Size at Birth, Fasting Glucose and Insulin Levels and Insulin Resistance in Adult Twins

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Studies in singletons have found an association between birthweight and Type 2 diabetes in adult life. The aim of this study was to investigate whether this association could also be seen in twins. 59 monozygotic (MZ) and 69 dizygotic (DZ) same-sex twin pairs aged 19–50 years and 89 singleton controls matched for age, gestational age, gender, maternal age and parity were recruited from a local obstetric database. Associations between adult glucose, HbA_1C and insulin levels and insulin resistance and birthweight were assessed by linear regression with adjustment for confounding variables. Twins were significantly lighter at birth than singleton controls, but there were no significant differences in adult weight, glucose, HbA_1C and insulin levels or insulin resistance between twins and controls. The relationship between birthweight and fasting glucose and insulin levels, and insulin resistance was not significantly different from zero in either twins or controls, but birthweight was significantly negatively associated with HbA_1C only in controls. There was no evidence of a difference between MZ and DZ twins in unpaired or within-pair analysis. These results provide little evidence that low birthweight in twins increases the risk of impaired glucose-insulin metabolism in young adults or that genetic factors can account for the association observed in singletons.

The "fetal origins hypothesis" pioneered by Barker and colleagues proposes that low birthweight is associated with the risk of developing Type 2 diabetes mellitus and the metabolic syndrome in adult life (Barker, 1998). A study in Hertfordshire was the first to show that 64-year-old men with low birthweight had higher rates of Type 2 diabetes in later life (Hales et al., 1991). A number of epidemiological studies in singletons have revealed similar inverse relationships between birthweight and the risk of developing Type 2 diabetes (Curhan et al., 1996; Phipps et al., 1993; Ravelli et al., 1998; Rich-Edwards et al., 1999). Studies in rats have shown that early growth retardation due to maternal protein restriction leads to the development of diabetes in old male rat offspring (Petry et al., 2001). Glucose tolerance progressively declines with age, resulting in a high prevalence of Type 2 diabetes and impaired glucose tolerance in the older population (Halter, 1995). The association of reduced fetal growth with insulin resistance is less consistent and the age of onset may depend on the degree of genetic predisposition of the population (Jaquet et al., 2003). The mechanisms underlying the development of the insulin resistance associated with reduced fetal growth remain unclear.

Twin studies have been identified as providing a potentially highly informative contribution to assessing the fetal origins hypothesis for two reasons. First, twins are smaller at birth compared to singletons and thus it is of direct interest to know whether they also are at increased risk of cardiovascular disease and other conditions linked in observational studies of singletons to size at birth (Leon, 2001). Second, twin studies could shed light on the underlying mechanisms, particularly discriminating between the influence of the early environment and the influence of genetic factors (Phillips et al., 2001). Only through assessment of whether the within-pair association differs from unpaired association can insights be gained into the particular importance of maternal factors (Dwyer et al., 2002). Furthermore, using within-pair analysis for MZ and DZ twins it is possible to see whether the association between birthweight and adult disease might be explained by maternal or genetic factors.

Two recent studies of twins who were discordant for Type 2 diabetes have provided support for the Barker hypothesis that the fetal environment plays an important role in determining future susceptibility to adult onset diabetes. These studies found that birthweights were significantly lower in diabetic MZ twins compared with their non-diabetic co-twins (Bo et al., 2000; Poulsen et al., 1997). It was concluded that the higher discordance rate of Type 2 diabetes in MZ compared to DZ twins could be explained by their different intrauterine environment and undernutrition rather than genetics per se.

However, the most recent studies of twins provide inconsistent evidence of the effect of birthweight on glucose-insulin metabolism. The Birmingham Twin Study found no association between birthweight and glucose tolerance (Baird et al., 2001). The East Flanders Prospective Twin Survey found similar negative findings between birthweight and

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insulin resistance (Loos et al., 2002). In contrast, low birthweight was associated with insulin resistance and low insulin secretion in elderly MZ twins in the most recent study from the Danish Twin Registry (Poulsen et al., 2002).

