inc., Minneapolis, MN, USA) respectively, following the manufacturer's instruction. Serum albumin level was measured by the bromocresol green assay using Architect c8000 (Abbott Laboratories Ltd., Wiesbaden, Germany). An automated complete blood count was obtained by Advia 2120 hematology system (Siemens, Erlangen, Germany).

2.2. Statistical analysis

The standardized BMI for age and gender recommended by The International Obesity Task Force was used as a reference to classify current BMI of the CCP into thinness (BMI < 18.5 kg/m^2, normal weight (BMI 18.5– < 25 kg/m^2) and overweight (BMI ≥ 25 kg/m^2) using a Stata software (Lahti-Koski et al., 2004; Vidmar et al., 2013). GMFCS level 1 to 5 were categorized to each participant. Proportions of CCP in different weight categories and GMFCS classification were analyzed using a chi-square test. The serum concentrations of leptin, adiponectin, resistin, albumin, hemoglobin, leukocytes and platelets count were checked for their normality. Thereafter, they were compared among groups using one-way ANOVA then followed by Bonferroni adjustment in order to identify differences between each group. A multivariate regression model was used to evaluate effects of these variables on BMI and GMFCS classifications. Each variable was calculated for multi-collinearity. The correlations between serum adipokine levels and BMI were calculated using Pearson's pairwise correlation (r) test. The correlations between GMFCS classifications and serum

adipokine levels were examined using Spearman's rho (ρ) test. Statistical analysis was performed using Stata version 13 software (StataCorp LP, College Station, TX, USA). P-values < 0.05 were considered statistically significant.

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (COA No. 675/2014) and complied with all of the ethical principles set forth in the Declaration of Helsinki (1964) as revised in 2000. Written informed consent was obtained from parents or legal guardians and assent to participate was acquired from children, when possible.

3. Results

During the study period, 72 CCP (38 males, 52% and 34 females, 48%) with a mean age of 8.7 ± 1.9 years (range 4.6–11.8 years) were eligible and recruited. Twenty-four per cent were categorized as overweight; in addition, this group were significantly younger compared to the other BMI groups. Clinical and biochemical outcomes arranged by standardized BMI for age and gender were shown in Table 1. No statistically significant differences were observed between the serum levels of the three adipokines and genders. Serum leptin levels were significantly different among the BMI groups and the highest serum leptin level was observed in CCP with overweight group. In contrast, the adiponectin and resistin concentrations did not show statistically significant differences between groups. Fig. 1 demonstrated the dispersing of serum adipokine levels among BMI categories. In the multivariate regression model, age, TST, serum leptin and hemoglobin levels had a significant association with BMI with p-value at 0.002, 0.006, 0.05 and 0.05 respectively. It must be pointed out that no difference was observed in each clinical and biochemical parameter arranged by GMFCS classification (Table 2). Similarly, the multivariate model did not show any significant effect of variables on GMFCS classification.

Fig. 2 demonstrates a positive correlation between BMI and serum leptin levels (A) whereas the levels of adiponectin (B) and resistin (C) negatively correlated to the BMI. After correcting for the outliers of serum levels of leptin and resistin, the correlation coefficients were 0.49 ($p < 0.001$) for leptin and −0.08 ($p = 0.52$) for resistin respectively. As shown by Spearman's rank correlation test, all three adipokine levels did not correlate with GMFCS classification in this study. Spearman's rho correlation coefficient (ρ) for GMFCS and serum leptin, adiponectin and resistin levels were 0.009 ($p = 0.94$), 0.06 ($p = 0.63$) and 0.15 ($p = 0.22$) respectively.

