

Greater early weight gain and shorter breastfeeding are associated with low adolescent adiponectin levels

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Received 23 October 2015; revised 6 December 2016; accepted 5 January 2017

Summary

Background: Early life factors can programme future risk for cardiovascular disease.

Objectives: We explored associations between adolescent adiponectin levels and concomitant metabolic alteration and also looked at the association between early life factors and adolescent adiponectin levels.

Methods: We studied a longitudinal cohort of low-income to middle-income Chilean adolescents who were enrolled in an infancy iron-deficiency anaemia preventive trial and follow-up studies at the Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile. In the 577 adolescents who were assessed as part of the 16-year follow-up, we evaluated independent associations between adiponectin levels and metabolic disturbances during adolescence. We also assessed the association between early life factors [short breastfeeding (<6 months) and infancy weight gain] and adolescent adiponectin levels.

Results: Participants were 16.8 years old (16.4–18.1), 48% female and 38% overweight/obese. Adolescent adiponectin levels were inversely associated with metabolic disturbances: altered homeostatic model assessment of insulin resistance and high-density lipoprotein cholesterol [odds ratios {95% confidence interval} = 0.87 {0.79–0.95}, *p*-value = 0.002, and 0.90 {0.87–0.94}, *p*-value < 0.001, respectively], adjusting for sex and fat mass index. Early life factors were independently associated with adolescent adiponectin levels, which decreased 0.88 ug mL⁻¹ per each unit increase in weight-for-age z-score between 0 and 6 months and was 1.58 ug mL⁻¹ lower among participants with short breastfeeding.

Conclusions: Higher adolescent adiponectin levels were independently associated with lower odds of metabolic disturbances. Greater weight gain during infancy and shorter breastfeeding were associated with lower adolescent adiponectin levels, supporting research indicating early life as a window of opportunity for prevention of later cardiovascular alterations. © 2017 World Obesity Federation

Keywords: Adiponectin, adolescence, breastfeeding duration, developmental origins of disease, infancy growth.

Abbreviations: AT, adipose tissue; BF, breastfeeding as the sole source of milk; BMI, body mass index; HDL-c, high-density lipoprotein cholesterol; INTA, Institute of Nutrition and Food Technology; SES, socioeconomic status; WAZ-score, weight-for-age z-score; WHO, World Health Organization

Introduction

As obesity prevalence continues to rise, cardiometabolic disturbances associated with excess fat mass have become important health and economic burdens facing both developed and developing nations (1). Children and adolescents are not immune to health impairments associated with obesity, which

could result in important reductions in healthy lifespan (2). However, about 25–35% of people are discordant in terms of adipose tissue (AT) amount and metabolic consequences, i.e. obese individuals metabolically healthy or normal weight individuals with metabolic alterations (3). Some AT features such as the topography or the adipokine secretory profile may explain the discordancy (4,5). Specifically,

the ability to secrete adiponectin is a key feature, because adiponectin is an insulin-sensitizing and cardioprotective hormone that improves the metabolism of lipids and carbohydrates and has anti-inflammatory effects (6). Its levels have been associated with cardiometabolic parameters, independent of adiposity (7,8), and have been implicated in discordant adiposity-metabolic profiles in both obese and normal weight participants (9). Low adiponectin has also been shown to independently predict metabolic alterations among children and adolescents (10,11). Several factors at the cellular or tissue level have been implicated in poor adiponectin secretion (12). However, the causes for the development of such factors are not well understood and therefore cannot be targeted.

It has been suggested that events in early life might influence adiponectin levels (10,13–15). At least two prior studies have shown that infancy weight gain correlates to later adiponectin levels (10,14). In addition, prior research has shown relationships between early nutrition and leptin (16). The hypothesis that early life factors relate to adiponectin is in line with the developmental origin of health and diseases concept. In a group of healthy adolescents who were part of a cohort followed since infancy, we aimed to (i) confirm previous findings regarding the associations between adolescent adiponectin levels and concomitant metabolic alterations, regardless of adiposity and sex, and (ii) to explore potential effects of early life factors on adolescent adiponectin levels.

