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Fetal and infant growth and impaired glucose tolerance at age 64

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Abstract

Objective—To discover whether reduced fetal and infant growth is associated with non-insulin dependent diabetes and impaired glucose tolerance in adult life.

Design—Follow up study of men born during 1920-30 whose birth weights and weights at 1 year were known.

Setting—Hertfordshire, England.

Subjects—468 men born in east Hertfordshire and still living there.

Main outcome measures—Fasting plasma glucose, insulin, proinsulin, and 32-33 split proinsulin concentrations and plasma glucose and insulin concentrations 30 and 120 minutes after a 75 g glucose drink.

Results—93 men had impaired glucose tolerance or hitherto undiagnosed diabetes. They had had a lower mean birth weight and a lower weight at 1 year. The proportion of men with impaired glucose tolerance fell progressively from 26% (6/23) among those who had weighed 18 lb (8.16 kg) or less at 1 year to 13% (3/24) among those who had weighed 27 lb (12.25 kg) or more. Corresponding figures for diabetes were 17% (4/23) and nil (0/24). Plasma glucose concentrations at 30 and 120 minutes fell with increasing birth weight and weight at 1 year. Plasma 32-33 split proinsulin concentration fell with increasing weight at 1 year. All these trends were significant and independent of current body mass. Blood pressure was inversely related to birth weight and strongly related to plasma glucose and 32-33 split proinsulin concentrations.

Conclusions—Reduced growth in early life is strongly linked with impaired glucose tolerance and non-insulin dependent diabetes. Reduced early growth is also related to a raised plasma concentration of 32-33 split proinsulin, which is interpreted as a sign of β cell dysfunction. Reduced intrauterine growth is linked with high blood pressure, which may explain the association between hypertension and impaired glucose tolerance.

Introduction

Recent findings suggest that retardation of growth during fetal life and infancy is associated with increased death rates from cardiovascular disease in adult life.¹ Among 5654 men followed up from birth, those who had had the lowest weights at birth and at 1 year had the highest death rates from ischaemic heart disease as adults. That study was carried out in the county of Hertfordshire, where since 1911 all babies have been weighed at birth and in infancy. The findings pose the question of what processes link retarded fetal and infant growth with cardiovascular disease. Blood pressure may be one such link. In a study of men and women aged 50 higher blood pressure was strongly related to lower birth weight and higher placental weight.² Impaired glucose tolerance

may be another link as it is a known risk factor for ischaemic heart disease,³ and non-insulin dependent diabetes is associated with hypertension.⁴ We therefore examined a sample of the men born in Hertfordshire and measured their glucose tolerance.

There is controversy about the relative importance of insulin deficiency due to pancreatic β cell dysfunction and insulin resistance in the genesis of impaired glucose tolerance and non-insulin dependent diabetes. Recent advances in assay methodology make it possible to measure specifically plasma concentrations of insulin and its precursors, intact and 32-33 split proinsulin.⁵ People with non-insulin dependent diabetes have raised plasma concentrations of these precursors, which has been interpreted as evidence of β cell dysfunction.⁶ We therefore measured insulin and its precursors in the Hertfordshire men to discover whether retarded early growth is linked to β cell dysfunction.

Subjects and methods

In Hertfordshire from 1911 onwards each birth was notified by the attending midwife. A health visitor saw the child at home periodically throughout infancy and recorded birth weight and weight at 1 year. Weights were measured in pounds (lb; 2.2 lb=1 kg) and were often rounded to the nearest half pound or pound. We therefore used the original units. We traced singleton boys born in east Hertfordshire during 1920-30 who had both birth weight and weight at 1 year recorded. A total of 1157 of the men were still living there, and 845 of them agreed to be interviewed at home.