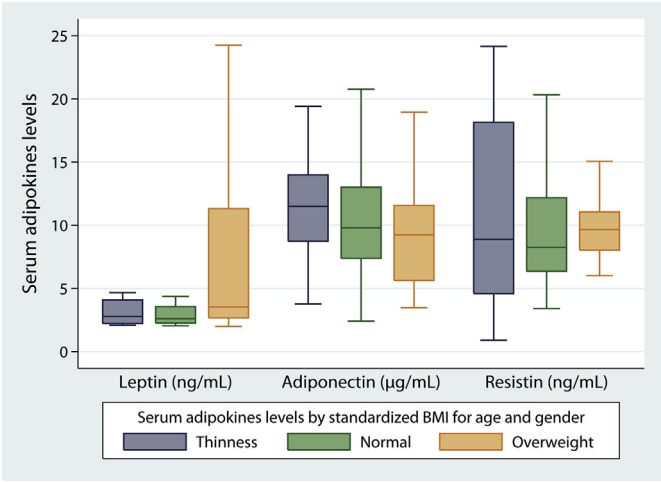

Fig. 1. Boxplot graph demonstrated serum adipokine levels and body mass index categories.

4. Discussion

As in the general children population, overweight and obesity in CCP have become an emerging problem (Lahti-Koski et al., 2004; Rogozinski et al., 2007; Trivedi et al., 2014; Pyrzak et al., 2010; Antunes et al., 2009), which could burden health care systems (Rogozinski et al., 2007; Peterson et al., 2013). Compared with typically developed children of the same age and gender, the CCP are less active. As a consequence, they can potentially develop health problems related to lack of physical activities, for instance, overweight, obesity and decreasing of bone health (Sheung-Tung, 2012; Peterson et al., 2013; Bauman, 2009).

Overweight and obesity cause chronic low-grade inflammation and promote pro-inflammatory milieu since the perinatal period which would, later on, generate several metabolic disorders, e.g., hypertension, dyslipidemia or insulin resistance (Wang, 2013; Albataineh et al., 2019; Trayhurn and Wood, 2004; Nappo et al., 2017; Kunath and Klöting, 2016). In this study, we evaluated the possible correlations between the serum levels of leptin, adiponectin and resistin and BMI together with the functional status in CCP, represented by GMFCS. BMI is convenient for a clinical setting and has high specificity for excess body fat (Duran et al., 2018). The highest serum level of leptin was observed in the overweight group who the average age was younger than CCP in other groups, corresponding to prior studies (Valle et al., 2005; Hamidi et al., 2006). Expectedly, BMI associated with the amount of body fat as demonstrated by TST and serum leptin levels in a multivariate regression model in our study.

Serum levels of leptin were positive while adiponectin showed a negative correlation with BMI, which was also consistent with previous reports (Antunes et al., 2009; Valle et al., 2005; Hamidi et al., 2006; Cambuli et al., 2008). Although we did not evidence any correlation between the serum level of resistin and BMI, our findings could suggest that leptin and adiponectin may represent good biomarkers for a metabolic assessment in overweight CCP, taking the outliers results into consideration. Leptin controls lipid metabolism by controlling appetite through a feedback loop via hypothalamus (Hamidi et al., 2006). Serum leptin levels were linked to the levels of tumor necrosis factor-α and interleukin-6, a well-known pro-inflammatory cytokines (Trivedi et al., 2014). Moreno et al. demonstrated that serum leptin level related to the development of a metabolic syndrome in overweight children (Moreno et al., 2002). In contrast, adiponectin provides a protective effect to several chronic diseases via its anti-inflammatory function (Pyrzak et al., 2010; de Castro Ferreira Vicente et al., 2017). Several reports found that an increase of adiponectin level associates with weight reduction; the level could be used as an indicator for weight-controlled intervention (Albataineh et al., 2019; Cambuli et al., 2008). Association between high serum leptin and low serum adiponectin levels and metabolic syndrome was established (Nappo et al., 2017; Valle et al., 2005). Resistin could act as a hormonal link between obesity, insulin resistance and diabetes mellitus (Gomez-Ambrosi et al., 2008). Chen et al. showed a correlation between serum resistin level and bodyweight, which advocated the underlying role of resistin in metabolic syndrome in overweight children (Chen et al., 2013).