Methods

Study design

The sample is from a longitudinal study that began as an infancy iron-deficiency anaemia preventive trial in Santiago, Chile (1991–1996; total $n = 1657$) (17). Infants were screened at community clinics to enrol healthy, singleton full-term infants, with birthweights ≥ 3 kg, who did not have iron-deficiency anaemia at 6 months. The infants were randomized to high-iron or low-iron supplementation or usual nutrition. The participants were subsequently followed at 5, 10 and 16 years to determine long-term effects of infancy iron supplementation. At 16 years, they were invited to participate in a study of biopsychosocial determinants of obesity and cardiovascular risk.

Sample

For the current analysis, we included 577 adolescents (299 boys and 278 girls) seen at 16 years and who weighed < 4 kg at birth and had complete data on

adolescent adiponectin. The analytic sample did not vary from the overall sample with respect to sex, age of first bottle of formula/cow milk and length and weight at 6 months. The analytic sample weighed less at birth (3.4 vs. 3.7 kg) and had a lower birth length (50.4 vs. 51.3 cm) compared with the overall sample, a difference related to the exclusion criteria of weighing ≥ 4 kg at birth. The analytic sample included participants who did not receive ($n = 235$) and who received iron supplementation (high-iron group, $n = 283$; low-iron group, $n = 13$) during infancy; iron supplementation group was considered as a covariate in the multivariate models.

Infancy data

Beginning at 4–6 months, infants were followed with monthly anthropometric measurements at the Institute of Nutrition and Food Technology (INTA), University of Chile; previous anthropometric data (i.e. birth to the recruitment age) were obtained from medical records. Changes in weight-for-age z-score (WAZ-score) between birth and 6 months (Δ_{0-6} WAZ-score) were computed as the difference between WAZ-scores at 6 months and birth [according to World Health Organization {WHO}, using AnthroPlus Software]. For those receiving formula/cow milk supplementation to breastfeeding at 4 months, the date of the first bottle was recorded based on maternal report ($n = 298$). For all other infants ($n = 256$), this information was obtained prospectively. The duration of breastfeeding as the sole source of milk (BF) was computed. Shorter BF was defined as supplementation prior to < 6 months (cut-off chosen given Chilean paediatricians' recommendation). We did not collect data on introduction of complementary food (pureed fruits were typically introduced after 4 months) (18), nor do we have data on consumption of water or fruit juices. Thus, in our study, infants may have received water or juice and almost certainly received complementary foods after 4 months. Therefore, BF is not equivalent to exclusive breastfeeding as defined by WHO (19).

Adolescent data

Participants were assessed, after an overnight fast, by trained medical professionals at INTA. Participants were weighed and measured twice in the Frankfurt position wearing underwear and without shoes. Body mass index (BMI) z-score were computed using WHO standards (using AnthroPlus software). BMI z-scores were used to classify participants as normal weight (z-score < 1), overweight (z-score ≥ 1 to < 2) or obese (z-score ≥ 2). Body composition was assessed using

Lunar Prodigy Dual Energy X-Ray Absorptiometry scan, according to standard protocols. Body fat mass was used for computing fat mass index [fat mass {kg}/height {m}²]. Fasting blood samples were processed, stored (−80°C) and analyzed at the Micronutrient Laboratory, INTA, following standard quality assurance and quality control procedures. Glucose and high-density lipoprotein cholesterol (HDL-c) were measured using enzymatic-colorimetric tests (QCA S. A. Amposta, Spain). Insulin was determined by radioimmunoassay I¹²⁵ (Siemens Healthcare diagnostic Inc.). Adiponectin was determined by enzyme-linked immunosorbent assay Quantikine, with a minimum detectable concentration ranging from 0.079 to 0.891 ng mL^{−1}. Criteria from the International Diabetes Foundation were used to define altered HDL-c (<40 mg/dL for boys, <50 mg/dL for girls) (20). Altered homeostatic model assessment of insulin resistance (HOMA-IR) was defined by local criteria as >3.3 (21). The study was approved by the Institutional Review Boards of the University of California, San Diego, for the adolescent wave and of the University of Michigan and INTA, University of Chile, for all waves of the study. Adolescent assent and parental consent were obtained.

