Symposium on ‘Nutrition in early life: new horizons in a new century’

Session 7: Early nutrition and later health
Early developmental pathways of obesity and diabetes risk

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Size at birth and patterns of postnatal weight gain have been associated with adult risk for the development of type 2 diabetes in many populations, but the putative pathophysiological link remains unknown. Studies of contemporary populations indicate that rapid infancy weight gain, which may follow fetal growth restriction, is an important risk factor for the development of childhood obesity and insulin resistance. Data from the Avon Longitudinal Study of Pregnancy and Childhood shows that rapid catch-up weight gain can lead to the development of insulin resistance, as early as 1 year of age, in association with increasing accumulation of central abdominal fat mass. In contrast, the disposition index, which reflects the β-cells ability to maintain insulin secretion in the face of increasing insulin resistance, is much more closely related to ponderal index at birth than postnatal catch-up weight gain. Infants with the lowest ponderal index at birth show a reduced disposition index at aged 8 years associated with increases in fasting NEFA levels. The disposition index is also closely related to childhood height gain and insulin-like growth factor-I (IGF-I) levels; reduced insulin secretory capacity being associated with reduced statural growth, and relatively short stature with reduced IGF-I levels at age 8 years. IGF-I may have an important role in the maintenance of β-cell mass, as demonstrated by recent studies of pancreatic β-cell IGF-I receptor knock-out and adult observational studies indicating that low IGF-I levels are predictive of subsequent risk for the development of type 2 diabetes. However, as insulin secretion is an important determinant of IGF-I levels, cause and effect may be difficult to establish. In conclusion, although rapid infancy weight gain and increasing rates of childhood obesity will increase the risk for the development of insulin resistance, prenatal and postnatal determinants of β-cell mass may ultimately be the most important determinants of an individual’s ability to maintain insulin secretion in the face of increasing insulin resistance, and thus risk for the development of type 2 diabetes.

Childhood obesity: Insulin resistance: Catch-up growth: Insulin-like growth factor-I

It is over 15 years since Barker and Hales (Hales et al. 1991; Hales & Barker, 1992) first published their observations of the relationship between size at birth and adult risk for the development of impaired glucose tolerance and type 2 diabetes (T2D). Through study of historical birth records they noted a continuous increase in risk for impaired glucose tolerance and T2D with decreasing birth weight; the smallest babies having an OR of 6.6 compared with those with the highest birth weight (Hales et al. 1991). These observations have been replicated in other
populations and do not appear to be confounded by socio-economic and other environmental factors. Eriksson et al. (2003) have studied a large Finnish birth cohort and have described size at birth and early postnatal growth patterns for 290 adults with T2D. It was found that 66% of the subjects with T2D were born smaller than average, and they showed rapid weight gain during the first 2 years of life and continued to gain weight rapidly. Furthermore, 34% of subjects with T2D had relatively large birth weights, possibly as a result of gestational diabetes, and these subjects demonstrated initial losses in weight and length centile position; but again from the age of 2 years these children gained in weight centile progressively and became obese. Several other studies (Pettitt et al. 1987; Silverman et al. 1991; Dabelea et al. 2000; Sobngwi et al. 2003) have shown that offspring of mothers with gestational diabetes, type 1 diabetes or T2D are at increased risk for the development of obesity and T2D.

These epidemiological data have been gathered largely through the retrospective study of birth records of subjects who had subsequently developed T2D. Thus, they are robust in relation to the outcome measures, but the birth and growth data are limited and pathophysiological mechanisms underlying these associations remain unclear. A considerable amount of information has become available from a variety of animal models showing that prenatal fetal undernutrition can lead to reductions in β-cell mass and confer risk of diabetes, particularly if the animals are overfed in the early postnatal period (Reusens & Remacle, 2006). In human subjects the study of contemporary birth cohorts, such as the Avon Longitudinal Study of Parents and Children (ALSPAC; Ness, 2004; Ong & Dunger, 2004), has provided detailed information on pregnancy and follow-up measurements through early infancy into adolescent years. Other population studies (Ibanez et al. 2006; Iniguez et al. 2006) have compared children born small-for-gestational age with subjects who were appropriate-for-gestational age. It is the purpose of the present article to review what has been learned about how the pathways from smaller size at birth through rapid infancy weight gain lead to future risk of T2D.