We have recently carried out a study of 131 adult twin pairs to assess whether the influence of size at birth on fasting glucose, HbA_1C and insulin levels, and insulin resistance differed within twins. We also compared the effect of birthweight on glucose and insulin metabolism in singleton controls matched for age, gestational age, gender, maternal age and parity. Details of associations between birthweight and blood pressure have been published elsewhere (McNeill et al., 2003).

Materials and Methods

Subjects

A total of 792 same gender live-born twin pairs were identified from the Aberdeen Maternity Neonatal Databank as having been born in Aberdeen Maternity Hospital between 1949 and 1980. Of these, 619 twin pairs (78.2%) were traced and the names and addresses of 465 twin pairs where one or both twins were still living in the Grampian region were obtained via the local Community Health Index.

To identify singleton controls, up to four live singleton deliveries were matched to each twin pair for gestational age (± 1 week), gender, maternal age (± 5 years) and parity (0, 1 or 2+), and year of birth (± 1 year). As a result, a total of 798 controls were identified of whom 577 (72.3%) were traced and the addresses of 442 still living in Grampian were obtained from the Community Health Index.

A total of 31 subjects (15 twin pairs and 1 control) were excluded by their family doctors for medical reasons. All others were sent a letter of information about the study and invited to participate. The overall subject response rate was 32.8% in twins and 21.9% in controls. Two hundred and sixty two twins, among whom there were 131 twin pairs, and 93 singleton controls attended for measurements. Four controls were later excluded as they were found to have been incorrectly matched with the twin deliveries. An insulin-dependent diabetic twin was excluded from the analysis leaving a total of 261 twins and 89 controls. In multiple linear regression analysis, the results for one twin pair, one of whom was a diabetic and had already been excluded above, and two DZ twin pairs with a within-pair difference in BMI > 15, were excluded. Six twins were also excluded as their gestational age was missing from the obstetric records, leaving 250 twins for regression analysis. Insulin results for two twin subjects were missing.

Measurements were made of height, weight and waist circumference in each subject. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Body fat was measured by bioelectrical impedance analysis using the Bodystat® 1500 (Bodystat Ltd, Isle of Man). Medical details, smoking and occupation were recorded by a questionnaire based on that used in the Scottish MONICA study (Smith et al., 1989). The physical activity questions were a modified version of those used for the Framingham Physical Activity Index (Kannel & Sorlie, 1979). Diet was assessed using version 6.31 of the Scottish Collaborative Group semi-quantitative food frequency questionnaire (Masson et al., 2003). Zygosity analysis was determined by DNA fingerprinting using a venous blood sample.

A fasting blood sample was taken for measurements of glucose, HbA_1C and insulin. Glucose was determined by the glucose oxidase method on an ADVIA® 1650 Chemistry System (Bayer Diagnostics, Tarrytown, USA). Glycated hemoglobin (HbA_1C) was measured using the Primus CLC385™ system (Primus Corporation, Kansas City, USA). Insulin was determined using a MEDGENIX INS-IRMA immunoradiometric assay kit (Medgenix Diagnostics, Brussels, Belgium) for human insulin. For insulin the interassay coefficient of variance was < 12.2%. For all other assays it was < 2%. The insulin assay was not included in any external Quality Assurance schemes, but performed well within the manufacturer's specifications. All other analytes were included in the relevant United Kingdom National Quality Assurance Scheme. Insulin Resistance was calculated using the homeostatic model assessment (HOMA): fasting insulin levels (uU/ml) x fasting glucose (mmol/L)/ 22.5 (Matthews et al., 1985).

Birthweight, gestational age, maternal age and parity information for both twins and controls were obtained from medical records stored on the Aberdeen Maternity Neonatal Databank. Self-reported birth order was used to obtain the relevant obstetric information from the Aberdeen Maternity Neonatal Databank on individual twins from each pair.

The study protocol was approved by the Grampian Research Ethics Committee, and all subjects gave informed written consent to participate.

