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Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals

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Abstract

Aims/hypothesis. A study of 7086 men and women born in Helsinki, Finland, has shown that the development of Type II (non-insulin-dependent) diabetes mellitus is associated with low birth weight followed by accelerated gain in height and weight during childhood and with high maternal BMI but the processes which underlie these associations are largely not known.
Methods. We carried out standard oral glucose tolerance tests, and measured plasma insulin and proinsulin, serum lipid concentrations and blood pressure in 474 patients from the Helsinki cohort.
Results. We used four indices of insulin resistance: fasting and 2-h plasma insulin, and fasting proinsulin and 32–33 split proinsulin concentrations. These were associated with small body size at birth and during childhood, rapid growth in height and low maternal BMI.
Conclusion/interpretation. Insulin resistance and Type II diabetes share common associations with retarded fetal growth and accelerated growth during childhood. They are dissimilar, however, in that insulin resistance is associated with thinness in childhood and low maternal BMI, while Type II diabetes is associated with high BMI in childhood and high maternal BMI. [Diabetologia (2002) 45: 342–348]

Keywords Fetal growth, childhood growth, maternal weight, insulin resistance, Type II diabetes.

Men and women who had low birth weight as a result of slow fetal growth have increased rates of glucose intolerance in adult life [1–4]. This has led to the hypothesis that Type II (non-insulin-dependent) diabetes mellitus originates through adaptations which the fetus makes when it is undernourished. These adaptations, which include reduced rates of growth, permanently change the structure, physiology and metabolism of the body [5, 6]. People who had low birth weight also have increased rates of the insulin resistance syndrome, in which hyperinsulinaemia and impaired glucose tolerance are associated with raised blood pressure, dyslipidaemia and central obesity [7, 8]. Insulin plays a central role in the regulation of fetal growth and one of the fetus's adaptations to undernutrition is to alter its insulin and glucose metabolism. Both insulin resistance and insulin deficiency are found in subjects with Type II diabetes and both could be initiated in utero.

We have previously reported on 471 patients with Type II diabetes within a cohort of 7086 men and women who were born in Helsinki, Finland, during 1924–1933 and whose body size at birth and growth during school years – from 7 to 15 years of age – was recorded [4]. As expected the incidence of Type II diabetes was higher in those who had low birth weight and short body length at birth. By 7 years of age, however, the mean heights and weights of the children who later developed Type II diabetes were around the average for all the children. Thereafter

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Table 1. Maternal, neonatal, childhood and characteristics at an elderly age of men and women in the study sample

		Means (SD)	
		Men (n = 176)	Women (n = 298)
Mothers	Height (cm)	158.5 (5.4)	158.4 (5.3)
	Weight (kg) in pregnancy	66.9 (7.7)	67.1 (9.5)
	BMI (kg/m^2)	26.6 (2.9)	26.7 (3.4)
Neonatal	Birth weight (g)	3452 (447)	3297 (456)
	Crown to heel length (cm)	50.3 (1.7)	49.7 (1.8)
	Ponderal index (kg/m^3)	27.1 (2.4)	26.8 (2.2)
Childhood 7 years	Height (cm)	120.4 (4.5)	118.9 (4.8)
	Weight (kg)	22.4 (2.4)	21.7 (2.9)
	BMI (kg/m^2)	15.4 (1.0)	15.3 (1.3)
Adult/elderly age	Height (cm)	174.4 (5.7)	160.3 (5.6)
	Weight (kg)	82.4 (12.5)	70.9 (12.1)
	BMI (kg/m^2)	27.1 (3.8)	27.6 (4.5)
	Age (years)	69.5 (3.0)	69.6 (2.7)

they continued to gain in height and weight rapidly. We examined a sample of 474 men and women from the cohort to determine whether components of the insulin resistance syndrome form the link between small size at birth, accelerated childhood growth and the development of impaired glucose tolerance and Type II diabetes in adult life.

Subjects and methods

The cohort of 7086 men and women born as singletons has been described [4]. They were born at Helsinki University Central Hospital during 1924–1933 and went to school in the city. Details of their birth and school health records have also been described previously [9,10]. The school records include a mean of 10 (SD 4) measurements of height and weight of each child between 6 and 16 years of age.