Statistical analysis

All continuous variables were tested for normality and were described as mean (standard deviation) or median (interquartile range). Categorical variables were expressed as percentages. Comparisons between weight status (normal, overweight and obese) were stratified by sex and tested using analysis of variance and Kruskal–Wallis (*post hoc* comparisons) or chi-squares tests. Adiponectin levels were grouped according to sex and weight status for density curve construction, which are similar to histograms but allow smoothing the curve and model the probability of having a specific value on the *x*-axis (Supporting Information). Logistic regressions were performed to explore the association between adolescent adiponectin levels and concomitant insulin resistance or altered HDL-c, adjusted for sex and fat mass index. In both models, we tested for an interaction between sex and adiponectin. The interaction was not statistically significant and was removed for parsimony. A multivariate linear regression model was used to study the association between early life factors (Δ_{0-6} WAZ-score and short BF) and adolescent adiponectin values, adjusting for fat mass index and adolescent haemoglobin levels (given the recently reported association between iron status and adiponectin levels) (22). The initial linear model also considered

other covariates such as sex, maternal education (as a proxy of social economic status) and iron supplementation group at infancy (received iron supplementation yes versus no), but these covariates were removed for parsimony because they did not significantly influence (<10%) the magnitude of the studied associations. Additionally, we have confirmed the findings with a sensitivity analysis including only participants in the no-iron treatment group (data not shown). The potential interaction between BF and early weight gain was also studied and discarded. Results were considered as statistically significant when *p*-value <0.05. Analyses and graphs were performed using STATA 12 (STATA Corp., College Station, TX, USA).

Results

This analysis included 577 adolescents (48.2% girls). The mean weights were 3.44 ± 0.27 kg at birth (WAZ-score = 0.3 ± 0.6) and 7.97 ± 0.87 kg at 6 months (WAZ-score = 0.3 ± 0.9). Thus, the mean WAZ-score did not change between birth and 6 months. The median age of the first milk/formula bottle was 92 (31–180) d; 74.7% of the sample received the first bottle before 6 months. Adolescents averaged 16.8 ± 0.3 years of age, ranging from 16.4 to 18.1 years; 23.7% of the sample was overweight and 13.9% was obese.

As shown in Table 1, girls who were obese in adolescence had higher WAZ-scores at birth and 6 months, compared with their normal weight counterparts (WAZ-score birth: 0.31 ± 0.54 vs. 0.57 ± 0.63, and WAZ-score 6 months: 0.18 ± 0.76 vs. 0.53 ± 0.78, for normal weight versus obese, respectively; both *p*-values <0.05). However, changes in WAZ-score between birth and 6 months were similar between the different weight status groups (−0.14 ± 0.83 vs. 0.01 ± 0.84 for normal weight versus obese, respectively; *p*-value >0.05). Among the boys, infant anthropometric parameters did not differ by adolescent weight status (WAZ-score birth: 0.22 ± 0.55 vs. 0.35 ± 0.54, for normal weight versus obese, respectively; *p*-value >0.05). Age at the first milk/formula bottle did not differ by sex (117.9 ± 101.5 vs. 117.1 ± 97.1, for boys versus girls, respectively; *p*-value >0.05) or adolescent weight status (113.1 ± 86.4 vs. 133.1 ± 97.1, for normal weight versus obese, respectively; *p*-value >0.05).

Compared with normal weight participants, obese participants had significantly higher insulin and HOMA-IR and lower HDL-c; overweight participants had significantly higher insulin and HOMA-IR; only overweight boys had lower HDL-c (Table 1).

