Pediatric RESEARCH

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CLINICAL RESEARCH ARTICLE

Effects of low-glycemic index diet on plasma adipokines in obese children

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BACKGROUND: A low-glycemic index (GI) diet may modulate adipocyte-produced adipokines linking to insulin resistance.
METHODS: The stored plasma samples from the RCT of a low-GI vs. conventional diet in obese children were analyzed for adipokines: leptin, adiponectin, resistin, and visfatin. Their relationships with clinical outcomes were assessed.
RESULTS: Fifty-two participants completed the 6-month intervention trial (mean age: 12.0 ± 2.0 years, 35 boys). Both groups had significantly decreased BMI *z*-scores from baseline whereas the low-GI group had significant reduction in fasting insulin and HOMA-IR. There were no differences in adipokines between the groups before and after the intervention. However, there was an association between baseline leptin and the change of fat mass index (FMI) but not the insulin resistance in both groups. The higher the baseline leptin was, the lower the changes were for FMI after the intervention.
CONCLUSION: Despite no demonstrable effect of low-GI diet on plasma adipokines, the higher baseline leptin was correlated with lower reduction of fat mass. Leptin resistance may have a detrimental effect on the reduction of adiposity in obese children. Baseline leptin could be a useful predictor of the change in body composition in an obesity intervention trial.

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IMPACT:

- Leptin resistance may have a detrimental effect in reducing the adiposity in obese children.
- This study is the first of its kind to compare the plasma adipokine concentrations of obese children on low-GI diet and conventional diet. We found that serum leptin was significantly correlated with the reduction of BMI *z*-score and FMI in both groups.
- Baseline leptin could be a useful predictor of the change in body composition in an obesity intervention trial.

INTRODUCTION

Prevalence of childhood and adolescent obesity are increasing in both developed and developing countries. In Thailand, there was an increasing trend of overnutrition among children compared to undernutrition.[1] Obese children have multiple health problems, such as obstructive sleep apnea, deformity of bone and joints, and metabolic syndrome similar to that of obese adults. Therefore, childhood obesity and the metabolic syndrome are an emerging health problem that needs early interventions, including dietary control, increased physical activity, and behavior modification. The metabolic syndrome consists of insulin resistance, hypertension, dyslipidemia (hypertriglyceridemia and low high-density lipoprotein cholesterol), and central obesity.[2] It is postulated that obese children have accumulated excess adipose tissue, especially those with central adiposity in which free fatty acids may be released and deposited in the muscles, the liver, and the pancreas. Adipocytes play an important role as an endocrine organ that regulates metabolism and energy homeostasis. Several adipokines are released from the adipocytes, including leptin, visfatin, and resistin. These adipokines cause a chronic low-grade inflammatory state. On the other hand, adiponectin, another adipokine, has an anti-inflammatory effect and increases insulin sensitivity which are suppressed in obese individuals. All of these changes may disturb the insulin signaling and eventually result in insulin resistance.[3]

Leptin suppresses appetite and increases energy expenditure by acting through the hypothalamus. Studies in Caucasians and Asians found that overweight and obese children, especially obese children with metabolic syndrome, had higher plasma leptin than normal-weight children.[4,5] Another study showed that a lifestyle intervention in obese children reduced leptin and increased soluble leptin receptor.[6]

Adiponectin is an insulin-sensitizing hormone that decreases circulating glucose levels by suppressing gluconeogenesis in the liver and enhancing insulin signaling in the skeletal muscle. A previous study showed that plasma adiponectin is inversely associated with obesity.[7]

A newly discovered adipokine, visfatin, mimics the action of insulin via a distinct binding site on the insulin receptor. Therefore, it potentially increases the risk for insulin resistance. In animal models, visfatin is produced mainly in the visceral adipose tissue.[8] A cross-sectional study conducted in 56 obese Japanese children

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reported that there was a good correlation between the visceral adipose tissue and plasma visfatin.[9] Yet, there was no supporting evidence that visfatin had any associations with insulin resistance or other components of the metabolic syndrome.

Resistin is a cytokine that is expressed in the adipose tissue. Although the role of resistin in obesity and insulin resistance has been demonstrated in animal models, its role in humans is still controversial.