According to previous studies, ambulatory CCP were likely to become overweight and obese, similarly to a healthy children population (Rogozinski et al., 2007; Houlihan, 2014). CCP with GMFCS 2 had the highest BMI and average TST (Rogozinski et al., 2007). This could be explained as the CCP with GMFCS 1 and 2 obviously lack of physical activity compared with typically developed children. CCP with GMFCS 3–5 are usually less active than those with GMFCS 1–2, however, not many of them were classified as overweight because they might experience a lack of nutrition at some stages of life (Amarase et al., 2016; Hurvitz et al., 2008). Bartlett et al. urged a protocol to prevent this condition by optimizing a nutritional status (Bartlett et al., 2010). In contrast, Duran et al. found that excess body fat is more prevalent in CCP with GMFCS 3–5 which was explained by a low sensitivity of the

Table 2
Demographics and biochemical data of children with cerebral palsy grouped by Gross Motor Function Classification System.

	GMFCS level				P-value
	2	3	4	5	
N	9	30	24	9	
age (years)	8.4 ± 1.9 (5.7–10.9)	9.3 ± 1.8 (4.6–11.8)	8.0 ± 1.9 (4.6–11.4)	8.9 ± 1.3 (7.0–11.1)	0.08
BMI (kg/m^2)	16.6 ± 4.9 (11.9–28.7)	16.2 ± 3.9 (10.7–25.1)	17.6 ± 2.9 (13.3–26.3)	16.4 ± 2.3 (13.6–20.4)	0.58
TST (mm)	9.9 ± 5.9 (4.3–24.3)	8.5 ± 3.2 (4.0–16.0)	8.6 ± 4.2 (4.2–20.3)	7.7 ± 2.5 (5.0–11.7)	0.67
leptin (ng/mL)	4.6 ± 5.8 (2.1–19.4)	4.8 ± 5.3 (2.0–24.3)	4.9 ± 6.2 (2.0–31.0)	6.4 ± 8.3 (2.1–27.7)	0.91
adiponectin (μg/mL)	10.2 ± 3.0 (4.7–14.6)	10.1 ± 3.8 (2.7–19.4)	10.2 ± 4.7 (2.4–18.9)	11.7 ± 5.3 (3.8–20.8)	0.77
resistin (ng/mL)	11.8 ± 7.4 (3.3–23.8)	8.5 ± 4.9 (0.9–24.2)	12.0 ± 11.3 (4.0–60.5)	12.7 ± 9.1 (6.2–36.4)	0.35
albumin (g/L)	46.6 ± 3.2 (40–51)	46.0 ± 1.8 (43–51)	45.8 ± 2.5 (43–51)	45.6 ± 1.5 (43–48)	0.77
hemoglobin (g/L)	123.6 ± 9.6 (107–139)	129.4 ± 10.7 (106–151)	130.8 ± 8.9 (117–149)	127 ± 10.1 (116–151)	0.28
leucocyte (x10^3/μL)	10.2 ± 4.6 (6.5–21.8)	8.0 ± 2.0 (5.2–13.6)	8.6 ± 1.9 (5.5–12.9)	8.9 ± 3.1 (6.1–14.3)	0.17
platelets (x10^9/L)	336.0 ± 82.0 (292–528)	325.1 ± 66.5 (193–471)	350.4 ± 101.4 (174–568)	342.1 ± 42.5 (270–396)	0.49

Data were presented as number or mean ± standard deviation (range) as appropriate. Statistical analysis was performed utilizing a one way ANOVA with Bonferroni adjustment test.
BMI; body mass index, GMFCS; gross motor function classification system, TST; triceps skinfold thickness.