Table 1 Descriptive data according to weight status and sex (N = 577)

	Boys			Girls		
	Normal weight (n = 193)	Overweight (n = 65)	Obese (n = 41)	Normal weight (n = 167)	Overweight (n = 72)	Obese (n = 39)
Infancy data						
WAZ-score birth	0.22 (0.55)	0.29 (0.52)	0.35 (0.54)	0.31 (0.54)a	0.40 (0.55)a	0.57 (0.63)b
WAZ-score 6 m ⁺	0.19 (0.88)	0.44 (0.98)	0.47 (0.93)	0.18 (0.76)a	0.45 (0.83)a	0.53 (0.78)b
Δ ₀₋₆ WAZ-score ⁺	-0.04 (0.93)	0.15 (0.92)	0.09 (0.94)	-0.14 (0.83)	0.07 (0.82)	0.01 (0.84)
Age of first bottle (d) ^{**}	115.40 (92.41)	118.48 (110.63)	128.59 (126.84)	110.84 (78.95)	116.14 (101.77)	139.44 (120.95)
Adolescent data						
BMI z-score	-0.16 (0.79)a	1.44 (0.30)b	2.54 (0.43)c	-0.03 (0.69)a	1.42 (0.27)b	2.57 (0.52)c
Fat mass index (kg m ⁻²)	3.63 (1.33)a	7.29 (1.57)b	11.58 (2.18)c	6.80 (1.52)a	10.68 (1.39)b	15.26 (2.65)c
Adiponectin (ug mL ⁻¹)	11.06 (4.94)a	8.90 (4.50)b	7.80 (4.15)b	13.42 (5.70)a	12.32 (4.62)a	9.04 (4.64)b
Glucose (mg dL ⁻¹)	90.52 (8.61)	90.30 (9.30)	94.41 (14.54)	85.98 (9.00)	86.71 (9.98)	88.89 (8.99)
Insulin (μU dL ⁻¹)†	5.30 (3.99-7.54)a	7.85 (4.84-11.18)b	11.76 (9.09-19.22)c	6.40 (4.43-8.20)a	7.37 (5.91-10.88)b	11.43 (9.11-17.30)c
HOMA-IRT	1.21 (0.85-1.73)a	1.81 (1.09-2.39)b	2.85 (1.85-4.74)c	1.33 (0.92-1.79)a	1.61 (1.22-2.32)b	2.46 (1.83-4.05)c
HOMA-IR ≥ p75 (%) [‡]	1.6	9.2	43.9*	1.8	9.7	35.9*
HDL-c (mg dL ⁻¹)	40.33 (10.01)a	35.04 (9.18)b	31.06 (6.24)b	44.08 (11.63)a	42.70 (9.72)a	37.17 (7.47)b
Altered HDL-c (%) [‡]	54.4	73.8	95.1*	68.9	75.0	94.9*

*p-value <0.05 between weight status within each sex (chi-squared).

†N = 526.

**N = 574.

Values indicate mean (SD), median (IQR) † or percentage ‡. (a,b,c) Differing letters indicate significant differences between weight status groups, within sex (ANOVA/Bonferroni or Kruskal-Wallis/Bonferroni). Values that do not differ by weight status group, within sex, are indicated by matching letters.

HOMA-IR ≥3.3, altered HDL-c: <40 mg dL⁻¹ for boys and <60 mg dL⁻¹ for girls[†].

ANOVA, analysis of variance; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; IQR, interquartile range; SD, standard deviation.

Adiponectin levels were lower in those with higher adiposity and differed by weight status and sex. Both overweight and obese boys had significantly lower adiponectin levels than normal weight boys. Obese girls had significantly lower adiponectin levels than overweight/normal weight girls (Table 1). Density curves describe these differences and illustrate the wide range of values in each weight category (Figure S1).

Adiponectin levels were inversely and independently associated with metabolic disturbances. Higher adiponectin levels were associated with decreased odds of having altered HOMA-IR and HDL-c, after controlling for fat mass index and sex (Table 2). Results were similar when adjusting for BMI, rather than fat mass index (results not shown). This association was not found for other cardiometabolic variables, such as blood pressure, triglycerides or low-density lipoprotein cholesterol (data not shown). There were no interactions between adiponectin levels and either fat mass index or sex.

Adolescent adiponectin level was independently associated with BF duration and weight gain during the first 6 months of life, taking into account adolescent adiposity and haemoglobin levels (Table 3). Being breastfed as the sole source of milk for <6 months was independently associated with lower adolescent adiponectin levels. Participants with short BF had 1.58 ug mL⁻¹ lower adiponectin levels compared with participants with long BF, adjusting for early weight gain, adolescent fat mass index and haemoglobin. Changes in WAZ-score between birth and 6 months were also independently and significantly associated with lower adolescent adiponectin levels. Adiponectin levels were 0.88 ug mL⁻¹ lower per each unit increase of WAZ-score in the first 6 months, adjusting for BF, adolescent fat mass index and haemoglobin.