Longitudinal and interventional studies of the change in these adipokines after lifestyle modifications to reduce the body fat are still scarce. This information could enlighten the pathophysiological changes and the relationships between these biomarkers and body fat that occur in childhood obesity and metabolic syndrome. In our previously published randomized controlled trial (RCT) of low-glycemic index (low-GI) diet effects on insulin resistance, we found that the low-GI diet may improve insulin sensitivity in obese children with high baseline insulin.[10] Using samples from this RCT, we aimed to compare the change in plasma adipokines (leptin, adiponectin, resistin, and visfatin) in obese Thai children on low-GI diet (intervention group) and conventional diet (control group) before and after a 6-month period of interventions. Secondly, we aimed to study the relationships of plasma adipokines on the changes of the body composition and the risks for developing metabolic syndrome.

METHODS

Study design

The study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Thailand. This trial was registered at clinicaltrials.gov (NCT02049788). This study was a single center, prospective, RCT. The detailed methodology has been published elsewhere.[10] In brief, eligible participants with a body mass index (BMI) higher than the International Obesity Task Force cut-off of 30 kg/m^2 in adults[11] were enrolled into this study. We did not intentionally recruit nor exclude children with metabolic syndrome in this study. The participants were randomized into the intervention group (low-GI diet) or the control group. In the intervention group, the individual goal for weight management was set and a low-GI diet instruction was provided to each participant. A dietitian emphasized the selection of low-GI carbohydrates which was adapted from the table by Foster-Powell et al.[12] The control group received conventional management instructions at the Nutrition Clinic, including caloric restriction, low-fat, and high-fiber diet. All participants received the same instructions to increase their physical activity and were asked to maintain monthly visits for 6 months. At every visit, the parents and the participants came and received all of the instructions together. A 3-day dietary record and a physical activity questionnaire were collected at each visit and analyzed. Blood samples were collected in the morning after 12 h of fasting at the first and sixth visits. The plasma was separated using cold centrifuge and stored at −80 °C until analysis as per the main RCT's plan. The primary outcome was the difference in adipokines including plasma leptin, adiponectin, resistin, and visfatin within and between randomized groups after 6 months. These adipokines were measured by ELISA KIT (R&D System Inc., Minneapolis, USA for leptin, adiponectin, and resistin; and Adipogen Life Sciences, Liestal, Switzerland for visfatin). The Revelation Quicklink software version 4.25 was used to analyze the data. The secondary outcomes were the correlations between the adipokines and BMI *z*-score, body composition, and other clinical outcomes. The BMI *z*-score was calculated based on World Health Organization (WHO) 2007's growth reference using the WHO AnthroPlus program.[13] The body composition was evaluated by using dual-energy X-ray absorptiometry (Hologic QDR Discovery A) on the first and sixth visits. Fat mass index (FMI) and fat-free mass index (FFMI) were calculated by fat mass (FM) or fat-free mass (FFM) in kilograms divided by the square of the height in meters (kg/m^2).[14]

Statistical analysis

Descriptive statistics were used to summarize all quantitative data. Categorical data were summarized using percentages. Continuous variables were reported as mean ± standard deviation (SD). The comparisons between the control and intervention groups were performed by an independent sample *t*-test. A paired *t*-test for dependent samples was used to evaluate the changes from the baseline within each group (before and after the 6-month period of the intervention). The results were not adjusted for any confounding variables except for homeostatic model of assessment-insulin resistance (HOMA-IR). The associations between BMI *z*-score, waist circumference (WC), body composition, insulin resistance, adipokines, and lipid profiles were evaluated by using a linear mixed model and presented as forest plots. Statistical significance was defined as a p value < 0.05. Analyses were performed using SPSS 23.0 (SPSS Inc., Chicago, IL) and R Program (Free Software Foundation, Inc., Boston, MA, USA).

RESULTS

Seventy participants (47 boys and 23 girls) were enrolled and randomized into two groups as shown in the flow diagram in our previous publication: control group ($n = 35$) and intervention group ($n = 35$).[10] There were 52 out of 70 participants who completed all six visits (27 in the control group; 19 boys, 8 girls and 25 in the intervention group: 16 boys, 9 girls). The mean age of the control group was 12.0 ± 2.1 years and the intervention group was 11.9 ± 1.9 years. The other baseline characteristics were shown elsewhere.[10] The proportion of children with metabolic syndrome was 2/27 (7%) and 1/25 (4%) in the control and the intervention groups, respectively. All analyses followed the intention-to-treat principle. The details about energy intakes and GI values compared within and between groups were shown in the report of the main RCT.[10] In brief, total energy intake in the intervention group significantly declined during the 6-month period. In addition, daily intake of the low-GI diets, which was calculated as items/day, significantly increased in the intervention group whereas in the control group, there were no changes. Brisk walking was the most common type of exercise used in both groups and around half of the participants in both groups were physically active.[10] There were significant differences in plasma insulin levels and HOMA-IR between the two groups at the first visit. There were no significant differences in adipokines between the two groups at the first and sixth visits (Table 1).