Each man was visited by one of four fieldworkers. The fieldworkers had not seen the infant data recorded for the man. Height was measured with a portable stadiometer and weight with a portable Seca scale. Waist circumference and hip girth were measured. Blood pressure was measured with an automated recorder (Dinamap) with the man sitting. Readings were taken on the left arm using the cuff size recommended for the arm circumference. Two readings were taken and the average used in the analysis. Room temperature was measured. The man was asked about his medical and social history. Father's occupation was used to define social class at birth, and current social class was derived from the man's occupation.⁷ Before starting the study the procedures for the measurements were standardised and the fieldworkers trained.

After the interview the man was asked if he would be willing to attend a local clinic one morning after an overnight fast to have a standard 75 g oral glucose tolerance test. Men known to have diabetes were excluded. A total of 468 men agreed to attend the clinic and have a fasting blood sample taken; 408 had a full glucose tolerance test. Measurements on the blood samples included plasma glucose and insulin concentrations at zero, 30, and 120 minutes and proinsulin and 32-33 split proinsulin concentrations at zero time

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only. Ethical approval was obtained from the east Hertfordshire ethics committee.

Plasma glucose was measured by a hexokinase method.⁸ Plasma insulin, proinsulin, and 32-33 split proinsulin concentrations were determined by two site immunometric assays with either iodine-125 or alkaline phosphatase as labels.^{5,9} The insulin assay was standardised against the first international reference preparation coded 66/304 and the intact and split proinsulin assays against standards obtained from Lilly Research Laboratories (Indianapolis, USA).

Because plasma measurements of glucose, insulin, proinsulin, and 32-33 split proinsulin have skewed distributions we transformed them to normality in the analysis by using logarithms. Values below the lower limit of detection were assigned the value of the lower limit. We analysed the data using linear regression, two sample *t* tests and logistic regression for calculating odds ratios.

Results

The 468 men who attended the clinic fasting were aged 59-70 (mean 64) years. Of the 408 who had a glucose tolerance test, 370 had complete measurements on all blood samples. Our analysis is based on the 468 fasting blood samples and the 370 samples from complete glucose tolerance tests. Of the 370 men who had complete measurements on all samples, 66 had impaired tolerance, defined as a two hour plasma glucose concentration of 7.8-11.0 mmol/l, and 27 had diabetes, defined as a two hour plasma glucose concentration of 11.1 mmol/l or over. Compared with the 277 other subjects these men were on average 0.5 lb (227 g) lighter at birth and 1.0 lb (450 g) lighter at 1 year (table I). They were heavier and had higher body mass indices (weight (kg)/(height (m))²) and waist to hip ratios. They had higher systolic and diastolic blood pressures. Their fasting glucose concentrations were 1.0 mmol/l higher (6.8 mmol/l compared with 5.8 mmol/l).

Men with impaired glucose tolerance or diabetes had higher mean insulin concentrations two hours after oral glucose (284 pmol/l compared with 124 pmol/l). They had higher mean fasting proinsulin concentrations (4.06 pmol/l compared with 2.66 pmol/l) and higher 32-33 split proinsulin concentrations (4.67 pmol/l compared with 2.72 pmol/l). All these differences were significant at the 5% level.

Tables II and III show that the proportions of men with impaired glucose tolerance or diabetes fell progressively with increasing birth weight and weight at 1 year.

Tables IV and V show the trends with birth weight and weight at 1 year in glucose, insulin, and proinsulin concentrations and blood pressure. Each of these measurements varied with body mass index, which tended to increase with birth weight and weight at 1

TABLE I—Mean weight, height, body mass index, waist to hip ratio, and systolic and diastolic blood pressures in men with and without impaired glucose tolerance or newly diagnosed diabetes as defined by plasma glucose concentrations two hours after 75 g oral load

	Two hour glucose concentration (mmol/l)		Difference (95% confidence interval)	p Value
	<7.8 (n=277)	≥7.8 (n=93)		
Birth weight* {lb g	8.0 3621	7.5 3411	-0.5(-0.8 to -0.2) -210(-351 to -69)	0.004
	Weight at 1 year* {lb kg	22.8 10.3	21.8 9.9	
Height (m)		1.72	1.71	-0.01(-0.02 to 0.01)
Weight (kg)	78.5	81.7	3.2(0.4 to 5.9)	0.02
Body mass index (kg/m ²)	26.6	27.9	1.4(0.6 to 2.2)	0.001
Waist to hip ratio	0.93	0.95	0.02(0.01 to 0.03)	0.001
Systolic blood pressure (mm Hg)	163	174	11(6 to 17)	<0.001
Diastolic blood pressure (mm Hg)	89	92	3(0 to 6)	0.02

*Original measurements were expressed in pounds (lb) and were rounded.

