

ORIGINAL ARTICLE

## Premature Birth and Later Insulin Resistance

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### ABSTRACT

#### BACKGROUND

Term infants who are small for gestational age appear prone to the development of insulin resistance during childhood. We hypothesized that insulin resistance, a marker of type 2 diabetes mellitus, would be prevalent among children who had been born prematurely, irrespective of whether they were appropriate for gestational age or small for gestational age.

#### METHODS

Seventy-two healthy prepubertal children 4 to 10 years of age were studied: 50 who had been born prematurely (32 weeks' gestation or less), including 38 with a birth weight that was appropriate for gestational age (above the 10th percentile) and 12 with a birth weight that was low (i.e., who were small) for gestational age, and 22 control subjects (at least 37 weeks' gestation, with a birth weight above the 10th percentile). Insulin sensitivity was measured with the use of paired insulin and glucose data obtained by frequent measurements during intravenous glucose-tolerance tests.

#### RESULTS

Children who had been born prematurely, whether their weight was appropriate or low for gestational age, had an isolated reduction in insulin sensitivity as compared with controls (appropriate-for-gestational-age group,  $14.2 \times 10^{-4}$  per minute per milliunit per liter [95 percent confidence interval, 11.5 to 16.2]; small-for-gestational-age group,  $12.9 \times 10^{-4}$  per minute per milliunit per liter [95 percent confidence interval, 9.7 to 17.4]; and control group,  $21.6 \times 10^{-4}$  per minute per milliunit per liter [95 percent confidence interval, 17.1 to 27.4];  $P=0.002$ ). There were no significant differences in insulin sensitivity between the two premature groups ( $P=0.80$ ). As compared with controls, both groups of premature children had a compensatory increase in acute insulin release (appropriate-for-gestational-age group, 2002 pmol per liter [95 percent confidence interval, 2153 to 2432]; small-for-gestational-age group, 2253 pmol per liter [95 percent confidence interval, 1622 to 3128]; and control group, 1148 pmol per liter [95 percent confidence interval, 875 to 1500];  $P<0.001$ ).

#### CONCLUSIONS

Like children who were born at term but who were small for gestational age, children who were born prematurely have an isolated reduction in insulin sensitivity, which may be a risk factor for type 2 diabetes mellitus.

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**T**HE INTRAUTERINE ENVIRONMENT and early postnatal life are now generally accepted as important determinants of the risk of disease in adulthood. Low birth weight, a marker of intrauterine adversity, has consistently been associated with a variety of adult-onset diseases, including type 2 diabetes mellitus, essential hypertension, dyslipidemia, coronary artery disease, and cerebrovascular accidents.<sup>1-8</sup> Attempts to establish the cause of these associations have led to the recognition that subjects with low birth weights have an early and consistent reduction in insulin sensitivity.<sup>9,10</sup> Insulin resistance (i.e., reduced insulin sensitivity) is a well-recognized, early metabolic abnormality in the pathogenesis of these adult-onset diseases and usually precedes clinically apparent symptoms.<sup>11-14</sup> Indeed, insulin resistance and compensatory hyperinsulinemia may be the prime pathogenic mechanisms underlying these diseases.<sup>15</sup>

To date, almost all studies linking children whose birth weights were low to the propensity toward disease in adulthood have focused on those who were small for gestational age and born at term. Low birth weight, however, is even more prevalent among children born prematurely, most of whom are smaller at birth than term infants. Similar to infants born at term, premature infants can be further classified on the basis of birth weight as either small or appropriate for gestational age. Improvements in neonatal care have dramatically increased survival among premature infants; currently over 90 percent of infants weighing less than 1500 g at birth (equivalent to the 50th percentile of birth weight for those born at 30 weeks' gestation) survive in the long term, as compared with fewer than 50 percent in the 1970s.<sup>16</sup>

Data obtained in 2000 on neonates in the United States indicate that 11.6 percent of all live-born infants were less than 37 weeks' gestation and that 1.4 percent weighed under 1500 g.<sup>17</sup> The costs of neonatal and early health care for these infants are considerable but may be even more substantial if one considers that they appear to be at increased risk for disease in adulthood, with its attendant costs. Prematurely born children represent a relevant and increasing proportion of society.