Despite decreased BMI *z*-score between the first and the sixth visits in the intervention group ($p < 0.0001$), leptin and visfatin decreased while adiponectin increased, but these were not significantly different between the first and the last visits. Table 2 showed that in the intervention group, there was no significant differences in the changes of body composition, adipokines, and lipid profiles; however, the fasting insulin and HOMA-IR significantly decreased from baseline to the sixth visit (−8.5 ± 13.5 mU/L, $p = 0.032$ and −1.9 ± 3.2, $p = 0.019$, respectively). The correlations between the baseline adipokines and the change of metabolic parameters are shown in Fig. 1. There were significant associations between baseline leptin and the change of FMI in the control and intervention groups (95% CI: 0.07, 0.69, $p = 0.02$ and 95% CI: 0.04, 0.71, $p = 0.03$, respectively). The higher the baseline leptin was, the lower the changes were for FMI after the intervention. There were no correlations between other baseline adipokines and the changes in body composition in both groups. But, there was a tendency for the association between baseline leptin and changes in insulin and HOMA-IR in the intervention group. Higher baseline leptin was related with lower reduction in plasma insulin and HOMA-IR. There was a tendency of a negative association between baseline adiponectin and change in FFMI in the control group whereas this tendency was not observed in the intervention group. Further analysis of the change in the individual adipokines

Table 1. Comparison of BMI *z*-score, waist circumference, body composition measured by DXA, fasting insulin, HOMA-IR, adipokines, and lipid profiles between the control and intervention groups ($n = 52$).

Parameters	Control ($n = 27$)	Intervention ($n = 25$)
Visit 1		
BMI *z*-score[a]	3.6 ± 1.6[b]	3.7 ± 0.9
Waist circumference (cm)	103.1 ± 14.9	105.8 ± 7.7
% Fat[c]	41.1 ± 6.0	42.1 ± 4.8
FMI (kg/m^2)	14.0 ± 4.5	14.7 ± 3.8
FFMI (kg/m^2)	18.8 ± 2.9	19.1 ± 2.6
Laboratory test		
Fasting plasma glucose (mmol/L)	5 ± 1	5 ± 0
Fasting insulin (mU/L)*	15 ± 8	22 ± 14
HOMA-IR*	3.1 ± 1.7	4.8 ± 3.3
Leptin (ng/mL)	27.8 ± 14	27.1 ± 11.7
Adiponectin (ng/mL)	1988.3 ± 1766.8	1927.5 ± 1356.7
Resistin (ng/mL)	15 ± 8	12.3 ± 5.7
Visfatin (ng/mL)	13.2 ± 13.7	17.3 ± 16
Serum total cholesterol (mmol/L)	4.5 ± 0.8	4.7 ± 0.8
Serum triglyceride (mmol/L)	1.1 ± 0.5	1.2 ± 0.4
Serum HDL (C) (mmol/L)	1.2 ± 0.2	1.2 ± 0.4
Serum LDL (C) (mmol/L)*	2.7 ± 0.7	3.1 ± 0.6
Visit 6		
BMI *z*-core	3.4 ± 1.3	3.4 ± 0.9
Waist circumference (cm)	104.2 ± 15.8	106.3 ± 9.5
% Fat	40.2 ± 8.7	43.1 ± 6.1
FMI (kg/m^2)	14.4 ± 4.5	15.2 ± 4.4
FFMI (kg/m^2)	18.8 ± 3.4	18.8 ± 2.6
Laboratory test[d]		
Fasting plasma glucose (mmol/L)	5 ± 1	5 ± 0
Fasting insulin (mU/L)	14 ± 10	14 ± 11
HOMA-IR	3.2 ± 2.6	2.9 ± 2.3
Leptin (ng/mL)	30 ± 18.6	26.4 ± 14.8
Adiponectin (ng/mL)	2288.5 ± 2,283.2	2311.4 ± 1608.6
Resistin (ng/mL)	14.1 ± 6.9	12.7 ± 9.2
Visfatin (ng/mL)	15.2 ± 12.9	15.2 ± 15
Serum total cholesterol (mmol/L)	4.4 ± 0.9	4.7 ± 0.7
Serum triglyceride (mmol/L)	1.1 ± 0.6	1.1 ± 0.4
Serum HDL (C) (mmol/L)	0.1 ± 0.2	1.3 ± 0.3
Serum LDL (C) (mmol/L)	2.7 ± 0.9	3 ± 0.7