A total of 674 people from the original study cohort, who were known to be living in the greater Helsinki area, were invited to attend a clinic in the morning after an overnight fast. Altogether 500 of them (74 per cent) did so. Of these, 26 were on medication for Type II diabetes and were excluded from the study because their medication could have altered their plasma glucose and insulin concentrations. An OGTT (75 g glucose) was done. Plasma glucose and insulin concentrations were measured at 0 min, 30 min and 120 min. Plasma glucose was measured by the hexokinase method and plasma insulin, proinsulin and 32–33 split proinsulin concentrations were determined by two-site immunometric assay [11, 12]. We defined Type II diabetes on the basis of fasting and 120-min plasma glucose concentrations, using the 1985 WHO criteria. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride concentrations were measured using standard enzymatic methods [13–15]. Low-density lipoprotein cholesterol concentrations were derived by the Freidwald formula [16]. The patients' height was measured using a Kawi stadiometer; weight was measured on a Seca alpha 770 scale. Waist and hip circumferences were measured using a soft tape according to standard practice. Blood pressure was measured from the right arm in the sitting position and was recorded as the mean of two successive readings using a standard sphygmomanometer.

We used fasting and 2-h plasma insulin, and fasting proinsulin and 32–33 split proinsulin concentrations, as indices of insulin resistance. These correlate strongly with insulin resistance as assessed by the glucose response to intravenous injection of insulin [17]. The acute insulin response to glucose was calculated as the difference between 30 min plasma insulin and fasting plasma insulin.

Statistical methods. Data were analysed by tabulation of means and multiple linear regression. Significance refers to analyses of continuous variables by regression. Plasma glucose, insulin, proinsulin, triglyceride and HDL cholesterol concentrations had skewed distributions and were therefore log-transformed for analysis. We adjusted blood pressure, plasma glucose, insulin, proinsulin and lipid concentrations for age, sex and BMI using linear regression. Z-scores for height, weight and BMI were calculated for the whole cohort of 7086 men and women, as previously described [9, 10].

Results

The maternal, neonatal, childhood and characteristics at an elderly age of the 176 men and 298 women are shown in Table 1. There were 76 subjects with undiagnosed or diet-treated Type II diabetes and 141 with impaired glucose tolerance. Their characteristics are shown in Table 2. Those with Type II diabetes had the highest mean current body mass indices, and the highest waist-to-hip ratios after adjusting for age, sex and BMI. In comparison with normoglycaemic subjects they had high 2-h plasma insulin and fasting proinsulin and 32–33 proinsulin concentrations. These indices of insulin resistance were strongly and positively related to BMI and waist-to-hip ratio.

Size at birth. We examined the associations between body size at birth and components of the insulin resistance syndrome. Because plasma glucose, insulin, triglyceride and cholesterol concentrations and blood pressure rose with increasing BMI, we adjusted for

Table 2. Characteristics of men and women according to their glucose tolerance

	Normal (n = 257)	Impaired glucose tolerance (n = 141)	Undiagnosed or diet-treated Type II diabetes (n = 76)
Women n (%)	167 (65)	90 (64)	41 (54)
Birth weight (g)	3351	3378	3322
BMI (kg/m^2)[a]	26.4	28.3	29.1
Waist-to-hip ratio (%)[b]	88.5	89.2	91.3
Fasting glucose (mmol/l)	5.3	5.4	6.6
2-h glucose (mmol/l)	6.1	8.9	13.0
Fasting insulin (pmol/l)	64	65	79
2-h plasma insulin (pmol/l)[c b]	406	638	631
Fasting proinsulin (pmol/l)[c b]	2.9	2.8	3.9
Fasting 32–33 split proinsulin (pmol/l)[a, b]	7.2	8.2	10.6
Maternal BMI (kg/m^2)	26.8	26.4	26.3

[a] Values adjusted for age and sex
[b] Values are adjusted for age, sex and BMI
[c] Values are geometric means

Table 3. Mean values of components of the insulin resistance syndrome, according to BMI at 7 years of age

	BMI (kg/m^2) at 7 years						
	< 14.3	- 14.9	- 15.5	- 16.2	> 17.5	All	p
Patients (n)	98	89	96	91	100	474	
Fasting glucose (mmol/l)[a]	5.6	5.5	5.5	5.5	5.4	5.5	0.06
2-hour glucose (mmol/l)[a]	7.8	7.7	7.6	7.5	7.7	7.7	0.29
Fasting insulin (pmol/l)[a]	69	73	62	68	63	67	0.21
2-hour insulin (pmol/l)[a]	550	590	433	485	457	498	0.005
Acute insulin response (pmol/l)	484	487	445	481	473	474	0.922
Fasting proinsulin (pmol/l)[a]	3.3	3.4	2.7	3.1	2.7	3.0	0.01
Fasting 32–33 split proinsulin (pmol/l)[a]	8.6	8.7	7.3	7.6	7.7	8.0	0.12
Triglyceride (mmol/l)[a]	1.31	1.45	1.22	1.30	1.25	1.30	0.22
LDL cholesterol (mmol/l)	3.8	3.9	3.8	3.9	3.8	3.8	0.95
HDL cholesterol (mmol/l)[a]	1.43	1.40	1.47	1.42	1.45	1.43	0.97
Systolic pressure (mmHg)	162	159	159	158	154	158	0.005
Diastolic pressure (mmHg)	90	91	89	89	86	89	0.002