TABLE II—Proportions of men aged 64 with impaired glucose tolerance or diabetes according to birth weight

Birth weight*	No of men	No (%) of men with two hour glucose (mmol/l) of:			Odds ratio (95% confidence interval)†	
		7.8-11.0	≥11.1	≥7.8		
≤5.5	≤2495	20	6 (30)	2 (10)	8 (40)	6.6 (1.5 to 28)
-6.5	-2948	47	10 (21)	6 (13)	16 (34)	4.8 (1.3 to 17)
-7.5	-3402	104	26 (25)	6 (6)	32 (31)	4.6 (1.4 to 16)
-8.5	-3856	117	18 (15)	8 (7)	26 (22)	2.6 (0.8 to 8.9)
-9.5	-4309	54	2 (4)	5 (9)	7 (13)	1.4 (0.3 to 5.6)
>9.5	>4309	28	4 (14)	0	4 (14)	1.0
Total		370	66 (18)	27 (7)	93 (25)	

*Original measurements were expressed in lb and were rounded.

†Odds ratio for two hour glucose concentration of ≥7.8 mmol/l adjusted for body mass index (χ^2 for trend=15.4; $p<0.001$).

TABLE III—Proportions of men aged 64 with impaired glucose tolerance or diabetes according to weight at 1 year

Weight at 1 year*	No of men	No (%) of men with two hour glucose (mmol/l) of:			Odds ratio (95% confidence interval)†	
		7.8-11.0	≥11.1	≥7.8		
≤18	≤8.16	23	6 (26)	4 (17)	10 (43)	8.2 (1.8 to 38)
-20	-9.07	63	13 (21)	7 (11)	20 (32)	4.8 (1.2 to 19)
-22	-9.98	107	24 (22)	8 (7)	32 (30)	4.2 (1.1 to 16)
-24	-10.89	105	14 (13)	5 (5)	19 (18)	2.1 (0.5 to 7.9)
-26	-11.79	48	6 (13)	3 (6)	9 (19)	2.1 (0.5 to 9.0)
≥27	≥12.25	24	3 (13)	0	3 (13)	1.0
Total		370	66 (18)	27 (7)	93 (25)	

*Original measurements were expressed in lb and were rounded.

†Odds ratio for two hour glucose of ≥7.8 mmol/l adjusted for body mass index (χ^2 for trend=14.9; $p<0.001$).

year, though the trends were weak. We therefore allowed for body mass index when calculating the significance of trends with early weight. Plasma glucose concentration at two hours fell with increasing birth weight and weight at 1 year (tables IV and V). Plasma glucose concentration at 30 minutes showed similar trends. Fasting plasma glucose values showed no trends. Table VI shows the plasma glucose concentrations at two hours with the men divided into approximate thirds according to weight at 1 year and adult body mass index. The values rose from 5.8 mmol/l in men with the highest weights at 1 year and lowest body mass indices to 7.7 mmol/l in men with the lowest weights at 1 year and highest body mass indices.

Similarly to plasma glucose, plasma insulin concentrations at two hours fell with increasing birth weight and weight at 1 year (tables IV and V). Thirty minute and fasting plasma insulin values showed no trends with early weights.

