Endocrinology and diabetes

G11 THE SPECTRUM OF HYPOCALCAEMIA IN AUTOIMMUNE POLYENDOCRINOPATHY, CANDIDIASIS, ECTODERMAL DYSPLASIA AND THE PHENOMENON OF TREATMENT RESISTANCE

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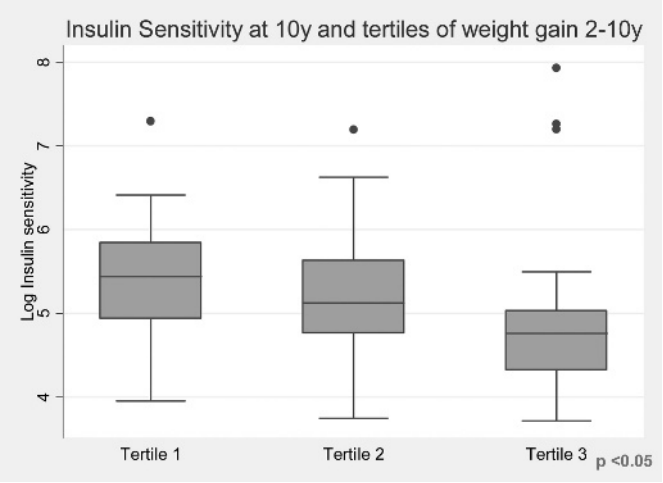
Background: Patients with autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia (APECED) (*AIRE* mutation positive) are particularly susceptible to hypocalcaemia. This is due to a complex interplay between hypoparathyroidism, autoimmune enteropathy and as yet unknown factors.
Aim: We describe the spectrum of hypocalcaemia encountered in patients with APECED and the range of therapies used in its treatment, from low-dose alfacalcidol (1-alpha) to major immunosuppressive therapy.
Methods: Data were collated from the Irish APECED population (n = 31).
Patients: 26 patients had hypoparathyroidism, all treated with 1-alpha. Hypocalcaemia secondary to hypoparathyroidism initially presented at a mean of 7 years.
Results: Many patients required supraphysiological dosages of 1-alpha. In addition, four patients required daily subcutaneous parathyroid hormone (PTH) injections, of which three progressed to intravenous calcium dependency (after up to 4 years of PTH). They had four episodes of prolonged intravenous dependency with requirements for very high calcium dosages (up to 0.99 mmol/kg per day). All patients had comorbid autoimmune enteropathy. All patients had normal serum albumin. The urinary calcium : creatine ratio was appropriately suppressed in all patients; however, all had preceding nephrocalcinosis. At present, one patient is maintained on a daily bolus of intravenous calcium, in addition to 1-alpha 25 μg twice a day. One patient was weaned from intravenous calcium after 6 days with intramuscular vitamin D stosstherapy and megadose 1-alpha (20 μg twice a day). One patient remained on continuous intravenous calcium infusion for a total of 48 days and was weaned after therapy with high-dose prednisolone, mycophenolate mofetil and intravenous 1-alpha. Previous unsuccessful treatments included pulsed methylprednisolone, vitamin D stosstherapy and azathioprine.
Conclusion: The range of hypocalcaemia in patients with APECED is wide and evolving treatment resistance may be difficult to manage, necessitating continuous calcium infusion for the maintenance of a normal serum level. There may be a beneficial role for large doses of 1-alpha vitamin D and immunosuppression.



G12 Figure Insulin sensitivity at 11 years and tertiles of weight gain from 2 to 11 years.