Values adjusted for age, sex and adult BMI
[a]Values are geometric means
p values are given for trends for each component of the metabolic syndrome

age, sex and BMI in all analyses. We found that 2-h plasma insulin and fasting proinsulin concentrations fell with increasing birth weight (p for trend = 0.02 and 0.03, respectively). There were similar trends with serum HDL-cholesterol concentrations (p = 0.06) and systolic blood pressure (p = 0.08). We also examined the trends with other indices of body size at birth. The 2-h plasma insulin concentrations also fell with increasing ponderal index (p = 0.03), while serum HDL-cholesterol concentrations rose (p = 0.07). Systolic blood pressure was related to short length at birth (p = 0.04). Birth weight was positively related to BMI (p = 0.03) but not to the waist-to-hip ratio, in adult life.

Growth in childhood. At each age from 7 to 15 years, a lower BMI was associated with higher 2-h plasma insulin, raised fasting proinsulin concentrations and raised systolic and diastolic blood pressure. Table 3 shows these associations for BMI at 7 years of age, the youngest age for which there are data. These associations were little changed by adjusting for birth weight or ponderal index at birth. At all ages BMI in childhood correlated with current BMI (correlation coefficient = 0.28, $p < 0.0001$ at age 7 years), but there were no correlations with the waist-to-hip ratio.

We also examined associations with rates of childhood growth. Table 4 shows the associations with rates of growth in height, expressed as change in standard deviation scores between 7 and 15 years of age. Rapid gain in height was associated with raised values of the four indices of insulin resistance, fasting and 2-h plasma insulin and fasting proinsulin and 32–33 split proinsulin concentrations. Rapid height gain was also associated with reduced serum HDL-cholesterol concentrations. Trends with the rate of change in weight were similar, though weaker, and only the trend with 32–33 split proinsulin concentrations was statistically significant (p = 0.04). There were no trends with rate of change in BMI.

Table 4. Mean values of components of the insulin resistance syndrome, according to change in standard deviation score for height between 7 and 15 years

	Change in standard deviation scores for height						
	> 0.17 fall	0.17 fall to 0.06 rise	0.06 to 0.31 rise	0.31 to 0.63 rise	> 0.63 rise	All	*p*
Patients (*n*)	94	95	95	95	95	474	
Fasting glucose (mmol/l)[a]	5.5	5.4	5.5	5.7	5.6	5.5	0.19
2-h glucose (mmol/l)[a]	7.7	7.4	7.8	7.6	7.7	7.7	0.80
Fasting insulin (pmol/l)[a]	61	71	62	69	72	67	0.04
2-h insulin (pmol/l)[a]	442	517	516	519	501	498	0.05
Acute insulin response (pmol/l)	445	455	471	518	479	474	0.28
Fasting proinsulin (pmol/l)[a]	2.8	2.9	2.6	3.6	3.3	3.0	0.04
Fasting 32–33 split proinsulin (pmol/l)[a]	6.9	7.6	7.1	10.2	8.6	8.0	0.001
Triglyceride (mmol/l)[a]	1.29	1.28	1.32	1.30	1.32	1.30	0.32
LDL cholesterol (mmol/l)[a]	3.8	4.0	3.9	3.8	3.8	3.8	0.34
HDL cholesterol (mmol/l)[a]	1.49	1.47	1.42	1.37	1.43	1.43	0.04
Systolic pressure (mmHg)	159	160	159	157	157	158	0.43
Diastolic pressure (mmHg)	88	90	89	89	88	89	0.75

Values are adjusted for age, sex and adult BMI
[a]Values are geometric means
p values are given for trends for each component of the metabolic syndrome

Table 5. Mean 2-h plasma insulin and serum HDL cholesterol concentrations according to BMI at 7 years of age and current BMI