Statistical Analysis

The distribution of all variables was tested for normality by the Kolmogorov-Smirnov test. Differences between twins and controls were compared using *t* tests for two samples. Paired *t* test or Wilcoxon tests for non-normally distributed data were used to test for differences in the birthweight, anthropometric variables and glucose and insulin measurements within twin pairs. In within pair analysis differences between first and second born twins were used rather than those between heavier and lighter twins at birth, as the distribution of birthweight differences is normally distributed for the former but not the latter (Bring & Wernoth, 1999). Therefore, the difference in all variables between twins in each pair was calculated as (first born – second born). The relationship between birthweight and adult glucose and insulin metabolism was tested by linear regression with adjustment for confounding variables.

Results

The birthweight and adult characteristics of the participating twins and controls are given in Table 1. There were no significant differences in current age, birthweight, gestational age or maternal parity between those who participated and those who did not participate in either the twins or the controls (data not shown). Male participants were a little older than female participants in both twins ($p < .001$) and controls ($p < .05$). The birthweight difference between all twins ranged from 1–1840g, with a

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Table 1

Birthweight, Adult Characteristics, Fasting Glucose, HbA_1C and Insulin Levels, and Insulin Resistance of Twins and Controls — Mean (SEM)

	Males				Females			
	MZ	DZ	All twins	Controls	MZ	DZ	All twins	Controls
	n = 43	*n* = 62	*n* = 105	*n* = 46	*n* = 76	*n* = 80	*n* = 156	*n* = 43
Birthweight (g)	2,520 (77.2)	2,667 (70.4)	2,607 (52.4)	2,956[a] (71.8)	2,377 (61.4)	2,420 (58.1)	2,399 (42.1)	2,927[a] (106.1)
Gest. age (weeks)	37.4 (0.49)	37.1 (0.33)	37.2 (0.28)	36.7 (0.33)	37.5 (0.32)	37.1 (0.31)	37.3 (0.22)	37.2 (0.42)
Current age (years)	34.6 (1.32)	37.4 (1.09)	36.3 (0.85)	35.7 (1.44)	29.4 (1.06)	32.6 (0.91)	30.5 (0.70)	31.1 (1.43)
Adult height (cm)	177.1 (1.08)	177.4 (0.84)	177.3 (0.66)	176.0 (0.85)	162.2 (0.80)	162.8 (0.72)	162.5 (0.54)	162.0 (1.01)
BMI (kg/m^2)	24.5 (0.51)	26.2 (0.49)	25.5 (0.36)	26.0 (0.57)	23.7 (0.42)	24.7 (0.63)	24.2 (0.39)	22.9[b] (0.46)
Glucose (mmol/l)	4.91 (0.08)	4.88 (0.06)	4.89 (0.05)	4.93 (0.05)	4.71 (0.05)	4.70 (0.05)	4.70 (0.04)	4.61 (0.06)
HbA_1C (%)	5.20 (0.04)	5.23 (0.04)	5.22 (0.03)	5.24 (0.05)	5.09 (0.06)	5.19 (0.04)	5.14 (0.04)	5.09 (0.04)
Insulin (μIU/ml)	11.0 (0.95)	11.3 (0.67)	11.2 (0.55)	11.5 (0.98)	11.2 (0.58)	11.1 (0.64)	11.2 (0.43)	9.93 (0.58)
Insulin Resistance (HOMA)	2.56 (0.25)	2.47 (0.16)	2.51 (0.14)	2.50 (0.21)	2.35 (0.13)	2.34 (0.15)	2.34 (0.10)	2.06 (0.14)

Note: [a] significantly different from all twins of the same gender $p < .001$

[b] significantly different from all twins of the same gender $p < .05$

Table 2

Regression Coefficients (95% CI) for the Relationship Between Glucose, HbA_1C, Insulin Levels and Insulin Resistance per kg Birthweight Adjusted for Current Age, Gender, Gestational Age, BMI and Smoking in Twins and Controls

