Prematurity – Another Example of Perinatal Metabolic Programming?

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Key Words

Prematurity • Insulin resistance • Catch-up growth

Abstract

Low birth weight is associated with both later adult diseases such as type 2 diabetes mellitus and a number of metabolic abnormalities, the foremost of which is insulin resistance. Indeed the link between an adverse perinatal environment, manifested by low birth weight, and adult life pathology may be an early, permanent reduction in insulin sensitivity. A reduction in insulin sensitivity has been demonstrated in small for gestational age (SGA), term subjects from childhood through to adulthood. Less is known about children born premature into an adverse neonatal environment. We present data demonstrating that premature infants also have metabolic abnormalities similar to those observed in term, SGA children and that these occur irrespective of whether they are SGA or appropriate for gestational age (AGA).

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Introduction

The link between low birth weight (primarily term, small for gestational age (SGA) subjects) and adult disease was first described by Barker and subsequently confirmed by several other groups [1–9]. Low birth weight

has been significantly correlated with an increased risk of adult onset type 2 diabetes mellitus, hypertension, obesity, ischemic heart disease and cerebrovascular accidents. This combination of diseases is often referred to as the ‘metabolic syndrome’. Associated metabolic abnormalities in these subjects have included dyslipidemia, a procoagulation state, and insulin resistance. Of these abnormalities, insulin resistance has been demonstrated to be an early and consistent finding and it is likely that insulin resistance plays a prime role in the pathogenesis of the metabolic syndrome [10].

The evidence that isolated insulin resistance has long-term health implications is now well established. For instance, the risk of developing type 2 diabetes mellitus over a 20-year period in a group of young adults with a strong family history of type 2 diabetes was predicted by isolated insulin resistance [11]. In subjects who were insulin resistant the risk of developing diabetes was 40% as compared to <5% in those who were insulin sensitive. Insulin resistance has also been recognized as an early finding in essential hypertension and is observed in normotensive first-degree relatives of hypertensive subjects [12, 13]. A reduction in insulin sensitivity has also been associated with an increase in adult disease morbidity. Facchini et al. [14] divided otherwise healthy adult subjects into tertiles based on insulin sensitivity and observed them over a 4- to 11-year period.

Those subjects with moderate or severe insulin resistance had a marked increase not only in hypertension,

Table 1. Group characteristics

	Premature AGA	Premature SGA	Term controls	Term SGA
n	38	12	22	13
Age, years	6.7 ± 1.2	6.5 ± 1.8	7.4 ± 1.4	8.9 ± 2.3
Male sex, %	15 (39)	6 (50)	15 (68)	8 (62)
Gestation, weeks	27.6 ± 2.2	30.5 ± 3.1	39.3 ± 1.2 ^a	38.6 ± 1.8
Birth weight, g	1,098 ± 362	1,062 ± 340	3,311 ± 417 ^a	2,114 ± 490
Birth weight, SDS	-0.05 ± 0.76	-2.16 ± 0.80	-0.18 ± 0.74 ^b	-2.65 ± 1.29
Height, SDS	-0.2 ± 1.37	-1.24 ± 1.20	-1.50 ± 1.57 ^c	-2.45 ± 0.80
MPHSDS	0.22 ± 1.07	-0.62 ± 1.34	-0.41 ± 0.97 ^d	-0.47 ± 1.29
WLI, %	101 ± 22	92 ± 15	92 ± 16	86 ± 12

Characteristics of the premature and term controls cohorts. MPHSDS = Mid-parental height standard deviation score; WLI = weight for length index. The term SGA cohort represent historical data from a previous study and have been included for comparison only.

^ap < 0.0001 vs. premature groups, ^bp < 0.001 vs. premature SGA, ^cp < 0.01 vs. premature AGA, ^dp < 0.05 vs. premature AGA, values expressed as mean ± SDs.

coronary heart disease, type 2 diabetes and cerebrovascular accidents but also malignancy. Thus, an isolated reduction in insulin sensitivity is associated with many adult diseases characteristic of those associated with being born SGA.

