Behavior of Insulin Resistance and Its Metabolic Correlates in Prepubertal Children

A Longitudinal Study (EarlyBird 32)

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Secular trends in childhood obesity suggest that many children are gaining excess fat, thereby contributing to an emerging epidemic of type 2 diabetes in young people (1,2). However, it is normal for children to accumulate some fat in the years before puberty (3). These considerations highlight the difficulty in distinguishing pathological from physiological fat accumulation. Longitudinal data in healthy children are required in order to properly examine the relationships between adiposity and metabolic health. We prospectively studied a cohort of healthy prepubertal British school children and report here some unexpected temporal relationships between adiposity and insulin resistance.

RESEARCH DESIGN AND METHODS

— EarlyBird is a prospective nonintervention study investigating the emergence of insulin resistance in childhood. A cohort of 307 healthy children was recruited in 2000–2001 from randomly selected schools in Plymouth, U.K. Most are Caucasian, with a wide socioeconomic mix. Mean ± SD age at recruitment was 4.9 ± 0.25 years. The protocol has previously been described in detail (4). Results are reported for the first 4 study years, when the children were aged 5, 6, 7, and then 8 years. Only children who attended at all four time points (130 boys and 100 girls) were included for analysis. Those excluded (40 boys and 37 girls) did not differ anthropometrically or in metabolic measures at age 5 years (*t* tests; all $P > 0.05$). The male preponderance resulted from random recruitment. Results are presented separately by sex.

Annual measures

Annual measures included height, weight, BMI standardized to 1990 U.K. reference data (SD scores), sum of five skinfolds (SSF) (skinfolds measured twice over biceps and triceps of the left arm and the subscapular, suprailiac, and paraumbilical areas and the mean calculated for each measure); body composition by bioimpedance at ages 6–8 years, and body composition assessed by dual-energy X-ray absorptiometry at age 7 years (used to validate SSF as a measure of percentage of body fat). Fasting blood tests included serum glucose, insulin, triglycerides, HDL cholesterol, and total adiponectin. Homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) and β-cell function (HOMA-B) were derived by HOMA2 (5), validated for use in children (6). Serum adiponectin concentrations were determined using enzyme-linked immunosorbent assay on serum stored at −80°C.

Statistical analyses

Statistical analyses were performed using SPSS (version 14.0; SPSS, Chicago, IL). Means were compared using paired *T* tests and linear associations by Pearson's correlation. Insulin resistance, triglycerides, waist circumference, and SSF were log transformed for all analyses to achieve normal distributions and the results back transformed for tabulation. Effect size (ES) ([mean at 8 years − mean at 5 years]/SD at 5 years) was calculated because it provides a useful indicator of the practical/clinical significance and is scale free (7), allowing comparisons across different variables. Differences and associations, respectively, of ES = ±0.25 and $r = \pm 0.24$ in boys and ES = ±0.29 and $r = \pm 0.28$ in girls would be statistically significant ($P < 0.05$) with 80% power. A difficult characteristic of this age-group is that many fasting insulin levels are below conventional detection limits of assays. To derive a HOMA value, each was arbitrarily allocated an insulin concentration of 1.5 mU/l. For assurance, we compared the metabolic trends in children with detectable insulin levels with findings in the entire cohort.

RESULTS

Adiposity

BMI at 5 years was significantly greater than the 1990 U.K. standard (8) in both boys and girls but increased only slightly from 5 to 8 years (Table 1). Skinfold thickness provides a more reliable measure of adiposity, correlating closely with dual-energy X-ray absorptiometry percentage of body fat in the EarlyBird cohort at age 7 years ($r = 0.93$; $P < 0.001$). Skinfold thickness increased significantly in both sexes from 5 to 8 years. Body composition was measured by bioelectrical impedance at ages 6–8 years, during

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Abbreviations: ES, effect size; HOMA, homeostasis model assessment; HOMA-B, HOMA of β-cell function; HOMA-IR, HOMA of insulin resistance; SSF, sum of skinfolds.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Trend of metabolic markers in children measured at 4 annual time points (from ages 5 to 8 years)*