Plasma proinsulin concentrations showed no trend with either birth weight or weight at 1 year. Plasma 32-33 split proinsulin concentrations fell slightly with increasing birth weight but showed a strong downward trend with increasing weight at 1 year (tables IV and V). Table VII shows the plasma 32-33 split proinsulin concentrations with the men divided into approximate thirds according to weight at 1 year and adult body mass index. The values rose from 2.1 pmol/l in men with the highest weights at 1 year and lowest body mass indices to 4.8 pmol/l in men with the lowest weights at 1 year and highest body mass indices.

Systolic blood pressure fell with increasing birth weight and weight at 1 year (tables IV and V). The trend with weight at 1 year was abolished by adjustment for birth weight. Systolic pressure rose with increasing plasma glucose concentration at two hours ($p=0.02$) independently of body mass index. The trend with plasma glucose concentration at 30 minutes was stronger ($p=0.0006$). Systolic pressure also rose with increasing plasma 32-33 split proinsulin concentration ($p=0.005$), again independently of body mass index. Diastolic pressure varied with plasma glucose

and proinsulin concentrations in the same way as systolic pressure, but the trends were weaker.

The men's social class either at birth or currently was not related to plasma glucose, insulin, or proinsulin concentration. Adjustment for social class did not change the associations with birth weight and weight at 1 year.

Discussion

In this study of men aged 59-70, 18% (66/370) were found to have impaired glucose tolerance and 7% (27/370) were newly discovered diabetics. These figures are consistent with other surveys.¹⁰ Our study shows that adults with impaired glucose tolerance and non-insulin dependent diabetes have lower weight gain prenatally and during infancy. The proportion of men with impaired glucose tolerance and diabetes fell progressively up to the highest values of birth weight and weight at 1 year (tables II and III). There were threefold differences in the prevalence of impaired glucose tolerance and diabetes between men with the lowest and highest early weights. These trends paralleled the fall in death rates from ischaemic heart disease with increasing birth weight and weight at 1 year which we described recently.¹ They suggest that impaired glucose tolerance and ischaemic heart disease may both be determined by influences which reduce fetal and infant growth.

Tables VI and VII illustrate how fetal and infant growth protect against the deleterious effect of higher body mass in adult life and, conversely, how lower body mass protects against the deleterious effect of reduced early growth. Twenty six per cent of men (14/53) whose birth weights and weights at 1 year were below the median and whose body mass indices were

TABLE VI—Geometric mean plasma glucose concentration (mmol/l) two hours after 75 g oral glucose load according to weight at 1 year and adult body mass index. (Numbers of men given in square brackets)

Adult body mass index (kg/m ²)	Weight at 1 year in lb (kg)*			Total
	≤21.5 (≤9.75)	-23.5 (-10.66)	>23.5 (>10.66)	
≤25.4	6.6 [45]	6.1 [39]	5.8 [36]	6.2 [120]
-28	6.7 [47]	6.9 [44]	5.9 [36]	6.5 [127]
>28	7.7 [39]	7.4 [43]	6.6 [41]	7.2 [123]
Total	7.0 [131]	6.8 [126]	6.1 [113]	6.6 [370]

*Original measurements were expressed in lb and were rounded. Geometric standard deviation of plasma glucose=1.4.

TABLE VII—Geometric mean plasma 32-33 split proinsulin concentration (pmol/l) according to weight at 1 year and adult body mass index. (Numbers of men given in square brackets)

Adult body mass index (kg/m ²)	Weight at 1 year in lb (kg)*			Total
	≤21.5 (≤9.75)	-23.5 (-10.66)	>23.5 (>10.66)	
≤25.4	2.5 [57]	2.2 [56]	2.1 [49]	2.2 [162]
-28	3.2 [57]	3.6 [49]	3.1 [41]	3.3 [147]
>28	4.8 [48]	3.8 [59]	3.9 [52]	4.1 [159]
Total	3.3 [162]	3.1 [164]	2.9 [142]	3.1 [468]

*Original measurements were expressed in lb and were rounded. Geometric standard deviation of plasma 32-33 split proinsulin=2.1.

above the median had impaired glucose tolerance. Only 5% of the men (3/64) who were above the median for early weights and below the median for body mass index had impaired tolerance. The corresponding figures for diabetes were 15% and 2% (8/53 and 1/64). The study sample comprised 40% of men who were born in east Hertfordshire and still living there. As our analysis was based on internal comparisons the selection of the sample would introduce bias only if the relations between early growth and plasma glucose, insulin, and proinsulin concentrations were different in those selected and not selected. This is unlikely. The same relations were found in each social class and each body mass group (tables VI and VII).