G12 INSULIN SENSITIVITY AND BODY COMPOSITION IN 11-YEAR-OLD CHILDREN BORN PRETERM

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Background: Term infants born small for gestational age who show rapid weight gain during infancy are more likely to develop diabetes in later life. However, little is known about such outcomes in preterm infants.
Objective: To examine the relationship between growth and insulin sensitivity in children born preterm.
Design/Methods: 164 children born at a median gestational age of 30.9 weeks (interquartile range (IQR) 29.1–32.4) and birth weight 1390 g (IQR 1155–1630) were recruited from a controlled trial of post-discharge nutritional intervention. The assessment included auxology, body composition using dual *x* ray absorptiometry (n = 139), fasting and 30 minute plasma glucose and insulin and fasting lipid profiles (n = 109).
Results: The median age at assessment was 11.3 years (IQR 9.5–12.5). Girls had a greater total fat percentage (median 33.1; IQR 26.9–39.3) than boys (median 25.5; IQR 20.8–37.7; p = 0.0009). Birth weight SD scores and gestational age did not influence insulin sensitivity. Insulin sensitivity decreased with the increasing weight gain tertile from 2 to 12 years (see fig) but this effect was only significant in pubertal children. Using a step-wise regression model, only current age, puberty and percentage of total fat were significantly associated with insulin sensitivity. 20/109 children had a low-density lipoprotein cholesterol level of more than 3 mmol/l.
Conclusions: Changes in insulin sensitivity, fat deposition and bone mineral content at 10 years in children born preterm are sex dependent and are largely explained by childhood growth and pubertal status. Markers of the metabolic syndrome are prevalent in this population.

G13 INFANTS OF MOTHERS WITH DIABETES DEMONSTRATE ALTERED ADIPOSITY AT BIRTH IN COMPARISON WITH HEALTHY TERM NEONATES

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Background and Aims: Infants of mothers with diabetes are at an increased risk of obesity and type 2 diabetes. Increased adipose tissue and altered adipose tissue partitioning are biomarkers for metabolic risk. It is uncertain whether infants of mothers with diabetes have increased adipose tissue and lean body mass (LBM) at birth. We aimed to compare adipose tissue content, distribution and LBM in infants of mothers with diabetes and healthy term neonates.
Methods: We performed whole-body adipose tissue magnetic resonance imaging in natural sleep within 2 weeks of birth in accordance with our previously described techniques. Research ethics approval and parental consent were obtained. We calculated that 26 infants in each group would have 80% power (5% significance) to detect a difference of 0.168 litres in total adipose tissue. Images were analysed to predefined parameters, blind to group allocation. Superficial subcutaneous, deep subcutaneous and internal adipose tissue compartments were quantified. Adipose tissue volume was converted to mass assuming a density of 0.8 g/ml.
Results: To date eight infants of mothers with diabetes from pregnancies with good glycaemic control and 26 healthy term neonates have been studied (see table).
Conclusions: This preliminary study shows that in comparison with healthy term neonates, infants of mothers with diabetes are longer, and despite no significant difference in body weight or LBM, have a significant increase in whole-body adiposity involving

G13 Table Comparisons between infants of mothers with diabetes and healthy term neonates

Comparisons made to an adjusted age of 40.8 weeks' gestation	Infants of mothers with diabetes n = 8	Healthy term neonates n = 26	95% CI for difference	p Value
% Whole-body adiposity	23.6	18.9	0.9 to 8.5	0.02
Body weight (kg)	3.656	3.340	−0.079 to 0.712	0.12
Head circumference (cm)	36.2	35.4	−0.3 to 1.9	0.26
Length (cm)	54.5	51.3	0.7 to 5.8	0.004
Ponderal index	23.8	24.8	−4.4 to 2.3	0.20
Lean body mass (kg)	2.810	2.699	−0.176 to 0.399	0.40
Total adipose tissue (litres)	0.940	0.712	0.034 to 0.421	0.02
Superficial subcutaneous adipose tissue (litres)	0.837	0.614	0.054 to 0.393	0.01
Deep subcutaneous adipose tissue (litres)	0.037	0.025	0.00009 to 0.025	0.048
Internal adipose tissue (litres)	0.065	0.074	−0.03 to 0.014	0.4

superficial and deep subcutaneous compartments. If confirmed, the early introduction of metabolic monitoring and family dietary and lifestyle education may be indicated.