BMI (Duran et al., 2018). Although the three adipokines in our study did not associate with GMFCS classification, increasing weight combined with poor physical ability could lead to other problems such as poor compliance to the rehabilitation program, fall or fractures (Atay and Bereket, 2016; Sheung-Tung, 2012; Houlihan, 2014; Tosun et al., 2017). Abnormal levels of leptin, adiponectin and resistin demonstrated a negative effect on the osteoblast and osteoclast functions and risk of low bone mineral content was higher in CCP who are non-ambulatory (Gomez-Ambrosi et al., 2008; Tosun et al., 2017). We recommend that overweight and obesity should be focused more on ambulatory CCP while non-ambulatory CCP might have an increasing risk of becoming underweight (Rogozinski et al., 2007; Musiol et al., 2014; Amarase et al., 2016; Hurvitz et al., 2008). More importantly, comprehensive treatment program including appropriate rehabilitation protocols, surgical procedures aimed to maximize physical capability and control weight should benefit overweight CCP in order to decrease the development of metabolic syndrome, e.g. diabetes mellitus or cardiovascular risks in the long term (Rogozinski et al., 2007; Trivedi et al., 2014; Bauman, 2009). As previously observed in overweight children in general (Lahti-Koski et al., 2004; Albataineh et al., 2019), we hypothesize that such interventions will likely reduce the levels of serum leptin and increase the levels of adiponectin. It is well accepted that the overall strength related to weight usually decreases in CCP when they reach adolescent and young adult life (Davids et al., 2015; Peterson et al., 2013; Bartlett et al., 2010). BMI in childhood has to be accentuated that it strongly associated to adulthood metabolic syndromes (Sandstrom et al., 2004; Bauman, 2009). This is further supported by the multivariate regression model in our study that age, amount of fat tissue and serum leptin levels correlated with the BMI. Taken together, the outcomes of our study underscore the importance to monitor, younger CCP with overweight problems in particular, for the prevention of metabolic syndromes later in life.

Although, in the present study, comparable levels of the three adipokines among male and female CCP were shown, recent studies produced opposite results (Antunes et al., 2009; Hamidi et al., 2006). This discrepancy apparently attributed to the enrolled population of our study were focused on children group not adolescent and adult CP. Moreover, the other biochemical markers, which generally designate metabolic statuses, e.g. serum albumin and complete blood count, were not different among BMI groups in our CCP cohort. This indicates that their levels might associate with other bodily conditions rather than body weight and they should be utilized in another appropriate circumstance.

There are limitations related to this study. Unfortunately, data on serum adipokine levels from a healthy age- and gender-matched cohort with the same ethnicity were not available. Such direct comparison would provide a more insightful appraise of the problem. Secondly, as the children's BMI could change during growth, the cross sectional study might not represent the actual weight status of each child. However, using standardized BMI references could mitigate this issue (Vidmar et al., 2013). In addition, BMI derived from the calculated height could carry a potential error from height calculation (Haapala et al., 2015; Bell et al., 2012; García-Contreras et al., 2016). Nevertheless, recent studies supported the estimation of the patient height based on the knee height and a population-specific equation (Bell et al., 2012; García-Contreras et al., 2016). Moreover, a further study to direct assessing fat mass by dual-energy X-ray absorptiometry would be helpful (Duran et al., 2018). Diet analysis of the studied cohort would also benefit this study. Finally, a long-term follow up is needed to characterize the alteration of serum adipokine levels related to BMI, GMFCS and the potential metabolic consequences in cerebral palsy population.

In conclusion, overweight and obesity in CCP are prevalent. Differences in serum leptin and adiponectin levels were correlated with BMI and might reflect an abnormal energy metabolism, which could lead to metabolic disorders. An appropriate CCP's care should be undertaken by multidisciplinary in order to control weight and maximize their functional abilities, to balance levels of serum adipokines, and especially to minimize the potential metabolic disorders. The CCP's quality of life would be improved in long term.

Ethical approval

This study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (COA No. 675/2014).