BMI at 7 years (kg/m^2)	Current BMI (kg/m^2)			
	- 25.5	- 28.8	> 28.8	All
	2-h plasma insulin (pmol/l[a])			
- 14.7	458 (74)	502 (55)	678 (27)	506 (156)
- 15.7	415 (47)	483 (55)	558 (51)	484 (153)
> 15.7	313 (38)	525 (52)	640 (68)	505 (158)
All	406 (159)	503 (162)	617 (146)	498 (467)
	Fasting serum HDL cholesterol (mmol/l[a])			
- 14.7	1.53 (75)	1.44 (56)	1.39 (27)	1.47 (158)
- 15.7	1.50 (48)	1.47 (55)	1.34 (54)	1.43 (157)
> 15.7	1.73 (38)	1.44 (53)	1.23 (68)	1.41 (159)
All	1.56 (161)	1.45 (164)	1.30 (149)	1.43 (474)

Figures in parentheses are numbers of subjects
[a]Values are geometric means, adjusted for age and sex

We examined interactive effects between BMI in childhood and current BMI. There was an interaction on 2-h plasma insulin concentrations (p for interaction = 0.04 at age 7 years). Table 5 shows this interaction with the patients divided by tertiles of BMI at 7 years of age and tertiles of current BMI. The highest concentrations of 2-h plasma insulin were in people who had a low childhood BMI, but a high current BMI. Conversely the lowest concentrations were in those with a high childhood BMI but a low current BMI. Although serum HDL cholesterol concentrations were not related to childhood BMI (Table 3), there was nevertheless a strong interactive effect on serum HDL between childhood and adult BMI (p for interaction = 0.001 at age 7 years). This was similar, though inverse, to the effect on 2-h plasma insulin concentrations (Table 5), so that the highest serum HDL cholesterol concentrations were in people who had a high childhood BMI but a low current BMI.

Maternal BMI. Table 6 shows that 2-h plasma glucose, fasting and 2-h plasma insulin, and fasting proinsulin and 32–33 proinsulin concentrations fell with increasing mother's BMI in late pregnancy. The mother's BMI was not related to lipid concentrations or blood pressure. The mother's BMI was positively associated with ponderal index at birth (correlation coefficient = 0.17) and BMI in childhood (r = 0.29 at 7 years). In simultaneous regressions with ponderal index at birth, BMI at 7 years and change in standard deviation score for height, maternal BMI continued to show associations with fasting plasma insulin (p = 0.02), 2-h plasma insulin (p = 0.003), and fasting proinsulin concentrations (0.009) but not with 32–33 split proinsulin. We found no interaction between the effects of a mother's BMI and current BMI. The mother's BMI was related to current BMI (correlation coefficient = 0.20, $p < 0.0001$), but was not correlated with the waist-to-hip ratio.

Table 6. Mean values of components of the insulin resistance syndrome, according to maternal BMI in late pregnancy

	Maternal BMI (kg/m^2)						
	< 24	- 25.5	–27	–29	> 29	All	*p*
Patients (*n*)	87	87	86	90	86	436	
Fasting glucose (mmol/l)[a]	5.5	5.5	5.6	5.5	5.5	5.5	0.44
2-h glucose (mmol/l)[a]	7.9	7.7	8.5	7.0	7.2	7.7	0.007
Fasting insulin (pmol/l)[a]	77	70	67	59	62	67	0.01
2-h insulin (pmol/l)[a]	577	546	516	469	405	499	< 0.001
Acute insulin response (pmol/l)	506	526	409	477	453	474	0.04
Fasting proinsulin (pmol/l)[a]	3.4	3.5	3.0	2.7	2.5	3.0	0.001
Fasting 32–33 split proinsulin (pmol/l)[a]	8.5	8.7	7.6	7.8	7.2	7.9	0.08
Triglyceride (mmol/l)[a]	1.31	1.35	1.33	1.27	1.20	1.29	0.20
LDL cholesterol (mmol/l)	4.0	3.8	3.9	3.8	3.8	3.9	0.91
HDL cholesterol (mmol/l)[a]	1.42	1.39	1.51	1.44	1.42	1.44	0.67
Systolic pressure (mmHg)	158	161	159	156	160	159	0.57
Diastolic pressure (mmHg)	90	88	90	87	90	89	0.95

p values are given for trends for each component of the metabolic syndrome

Values are adjusted for age, sex and adult BMI

[a]Values are geometric means

Discussion

We examined 474 men and women around 69 years of age who belonged to a cohort of 7086 people born in Helsinki during 1924–1933. In this cohort, those receiving medication for Type II diabetes had low birth weight, with either short body length or thinness at birth, followed by accelerated height and weight gain in childhood [4]. Their mothers had a high BMI in pregnancy. We examined the associations between early growth and four indices of insulin resistance – fasting and 2-h plasma insulin and fasting proinsulin and 32–33 split proinsulin concentrations. Applying these criteria, and after allowing for current BMI, insulin resistance was associated with thinness at birth, with continued thinness in childhood but rapid growth in height and with low maternal BMI in pregnancy. Therefore, although insulin resistance and Type II diabetes are both associated with small body size at birth and obesity in adult life, insulin resistance does not seem to be the process which links high maternal body mass with increased risk of Type II diabetes.