Prematurity and Reduced Insulin Sensitivity

Premature birth (<37 weeks' gestation) is not uncommon comprising 11.6% of births in the USA [15]. Even very premature infants (<33 weeks' gestation) now comprise 2.5% of total annual births. This increasing prevalence of premature survivors is a reflection on the rapid and dramatic improvements in neonatal care over the past 30 years. Indeed, long-term survival with gestational ages from 24 to 32 weeks has become an almost expected outcome over the past two decades [16]. With this improvement in outcome, the focus has shifted from solely resuscitation and neonatal survival to include the later consequences of prematurity. Not surprisingly there has been an emphasis on improving developmental outcome, behavioral problems and growth in premature children. However, recent research has indicated that metabolic abnormalities are also present, and in particular a reduction in insulin sensitivity.

We have recently published data on 50 very premature children (born <33 weeks' gestation), 22 control children (born at term of normal birth weight) and 12 term SGA children (birth weight <10th percentile) [17]. All subjects

were healthy, aged 4–10 years old, developmentally normal and prepubertal (table 1). Intravenous glucose tolerance tests were performed and Bergman's Minimal Model used to estimate parameters of glucose homeostasis (table 2). Our data indicated the premature children had an approximately 40% reduction in insulin sensitivity compared to the control children. Further support for an early alteration in insulin sensitivity has come from studies in the neonatal and early infant period [18–20]. These studies indicate that, like term SGA subjects, metabolic abnormalities in prematurely born subjects occur early in life. As term SGA and premature children had a similar reduction in insulin sensitivity, it is possible that prematurity may also be associated with an increased risk of later adult diseases.

The Developmental Origins of Disease

Fetal programming has been proposed by Barker and Hales to explain the observations linking early life events such as low birth weight and later adult pathology. During proposed critical periods of fetal and early infant life, it has been hypothesized that subjects exposed to an adverse environment develop compensatory responses to survive that become permanent or programmed. These responses can become maladaptive if the environment for which they were developed is not that expected or predicted by the intrauterine environment. This would occur, for instance, in SGA children who were undernour-

Table 2. Glucose regulation parameters

	Premature AGA	Premature SGA	Term controls	Term SGA
S_I ($10^{-4}/\text{min}^{-1}$), mU/l	14.2 (11.5–16.2) ^a	12.9 (9.7–17.4) ^b	21.6 (17.1–27.4)	15.1 (11.4–19.9)
AIR, pmol/l	2,002 (1,434–2,432) ^c	2,253 (1,622–3,128) ^c	1,148 (875–1,500)	1,370 (940–2,002)
S_g ($10^{-2}/\text{min}^{-1}$)	1.92 (1.64–2.21)	2.08 (1.59–2.55)	2.34 (1.95–2.74)	2.64 (2.00–3.28)
K_g ($10^{-2}/\text{min}^{-1}$), mg/day	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/l	26.8 (17.5–41.0)	26.0 (21.8–31.5)	32.3 (25.0–41.7)	39.1 (35.3–43.2)

S_I = Insulin sensitivity index; AIR = acute insulin response (insulin release over the first 10 min of the IVGTT); S_g = glucose effectiveness (the ability of glucose to increase its own uptake and reduce its own production); K_g = glucose disposal coefficient (the negative log of the slope of glucose decline from 10 to 19 min during an IVGTT). Values are means with 95% confidence intervals in parentheses. ^a $p < 0.005$ vs. term controls; ^b $p < 0.01$ vs. term control; ^c $p < 0.001$ vs. term controls.