	Glucose (mmol/l)	HbA_1C (%)	Insulin (μIU/ml)	Insulin Resistance
MZ twins (*n* = 116)				
Unpaired	–0.03 (–0.25 to 0.18)	–0.12 (–0.35 to 0.11)	–1.32 (–3.71 to 1.06)	–0.32 (–0.92 to 0.29)
Within–pair	0.19 (–0.11 to 0.49)	0.15 (–0.33 to 0.63)	1.05 (–2.68 to 4.77)	0.15 (–0.52 to 0.82)
DZ twins (*n* = 134)				
Unpaired	–0.13 (–0.32 to 0.07)	–0.01 (–0.14 to 0.12)	–1.11 (–2.94 to 0.72)	–0.32 (–0.74 to 0.10)
Within–pair	–0.00 (–0.35 to 0.34)	0.07 (–0.17 to 0.31)	–0.70 (–4.92 to 3.53)	–0.47 (–0.86 to 0.76)
All twins (*n* = 250)				
Unpaired	–0.08 (–0.22 to 0.06)	–0.03 (–0.15 to 0.10)	–1.11 (–2.56 to 0.33)	–0.30 (–0.65 to 0.05)
Within-pair	0.09 (–0.13 to 0.31)	0.12 (–0.23 to 0.37)	–0.50 (–3.20 to 2.20)	–0.27 (–0.52 to 0.47)
All controls (*n* = 89)	–0.04 (–0.22 to 0.13)	–0.15 (–0.29 to –0.01)[b]	–0.23 (–2.56 to 0.33)	–0.55 (–0.62 to 0.51)

Note: [b] $p < .05$

median difference of 280g. The median within-pair birthweight differences were similar for MZ and DZ twin pairs (340g and 267g, respectively; $p = 0.4$).

The birthweight of controls was heavier than that of twins by an average of 459g ($p < .001$). Both male and female controls were, on average, heavier at birth than male and female twins (by 349g and 528g respectively, $p < .001$ for both genders). There were no significant differences in gestational age, current age or adult anthropometric characteristics between twins and controls in either males or females, apart from BMI which was significantly higher in twins than in controls among the females ($p < .05$) but not the males.

Fasting glucose, HbA_1C and insulin levels, and insulin resistance of twins and controls are also given in Table 1. There were no significant differences in glucose, HbA_1C and insulin levels, and insulin resistance between twins and controls for either males or females, and there were no significant differences between MZ and DZ pairs. Percentage of energy from fat, polyunsaturated: saturated fat ratio (P:S ratio), alcohol intake, physical activity level (PAL) and smoking also showed no significant differences between twins and controls, for either males or females (data not shown). There were also no significant differences between MZ and DZ pairs.

Regression coefficients for the association between birthweight and fasting glucose, HbA_1C and insulin levels, and insulin resistance in twins and controls, adjusted for possible confounding variables, are shown in Table 2. In

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controls, fasting glucose, HbA_1C and insulin levels, and insulin resistance were inversely associated with birthweight, there being a significant negative association only between birthweight and HbA_1C. In twins there was the same trend, but the associations between birthweight and fasting glucose, HbA_1C and insulin levels, and insulin resistance were not significantly different from zero.

In within pair analysis, there was a wide range of differences in all variables (e.g., up to 1.8kg in birthweight and up to 1.5 mmol/l in fasting glucose), but within-pair differences in fasting glucose, HbA_1C and insulin levels, and insulin resistance were very similar in MZ and DZ twin pairs (data not shown). The adjusted regression coefficients for the association between intra-pair differences in fasting glucose, HbA_1C and insulin levels, and insulin resistance and intra-pair differences in birthweight are also given in Table 2. In within-pair analysis there was no significant relationship between differences in birthweight and differences in glucose, HbA_1C, insulin and insulin resistance in either MZ or DZ twin pairs.

