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Thinness at birth and insulin resistance in adult life

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Summary Type 2 (non-insulin-dependent) diabetes mellitus may originate through impaired development in fetal life. Both insulin deficiency and resistance to the action of insulin are thought to be important in its pathogenesis. Although there is evidence that impaired fetal development may result in insulin deficiency, it is not known whether insulin resistance could also be a consequence of reduced early growth. Insulin resistance was therefore measured in 81 normoglycaemic subjects, and 22 subjects with impaired glucose tolerance, who were born in Preston, UK, between 1935 and 1943. Their birth measurements had been recorded in detail. Insulin resistance was measured by the insulin tolerance test which uses the rate of fall in blood glucose concentrations after intravenous injection of insulin as an index of insulin resistance. Men and women who were thin at birth, as measured by a low ponderal index, were more insulin resistant. The association was statistically significant ($p = 0.01$) and independent of duration of gestation, adult body mass index and waist to hip ratio and of confounding variables including social class at birth or currently. Thinness at birth and in adult life has opposing effects such that resistance fell with increasing ponderal index at birth but rose with increasing adult body mass index. It is concluded that insulin resistance is associated with impaired development in fetal life. [Diabetologia (1994) 37: 150–154]

Key words Type 2 (non-insulin-dependent) diabetes mellitus, insulin resistance, fetal growth, metabolic programming.

There is accumulating evidence that impaired development in utero and during infancy appears to be one of the factors which causes Type 2 (non-insulin-dependent) diabetes [1–4]. In a study of men aged 59 to 70 years, in Hertfordshire, UK, those who had lower birthweights and weights at one year had a higher prevalence of Type 2 diabetes and impaired glucose tolerance [1]. A subsequent study in 50-year-old men and women in Preston, UK, confirmed the association and showed that it depended on babies who were small in relation to their gestational age rather than babies who were born prematurely [2]. The association has also been demonstrated in young adults [3, 4].

Both deficiency of insulin and resistance to its action are thought to play a role in the pathogenesis of Type 2 diabetes [5, 6]. There is an obvious link between reduced early growth and subsequent insulin deficiency. Much of the development of the pancreatic islet cells occurs in utero and babies with intra-uterine growth retardation have marked reductions in size of the endocrine pancreas and in plasma insulin concentrations [7, 8] and evidence of reduced beta-cell function in adult life [9]. There is no known link between reduced early growth and the development of insulin resistance. The processes which underlie insulin resistance at tissue and cellular level are unknown. The main influences known to be associated with it are obesity and physical inactivity in adult life [10, 11]. A link with reduced fetal growth is suggested, however, by the association between low birthweight and the development of so-

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called syndrome X, [4, 12] the co-existence of impaired glucose tolerance, hypertension and high serum triglyceride concentrations [13]. People with this disorder are insulin resistant.

Insulin action can be directly measured by the fall in plasma glucose concentrations after intravenous injection of insulin [14]. We have used this to examine the association between body size at birth and insulin resistance in a sample of the men and women who took part in the Preston study [2].

Subjects and methods

From 1932 a standardised record was kept for each woman admitted to the labour ward at Sharoe Green Hospital, Preston, Lancashire. The record included the baby's birthweight, placental weight, length from crown to heel, and head circumference. Weights were measured in pounds (1 pound = 0.45 kg) and lengths and head circumferences in inches (1 inch = 2.54 cm) and were often rounded. The records also included the date of the mothers' last menstrual period which we used to estimate the duration of gestation. As previously described we used the National Health Service central register to trace 393 of the singleton infants born in Sharoe Green Hospital, Preston during 1935–1943 who still live in or close to the city [2]. After six people previously diagnosed as having diabetes were excluded the remainder were asked to have a full 75-g oral glucose tolerance test. Of these 266 (69%) agreed to do so. Normoglycaemia, established by a 2-h plasma glucose concentration below 7.8 mmol/l was found in 232. Impaired glucose tolerance was found in 29 with a 2-h plasma glucose concentration of 7.8 to 11.1 mmol/l. Type 2 diabetes was established in 5 subjects, with a 2-h plasma glucose concentration of 11.1 mmol/l and over.