These values were derived from the Minimal Model for premature and term control cohorts. Age, sex, height SDS, weight for length index (WLI; a measure of relative adiposity with 100% being normal), birth weight SDS and mid-parental height SDS (MPHSDS) were controlled for in this analysis. Term SGA data is historical and for comparison only.

ished in utero and are then born into an environment of plenty. Similarly, the neonatal environment for premature infants (developmentally equivalent to the third trimester of pregnancy) is abnormal compared to in utero and could result in premature neonates perceiving a nutrient-restricted environment. Despite expert neonatal care, premature delivery results in poor early growth, inadequate and imbalanced nutrient delivery and increased physiological stress. The Fetal Salvage Hypothesis proposed by our group suggests that in a nutrient-poor in utero environment (such as that experienced in a pregnancy complicated by utero-placental insufficiency) all available glucose needs to be diverted to essential organs [21]. The development of insulin resistance diverts glucose away from muscle and fat to these organs, while still maintaining some insulin secretion, a hormone that plays other essential roles in fetal homeostasis (such as regulation of the IGF-I axis) separate from its role in carbohydrate metabolism. A similar mechanism may occur in very premature infants who are either unable to utilize or obtain adequate nutrition. Once nutrition is more readily available maladaptive responses related to this reduced insulin sensitivity could occur.

The evidence that prematurity is associated with later adult disease is scant, primarily due to a lack of older survivors. High survival rates from more extreme prematu-

rity are a modern phenomenon (20–30 years) and these survivors are not yet in the at-risk age group for the diseases identified from SGA studies. There has been one publication in prematurely born young adults (mean age 24 years) that indicated elevated systolic and diastolic blood pressures compared to a term normal birth weight cohort [22]. These subjects also had slightly but significantly elevated fasting insulin levels suggesting they may have reduced insulin sensitivity. Prematurity may also increase the risk of developing abdominal obesity [23]. If this is the case, then any underlying impairment in insulin sensitivity will be amplified.

Potential Causes for the Reduced Insulin Sensitivity in Prematurity

As prematurity results in what appears to be an early and permanent reduction in insulin sensitivity, what perinatal event or events may have caused this change? We found no association between insulin resistance and either birth weight or gestational age (<33 weeks) [17]. Similarly no difference was found in insulin sensitivity between appropriate for gestational age (AGA) or SGA premature children, although there was a nonsignificant reduction in insulin sensitivity (~15%) in the SGA group.

Table 3. Neonatal characteristics of premature subjects

	Premature AGA (n = 27)	Premature SGA (n = 7)	p value*
Preeclampsia, %	6 (22)	5 (71)	0.02
Vaginal delivery, %	13 (48)	0 (0)	0.02
Antenatal steroids, %	19 (70)	4 (57)	0.4
Postnatal steroids, %	11 (41)	2 (29)	0.4
Subjects ventilated, %	7 (26)	5 (71)	0.01
Days of ventilation (if ventilated)	8 (0–41)	9 (0–37)	0.99
Days of CPAP	14 (0–42)	6 (0–39)	0.4
Days of oxygen	14 (0–547)	2 (0–6)	0.5
Days of parenteral nutrition	13 (0–37)	12 (6–26)	0.98
Days until full oral feeding	15 (6–37)	20 (14–34)	0.2
Days on antibiotics	12 (2–30)	9.5 (5–36)	0.6

Neonatal characteristics of preterm AGA and SGA children where complete neonatal records available. Values are expressed as the number of subjects (percentage) or mean with 95% confidence intervals. * From Fisher's exact test for proportions and Mann-Whitney U for days of treatment.

Table 4. Actual intake vs. recommended intake

	Canadian recommended 0–4 weeks	Intake 0–4 weeks mean $\pm$ SEM	Canadian recommended 4–12 weeks	Intake 4–8 weeks mean $\pm$ SEM	Intake 8–12 weeks mean $\pm$ SEM
n		34		31	24
Energy, kJ/kg/day	402–508	454 $\pm$ 10	438–563	626 $\pm$ 10	577 $\pm$ 6
Protein, g/kg/day	2.9–3.75	2.34 $\pm$ 0.05	3.5–4.0	3.01 $\pm$ 0.08	2.26 $\pm$ 0.14
Lipid, g/kg/day	3.5–6	5.60 $\pm$ 0.18	4.5–6.8	8.15 $\pm$ 0.16	8.1 $\pm$ 0.1
CHO, g/kg/day	6.9–16.6	13.51 $\pm$ 0.2	7.5–15.5	15.95 $\pm$ 0.23	13.57 $\pm$ 0.29

Comparison of nutrient intake at 0–4, 4–8 and 8–12 weeks in premature children as compared to recommended macronutrient and total energy intake [52–54].