Table 2 Association between adiponectin level and altered HOMA-IR and altered HDL-c in adolescence

	Altered HOMA-IR ⁺	Altered HDL-c ⁺⁺
Adiponectin	0.87 (0.79–0.95)*	0.90 (0.87–0.94)*
Female	0.36 (0.17–0.78)*	0.83 (0.54–1.25)
Fat mass index	1.41 (1.28–1.54)*	1.08 (1.03–1.14)*

**p*-value < 0.05.

⁺*N* = 576.

⁺⁺*N* = 577.

Two different logistic regression models are presented, using adiponectin as predictor and adjusting for covariates (sex and fat mass index). Values correspond to OR (95% confidence interval).

HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; OR, odds ratio.

Table 3 Association between early life factors and adolescent adiponectin levels (*N* = 526)*

	Beta	<i>p</i> -value
Breastfed <6 months	-1.58	0.004
Δ ₀₋₆ weight-for-age	-0.88	0.002

*R*² = 0.07 (*p*-value < 0.05).

*Model adjusted for adolescent fat mass index and hemoglobin levels.

Discussion

In a cohort of healthy Chilean adolescents, we studied adiponectin levels, their metabolic correlates and early life determinants. We found that adiponectin levels exhibited wide and overlapping ranges across the three weight status groups and higher adiponectin levels were associated with decreased metabolic disturbance, taking fat mass and sex into account. The inverse association of adiponectin with various measures of adiposity is well established in both adults and children/adolescents (23,24). However, the heterogeneity of adiponectin levels within each weight status group (Figure S1) has garnered less attention. The variability of adiponectin levels unexplained by weight status highlights the need to identify additional factors associated with adiponectin concentrations, especially given its cardiovascular protective effect. The associations we observed between low adiponectin levels and cardiovascular risk factors, independent of fat mass or sex, are consistent with previous research. Volberg *et al.* showed similar positive associations between adiponectin and HDL-c and negative associations between adiponectin and triglycerides and blood pressure among ~150 nine-year-old children, adjusting for BMI (10). Other reports have shown similar independent associations between adiponectin and lipids or other metabolic parameters (11). Moreover, Weghuber *et al.* implicated adiponectin levels, among other factors, as responsible for the distinction between metabolically healthy and unhealthy overweight/obesity in youth (25). The results of our study and those of others suggest that differences in adiponectin levels may be related to the development of metabolic disturbances. Thus, adiponectin – either by itself or as a marker of AT dysfunction – is an important player in the concordance (or discrepancy) between fat mass and metabolic performance.

We were also interested in studying early life predictors and found that greater WAZ-score gain in the first 6 months of life and duration of BF <6 months was independently associated with lower adiponectin levels. This information is in line with previous reports

of greater early weight gain and early formula or cow milk as risk factors for later development of non-communicable diseases (23,26). Volberg *et al.* also studied the association of perinatal factors with adiponectin levels and found that infant weight gain during the first 6 months was inversely associated with adiponectin levels at 9 years, adjusting for child BMI ($n = 146$) (10). Infant nutrition was not included in their analysis. Volberg *et al.* also found that intrauterine growth influenced later adiponectin values. Larnkjaer *et al.* similarly (14) found that WAZ-score changes during the first 3 months were inversely related to adolescent adiponectin levels [divided by fat mass {kg}], taking breastfeeding into account ($n = 95$). Our results replicate their observations in a considerably larger sample. Most available studies have controlled for child BMI. Our study has the additional strength of having data on fat mass measured by DXA scan, which is an improvement on BMI adjustment because the latter is an indirect assessment of fat mass and thus is not an accurate measure of adiposity. One other prior study reported an association between breastfeeding and higher levels of high molecular weight adiponectin, which is a specific form of total circulating adiponectin (15). In 12-month-old infants ($n = 99$), de Zegher *et al.* found that formula-fed small-for-gestational-age infants had lower adiponectin levels than breastfed small-for-gestational-age infants at 4 and 12 months. For our study, there are no data on intrauterine growth, and by design, our cohort excluded low birth weight or small-for-gestational-age infants.