C cholesterol, *DXA* dual-energy X-ray absorptiometry, *FMI* fat mass index = fat mass (kg)/height (m^2), *FFMI* fat-free mass index = fat-free mass (kg)/height (m^2), *HOMA-IR* homeostatic model of assessment-insulin resistance = (FI × FPG)/22.5, *FI* fasting insulin concentration (mU/L), *FPG* fasting plasma glucose (mmol/L).
*$p < 0.05$.
[a]BMI z-scores were calculated using the WHO's growth reference 2007.[13]
[b]Means ± SDs (all such values) and independent sample *t*-test were used to evaluate the continuous variables. [c]Percentage of fat was calculated from fat mass (kg)/body weight (kg) × 100. [d]Data from 26 participants from the control group were analyzed because one of the participant did not have his laboratory result.

Table 2. Comparison of the changes in anthropometry, body composition measured by DXA, and laboratory tests between the control and intervention groups during the 6-month period ($n = 52$).

Changes in outcomes[a]	Control ($n = 27$)	Intervention ($n = 25$)
BMI *z*-score	−0.3 ± 0.5[b]	−0.3 ± 0.2
Waist circumference (cm)	1.1 ± 5.6	0.5 ± 4.1
FMI (kg/m^2)	0.3 ± 1.6	0.8 ± 3.5
FFMI (kg/m^2)	0.2 ± 0.8	0.8 ± 3.9
% Fat[c]	0.1 ± 2.8	0.1 ± 3.0
Fasting plasma insulin (mU/L)*	−0.8 ± 11.3	−8.5 ± 13.5
HOMA-IR*	0.1 ± 2.8	−1.9 ± 3.2
Leptin (ng/mL)	1.7 ± 12.5	−3.1 ± 12.8
Adiponectin (ng/mL)	306.4 ± 1135	518.7 ± 1132
Resistin (ng/mL)	−0.02 ± 4.9	1.2 ± 7.3
Visfatin (ng/mL)	3.4 ± 17.5	−4.9 ± 17.6
Serum total cholesterol (mmol/L)	−0.1 ± 0.6	−0.1 ± 0.7
Serum triglyceride (mmol/L)	0 ± 0.4	−0.1 ± 0.4
Serum HDL (C) (mmol/L)	0 ± 0.2	0 ± 0.3
Serum LDL (C) (mmol/L)	0 ± 0.5	−0.1 ± 0.5

C cholesterol, *DXA* dual-energy X-ray absorptiometry, *FFMI* fat-free mass index = fat-free mass (kg)/height (m^2), *FMI* fat mass index = fat mass (kg)/height (m^2), *HOMA-IR* homeostatic model of assessment-insulin resistance = (FI × FPG)/22.5, *FI* fasting insulin concentration (mU/L), *FPG* fasting plasma glucose (mmol/L).
*$p < 0.05$.
[a]Changes in outcomes between visit 6 and visit 1. [b]Means ± SDs (all such values) and independent sample *t*-test were used to compare the data between the two groups. [c]Percentage of fat = fat mass (kg) × 100/body weight (kg).

with changes in various outcomes was assessed using the general linear model which revealed two interesting relationships. Firstly, in the case of plasma leptin, we observed an association between the change in leptin from baseline, change in BMI, and in FMI. However, there was no significant difference in the magnitude of these associations between the control group ($r_{BMI} = 0.47$, 95% CI: 0.16, 0.74, $p = 0.006$ and $r_{FMI} = 0.73$, 95% CI: 0.48, 0.87, $p < 0.001$) and the intervention group ($r_{BMI} = 0.49$, 95% CI: 0.09, 0.75, $p = 0.019$ and $r_{FMI} = 0.56$, 95% CI: 0.19, 0.79, $p = 0.005$) (Fig. 2a). Secondly, we found a considerable difference in the nature of the associations between the change in visfatin with various outcomes (Fig. 2d). Specifically, the change in visfatin was strongly associated with changes in BMI among the controls ($r = 0.47$, 95% CI: 0.10, 0.72, $p = 0.014$) but not in the intervention group ($r = -0.047$, 95% CI: −0.46, 0.38, $p = 0.835$). A similar trend was seen in the change of FMI; however, there was no significant association between delta visfatin and delta FMI detected in the control or the intervention groups (Fig. 2d). Furthermore, there were no correlations between all adipokines and the GI diet intake (calculated as items/day[10]) at baseline and the sixth visit (data not shown).