Other studies have demonstrated differences between premature SGA and AGA premature and children with the SGA group being more insulin resistant [24]. Our findings may reflect a lack of sample size to detect a modest difference between groups, the more sensitive assessment of insulin sensitivity we used or possibly other factors unique to our cohort including local differences in neonatal care and etiology of the prematurity. Nevertheless, both the premature SGA and AGA group in our cohort were substantially more insulin resistant compared to the control term AGA group.

Other factors that may determine this reduction in insulin sensitivity could reflect maternal, placental, fetal or neonatal variables. To investigate this further we have examined the antenatal and neonatal course of 34 prema-

ture infants (27 AGA; 7 SGA) [17]. Insulin sensitivity was modeled against a number of variables such as cause for prematurity (e.g. preeclampsia), drug use prior to delivery (e.g. antenatal glucocorticoid therapy), severity of illness in the neonatal unit (e.g. days on ventilator, days on oxygen, days of antibiotic use), nutrition (e.g. total carbohydrate, protein and fat in g/kg/day), postnatal weight gain to term equivalent (40 weeks) and to 1 year of age. These results are summarized in table 3. None of the other variables demonstrated significant differences.

While not detecting differences between nutrition and insulin sensitivity our data demonstrated that macronutrient intake in our children during the neonatal period was consistently abnormal (table 4). During the first 3 months of life these children almost universally had a diet

deficient in protein and for much of that time had excess fat (mainly as intralipid or medium-chain triglyceride oil). Because diet was very similar among all the premature children, it is not surprising that no associations were made between diet and insulin sensitivity.

Animal models mimicking the metabolic syndrome in humans have used a number of maternal insults including severe dietary restriction, specific maternal protein restriction, uterine artery ligation and prenatal dexamethasone exposure [25–29]. It is noteworthy that protein restriction in the rat dams had similar metabolic effects in offspring compared to our subjects who were also protein restricted. Although in our case the protein restriction was postnatal, this may be a useful model to understand the pathogenesis of nutrient alteration. It could be argued that an extremely premature neonate is equivalent to a fetus in the third trimester of pregnancy and nutritional restriction at this time is equivalent to uteroplacental insufficiency in late pregnancy. If macronutrient intake is a determinant in the metabolic perturbations observed in prematurity, then optimization of nutrition may well be able to prevent these abnormalities to occur.

Insulin Sensitivity, Catch-Up Growth and Fat Mass: The Interaction

Pathological insulin resistance and the metabolic syndrome are not necessarily the inevitable consequences of an early, isolated reduction in insulin sensitivity. Insulin sensitivity is an interaction of both genetic and environmental factors, of which one is early life environment. Puberty, physical activity, diet and drug use can all modify insulin sensitivity. However, the greatest single variable contributing to insulin sensitivity in healthy children and adults is fat mass [30]. This was elegantly demonstrated by Hypponen et al. [31] who examined the prevalence of type 2 diabetes at 41 years of age in 10,683 subjects followed from birth. In this cohort, 88 subjects were diagnosed with type 2 diabetes; there was doubling of the risk of developing diabetes in those born in the lowest tertile. However, in subjects born with birth weights in the lowest tertile, all had body mass indexes in the upper tertile indicating the requirement for both to develop type 2 diabetes mellitus. Other studies have also confirmed that increased fat mass amplifies the reduction in insulin sensitivity and magnifies the metabolic problems in both term SGA and premature groups [32–34]. Thus, changes in body composition are relevant to the manifes-

tation of clinical pathology from these metabolic abnormalities in term SGA and premature subjects. In our study, we found no effect of catch-up growth either from birth to 40 weeks corrected age or to 1 year of age. This may have been because we controlled for weight in our regression modeling of insulin sensitivity. However, change in weight SDS from birth to childhood was correlated with insulin sensitivity ($r^2 = 0.32$), with greater weight gain associated with lower insulin sensitivity.