Although both premature infants and term infants who are small for gestational age are confronted with an adverse environment at a similar stage of biologic maturity, premature infants primarily face an adverse postnatal environment, whereas term in-

fants who are small for gestational age have experienced this adverse environment during intrauterine life. We hypothesized that if this adverse environment is responsible for the reduction in insulin sensitivity observed in term infants who are small for gestational age, then premature infants would have a similar, early, and permanent reduction in insulin sensitivity. If this hypothesis is correct, insulin resistance should be present in childhood.

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## METHODS

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### SUBJECTS

All subjects were recruited between June 1999 and December 2000 for this study, and all were healthy, developmentally normal, prepubertal children 4 to 10 years of age. Children who had been born prematurely (32 weeks' gestation or less) were assigned to two groups on the basis of birth weight. Those with a birth weight at or above the 10th percentile were defined as being appropriate for gestational age, and those with a birth weight below the 10th percentile as being small for gestational age.<sup>18</sup> Potential subjects were identified from the neonatal-unit database of the National Women's Hospital and Middlemore Hospital in Auckland, New Zealand. The families of 103 eligible children who had been born prematurely were contacted, and the parents or guardians of 50 children consented to enroll their child. A control group of healthy, developmentally normal children 4 to 10 years of age who had been born at at least 37 weeks' gestation and whose birth weights were at or above the 10th percentile were also recruited. This group included both subjects with normal-variant short stature recruited from endocrinology clinics at Starship Hospital, Auckland, and subjects with normal stature recruited by means of advertisements. Both short- and normal-stature children were combined, since height has previously been demonstrated not to influence insulin sensitivity in otherwise healthy children.<sup>18</sup> More than 90 percent of the subjects were of European ancestry, and the majority of the others were in part of European ancestry. Consequently, all the subjects were assessed according to the same growth charts. Race was determined by the parents' self-identification in a questionnaire.

Approval for the study was provided by the Auckland Ethics Committee. Written informed consent was obtained from the parents or guardians and also from the subjects who were able to do so.

Data on the glucose variables from a previously

described group of healthy prepubertal children who were 4 to 10 years old and who had been born at term but had been small for gestational age are also included.<sup>9</sup> These data, having been previously analyzed and published, were not included in the statistical analysis, but rather this group was added for comparison only, representing a term low-birth-weight cohort in which insulin resistance was well documented. The methods of the insulin assay changed between these studies, and samples from the previous study were reanalyzed with the use of current methods to ensure that appropriate comparisons could be made. Accordingly, the values for insulin sensitivity and acute insulin release in this article differ from those in our previous study.<sup>9</sup>

Exclusion criteria included evolving type 1 diabetes mellitus (as defined by the presence of antibodies against glutamic acid decarboxylase and tyrosine phosphatase), a diagnosis involving chromosomal abnormalities or syndromes, a first-degree relative with type 2 diabetes mellitus, and chronic illness or medical therapy known to influence insulin sensitivity. All short subjects (height SD scores less than -2) underwent clonidine stimulation to exclude growth hormone deficiency; a plasma growth hormone level of at least 7.0  $\mu\text{g}$  per liter in response to clonidine stimulation was necessary for participation. Birth weight and height were converted into SD scores to allow comparison of subjects with different gestational ages, chronological ages, and sexes.<sup>19,20</sup> The weight-for-length index was used to provide an age-adjusted evaluation of relative obesity.<sup>21,22</sup> Ideal body weight was defined as a weight-for-length index of 100 percent (normal range, 80 to 120 percent; obesity, above 120 percent; and extreme thinness, below 80 percent).

#### DATA COLLECTION

Insulin sensitivity was measured in all subjects with the use of Bergman's minimal model, in which paired insulin and glucose data obtained by frequent measurements during an intravenous glucose-tolerance test are modified for use in children, as previously described.<sup>18</sup> Values derived from the minimal model included the insulin sensitivity index, acute insulin release (the integrated insulin release during the first 10 minutes after the dextrose infusion), glucose effectiveness (the ability of glucose to increase its own disposal and reduce its own production), and the glucose disposal index (the negative natural logarithm of the slope of the de-

cline in glucose levels from minute 10 to minute 19 of the intravenous glucose-tolerance test).