DISCUSSION

To our knowledge, this is the first study that investigated the changes in adipokines in obese children and adolescents after receiving a low-GI diet instruction compared to the conventional instruction.

The results in our study showed that there were no significant differences in adipokines between the two groups at the first and

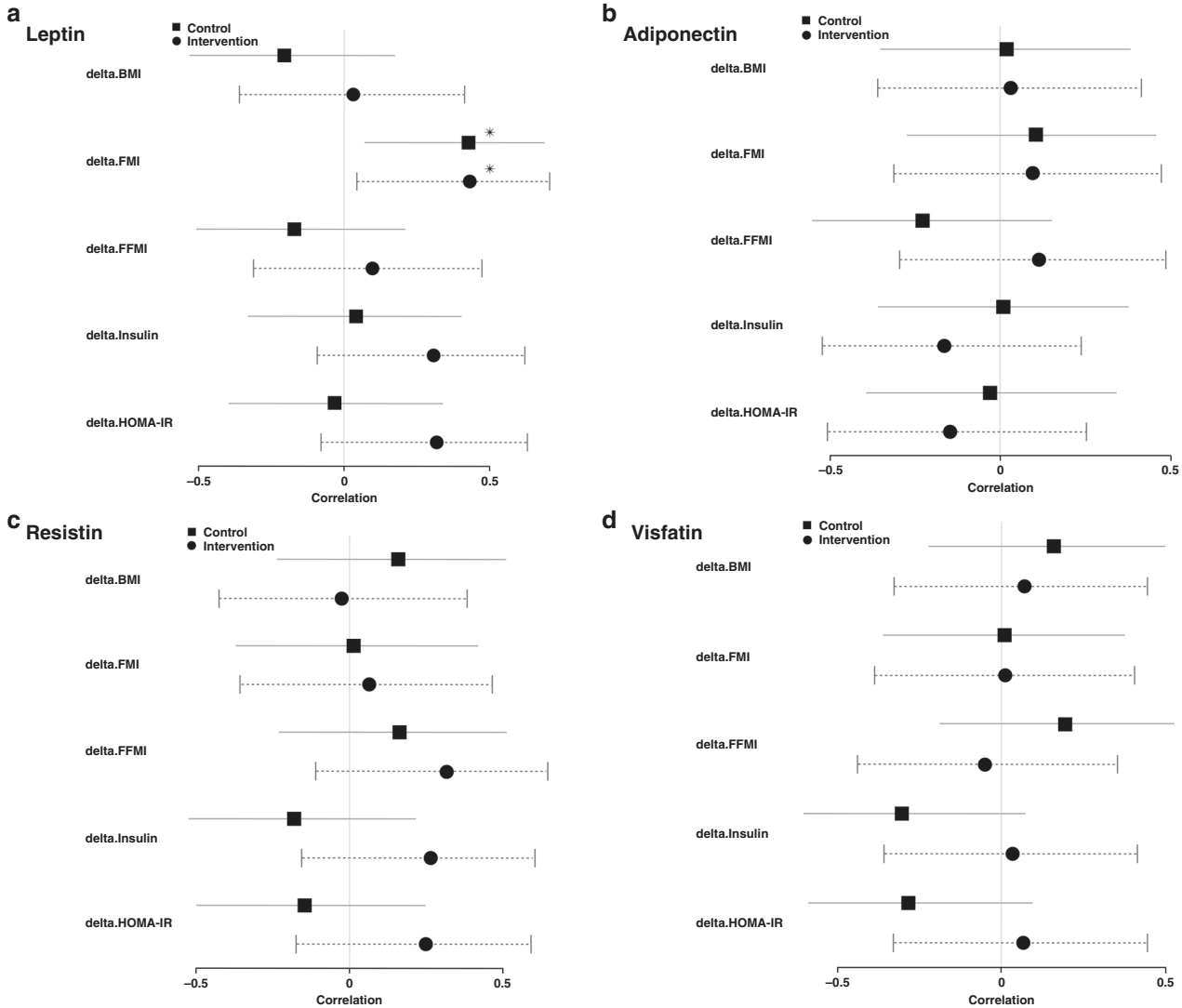

Fig. 1 Forest plots of the correlations between baseline adipokines and the changes (delta) in clinical outcomes. a Leptin, **b** Adiponectin, **c** Resistin, **d** Visfatin. The associations were analyzed by the linear mixed model and the plots were generated by R program. The error bars represent 95% CI, *$p < 0.05$. *FFMI* fat-free mass index = fat-free mass (kg)/height (m^2), *FMI* fat mass index = fat mass (kg)/height (m^2), *HOMA-IR* homeostatic model of assessment-insulin resistance = (FI × FPG)/22.5, *FI* fasting insulin (mU/L), *FPG* fasting plasma glucose (mmol/L).

sixth visit. The concentrations of leptin and visfatin were decreased whereas adiponectin was increased in both groups, but there were no significant differences between the first and the last visits. However, plasma leptin was strongly and linearly related to the BMI *z*-score and adiposity in both groups. In agreement with previous reports, the expression and secretion of leptin was positively correlated with BMI, WC, and FM.[15,16] Leptins in obese children and adolescents were significantly reduced after a weight reduction program because the leptins reflected the amount of adipose tissue.[17] However, there were no significant differences in plasma leptin between the first and the sixth visits in each group, and between the two groups. This might be because the BMI *z*-score was not significantly different between the groups and the decrease of BMI *z*-score from the baseline in both groups was too small to detect a change of leptins during the 6-month period. The results from another study suggested that in order to see the most favorable effects on leptin, a >10% weight loss along with a >10% visceral fat loss is most likely necessary.