G14 GROWTH AND BODY COMPOSITION IN PRETERM INFANTS AND RELATIONSHIPS WITH INSULIN-LIKE GROWTH FACTOR TYPE 1, ADIPONECTIN AND LEPTIN

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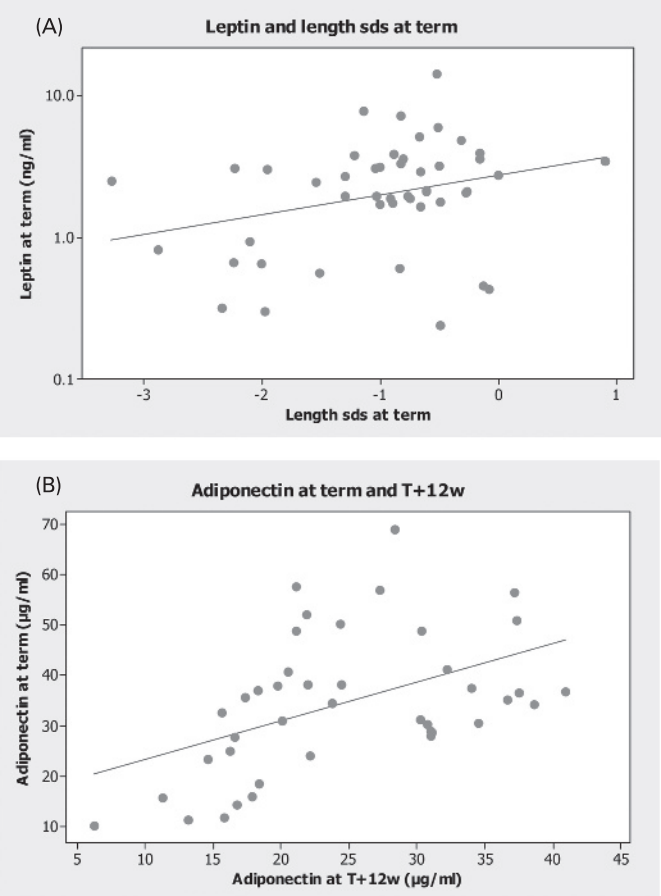
Background: Serum leptin correlates positively with the body mass index in term infants and body fat and appetite in childhood. Adiponectin is positively related to size at birth and neonatal adiposity, but is inversely correlated with adiposity in childhood. Data in preterm infants, however, are limited.

Objective: To describe the relationships between growth and body composition in preterm infants and serum concentrations of leptin, adiponectin and insulin-like growth factor type 1 (IGF-1).

Design/Methods: Preterm infants (34 weeks) who were enrolled in a trial of a post-discharge nutritional intervention had serum leptin, adiponectin (AutoDELFIA), and serum IGF-1 (Immulite autoanalyser) concentrations measured at term (corrected age) and 12 weeks post-term. Growth and body composition (dual *x* ray absorptiometry, Hologic 2000) were also assessed.

Results: We studied 71 infants with a median birth weight of 1400 g (interquartile range (IQR) 1197–1640) and median gestation 31.0 weeks (IQR 29.1–32.4) of whom 63 had paired data at both time points. There were significant associations between growth indices and adipokines and IGF-1 but not with DXA-derived parameters (see fig).

Conclusions: There are associations between adipokines, IGF-1 and growth in preterm infants following initial hospital discharge. The direction of effect and degree of correlation for leptin and adiponectin suggests that different mechanisms may exist to those that operate in later childhood or adult life.



G14 Figure Correlation between (A) leptin concentrations and length SDS at term corrected age; (B) adiponectin concentrations at term and term plus 12 weeks corrected age.