Because Type 2 diabetes and impaired glucose tolerance were not only associated with low birthweight but with low birthweight in relation to placental weight, which is thought to be a marker of fetal malnutrition [2], we selected our sample after stratifying for both birth and placental weights. From the 232 normoglycaemic men and women we selected a sample whose birthweights and placental weights were spread over the range for these two variables. The sample was randomly chosen from the three birthweight groups (≤ 2.9, –3.4 and > 3.4 kg) and the four placental weight groups (≤ 0.45, –0.6, –0.7, > 0.7 kg) used in our previous analyses [15]. Four men and four women were selected from each of the 12 birthweight and placental weight groups and asked to take part in insulin tolerance tests, of whom 23 subjects declined to do so. Where possible we replaced them with other people of the same sex from the same birthweight and placental weight groups. There were insufficient numbers in some groups and four of the subjects were found to be unsuitable for the insulin tolerance test because they had been diagnosed as having ischaemic heart disease or epilepsy. The final sample comprised 81 subjects. We also asked all of the 29 men and women found to have impaired glucose tolerance to take part in the study, of whom 23 agreed to do so. One was unsuitable for the insulin tolerance test because he had ischaemic heart disease, leaving 22.

At the clinic the subjects' height was measured with a portable stadiometer (CMS Weighing Equipment Ltd, Camden, London, UK). Weight was measured with a SECA scale (SECA Ltd, Birmingham, UK) and waist and hip circumferences with a steel tape measure. Blood pressure was measured with an automated recorder (Dinamap Model 1846SX; Critikon, Tampa, Fla., USA) in seated subjects with a cuff of appropriate size placed on the left arm as previously described [15]. Two readings were taken and the average used in the analysis. Subjects were also asked about their smoking and drinking habits. Alcohol consumption was converted into the total number of units each week (1 unit = 10 g ethanol). Occupation of the father was used to define social class at birth, and current social class was derived from the subject's or husband's occupation. Ethical approval for the study was obtained from the Preston District Hospital Ethics Committee and each participating subject gave informed consent.

The insulin tolerance tests were carried out between 08.30 and 11.00 hours. Subjects had fasted for 12 h overnight and had been asked to abstain from alcohol and not to smoke during the fasting period. A bolus of Human Actrapid insulin (Novo Laboratories, Basingstoke, UK) 0.05 IU/kg was injected into an antecubital vein and venous blood sampled through a retrogradely placed cannula from the dorsum of the hand on the same arm. In order to dilate the arterioles of the hand, and hence 'arterialise' the venous blood, the hand was placed in a water bath held at a constant temperature of 43 °C for 20 min before insulin injection and kept there until the end of the study [16]. Venous blood sampling was carried out 0, 3, 5, 7, 9, 11, 13, and 15 min after the insulin injection. The test was terminated by the injection of glucose. The blood samples were kept on ice and analysed for whole blood glucose with a Yellow Springs analyser (YSI, Yellow Springs, Ohio, USA).

Statistical analysis

Insulin resistance was measured by the half-life of blood glucose concentrations as estimated from the slope of the fall on a log scale from 3 to 15 min, the interval in which the decline in blood glucose was observed [17]. Because the measurements of resistance had a skewed distribution, we transformed them to normality by using reciprocals. In a pilot study repeat tests carried out on 18 normal subjects gave a within-subject coefficient of variation (CV) of 13% for the rate constant [18]. The interassay CV of the Yellow Springs analyser was 4.0% at 4.2 mmol/l.

Results

The 81 normoglycaemic subjects, 41 men and 40 women, were aged 47 to 55 (mean 52) years. They had a mean body mass index of 26.1 kg/m^2, a mean birthweight of 3.2 kg and a mean placental weight of 0.6 kg. The 22 subjects with impaired glucose tolerance, 12 men and 10 women, were of a similar age (range 47 to 56, mean 52 years). They had higher mean body mass index, 27.7 kg/m^2, lower mean birthweight, 2.9 kg, but similar mean placental weight, 0.6 kg.

The mean fasting blood glucose level in the normoglycaemic subjects was 4.7 mmol/l and in the glucose intolerant subjects 4.9 mmol/l. During the insulin tolerance test blood glucose levels fell to 2.9 (range 1.9 to 4.6) mmol/l in the normoglycaemic subjects and to 3.3 (range 2.3 to 5.1) mmol/l in the glucose intolerant subjects. The half-life ($t^1/_2$) of the fall in blood glucose ranged from 9.9 min in the least resistant subject to 46.6 min in the most resistant. The 22 subjects with impaired glucose tolerance were more resistant (mean $t^1/_2$ 21.2 min) than the 81 normoglycaemic subjects

Table 1. Mean insulin resistance ($t^1/_2$ min) in men and women aged 47–56 years according to body mass index, waist to hip ratio, age and systolic blood pressure