[18] More recently, a study in 4- to 17-year-old children showed that BMI explained most of the variability in leptin and concluded that total adiposity, but not insulin, is the main determinant of leptins in obesity.[19] In contrast, some studies demonstrated that leptins were associated with insulin and HOMA-IR.[20,21] The effect of GI on insulin resistance has been previously evaluated, but its results have been inconsistent. Several studies demonstrated the beneficial effects of low-GI diets on insulin resistance among children and adolescents, including our study.[10,22,23] Low-GI foods are absorbed and digested slowly which could prolong satiety and suppress the release of free fatty acid. Thus, the improvements in glucose tolerance, insulin sensitivity, and leptin may be observed following a low-GI diet.[24] However, these beneficial effects were also observed following a hypocaloric high-GI diet.[25] Based on these results, it is probable that the effect of caloric restriction is stronger than dietary GI. The effect of low-GI diet in our study may not be strong enough to demonstrate any significant change of leptin either within the group or between the groups. Leptin was not significantly related to the change in the insulin levels but there was a tendency for less insulin reduction in the low-GI diet group especially when the baseline leptin was high. The same tendency was also found in HOMA-IR and FMI among the children in the low-GI group.

Like leptin, adiponectin is a hormone secreted by adipocytes. A previous study reported an inverse association between body