The correlation of birth weight and weight at 1 year with glucose intolerance might result from a single influence acting prenatally which reduces fetal growth and continues to affect infant growth. The mechanisms which link low fetal and infant growth rates with adult glucose intolerance are still a matter for speculation. We know, however, that much of the development of the islets of Langerhans occurs in utero.¹¹ The exact timing of islet formation differs among species. In rats the numbers of islets increase rapidly in the last four to six days of intrauterine life. In humans β cell mass increases more than 130-fold between the 12th intrauterine week and the fifth postnatal month.

Overnutrition during intrauterine life is known to influence β cell development, in that diabetes during pregnancy—which has been likened to overnutrition—leads to β cell hyperplasia in the fetus.¹² There are few studies of the effects on β cell development of undernutrition during early life. In rats weaned on to a low protein diet for only three weeks the insulin response to glucose was permanently impaired. This led to the suggestion "that early malnutrition may predispose to diabetes."¹³ Infants who are small for dates have fewer β cells.¹⁴ There are conflicting reports on whether the β cell mass is reduced in patients with non-insulin dependent diabetes.¹¹ In one study, however, in which diabetic patients were compared with people of the same weight their β cell mass was found to be lower.¹⁵

A WORKING HYPOTHESIS

As a working hypothesis it seems reasonable to propose that nutritional and other factors determining fetal and infant growth influence the size and function

TABLE IV—Mean body mass index; geometric mean plasma glucose, insulin, and proinsulin concentrations; and mean systolic blood pressure according to birth weight

	Birth weight in lb (g)*						Trend test†
	≤5.5 (≤2495)	-6.5 (-2948)	-7.5 (-3402)	-8.5 (-3856)	-9.5 (-4309)	>9.5 (>4309)	
Fasting blood samples:							
No of men	21	61	144	141	68	33	468
Body mass index (kg/m ²)	26.7	26.8	26.4	26.9	26.8	29.1	26.9
Glucose (mmol/l)	6.2	6.0	6.1	6.1	6.0	5.8	6.1 0.17
Insulin (pmol/l)	45	44	41	41	40	46	42 0.15
Proinsulin (pmol/l)	3.5	2.8	3.0	3.0	2.9	2.9	3.0 0.24
32-33 Split proinsulin (pmol/l)	3.6	3.4	3.0	3.1	3.0	3.1	3.1 0.06
Systolic blood pressure (mm Hg)	173	165	166	164	161	161	164 0.001
Glucose tolerance tests:							
No of men	20	47	104	117	54	28	370
Glucose (mmol/l) { 30 minutes	10.1	9.9	9.7	9.3	9.2	8.9	9.5 0.001
{ 2 hours	7.5	6.9	6.8	6.5	6.3	5.9	6.6 0.002
Insulin (pmol/l) { 30 minutes	315	293	254	282	248	296	273 0.22
{ 2 hours	224	192	161	139	124	143	153 0.0005

*Original measurements were expressed in lb and were rounded.

†p Value adjusted for body mass index.