	5 years	6 years	7 years	8 years	Change from 5 to 8 years	
					ES	*P*
Boys (*n* = 130)						
BMI (SDS)	0.16 (−0.03 to 0.34)	0.15 (−0.04 to 0.33)	0.19 (0.00–0.37)	0.26 (0.07–0.46)	0.10	0.05
SSF (cm)*	3.66 (3.48–3.85)	3.83 (3.64–4.04)	4.13 (3.91–4.37)	4.56 (4.30–4.85)	0.74	<0.001
Insulin (mU/l)*	3.29 (2.94–3.67)	2.56 (2.29–2.86)	2.29 (2.12–2.51)	2.59 (2.36–2.83)	−0.36	0.001
Insulin resistance	0.46 (0.41–0.51)	0.34 (0.32–0.40)	0.33 (0.30–0.36)	0.38 (0.34–0.42)	−0.37	0.01
β-Cell function	86.13 (79.51–92.74)	66.74 (61.08–72.38)	54.08 (54.05–62.11)	54.87 (51.42–58.56)	−0.92	<0.001
Glucose (mmol/l)	4.31 (4.22–4.39)	4.52 (4.46–4.58)	4.63 (4.55–4.71)	4.78 (4.72–4.84)	1.05	<0.001
Triglycerides (mmol/l)*	0.59 (0.55–0.64)	0.56 (0.51–0.60)	0.57 (0.53–0.61)	0.57 (0.53–0.61)	−0.15	0.40
HDL cholesterol (mmol/l)	1.50 (1.44–1.56)	1.59 (1.53–1.65)	1.66 (1.60–1.72)	1.76 (1.70–1.83)	0.78	<0.001
Adiponectin (ug/ml)*†	13.83 (12.97–14.69)	12.92 (12.00–13.83)	12.73 (11.81–13.65)	12.54 (11.61–13.46)	−0.35	<0.001
Girls (*n* = 100)						
BMI (SDS)	0.51 (0.31–0.72)	0.51 (0.31–0.71)	0.54 (0.34–0.75)	0.56 (0.34–0.78)	0.04	0.49
SSF (cm)*	4.51 (4.25–4.80)	4.86 (4.54–5.20)	5.38 (5.01–5.77)	5.90 (5.50–6.33)	0.89	<0.001
Insulin (mU/l)*	4.66 (4.14–5.31)	3.63 (3.19–4.14)	2.89 (2.64–3.19)	3.10 (2.75–3.49)	−0.65	<0.001
Insulin resistance	0.66 (0.58–0.74)	0.51 (0.45–0.58)	0.42 (0.38–0.46)	0.44 (0.39–0.50)	−0.59	<0.001
β-Cell function	110.04 (100.71–119.37)	90.15 (82.66–97.64)	68.10 (63.66–72.54)	71.10 (65.79–76.41)	−1.02	<0.001
Glucose (mmol/l)	4.31 (4.22–4.40)	4.36 (4.30–4.43)	4.57 (4.51–4.64)	4.60 (4.54–4.67)	0.60	<0.001
Triglycerides (mmol/l)*	0.71 (0.65–0.76)	0.67 (0.59–0.75)	0.69 (0.63–0.75)	0.68 (0.60–0.77)	−0.28	0.02
HDL cholesterol (mmol/l)	1.41 (1.35–1.47)	1.52 (1.47–1.57)	1.56 (1.51–1.61)	1.65 (1.58–1.72)	0.78	<0.001
Adiponectin (ug/ml)*‡	13.67 (12.56–14.77)	12.59 (11.54–13.63)	13.19 (12.22–14.17)	12.62 (11.68–13.56)	−0.12	0.02

Data are means (95% CIs) or SDs unless otherwise indicated. Insulin resistance and β-cell function measured by HOMA. *Antilogged means and 95% CI; ES calculated on logged data. †n = 114. ‡n = 86. SDS, standard deviation scores.

which time percentage of fat mass rose (ES 0.32 and 0.91 SD in boys and girls, respectively; both $P < 0.001$)

Metabolic variables

HOMA-IR fell progressively and unexpectedly in both sexes from ages 5 to 7 years, tending to level off between ages 7 and 8 years (Table 1). Consistent with the fall in insulin resistance, HDL cholesterol rose significantly and triglyceride levels fell significantly in girls (though not significantly in boys). HOMA-B decreased significantly in both sexes, and glucose rose, crossing some 25% of its reference range. Adiponectin fell significantly.

The trends in insulin resistance and β-cell function were similar in each BMI tertile (data not shown). Fasting insulin was undetectable (<2.0 mU/l) in 19, 34, 35, and 35% of children at ages 5, 6, 7, and 8 years, respectively. However, the trends in insulin among children with detectable insulin levels at ages 5 and 8 years were the same as for the cohort as a whole: ES boys −0.35 SD, $P = 0.03$ and girls −0.55 SD, $P < 0.001$.

Correlations

Correlations between HOMA-IR and BMI were positive and tended to strengthen with age: at age 5 years, boys $r = 0.21$ ($P = 0.01$) and girls $r = 0.23$ ($P = 0.02$); by age 8 years, boys $r = 0.37$ and girls $r = 0.5$ (both $P < 0.001$). Correlations with SSF were similar: at age 5 years, boys $r = 0.12$ and girls $r = 0.07$ (both $P > 0.16$); at age 8 years, boys $r = 0.34$ and girls $r = 0.57$ (both $P < 0.001$). Insulin resistance was not significantly correlated with HDL cholesterol and correlated only weakly with adiponectin in boys aged 5 and 6 years. Fat mass calculated at ages 6, 7, and 8 years by bioimpedance correlated with insulin resistance better than fat-free mass (at 8 years, boys $r = 0.38$ and girls $r = 0.56$ [both $P < 0.001$] compared with boys $r = 0.28$ [$P = 0.001$] and girls $r = 0.43$ [$P < 0.001$], respectively).

CONCLUSIONS — The combination of findings was unexpected and has not been reported before. Despite rising adiposity, there was a fall in insulin resistance between ages 5 and 7 years, consistent with falling triglycerides and rising HDL cholesterol. It is of interest that the positive correlation between insulin resistance and adiposity continued to strengthen over this period. The linear rise in fasting glucose levels over the same time interval is

consistent with the substantial drop in HOMA-B (β-cell reserve).

The linearity of the changes and the precision of the assays suggest that the trends were systematic and the data sound. The trends in HOMA-IR and HOMA-B are unknown in up to one-third of children with undetectable insulin. However, the trends were the same among those with measurable insulin at each age, among children grouped by BMI tertile (data not shown), and in the group as a whole. It is unlikely that inclusion of insulin values <2.0 mU/l, had they been known, would have had any significant impact on the trends observed.

Puberty is a period of increasing insulin resistance (9,10) and, indeed, the fall in insulin resistance observed from ages 5 to 7 years appears to level off by age 8 years. The next 3 years will establish at what point it rises again and whether the heaviest children are compromised the most. The importance of our findings, which were only revealed by longitudinal study, lies with the apparent conundrum of falling insulin resistance and improving metabolic health, despite increasing adiposity. Intervention studies may be needed to resolve this paradox.

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