Other outcome measures of low birth weight subjects have been positively linked to greater postnatal catch-up growth including improved head growth, neurodevelopmental outcome and even later income [35–37]. Thus, early improvement in growth appears beneficial for a number of important outcomes. There have been several controversial studies suggesting that restricting postnatal catch-up after prematurity will avoid later metabolic abnormalities [38–40]. These papers, however, did not measure insulin sensitivity directly, and were not specifically designed to examine questions regarding postnatal growth sequelae. As indicated by our findings, if nutrition is involved then dietary restriction is more likely to be causal and it may be possible to alter this early metabolic programming by improving specific macro- or micronutrient deficiencies in the neonatal period. Caution should also be used in suggesting restricting catch-up growth given the importance of early postnatal growth to later neurocognitive outcome.

Although the effect of ‘catch-up’ postnatal growth on later metabolic sequelae remains debatable, in utero undernutrition does appear to increase the risk of obesity in adulthood [41]. Term SGA subjects who had greater catch-up growth in the first 2 years had an increased body fat mass and more central fat compared with children of normal birth weight [41]. This increase in fat mass accumulation occurs at least into early adulthood leading to a significantly increased body fat mass at 25 years of age compared with normal birth weight controls [42, 43].

There is limited data available examining body composition in prematurely born subjects and the longitudinal change in lean body mass and fat mass with age. Atkinson et al. [44], using DEXA analysis, found that preterm children, at 40 weeks’ corrected gestation, had differences in body composition with elevated fat mass and reduced lean mass compared to healthy term equivalents. Other studies using DEXA have demonstrated no difference in lean body mass or fat mass when adjusted for the smaller size of the preterm children [45]. Changes in body composition have been noted up to one year of age in premature infants who receive higher caloric nutri-

tion and demonstrate greater catch-up growth [46]. Not surprisingly, they had greater fat mass (both total and as a percentage of body weight) and greater lean mass than the less well nourished and smaller preterm infants. More recently, Uthaya et al. [23] using MRI have demonstrated specific abnormalities in the partitioning of fat in premature infants at the equivalent of 40 weeks' gestation versus a group of healthy term neonates. They demonstrated that there was an increase in visceral fat and a reduction in subcutaneous fat. Visceral adiposity is strongly associated with insulin resistance in adults and may be a cause for the insulin resistance we have observed. If this pattern of fat distribution persists into adulthood, it could greatly increase the risk of later type 2 diabetes, hypertension and atherosclerosis.

However, there is a paucity of longitudinal data on body composition in premature children with no information available after one year of age. Several longitudinal studies have evaluated postnatal growth and weight gain in preterm children and related these findings to size and measures of adiposity later in adolescence or adulthood [47–50]. Generally, increased adiposity was observed in early adulthood. Euser et al. [51] found that ear-

ly postnatal weight gain in preterm children was associated with a higher percentage of body fat, more abdominal fat and higher BMI at 19 years. However, their report lacked detail about body composition in early postnatal life and only showed data about weight, length and head circumference.

Conclusions

In summary, prematurity appears to convey a risk of reduced insulin sensitivity similar in magnitude to that observed in term SGA children. This metabolic perturbation likely occurs during the neonatal period and is probably a result of nutritional and other perinatal factors. It has not yet been demonstrated that this reduction in insulin sensitivity will translate into an increased risk of later adult disease but is likely to be an added risk factor. Unlike SGA children, the insult with prematurity is postnatal and therefore potentially correctable. By further identifying and understanding the pathogenesis of these metabolic changes it may be possible to modify this reduction in insulin sensitivity.

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