Body mass index (kg/m^2)			*p* value for trend
≤24	15.6	(36)	
–26	17.7	(27)	
–28	19.5	(16)	
>28	22.6	(24)	<0.001
Waist to hip ratio			
≤0.82	15.7	(31)	
–0.89	16.9	(25)	
–0.94	18.9	(23)	
>0.94	23.4	(24)	<0.001
Age (years)			
≤51	16.6	(32)	
–53	18.1	(32)	
>53	19.4	(39)	0.04
Systolic pressure (mm Hg)			
≤130	15.3	(18)	
–140	16.1	(21)	
–150	18.7	(18)	
–160	20.9	(22)	
>160	19.7	(24)	<0.001
Total	18.0	(103)	SD = 6.3

Numbers of subjects in parentheses

(mean $t^1/_2$ 17.3 min, $t = 2.58$, $p = 0.01$). Men were also significantly more resistant (mean $t^1/_2$ 19.9 min) than women (mean $t^1/_2$ 16.4 min, $t = 3.22$, $p = 0.002$). The differences between men and women and between normoglycaemic subjects and subjects with impaired glucose tolerance remained statistically significant after adjustment for current body mass index and/or gender.

Table 1 shows insulin resistance according to measurements in adults. In this and subsequent analyses the findings were similar in the normoglycaemic subjects and those with impaired glucose tolerance. We therefore combined the data for both groups. Resistance was greater in people with higher body mass ($p < 0.001$) and with increasing age ($p = 0.04$); the trends were present in both sexes. Insulin resistance also correlated with systolic blood pressure. Because systolic blood pressure rose with age, body mass index and waist to hip ratio and was higher in men than women, we adjusted for these variables by means of a multiple regression. Subjects with a higher systolic pressure were more insulin resistant ($p = 0.02$). Findings for diastolic pressure were not significant ($p = 0.08$). Insulin resistance was not, however, associated with social class, either at birth, or currently, or with smoking or alcohol consumption.

Table 2 shows the mean values of insulin resistance according to measurements of body size at birth. In Table 2 we have used the same divisions of birth measurements as in previous analyses of data from Preston

Table 2. Mean insulin resistance ($t^1/_2$ min) according to measurements of body size at birth and duration of gestation

Birthweight (kg)			*p* value for trend
≤2.9	19.2	(36)	
–3.4	17.8	(34)	
>3.4	17.1	(33)	0.13
Head circumference (cm)			
≤33.7	19.6	(29)	
–34.9	16.3	(21)	
–35.6	18.0	(33)	
>35.6	18.0	(20)	0.60
Length (cm)			
<50.8	19.5	(21)	
50.8	17.2	(43)	
–53.3	19.0	(19)	
>53.3	17.7	(20)	0.98
Ponderal index (kg/m^3)			
≤20.6	20.6	(26)	
–22.3	17.3	(37)	
–25.0	17.9	(23)	
>25.0	16.6	(17)	0.01
Length of gestation (weeks)			
≤38	18.7	(19)	
39	16.1	(15)	
40	17.6	(19)	
41	18.7	(22)	
≥42	17.4	(10)	
Not known	19.3	(18)	0.61
Placental weight (kg)			
≤0.45	16.7	(23)	
–0.6	19.8	(31)	
–0.7	17.5	(26)	
>0.7	17.9	(23)	0.98
Total	18.0	(103)	SD = 6.3

Numbers of subjects in parentheses

[15, 19]. Duration of gestation was not recorded for 18 subjects. Men and women who had lower birthweight were more insulin resistant, though the trend was not statistically significant ($p = 0.13$). Insulin resistance was not related to head circumference, length, gestational age, placental weight or to the ratio of placental weight to birthweight ($p = 0.30$). Nor was it related to the ratio of head circumference to length ($p = 0.54$), which we have previously used to define babies who were disproportionately short [19]. Insulin resistance was greater, however, in subjects who were thin at birth, defined by a low ponderal index (birthweight/length^3) at birth. This trend was statistically significant ($p = 0.01$). In a simultaneous regression of insulin resistance against placental weight, head circumference and gestational age the association with ponderal index remained strongly statistically significant ($p = 0.009$). There were, however, no statistically significant relationships between ponderal index at birth and sex, adult body mass index or waist to hip ratio.