Complete maternal and neonatal records were available for 34 of 50 premature subjects. The following retrospective data were obtained: the reason for premature delivery; the type of delivery; the number of days of ventilation, for those who received mechanical ventilation; use or nonuse of antenatal or postnatal glucocorticoid therapy, supplemental oxygen, respiratory assistance with continuous positive airway pressure, and antibiotics; the number of days of parenteral nutrition; and the number of days before full oral feeding was instituted.

#### ASSAYS

Levels of plasma glucose were measured by means of an automated random-access analyzer (model 911, Hitachi) that had an interassay coefficient of variation of 1.2 percent.<sup>23</sup> Insulin levels were determined by means of an enzyme immunoassay (IMX microparticle assay, Abbott) that had an interassay coefficient of variation of less than 5 percent. Antibodies against glutamic acid decarboxylase and tyrosine phosphatase were measured by means of a radioimmunoassay (either tyrosine phosphatase or glutamic acid decarboxylase) labeled with iodine-125 (RSR). The intraassay and interassay coefficients of variation were less than 5 percent for both antibody assays.

#### STATISTICAL ANALYSIS

Differences in demographic characteristics and clinical measures between control and premature groups were investigated by means of analysis of variance for continuous variables and the chi-square test for proportions. Differences in neonatal characteristics were evaluated with the use of Fisher's exact test for proportions and the Mann-Whitney U test for the number of days of treatment. General linear regression models were used to investigate differences in glucose-regulation variables among the three groups of subjects. The specific hypotheses tested were the difference in insulin sensitivity between appropriate- and small-for-gestational-age subjects within the premature groups and the difference in insulin sensitivity between the premature groups and the term group. Age, sex, height SD score, weight-for-length index, birth-weight SD score, and midparental height SD score were included in the models.

General linear regression models were also used to establish whether maternal or neonatal charac-

teristics affected insulin sensitivity in the premature subjects. These variables included age; sex; weight-for-length index; height SD score; birth-weight SD score; presence or absence of gestational hypertension, antenatal glucocorticoid treatment, and postnatal glucocorticoid therapy; number of days of oxygen administration; and number of days of antibiotic administration. The data on insulin sensitivity and acute insulin release were logarithmically transformed to meet the assumptions of normality.

## RESULTS

Fifty subjects who had been born prematurely (38 with an appropriate weight for gestational age and 12 with a low weight [i.e., who were small] for gestational age) and 22 control subjects who had been born at term with an appropriate weight for gestational age were enrolled. The characteristics of these groups plus the cohort of term infants who were small for gestational age are summarized in Table 1. Other than the expected differences in birth-weight SD score and the length of gestation among the groups, the premature appropriate-for-gestational-age group was taller ( $P=0.002$ ) than the premature small-for-gestational-age group, although the former group also had taller parents ( $P=0.03$ ).

The neonatal characteristics of the 35 subjects who had been premature (27 who were appropriate and 7 who were small for gestational age) for whom data were complete are summarized in Table 2. Children who had been born preterm and small for ges-

tational age were more likely to have had mothers with preeclampsia ( $P=0.02$ ), to have been born by cesarean section ( $P=0.02$ ), and to have received mechanical ventilation ( $P=0.01$ ).

The glucose-regulation variables are summarized in Table 3. When the groups of subjects who were appropriate and those who were small for gestational age were combined, insulin sensitivity was approximately 40 percent lower than that in term control subjects ( $P=0.002$ ). This isolated reduction in insulin sensitivity was similar in both the premature small-for-gestational-age group and the premature appropriate-for-gestational-age group ( $P=0.80$ ) and similar to that in the term small-for-gestational-age group. Insulin sensitivity was inversely associated with the weight-for-length index ( $P=0.003$ ), age ( $P=0.03$ ), and fasting insulin level ( $P=0.007$ ). Thus, heavier, older subjects with higher fasting insulin values were more resistant to insulin than were younger, lighter subjects with lower fasting insulin values. None of the following maternal, neonatal, or childhood factors influenced insulin sensitivity in premature subjects: presence or absence of gestational hypertension ( $P=0.08$ ), sex ( $P=0.30$ ), days of antibiotics received ( $P=0.60$ ), days of oxygen received ( $P=0.60$ ), presence or absence of prenatal glucocorticoid use ( $P=0.40$ ), presence or absence of postnatal neonatal glucocorticoid use ( $P=0.50$ ), birth-weight SD score ( $P=0.20$ ), or height SD score ( $P=0.90$ ).

