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

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Abbreviations

AT: adipose tissue

BMI: body mass index

BF: breastfeeding as the sole source of milk

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

What is already known about this subject

- Lower adiponectin levels are associated with concomitant cardiometabolic alterations, regardless of adiposity.

- Controlling for BMI, both intrauterine weight gain and weight gain during the first months of life are inversely and independently associated with later adiponectin levels.

- Among small-for-gestational-age infants, formula fed infants have lower adiponectin levels at 12 months of age compared to breastfed infants.

What this study adds

- Weight gain during the first months of life was inversely and independently associated with adolescent adiponectin levels, controlling for fat mass and other covariates.

- For normal weight infants, breastfeeding as the sole source of milk for 6 months or more was associated with greater adolescent adiponectin levels.

Abstract

Background. Early life factors can program future risk for cardiovascular disease.

Objective. 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- to middle-income Chilean adolescents who were enrolled in an infancy iron deficiency anemia preventive trial and follow-up studies at the Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile. In 577 adolescents who were assessed as part of the 16y 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 year-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 (ORs [95%CI]= 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 per each unit increase in weight-for-age z-score between 0 and 6 months, and was 1.58 ug/mL 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.

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, since 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 has 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 1) confirm previous findings regarding the associations between adolescent adiponectin levels and concomitant metabolic alterations, regardless of adiposity and sex and 2) to explore potential effects of early life factors on adolescent adiponectin levels.

Methods

Study design. The sample is from a longitudinal study, which began as an infancy iron deficiency anemia preventive trial in Santiago, Chile (1991-1996; total *n*=1657) (17). Infants were screened at community clinics to enroll healthy, singleton full-term infants, with birthweights ≥3 kg, who did not have iron-deficiency anemia 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 males and 278 females) 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, 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 to the overall sample, a difference related to the exclusion criteria of weighing ≥4 kg at birth. The analytic sample included participants who did not received (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 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 (cutoff chosen given Chilean pediatricians' 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 I^{125} (Siemens Healthcare diagnostic Inc). Adiponectin was determined by enzyme-linked immunosorbent assay (ELISA) Quantikine®, with a minimum detectable concentration ranging from 0.079–0.891 ng/mL. Criteria from the International Diabetes Foundation (IDF) were used to define altered HDL-c (**<**40 mg/dL for males, <50 mg/dL for females) (20). Altered homeostatic model assessment of insulin resistance (HOMA-IR) was defined by local criteria as greater than 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, obese) were stratified by sex and tested using ANOVA and Kruskal-Wallis (post-hoc comparisons) or Chi-square tests. Adiponectin levels were grouped according to sex and weight status for density curves construction, which are similar to histograms but allow smoothing the curve and model the probability of having a specific value on the x-axis (see Supplementary 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 hemoglobin 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 vs no), but were removed for parsimony since 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).

Results

This analysis included 577 adolescents (48.2% female). 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] days; 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 18.1y; 23.7% of the sample was overweight and 13.9% was obese.

As shown in Table 1, females who were obese in adolescence had higher WAZ-scores at birth and 6 months, compared to their normal weight counterparts (WAZ-score birth: 0.31±0.54 vs 0.57±0.63; and WAZ-score 6m: 0.18±0.76 vs 0.53±0.78 for normal weight vs 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 vs obese, respectively; p-value>0.05). Among

males, 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 vs 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 males vs females, respectively; p-value>0.05) or adolescent weight status (113.1±86.4 vs 133.1±97.1 for normal weight vs obese, respectively; p-value>0.05).

Compared to normal weight participants, obese participants had significantly higher insulin, HOMA-IR and lower HDL-c; overweight participants had significantly higher insulin and HOMA-IR; only overweight males had lower HDL-c (Table 1). Adiponectin levels were lower in those with higher adiposity and differed by weight status and sex. Both, overweight and obese males had significantly lower adiponectin levels than normal weight males. Obese females had significantly lower adiponectin levels than overweight/normal weight females (Table 1). Density curves describe these differences and illustrate the wide range of values in each weight category (Supplemental Figure 1).

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 LDL-c (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 sex and adolescent adiposity (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 lower adiponectin levels compared to participants with long BF, adjusting for early weight gain, adolescent fat mass index and hemoglobin. 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 lower per each unit increase of WAZ in the first 6 months, adjusting for BF, adolescent fat mass index and hemoglobin).

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 (Supplemental Figure 1) 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, is 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 9-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, were 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 breast-fed small-for-gestational-age infants at 4 and 12 months. For our study, there is no data on intrauterine growth, and by design, our cohort excluded low birth weight or small-for-gestational-age infants.

Since 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 since 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 hemoglobin 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. Since body composition was not measured during infancy, we cannot assess the role of greater fat mass gain in early life. However, previously reported data suggests 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 vs. 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, for example, topography of fat deposit (i.e. subcutaneous vs intra-abdominal) and/or other adipokines levels.

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- to middle-income Chilean adolescents, studied since infancy, may not be generalizable to individuals from other backgrounds. 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 center, 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- or over-reporting of duration. Having prospectively collected breastfeeding data provides confidence in describing findings using a cut-off value (<6 months versus ≥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 adds evidence that early life factors are related to later metabolic health, supporting the developmental origin of health and disease paradigm.

Conflict of interest statement: The authors have no conflicts of interest.

Acknowledgments

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

	Males			Females		
	Normal weight	**Overweight**	**Obese**	**Normal weight**	**Overweight**	**Obese**
	(n=193)	**(n=65)**	**(n=41)**	**(n=167)**	**(n=72)**	**(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 6m[+]	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 [days][++]	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]	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]	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 [µUI/dL]†	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-IR†	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]	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*

Values indicate either 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.

* indicates p-value<0.05 between weight status within each sex (Chi square).

HOMA-IR ≥3.3, altered HDL-c: 40 mg/dL for males and 50 mg/dL for females.

+ N=526

++N=574

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

adolescence

	Altered HOMA-IR #	Altered HDL-c Ψ
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)*

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) in 2 different logistic regressions.

*P-value<0.05

N=576

Ψ N=577

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

	Beta	p-value
Breastfed **< 6 m**	-1.58	0.004
Δ_{0-6} weight-for-age	-0.88	0.002

* Model adjusted for adolescent fat mass index and hemoglobin levels

R^2=0.07 (p-value<0.05)

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