**Prenatal exposures**

The critical windows of prenatal and early postnatal life proposed by Widdowson & McCance (1975) appear to be important in determining the long-term risk for diabetes. In human subjects, in addition to fetal genes, the maternal uterine environment is an important determinant of size at birth (Ong et al. 2000). The growth of first-born babies appears to be restrained as they are smaller at birth and then show postnatal rapid catch-up weight gain (Ong et al. 2002). In these first-borns birth weight correlations with maternal and grand-maternal birth weights are particularly strong (Ounsted et al. 1986, 1988). The nature of this maternal inheritance of birth weight is unclear. Associations between birth weight and common genetic variation in mitochondrial genes, which are inherited only from the mother, and imprinted genes, where only the maternal copy is expressed, have been described (Casteels et al. 1999; Petry et al. 2005). More recently, attention has turned to epigenetic mechanisms whereby the maternal uterine environment could permanently alter methylation marks on the genome and therefore later gene expression (Engel et al. 2004). Curiously, low birth weight in the mother is also associated with an increased risk of gestational diabetes in the offspring (Seghieri et al. 2002). This observation brings forth the paradox of associations between both low and high birth weights and increased risks for T2D. In the Cambridge Birth Cohort mothers of first-born babies were found to have higher blood glucose levels than others who were having their second or third baby (Petry et al. 2005), and it is possible that the mechanisms for maternal restraint of fetal growth could also, in genetically-susceptible individuals, lead to gestational diabetes (Fig. 1). The mechanisms underlying programming of diabetes risk *in utero* are likely to be complex and probably involve an interaction between fetal genes and the maternal uterine environment. It is becoming clearer that these prenatal interactions increase the subsequent risk for the development of insulin resistance and obesity, and may be associated with reduced β-cell mass and thus risk for T2D.

**Catch-up weight gain and insulin sensitivity**

In the ALSPAC cohort about 25% of infants were found to show postnatal rapid catch-up weight gain (they crossed

![Fig. 1. Maternal glucose levels at 1 h after an oral glucose load at 27–32 weeks of gestation in the Cambridge Birth Cohort, by mother’s H19 2992 genotype (CC, ■; T* (CT or TT), (□)) and stratified by birth order (primip, mother’s first child; non-primip, second or subsequent child). Values are means and 95% CI represented by vertical bars. Associations with mother’s genotype (CC v. T*) were only seen in first pregnancies (P = 0.01). (Reproduced from Petry et al. 2005, with the permission of BMC Genetics.)](https://www.cambridge.org/core/terms)
centiles upwards over the first 6–12 months), with approximately 25% exhibiting relative catch-down in weight relative to their birth centile (Ong et al. 2000). The remaining infants grew steadily along the weight centile on which they were born. It has been debated whether this realignment of growth patterns represents true 'catch-up' and 'catch-down' growth; observations in the ALSPAC cohort (Ong et al. 2000) would indicate that they are clearly related to prenatal factors such as parity, maternal smoking and maternal birth weight, indicating reversal of the effects of restraint or enhancement of fetal growth. Catch-up weight gain seems to be driven by satiety, as it can be predicted from cord blood leptin and ghrelin levels (Ong et al. 1999; Gohlke et al. 2005), and is associated with increased levels of nutrient intake at age 4 months (Ong et al. 2006). Catch-up in height also occurs in these infants, but is generally completed by the age of 6–12 months and growth then continues along a centile appropriate for mid-parental height. In contrast, the rapid weight gain may continue, and in the ALSPAC cohort the early-'catch-up' group was found to have the greatest BMI, percentage body fat and fat mass at age 5 years when compared with the no change or ‘catch-down’ groups (Ong et al. 2000). In addition, 'catch-up' infants were found to have an increased waist circumference at 5 years, which may be critical in relation to future metabolic risk.