Similar results were observed for insulin release (as assessed by acute insulin release), reflecting the

**Table 1. Baseline Characteristics of the Study Subjects.\***

Characteristic	Premature Appropriate-for-Gestational-Age Group (N=38)	Premature Small-for-Gestational-Age Group (N=12)	Term Controls (N=22)	Term Small-for-Gestational-Age Group (N=13)	P Value†
Age — yr	6.7±1.2	6.5±1.8	7.4±1.4	8.9±2.3	0.09
Male sex — no. (%)	15 (39)	6 (50)	15 (68)	8 (62)	0.10
Gestation — wk	27.6±2.2	30.5±3.1	39.3±1.2	38.6±1.8	<0.001
Birth weight					
Grams	1098±362	1062±340	3311±417	2114±490	<0.001
SD score	-0.05±0.76	-2.16±0.80	-0.18±0.74	-2.65±1.29	<0.001
Height SD score	-0.2±1.37	-1.24±1.20	-1.50±1.57	-2.45±0.80	0.002
Midparental height SD score	0.22±1.07	-0.62±1.34	-0.41±0.97	-0.47±1.29	0.03
Weight-for-length index — %	101±22	92±15	92±16	86±12	0.10

\* Plus-minus values are means ±SD. Data on the term small-for-gestational-age group are from Hofman et al.<sup>9</sup>

† Analysis of variance was used for continuous variables, and the chi-square test was used for proportions.

relative compensatory hyperinsulinemia required to maintain euglycemia in a state of reduced insulin sensitivity. Both the premature appropriate-for-gestational-age group and the premature small-for-gestational-age group had elevated acute insulin release, with values that were approximately 50 percent higher than those in the term control group ( $P < 0.001$ ). The acute insulin release was similar in both the premature small-for-gestational-age group and the premature appropriate-for-gestational-age group ( $P = 0.80$ ). Acute insulin release was associated with the weight-for-length index ( $P < 0.001$ ).

There were no significant differences among the groups in fasting insulin levels ( $P = 0.40$ ), the glucose disposal index ( $P = 0.90$ ), or glucose effectiveness ( $P = 0.30$ ). No variables were significantly associated with the glucose disposal index or glucose effectiveness, but the fasting insulin level was associated with the weight-for-length index ( $P < 0.001$ ).

DISCUSSION

Our observation that children 4 to 10 years of age who were born prematurely have an isolated reduction in insulin sensitivity suggests that they, like term infants who were small for gestational age, may be at increased risk for type 2 diabetes mellitus and other diseases of adulthood associated with insulin resistance. Children who were born at term but who were small for gestational age have a similar reduction in insulin sensitivity and have an increased risk of these adult-onset diseases.<sup>24</sup> The effect of low birth weight on the risk of disease in adulthood may be considerable; indeed, a meta-analysis estimated that up to 35 percent of the cases of type 2 diabetes mellitus are attributable to reduced birth weight.<sup>25</sup> Children born before 32 weeks' gestation are at least as common as term children who are born small for gestational age, comprising 1 to 2 percent of live-born children.

The reduction in insulin sensitivity in children who had been born prematurely was observed consistently among those with a gestational age of 32 weeks or less, with no effect of the length of gestation on the degree of insulin sensitivity. The subjects had a similar reduction in insulin sensitivity whether they had been born at 24 or 32 weeks' gestation, suggesting that there is a critical window during this time in which insulin sensitivity is permanently altered. This period would be equivalent to the early third trimester of pregnancy and may represent a critical time in utero for the occur-

rence of permanent metabolic changes. There remains debate about when permanent metabolic programming of the fetus occurs. Studies in animals and humans have suggested that there are probably several critical periods from the periconceptual period to later pregnancy.<sup>26,27</sup> Additional studies examining subjects who had been born prematurely would confirm the importance of this period and may provide further insight into the role of this critical period in the third trimester.