Our results could be influenced by a preferential survival of patients with particular glucose-insulin profiles. Although 74 % of people invited to take part did so our sample is not representative of the cohort. Altogether 63 % of the participants were women, which must in part reflect their longer life expectancy. Our findings, however, are based on internal comparisons within the sample and we do not think it is likely that the differences in the growth of subjects who developed Type II diabetes or insulin resistance can be attributed to selection bias.

The associations between indices of insulin resistance, serum HDL-cholesterol concentrations, and low birth weight and thinness at birth have been found before [1, 2, 6, 7, 18]. Babies that are thin at birth lack muscle, a deficiency which will persist as the critical period for muscle growth is around 30 weeks in utero and there is little cell replication after birth [19]. It has been suggested that altered sensitivity of muscle to insulin could underlie the association between low ponderal index at birth and insulin resistance in adult life [5, 6].

We found that indices of insulin resistance were associated with low BMI in childhood, after current body mass had been taken into account. This has not been shown before. A possible explanation for this is that a low childhood BMI reflects a low lean body mass, which persists into adult life so that at any current BMI there will be a raised ratio of fat to lean body mass. In this cohort of children, growing up in Finland during and after the Second World War, obesity was rare and a higher BMI would probably have indicated muscularity rather than excess body fat. We found that BMI in childhood modulated the effects of current BMI on 2-h plasma insulin concentrations so that the highest concentrations were among patients who had had a low childhood BMI but had a high current BMI. Childhood BMI and current BMI also had interactive effects on serum HDL cholesterol concentrations.

We found that rapid growth in height when patients were between 7 and 15 years of age was associated with all four indices of insulin resistance. The 32–33 split proinsulin concentrations were also associated with a rapid gain in weight. We have previously speculated that rapid growth following small size at birth might lead to Type II diabetes because it leads to excessive metabolic demand on a limited pancreatic beta-cell mass. Findings in this study, however, are more consistent with the hypothesis that insulin resistance is the result of over-activation of the IGF-system in association with accelerated post-natal growth [20].

We have confirmed that a low maternal BMI in late pregnancy is associated with insulin resistance in

offspring. Studies in Scotland, Holland and China have shown similar findings [8, 21, 22]. The study in China included the mother's BMI in both early and late pregnancy. The indices of insulin resistance were associated with both, and it could be that the association between low maternal BMI and insulin resistance in the offspring is established in early pregnancy. We found that the association was independent of the offspring's body size at birth and BMI in childhood. We do not know what aspect of maternal metabolism is associated with low BMI and leads to insulin resistance, low protein turnover is one possibility [23].

Consistent with the role of insulin resistance in determining Type II diabetes, these two conditions have similar associations in our study: low birth weight, rapid childhood growth and obesity in adult life. Type II diabetes is also associated with high maternal BMI which was not related to insulin resistance. It could, however, be related to insulin deficiency, as a consequence of impaired pancreatic beta-cell function. High maternal BMI is associated with maternal hyperglycaemia. Experiments in rats have shown that this is associated with beta-cell exhaustion and low insulin concentrations in the fetus [24]. In humans, two studies in Scotland and India found evidence that higher BMI or adiposity in the mother is associated with a low insulin increment, a crude marker of insulin deficiency in the offspring, though the associations were weak [25, 26].

Consistent with many previous studies, we found that low birth weight and short body length at birth were associated with raised blood pressure [27]. We have already shown that, in this cohort, hypertension requiring medication is associated with low birth weight and short length at birth [28]. The strong associations we found between both adult systolic and diastolic blood pressure and low BMI in childhood have not been shown before and seem to conflict with the known association between high BMI and high blood pressure measured in childhood.

In conclusion, the development of insulin resistance is associated with maternal thinness, low birth weight and thinness at birth, thinness in childhood, rapid growth in height in childhood and obesity in adult life. The development of Type II diabetes is similarly associated with low birth weight, rapid growth in weight and height in childhood and obesity in adult life as well as with high maternal body mass. This pattern of growth could be linked to the development of both insulin resistance and insulin deficiency.

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