TABLE V—Mean body mass index; geometric mean plasma glucose, insulin, and proinsulin concentrations; and mean systolic blood pressure according to weight at 1 year

	Weight at 1 year in lb (kg)*						Trend test†
	≤18 (≤8.16)	-20 (-9.07)	-22 (-9.98)	-24 (-10.89)	-26 (-11.79)	≥27 (≥12.25)	
Fasting blood samples:							
No of men	28	75	143	132	63	27	468
Body mass index (kg/m ²)	26.2	26.4	26.9	26.9	26.9	28.3	26.9
Glucose (mmol/l)	6.0	6.1	6.1	6.1	6.0	5.8	6.1 0.2
Insulin (pmol/l)	34	49	43	38	42	43	42 0.11
Proinsulin (pmol/l)	3.1	2.9	3.1	2.8	3.3	2.7	3.0 0.11
32-33 Split proinsulin (pmol/l)	3.4	3.3	3.2	2.8	3.4	2.5	3.1 0.008
Systolic blood pressure (mm Hg)	168	169	165	162	162	161	164 0.007
Glucose tolerance tests:							
No of men	23	63	107	105	48	24	370
Glucose (mmol/l) { 30 minutes	9.7	9.7	9.8	9.4	9.0	8.7	9.5 0.004
{ 2 hours	7.9	7.0	6.7	6.5	6.3	6.0	6.6 0.0006
Insulin (pmol/l) { 30 minutes	220	286	290	279	253	238	273 0.16
{ 2 hours	153	201	156	138	129	144	153 0.002

*Original measurements were expressed in lb and were rounded.

†p Value adjusted for body mass index.

of the adult pancreatic β cell complement. Plasma concentrations of 32-33 split proinsulin were higher in men with lower weight at 1 year (table V). A raised plasma 32-33 split proinsulin concentration may indicate production of insulin by a comparatively small complement of β cells. Whether and when non-insulin dependent diabetes supervenes will be determined by the rate of attrition of β cells with aging and by the development of insulin resistance, of which the most important known determinant is obesity. An alternative explanation of the raised 32-33 split proinsulin concentration is that it reflects increased insulin production secondary to insulin resistance. Further experiments are planned to investigate these possibilities or indeed whether processes leading to poor fetal and infant growth might lead to a combination of insulin deficiency and resistance.

An attractive feature of this explanation is that it provides an alternative to the "thrifty genotype" hypothesis.¹⁶ This hypothesis suggests that the high incidence of diabetes in Western or recently affluent societies results from the existence of diabetogenic genes which confer a survival advantage in conditions of subsistence living. We suggest that diabetes is a consequence of poor nutrition during critical periods of fetal life and infancy with consequent impaired development of β cell function. If poor nutrition continues the reduced ability to produce insulin is not a disadvantage. It becomes so only if nutrition becomes abundant, when increased demand for insulin outstrips the capacity for production. Ethiopian Jews who migrated to Israel experienced a change from poor to abundant nutrition and had a subsequent high incidence of diabetes.¹⁷ The long term effects of poor nutrition during early life may depend on the nature, timing, and intensity of deprivation, which will determine the specific tissues in which development is impaired. This phenomenon may underlie several Western diseases other than diabetes, most importantly ischaemic heart disease.¹⁸

Consistent with other studies,¹⁹ we have found that plasma glucose concentrations are strongly related to blood pressure levels independently of body mass index. Blood pressure was inversely related to birth weight, as has also been found before.² The association between blood pressure and 32-33 split proinsulin concentrations indicates that similar influences may impair vascular and pancreatic islet cell development in utero. The association of hypertension, non-insulin dependent diabetes, and hyperlipidaemia has been called syndrome X.²⁰ Insulin resistance has been proposed as the link between these abnormalities. Our study, however, raises the possibility that retarded intrauterine growth may be the link.

Our findings are open to the interpretation that a genetically determined deficiency of insulin production is manifested by growth failure in early life long before the onset of adult glucose intolerance. The high concordance of non-insulin dependent diabetes in monozygotic twins is often cited as strong evidence that the disorder is genetically controlled.²¹ Because maternal physique and nutrition have such a strong influence on fetal and infant growth we favour an environmental explanation of our findings. This would

necessarily put in question the genetic interpretation of concordance in monozygotic twins. The strong associations which we report suggest that research directed towards the causes of non-insulin dependent diabetes should examine the development of the pancreas in fetal life and infancy and the nutritional and other influences which regulate it.

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