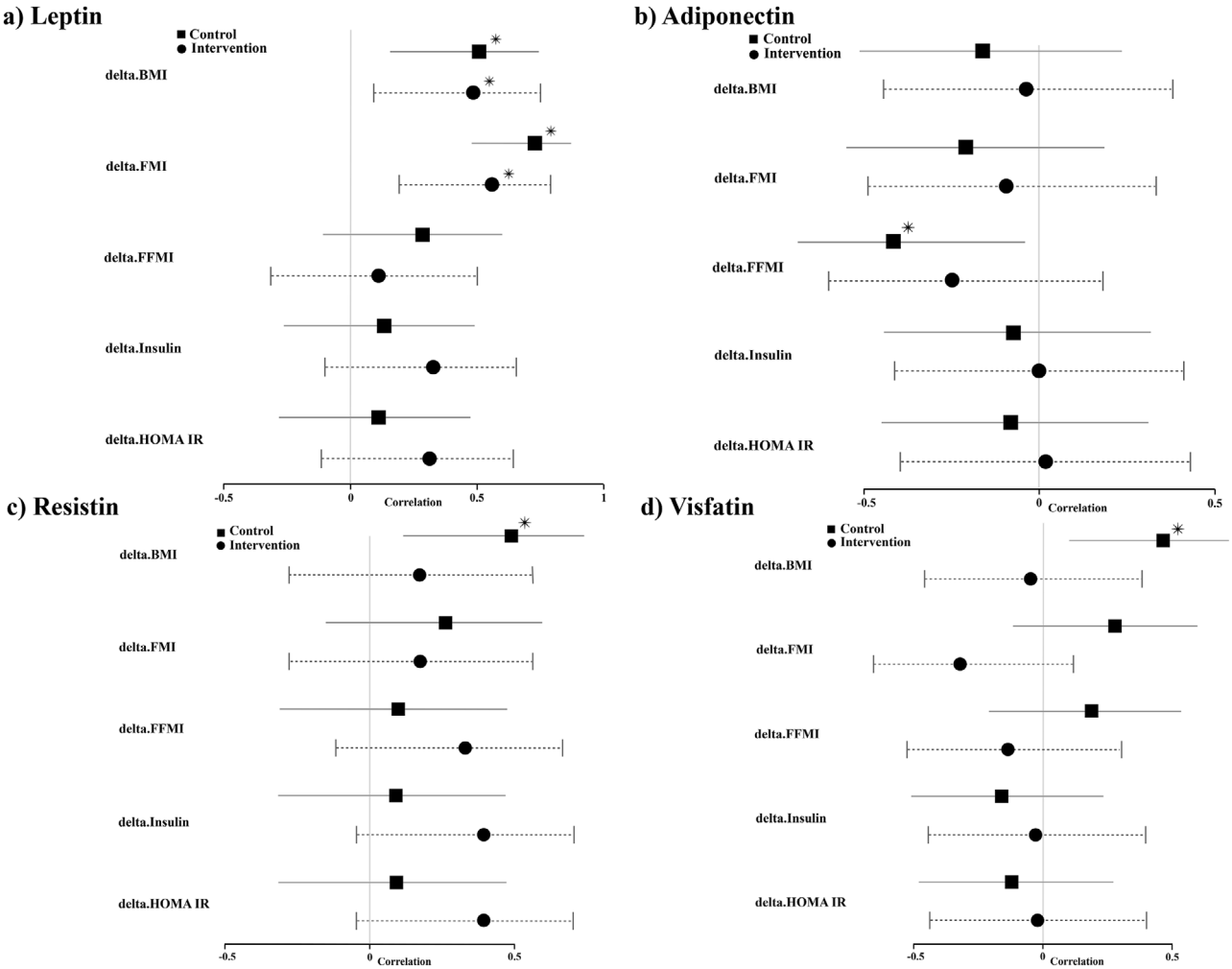

Fig. 2 Forest plots of the correlations between the changes of adipokines and the changes (delta) in clinical outcomes. a Leptin, **b** Adiponectin, **c** Resistin, **d** Visfatin. The associations were analyzed by the linear mixed model and the plots were generated by R program. The error bars represent 95% CI, *$p < 0.05$. *FFMI* fat-free mass index = fat-free mass (kg)/height (m^2), *FMI* fat mass index = fat mass (kg)/height (m^2), *HOMA-IR* homeostatic model of assessment-insulin resistance = (FI × FPG)/22.5, *FI* fasting insulin (mU/L), *FPG* fasting plasma glucose (mmol/L).

weight and circulating adiponectin; the amount of adiponectin was low among overweight and obese adults.[26] Additionally, a comparison between two meals with different GI showed that plasma adiponectin increased after a low-GI meal was consumed.[27] Another study demonstrated that lower adiponectin was associated with higher dietary GI and glycemic load (GL), which suggested that dietary modifications may improve the amount of adiponectin.[28] Higher baseline adiponectin may be related to greater reduction in FFMI in the control group as shown in this study while the intervention group did not have this tendency. Therefore, it is postulated that low-GI diet may be able to de-couple the association between the adiponectin and FFMI. Adiponectin is believed to improve insulin sensitivity through different mechanisms. Moreover, adiponectin has potent anti-apoptotic effects which are believed to prevent lipid-induced pancreatic beta cell apoptosis.[29] Thus, adiponectin could have protective effects against diabetes. There were no significant changes in plasma adiponectin between the first and the last visits within each group and between the two groups in this study. The possible reason may be because adiponectin did not respond to this small degree of BMI *z*-score change and that there was not enough loss of FM and/or increase of FFM over the course of the trial to see any changes on adiponectin levels. Previous reports described the degree of weight loss was related to the plasma adiponectin concentration and suggested that a decrease of >10% in the visceral fat may be necessary to increase the adiponectin level.[18,30]

As for resistin, there was no significant differences detected within each group and between the groups. Resistin was not correlated with the changes of BMI *z*-score and FMI in both the control and intervention groups. The adipose tissue may not play a role in the production of this protein. It is possible that adiposity and resistin generate cardiovascular and metabolic syndrome risks via different pathways.[31] The physiologic role of resistin on obesity and insulin resistance is still unclear and inconclusive. Hence, the role of resistin as an adipocytokine in children should be reevaluated.