Central adiposity and accumulation of visceral fat in particular are important risk factors for the development of insulin resistance (Garnett et al. 2001), and in a study of small-for-gestational-age infants v. appropriate-for-gestational-age infants an accretion of excess central fat in small-for-gestational-age infants between ages 2 and 4 years has been described (Ibanez et al. 2006). Garnett et al. (2001) have shown that for each tertile of weight at 8 years infants with low birth weight have the greatest percentage of abdominal fat. In the ALSPAC cohort it was found (Ong et al. 2004) that 'catch-up' infants are the most insulin resistant at age 8 years, and it is the overweight children aged 8 years with the lowest birth weight who are the most insulin resistant, but the effect of size at birth is only evident in those in the highest tertile of weight at 8 years (Fig. 2).

Rapid postnatal weight gain also appears to lead to more rapid maturation and earlier age at the onset of puberty (dos Santos Silva et al. 2002). This outcome has also become evident in the ALSPAC cohort, and there appears to be a strong trans-generational effect. The offspring of mothers with early age at menarche are relatively small at birth and show the classical catch-up weight gain growth pattern. In contrast, the offspring of mothers who had a late menarche are slightly larger at birth and show postnatal catch-down in weight (KK Ong and DB Dunger, unpublished results). This trans-generational effect again indicates the importance of maternal genes and may suggest epigenetic modulation of fetal genes.

**Height gain and insulin secretion**

Catch-up growth appears to be driven by decreased satiety (Ounsted & Sleigh, 1975), and it is a risk factor for the development of central adiposity and insulin resistance (Ong et al. 2004). However, insulin resistance per se only leads to diabetes if there is failure of β-cell compensation.

The relationship between insulin resistance and insulin secretion is parabolic and β-cell capacity is best described by the product of the two; the ‘disposition index’ (Stumvoll et al. 2005). In ALSPAC this index was assessed at age 8 years in >800 children using a short oral glucose-tolerance test with measurements of glucose and insulin at 0 and 30 min, in which insulin secretion was estimated by calculating the insulinogenic index and homeostasis model assessment gave an estimate of insulin sensitivity. A lower disposition index was shown to be associated with lower ponderal index at birth, but not with the rate of postnatal weight gain (Ong et al. 2004). It was also found to be closely related to height, mid-parental height and insulin-like growth factor-I (IGF-I) levels; the children showing the least gains in postnatal height and with the lowest IGF-I levels were found to have the lowest disposition index (Ong et al. 2004). Similar data have been reported from a Chilean cohort of small-for-gestational-age and appropriate-for-gestational-age infants studied at a much earlier age (Iniguez et al. 2006). The difference in height gain between children in the highest and lowest tertiles of insulin secretion adjusted for sensitivity and IGF-I levels at 8 years is striking. The children with relatively poor insulin secretion aged 8 years show a pronounced loss in height so
score and reduced levels of IGF-I between ages 6 months to 1 year (Fig. 3). This period is critical for determining height trajectory (Widdowson & McCance, 1975), which in early infancy is regulated by insulin and IGF-I (Silbergeld et al., 1989; Low et al., 2001; Ong et al., 2006).

Thus, following prenatal growth restraint catch-up growth driven by reduced satiety can lead to insulin resistance and visceral fat accumulation, but height gain and IGF-I levels may be more important markers of β-cell mass and the subsequent risk for the development of T2D. ALSPAC has shown that children with the least height gain by 8 years have the lowest insulin secretion, despite being relatively insulin sensitive. Indeed, the insulin sensitivity may be an adaptive response to poor insulin secretion. However, the children who probably give the greatest concern are those with the lowest insulin sensitivity, and although they show compensatory hyperinsulinaemia, their insulin secretion is less than that seen in the other subjects (B Salgin, KK Ong, CJ Petry, P Emmett and DB Dunger, unpublished results). The same relationship between height and IGF-I levels has been observed in adults who go on to develop T2D. However, studies of genetic defects associated with T2D in relation to size at birth (Hattersley et al., 1998) give variable results, with either no association or an association between genetic markers of T2D risk and larger, rather than smaller, size at birth. An alternative hypothesis is that the in utero environment effects epigenetic changes in transcription factors that regulate β-cell development and mass (Engel et al., 2004). A further proposal (Jensen et al., 2003) is that the in utero environment may programme hormonal axes that are important in maintaining β-cell mass.