**Table 2. Maternal and Neonatal Characteristics in the Two Groups of Premature Subjects.\***

Characteristic	Premature Appropriate-for-Gestational-Age Group (N=27)	Premature Small-for-Gestational-Age Group (N=7)	P Value†‡
<b>Maternal</b>			
Preeclampsia — no. (%)	6 (22)	5 (71)	0.02
Vaginal delivery — no. (%)	13 (48)	0	0.02
Glucocorticoids — no. (%)			
Antenatal	19 (70)	4 (57)	0.4
Postnatal	11 (41)	2 (29)	0.4
<b>Neonatal</b>			
Mechanical ventilation — no. (%)	7 (26)	5 (71)	0.01
Days of ventilation (if ventilation used)			0.99
Mean	8	9	
95 percent confidence interval	0–41	0–37	
Days of CPAP‡			0.4
Mean	14	6	
95 percent confidence interval	0–42	0–39	
Days of oxygen			0.5
Mean	14	2	
95 percent confidence interval	0–547	0–76	
Days of parenteral nutrition			0.98
Mean	13	12	
95 percent confidence interval	0–37	6–26	
Days until full oral feeding instituted			0.2
Mean	15	20	
95 percent confidence interval	6–37	14–34	
Days on antibiotics			0.6
Mean	12	10	
95 percent confidence interval	2–30	5–36	

\* Only subjects with complete neonatal records were included. Subjects who received ventilation therapy for less than 12 hours were recorded as having zero days of ventilation therapy.

† Fisher's exact test was used for proportions, and the Mann-Whitney U test was used for days of treatment.

‡ CPAP denotes continuous positive airway pressure.

Table 3. Indicators of Glucose Regulation.\*

Variable	Premature Appropriate-for- Gestational-Age Group	Premature Small-for- Gestational-Age Group	Term Controls	Term Small-for- Gestational-Age Group
	mean (95 percent confidence interval)			
Insulin sensitivity ( $\times 10^{-4}/\text{min}^{-1}$ [mU/liter])	14.2 (11.5–16.2) <sup>†</sup>	12.9 (9.7–17.4) <sup>‡</sup>	21.6 (17.1–27.4)	15.1 (11.4–19.9)
Acute insulin release (pmol/liter)	2002 (2153–2432) <sup>§</sup>	2253 (1622–3128) <sup>§</sup>	1148 (875–1500)	1370 (940–2002)
Glucose effectiveness ( $\times 10^{-2}/\text{min}^{-1}$ )	1.92 (1.64–2.21)	2.08 (1.59–2.55)	2.34 (1.95–2.74)	2.64 (2.00–3.28)
Glucose disposal index ( $\times 10^{-2}$ [mg/day]/ $\text{min}^{-1}$ )	2.66 (2.36–2.96)	2.56 (2.05–3.08)	2.72 (2.25–3.19)	2.23 (1.70–2.77)
Fasting insulin (pmol/liter)	26.8 (17.5–41.0)	26.0 (21.8–31.5)	32.3 (25.0–41.7)	39.1 (35.3–43.2)

\* Values were derived from the minimal model for premature and term control cohorts. Age, sex, height SD score, weight-for-length index, birth-weight SD score, and midparental height SD score were controlled for in this analysis. Data on the term small-for-gestational-age cohort are historical<sup>9</sup> and for comparison only.

<sup>†</sup> P=0.004 for the comparison with term controls.

<sup>‡</sup> P=0.009 for the comparison with term controls.

<sup>§</sup> P<0.001 for the comparison with term controls.