Another adipocytokine is visfatin. There was no significant differences in visfatin within each group and between the groups. However, the change in visfatin was strongly associated with changes in BMI among the controls but not in the intervention group, indicating that the treatment appears to have de-coupled the visfatin and BMI association, which is an interesting point that needs to be further investigated. The effects of visfatin in obese children are controversial. Davutoglu et al.[32] showed that visfatin levels were significantly correlated to weight, BMI, and WC in obese children. In another case–control study, it was found that visfatin levels were significantly associated with total abdominal fat, visceral fat, subcutaneous visceral fat, and HOMA-IR.[33] Nonetheless, a cross-sectional study conducted in 175 overweight and obese children showed that there was no relationship

between serum visfatin, BMI, or larger WC, which is similar to our study.[34] In addition, visfatin was not associated with insulin and HOMA-IR in this study. These findings were inconsistent with a study by Mitra Nourbakhsh et al.[35] They found a correlation of visfatin with insulin resistance indices and metabolic syndrome. Moreover, visfatin were higher in obese children and adolescents with metabolic syndrome compared to those without. In our study, we found low proportion of obese children with metabolic syndrome; hence, the association between visfatin and insulin resistance indices may not be strong enough to be detected at the end of the study. From the results of our study, plasma visfatin may not be a specific marker for insulin metabolism which is in line with another study.[9] In addition, lipid profiles were not correlated with any adipokines in the study. These relationships were inconsistent with previous reports. This discrepancy may be attributable to the differences in the degrees of fatty acid saturation within the triglyceride molecule from different dietary intake among the participants.[36]

The limitations of this study were the dietary intake of the participants. The actual caloric intake of both groups was higher than the instruction, even though there were significant changes in the amount of low-GI foods consumed in the intervention group. Therefore, this may cause subtle changes in the body composition and adipokines. Moreover, the changes of BMI *z*-score of 0.78 or higher is usually needed to demonstrate the change in the body composition and adipokines.[10] Although we wanted to study the effects of realistically achievable low-GI diet on all of the outcomes in the participants' daily lives, this intention-to-treat approach may underestimate the efficacy of the low-GI diet on adipokines. Previous studies showed that a decrease of more than 10% in visceral fat may be necessary to significantly change the adipokine levels. As a result of this, we could not detect any significant change in the adipokines in our study because there was not enough change in the adiposity. On the other hand, more intensive interventions may have a greater impact on the plasma adipokines such as a more strict calories control dietary intervention or bariatric surgery may reveal plausible associations among these adipokines.

In conclusion, baseline plasma leptin was strongly correlated with the changes of FMI in both groups. The higher the baseline leptin was, the lower the changes were for FMI after the intervention. These results indicated that leptin resistance may influence adipose tissue mass in obese children after the intervention, and could be a useful indicator to predict the change in adiposity. Thus, we could use leptin as a surrogate marker to determine which obese children should receive more intensive weight management program in order to decrease adiposity. However, there was insufficient evidence to consider other adipokines as a marker for adiposity and metabolic syndrome in obese children and adolescents. Identification of the receptor system for leptin, relevant signaling pathways, and their sensitivity state are needed to assess the role of adipokines in obese children. Other inflammatory markers may be considered to evaluate the effect of obesity among this population.

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AUTHOR CONTRIBUTIONS

Each author has met the Pediatric Research authorship requirements and each author has made the following contributions: C.V. substantially contributed in collecting the data, analyzed the data, interpreted the data, wrote the first draft of the manuscript, critically reviewed the manuscript's intellectual content, and finalized the manuscript for publication. C.H. substantially contributed in statistically analyzing the data, interpreted the data, and finalized the manuscript for publication. S.C. substantially contributed to the conception and design of the study, collected the data, analyzed the data, interpreted the data, critically reviewed the manuscript's intellectual content, and finalized the manuscript for publication.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

Patient consent: All the patients and their guardians have given the appropriate assents and consents for the study and for their stored samples to be used in future research.

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