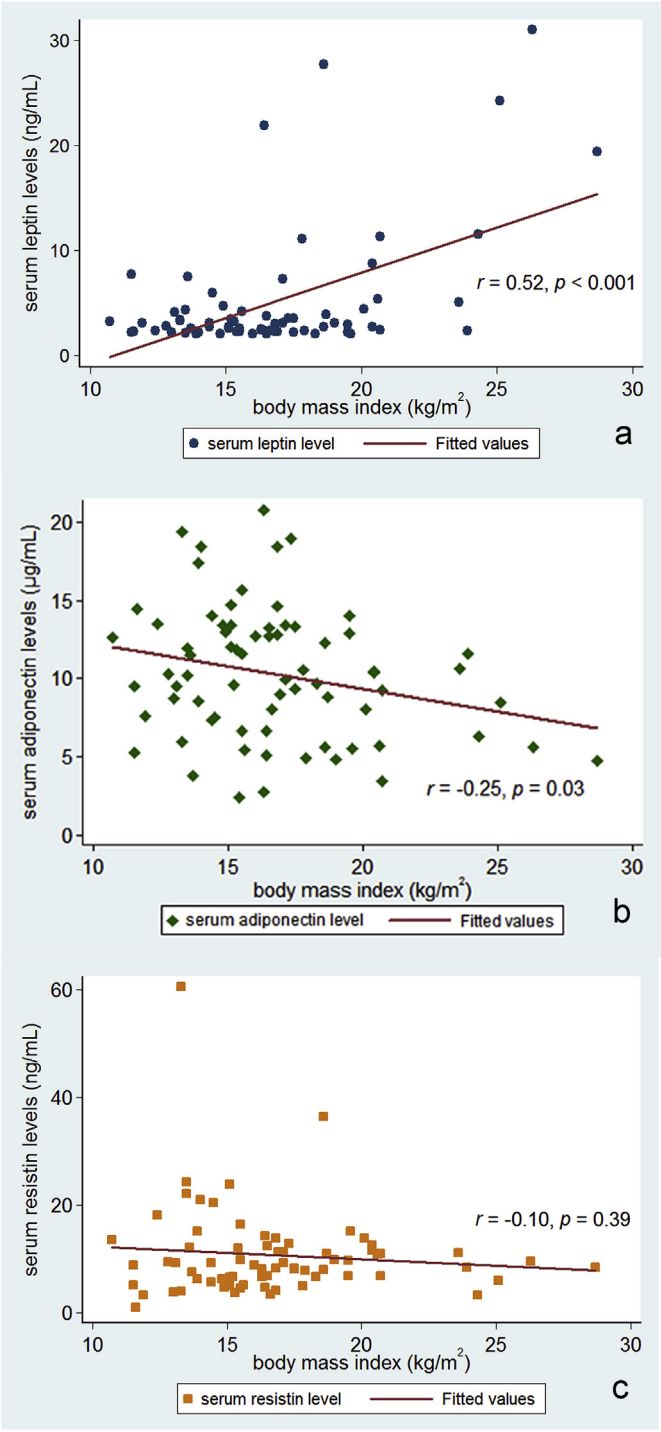

Fig. 2. Correlation graphs between serum leptin (a), serum adiponectin (b) and serum resistin (c) levels and body mass index.

Funding source

This study was supported by a grant from the Ratchadapiseksomphot Fund, Faculty of Medicine, Chulalongkorn University, Thailand (Grant number RA 58/040).

Declaration of competing interest

None.

Acknowledgments

We thank the staff of the *Foundation for the Welfare of the Crippled under the Royal Patronage of Her Royal Highness the Princess Mother, Thailand* for their invaluable support during the development of this project. We acknowledge the help by Stephen J. Kerr, Ph.D. for assistance with statistical analysis, Ms. Wanvisa Udomsinprasert for technical assistance and Professor Alain Jacquet, Ph.D. and Mr. Paul Hatton for assistance with English language editing. This study was supported by a grant from the Ratchadapiseksomphot Fund, Faculty of Medicine, Chulalongkorn University (Grant number RA 58/040).

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