A particular interest has been in the relationship between IGF-I levels, height gain and β-cell mass, which has been investigated in the ALSPAC cohort. Higher IGF-I levels at 5 years predict greater β-cell function at age 8 years (Ong et al., 2004), paralleling the observations made in the MRC Ely adult cohort (Sandhu et al., 2002). β-Cell function is closely related to height and lean body mass, which are regulated by IGF-I. Experimental knock-out studies of the IGF-I and insulin receptor genes in the β-cell leads to failure of β-cell development and loss of insulin secretion (van Haften & Twickler, 2004; Ueki et al., 2006). Furthermore, IGF-I deficiency in adults is associated with

**Maintenance of β-cell mass**

What is remarkable about these data linking size at birth, childhood gains in height and weight and risk for T2D is that the exposure occurs in early life yet the disease outcome may be delayed by 30–60 years. β-Cell mass increases continuously with growth and is known to accelerate in obese subjects and during pregnancy (Van Assche et al., 1978; Bonner-Weir et al., 1989; Bruning et al., 1997). Thus, β-cell mass is not a fixed entity and how early developmental influences could become ‘hard-wired’ needs to be understood. Fetal insulin secretion in utero is an important determinant of size at birth and it has been proposed (Fowden, 1989; Hattersley et al., 1998) that genetic defects affecting insulin secretion could explain both size at birth and disease outcome. However, studies of genetic defects associated with T2D in relation to size at birth (Hattersley et al., 1998) give variable results, with either no association or an association between genetic markers of T2D risk and larger, rather than smaller, size at birth. An alternative hypothesis is that the in utero environment effects epigenetic changes in transcription factors that regulate β-cell development and mass (Engel et al., 2004). A further proposal (Jensen et al., 2003) is that the in utero environment may programme hormonal axes that are important in maintaining β-cell mass.
gains in abdominal adiposity, insulin resistance and T2D risk (Sandhu et al. 2002; Dunger et al. 2003). Thus, impaired IGF-I production throughout childhood and adult life could be one element in explaining links between size at birth and adult T2D risk. However, as IGF-I levels are determined by insulin secretion (Holly et al. 1989), cause and effect may be difficult to identify, yet IGF-I may be a determinant of insulin secretion (Kulkarni et al. 2002; Xuan et al. 2002). This hypothesis can be tested and aetiological trials are currently being carried out in the MRC Ely cohort to look at the effects of low-dose growth hormone, which lead to small increases in IGF-I levels (Yuen et al. 2005), on insulin secretion and the risk for the development of impaired glucose tolerance (Yuen et al. 2004).

Conclusion

Understanding the mechanisms underlying links between size at birth and risk for T2D has important implications for public health. In countries such as India, where nutrition has recently improved, particularly with population migration from rural to urban environments or emigration, babies born small are at high risk for developing T2D (McKeigue et al. 1991; World Health Organization Expert Consultation, 2004). In contemporary Western countries the risks associated with low birth weight as a result of poor maternal nutrition during pregnancy are much lower (Godfrey et al. 1997; Rogers et al. 1998; Mathews et al. 1999); however, the risks related to increasing rates of maternal obesity and gestational diabetes are of greater concern (Reilly et al. 1999; Dabelea et al. 2000; Bundeed et al. 2001). A recent study of women in Eastern Europe (Hesse et al. 2003) has shown that an increase in maternal pregnancy weight gain is one of the first responses to socio-economic improvement. Data from the Pima Indians (Franks et al. 2006) demonstrate that even borderline increases in maternal blood glucose levels during pregnancy may increase risk of T2D in the offspring.

The complex interaction between the maternal uterine environment and fetal genes has evolved over many thousands of years to optimise maternal and fetal survival (Neel, 1962; Haig, 1996). The recent changes in the nutritional status of mothers and offspring may not just be associated with obesity, but could also alter the balance of risk for adult disease such as T2D.

References