Investigating the reasons for the reduction in insulin sensitivity in premature subjects may also increase our understanding of the similar permanent metabolic changes observed in term infants who were small for gestational age and had in utero growth restriction. Premature infants are more accessible than their in utero peers, and changes in their neonatal care may mitigate the later reduction in insulin sensitivity. Rodent models of insulin resistance (induced by a maternal diet low in protein, maternal total calorie deprivation, or maternal exposure to dexamethasone) to some degree mimic the metabolic abnormalities observed in term human infants with low birth weights.<sup>28–30</sup> Clinical similarities to these rodent models can be found in the early postnatal life of infants born prematurely who commonly have reduced neonatal protein and total caloric intakes or whose mothers have received courses of dexamethasone during pregnancy.

Despite these similarities to experimental models, we found no evidence that the severity of the neonatal course (as reflected by the use of antibiotic therapy and the duration of the requirement for supplemental oxygen), exposure to prenatal or postnatal glucocorticoids, or the presence of maternal gestational preeclampsia had any effect on insulin sensitivity. The pathogenesis of the alteration in insulin sensitivity in these children who were born prematurely remains to be elucidated, but further understanding of it might allow rational changes to

be made in neonatal care that will reduce the long-term complications.

A similar reduction in insulin sensitivity was observed in both children who had been born prematurely but were appropriate for gestational age and those who had been born prematurely but were small for gestational age. The combination of being both small for gestational age and premature indicates that growth restriction has occurred before delivery, reflecting an in utero insult before the third trimester. Since this combination did not result in greater insulin resistance than that seen in children who had been born at term, it is likely that an adverse in utero environment before the third trimester of pregnancy has minimal metabolic effect.

A recent study comparing preterm children who were appropriate for gestational age and preterm children who were small for gestational age, however, suggested that the in utero environment may be important, since preterm children who were small for gestational age had higher fasting insulin levels.<sup>31</sup> That study also used a short intravenous glucose-tolerance test and did not find a difference between children who were small for gestational age and those who were appropriate for gestational age using stimulated insulin release. Furthermore, no formal assessment of insulin sensitivity was performed with the use of these stimulated values. Fasting insulin levels have a relatively poor correlation with insulin sensitivity in children (r values between

0.40 and 0.60).<sup>9,22</sup> An appropriate assessment of insulin sensitivity in childhood requires the use of a well-accepted method, such as the hyperinsulinemic–euglycemic clamp or the minimal model, a point highlighted in our study.

A relatively large number of families declined to participate in our study, and the reason universally given was the invasive nature of the tests being performed. The subjects who had been born prematurely whose parents agreed to their participation, however, had neonatal characteristics similar to those of other surviving preterm children born at 32 weeks' gestation or less in Auckland.<sup>16</sup> Our cohort did have better clinical outcomes than the total cohort of surviving children who had been born prematurely, since we excluded subjects with major or moderate disability. On the basis of these neonatal characteristics and on the better developmental outcome of our cohort, we do not believe a selection bias occurred that influenced our findings.

The actual incidence of adult-onset type 2 diabetes mellitus among people who were born prematurely is unknown, since the first generation of very premature infants is only now surviving in substantial numbers. These survivors are currently young adults, and although there is a convincing epidemi-

ologic association between low birth weight and adult-onset disease, it remains to be established whether a similar relationship exists with prematurity. Our data support the need for close long-term monitoring of these subjects for diseases including obesity, type 2 diabetes mellitus, hypertension, and atherosclerosis.

The identification of an increased risk of disease well before any clinical manifestations occur leaves a large window of time in which to institute interventions that might delay or prevent overt disease. In adult populations at high risk for type 2 diabetes mellitus, healthy lifestyle choices or therapy with drugs that increase insulin sensitivity can delay the onset of disease.<sup>32</sup> Instituting lifestyle interventions in young adults or adolescents who are at risk might be even more beneficial, particularly in those with other risk factors such as weight gain and obesity.

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**CORRECTION**

**Premature Birth and Later Insulin Resistance**

Premature Birth and Later Insulin Resistance . On page 2179, line 11 under Results, and on page 2184, in Table 3, under the column heading Premature Appropriate-for-Gestational-Age Group, the 95 percent confidence interval for acute insulin release should have been 1434 to 2432, rather than 2153 to 2432, as printed.