Because breastfed infants gain more weight during the first 6 months (27), it is worth noticing that both early factors were associated with adiponectin levels independently of each other. Thus, on one hand, greater early weight is associated with lower adolescent adiponectin levels, regardless of the source of milk, and on the other hand, breastfeeding is associated with greater adiponectin levels, even when considering the potential differences in early weight gain. Moreover, both early factors were associated with adolescent adiponectin levels after taking into account fat mass index (among other covariates). This is relevant because both factors have been associated with later adiposity (28–30). Furthermore, given recent findings related to the association between iron and adiponectin levels (22) and because of the design of the original study, we also included both infancy iron supplementation group and adolescent haemoglobin level in the models. Only the latter was relevant in the studied model.

Our study was unable to evaluate potential mechanisms involved in the deleterious influences of greater

weight gain and shorter BF on adolescence adiponectin levels. Because body composition was not measured during infancy, we cannot assess the role of greater fat mass gain in early life. However, previously reported data suggest that both greater weight gain and shorter BF are associated with greater fat mass gain as early as 2 years (24). If this were the case among our participants, it would be plausible to hypothesize that the greater expansion of AT during a determined window of time could constitute a ‘biological challenge’ that impaired AT functionality. Adolescent adiponectin levels may reflect long-term consequences of such early biological changes in AT physiology. Future studies on the topic should focus on body composition changes in early life and throughout childhood (i.e. assessment of fat versus lean mass gain) in order to better understand the dynamics of AT expansion and its consequences. Additionally, future studies could also address AT functioning in a more comprehensive way by studying topography of fat deposit (i.e. subcutaneous versus intra-abdominal) and/or other.

There are additional limitations and important strengths of our study. Some participants received iron supplementation treatment during infancy, which could be associated with future adiponectin levels. We considered treatment group and adolescent iron status in multivariate models, but some residual confounding might still be present in the association. Furthermore, findings from our cohort of low-income to middle-income Chilean adolescents, studied since infancy, may not be generalizable to individuals from other backgrounds. Socioeconomic status (SES) was not associated to either predictors or the dependent variables (data not shown). We hypothesize that because we do not have the full range of SES represented in our sample, we were unlikely to find any confounding associations with SES. In addition, maternal obesity, a known predictor of infant and adolescent weight gain, was not collected. The strengths of the study include the large infancy cohort with longitudinal data into adolescence, anthropometry measured at a nutrition research centre, careful measurement of infant breast and bottle feeding and the availability of data on adolescent body composition, measured by DXA scan. Breastfeeding is often recalled years later, which could lead to under-reporting or over-reporting of duration. Having prospectively collected breastfeeding data provides confidence in describing findings using a cut-off value (<6 months vs. ≥ 6 months).

In our study of 577 Chilean adolescents studied since infancy, participants with lower levels of adiponectin were more likely to have insulin resistance

and/or low HDL-c. Weight status and sex alone did not adequately explain individual adiponectin levels. Early life factors including greater weight gain in the first 6 months and shorter BF were independently associated with lower adiponectin levels. Our findings regarding the influences of early postnatal factors on adiponectin levels and the associations of this hormone to metabolic parameters add evidence that early life factors are related to later metabolic health, supporting the developmental origin of health and disease paradigm.

Conflict of interest statement

No conflict of interest was declared.

Acknowledgements

This work was supported by the National Institutes of Health, Heart, Lung, and Blood Institute (HL088530, PI: Gahagan) and the National Institute of Child Health and Human Development (HD14122 and HD33487, PI: Lozoff). No funding source had a role in study design, data analysis or manuscript preparation. M. R., R. B., B. L. and S. G. conceived and designed the study; M. R., E. B. and S. G. analyzed and interpreted the data; M. R. and S. G. drafted the article; R. B., E. B., B. L. and S. G. critically revised the article for important intellectual content; all authors provided final approval of the article.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Figure S1. Supporting info item