Discussion

In this study there were no significant differences in any measurements between twins and controls apart from birthweight, which, as expected, was significantly lower in twins than controls. Twins at birth were, on average, smaller by 459g than controls matched for gestational age. The lack of difference in adult height and BMI between twins and controls suggests that the twins experienced post-natal catch-up growth. In terms of the Barker hypothesis, small size at birth followed by catch-up growth in singletons has already been proposed as an important coronary heart disease risk factor (Eriksson et al., 1999). Our finding that the twins did not have higher fasting glucose, HbA_1C and insulin levels, or insulin resistance than the controls suggests that in twins the combined effect of in utero growth restriction and catch-up growth on glucose-insulin metabolism levels is small.

In unpaired analysis of twins, there was no significant association between birthweight and glucose or insulin levels or insulin resistance. Similar findings have been reported in the East Flanders Prospective Twin Survey of 423 twin pairs (250 MZ and 173 DZ) aged between 18 and 34 years (Loos et al., 2002). Birthweight per se was also not associated with insulin secretion or action in 104 MZ twins and 88 DZ twins in two age groups (25–34 and 57–66 years) from the Danish Twin Register (Poulsen et al., 2002).

The results and general trends shown in unpaired analysis of twins remained similar in within-pair analysis. One possible reason for differences between studies could be age differences. The East Flanders Prospective Twin Survey (Loos et al., 2002) of young twins and the Birmingham twin study (Baird et al., 2001) of 58 MZ and 140 DZ twins with a mean age of 43.7 years produced similar observations. However, the Danish Twin Register found a significant association between low birthweight and both insulin resistance and low insulin secretion after both oral and intravenous glucose administration in 21 elderly MZ twin pairs (Poulsen et al., 2002). They concluded that ageing could play an important role by unmasking the influence of an adverse intrauterine environment on insulin resistance and low insulin secretion in twins.

In within-pair analysis, the effect of genetic and other parental factors (such as maternal diet, maternal size, gestational age, gender, parental smoking and socio-economic influences) were controlled. Genetic influences are totally removed in MZ and partially removed in DZ twin pairs. If genetic factors were important, the association (regression coefficient or slopes) between birth size and adult disease risk factors would be substantially reduced in MZ twins, but not in DZ twins. If there are no evident differences in the regression coefficients of either MZ twins or DZ twins, perhaps neither genetic nor maternal factors are involved. Our data showed no evidence of a difference between MZ twins and DZ twins in either within-pair or unpaired analysis. Furthermore, if maternal factors were important, the relationship (slopes) between birth size and later disease risk factors would be reduced in within-pair analyses in all twins rather than unpaired analyses. Again this trend was not evident in the present study. Consequently, the results of the study suggest that genetic and maternal factors had less of an influence on glucose-insulin metabolism, though our twins were young.

Chorion type is important for monochorionic MZ twins as they share one placenta and have therefore to share the limited nutrients available through the single foetal supply line. They may also suffer from problems due to unequal blood circulation between co-twins, resulting in MZ twins as a whole possibly having a more discordant in utero experience than DZ twins. According to Barker's programming hypothesis monochorionic MZ twins could therefore be more prone to develop various metabolic abnormalities. It was not possible to explore this aspect in the present study, as chorionicity information for only 29 (12 monochorionic and 17 dichorionic) of the 60 MZ twin pairs was available from the maternal records. However, there was no difference in within-pair birthweight difference between MZ and DZ twins.

In singleton controls birthweight was not associated with fasting glucose or insulin levels, or insulin resistance, except that there was a significant negative relationship between birthweight and HbA_1C. The influence of the intrauterine environment on the development of glucose-insulin metabolism and insulin resistance could be increased with age. Other studies that pointed to the possible importance of low birthweight in Type 2 diabetes were based on examination of samples of men and women in middle and late life (Phillips, 1998).

In conclusion, twins were smaller at birth than singleton controls matched for gestational age, but they did not have higher fasting glucose, HbA_1C and insulin levels, and insulin resistance than the controls. Birthweight was not associated with fasting glucose and insulin levels, and insulin resistance in both twins and controls suggests that in twins the combined effect of in utero growth restriction and catch-up growth on glucose-insulin metabolism levels is small. There was no evidence that low birthweight in twins increases the risk of impaired glucose-insulin metabolism in young adults.

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