Table 3. Mean insulin resistance according to ponderal index at birth and adult body mass index

Ponderal index (kg/m^3)	Body mass index (kg/m^2)				
	≤24.0	−26.0	−28.0	>28.0	All
≤20.6	17.9 (8)	18.0 (8)	23.1 (4)	30.7 (6)	20.6 (26)
−22.3	15.8 (16)	17.3 (11)	17.8 (6)	27.1 (4)	17.3 (37)
−25.0	14.4 (8)	20.7 (4)	21.0 (3)	20.4 (8)	17.9 (23)
>25.0	14.1 (4)	16.1 (4)	17.8 (3)	18.5 (6)	16.6 (17)
All	15.6 (36)	17.7 (27)	19.5 (16)	22.6 (24)	18.0 (103)

Numbers of subjects in parentheses

We used multiple regression to analyse the simultaneous relations of ponderal index, systolic blood pressure, body mass index, waist to hip ratio and age with insulin resistance. The effect of ponderal index remained statistically significant ($p = 0.007$) as did systolic blood pressure ($p = 0.007$), body mass index ($p < 0.001$) and waist to hip ratio ($p < 0.04$) but not age ($p = 0.85$). In separate regressions by sex the effect of ponderal index was seen in both men ($p = 0.08$) and women ($p = 0.02$).

Table 3 shows insulin resistance according to ponderal index at birth and current body mass index. At each body mass resistance fell between subjects with low and high ponderal index. At each ponderal index resistance was greater in people with high body mass. The highest mean resistance, 30.7 min, was in subjects with a ponderal index of 20.6 kg/m^3 or less and a current body mass index of more than 28 kg/m^2. The lowest mean resistance, 14.1 min, was in subjects with a ponderal index of more than 25.0 kg/m^3 and a current body mass index of 24 kg/m^2 or less.

Discussion

We have studied insulin resistance in men and women aged around 50 years whose body size at birth had been measured in detail. Our measure of insulin resistance was based on the fall in blood glucose concentration following intravenous insulin injection. Epidemiological studies of insulin resistance are usually based on fasting insulin concentrations, which are a weak measure of resistance. In both sexes those who had been thin at birth, as indicated by a low ponderal index, were resistant to insulin. The association was statistically significant and independent of length of gestation, of current body mass index and waist to hip ratio, and of potential confounding variables including social class at birth or currently. Being thin at birth and being thin as an adult had opposing effects on insulin resistance. People who were thin at birth but obese as adults were the most resistant to insulin.

The short insulin tolerance test which we used is a modification of the test used by Bonora et al. [14]. It measures insulin action by using the fall in plasma glucose concentrations over 15 min after intravenous insulin injection. Two studies have demonstrated that the results correlate well with estimates of insulin resistance obtained using a euglycaemic clamp, widely accepted as the reference method [14, 20]. Within this time interval there is no evidence of a counterregulatory response [14]. We have also demonstrated that the test has adequate reproducibility [18]. Consistent with findings in many other studies, we found that insulin resistance was associated with high body mass index, high waist to hip ratio, increasing age and high systolic blood pressure [13, 21–24].

The 103 men and women in our study were born in hospital and still live in Preston, and are therefore unrepresentative of all men and women born in the town. As our analysis was based on internal comparisons the selection of the sample would introduce bias only if the relationship between ponderal index at birth and insulin resistance in the adult was different in those selected and not selected, which is unlikely.

Thinness at birth is associated not only with later impaired glucose tolerance and insulin resistance but also with raised blood pressure [19, 25], and death from cardiovascular disease [26]. A survey of children aged 4 years, who were born in Salisbury, UK, showed that those who had a low ponderal index at birth had raised systolic and diastolic blood pressures [25]. A similar association was found among 50-year-old men and women in Preston [19]. A follow-up study of men born in a maternity hospital in Sheffield during 1907–1924 showed that those who had a low ponderal index or a small head circumference had raised death rates from cardiovascular disease [26]. Low ponderal index is thought to reflect impaired fetal growth in mid-gestation.

The processes which link thinness at birth with insulin resistance in adult life are not known. Studies of patients with Type 2 diabetes, using a euglycaemic clamp, have shown that peripheral tissues, particularly skeletal muscle, are an important site of insulin resistance [27]. Muscle biopsies have shown that insulin resistance is associated with a lower density of capillaries in muscle, a lesser proportion of Type 1 muscle fibres and a greater proportion of Type 2B fibres [28]. Transcapillary insulin transport is a rate-limiting step in insulin action [29]. Babies born at term with a low ponderal index have a reduced mid-arm circumference which implies that they have a low muscle bulk as well as less subcutaneous fat [30]. It is therefore possible that thinness in fetal life is associated with abnormalities in muscle structure and function that persist into adult life and interfere with the ability of insulin to promote glucose uptake.

Our findings suggest that thinness at birth and obesity in adult life are both independently associated with insulin resistance. People who were thin at birth and thereafter became obese were markedly resistant to insulin compared with those who were fat at birth but thin as adults. The prevalence of Type 2 diabetes in a population may therefore be related to the past prevalence of impaired fetal growth and the current prevalence of adult obesity [31].

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