G15 GENDER AND BODY MASS INDEX AT DIAGNOSIS ARE RISK FACTORS FOR OBESITY AMONG CHILDHOOD SURVIVORS OF SUPRASELLAR BRAIN TUMOURS

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Background: Excessive weight gain leading to severe obesity is a well-recognised late complication in children surviving suprasellar brain tumours. However, factors that predict obesity in these children have not been explored.

Aims: To assess the change in body mass index (BMI) from diagnosis to last follow-up among survivors of childhood suprasellar brain tumours, and to determine the factors that could predict which of these children are at risk of developing obesity.

Methods: We conducted a retrospective review of 46 children (16 boys) aged 7.6 ± 4.6 years at diagnosis of tumour and followed up for 4.9 ± 3.5 years. Height and weight at diagnosis and follow-up were ascertained from clinical records. BMI standard deviation scores (SDS) and changes in BMI SDS (ΔBMI SDS) during follow-up were calculated. Survival analyses were used to explore the risks of developing obesity (International Obesity Taskforce defined) during follow-up.

Results: Boys were slightly older than girls at diagnosis of tumour (9.0 ± 4.3 years vs 6.8 ± 4.6 years; p = 0.1), but there were no sex differences in the duration of follow-up (4.5 ± 2.8 years vs 5.1 ± 3.8 years; p = 0.6); tumour types (glioma (total n = 21),

craniopharyngioma (13), prolactinoma (4), other suprasellar tumours (8)); endocrinopathies (39); and treatment modalities (surgery (29), radiotherapy (23), chemotherapy (14), none (10)). The baseline BMI SDS was similar in boys (0.64 ± 1.51) and girls (0.70 ± 1.33); p = 0.9. ΔBMI SDS/year was significantly greater in girls (0.52 ± 0.81) than in boys (0.09 ± 0.34); p = 0.02, especially in the first year after diagnosis (1.24 ± 1.30 in girls vs 0.19 ± 0.89 in boys; p = 0.002). Three of the 46 children (6%), one boy and two girls, were obese at diagnosis of tumour, increasing to 20 (43%), three boys (19%) and 17 girls (57%), by last follow-up (p = 0.04). Eighteen of the 34 children (53%) whose baseline BMI SDS was greater than 0 developed obesity by the last follow-up, compared with only two of the other 12 children (17%) whose baseline BMI SDS was 0 or less (p = 0.02).

Conclusion: In our cohort, female gender and BMI greater than the 50th centile at the diagnosis of suprasellar brain tumours were risk factors for the subsequent development of obesity. Significantly greater increases in BMI among girls occurred soon after diagnosis. An early prediction of obesity risk in children surviving suprasellar brain tumours would allow early targeted interventions to minimise their weight gain and associated morbidities.

G16 DOES IMMEDIATE FEEDBACK OF GLYCOSYLATED HAEMOGLOBIN RESULT IN IMPROVE GLYCAEMIC CONTROL IN YOUNG PEOPLE WITH TYPE 1 DIABETES: A RANDOMISED CONTROLLED TRIAL

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Aims: Immediate feedback of glycosylated haemoglobin (HbA1c) using point-of-care testing is becoming established practice in childrens' diabetes clinics. It is expensive and there have been no studies in children to assess improvements in control. We aimed to determine whether glycaemic control improved and the method was acceptable and accurate.

Methods: Using a randomised block design, 95 children were assigned either to use a near-patient test (NPT) in clinic for assessing HbA1c with immediate feedback of results, or to the usual practice of a laboratory HbA1c with results sent out in a clinic letter. Laboratory HbA1c results were compared in both groups at 0 and 12 months. All NPT were compared with the laboratory, and questionnaires were used to determine the acceptability of the test to patients, families and staff and perceived levels of understanding.

Results: Baseline characteristics were comparable. Using analysis of covariance, a significant difference was found in laboratory HbA1c between the two groups at 12 months (mean difference 0.6%, p = 0.02) with a mean decrease in the NPT group of 0.4%. The NPT correlated well with the laboratory method at HbA1c levels less than 10.5%. The NPT was preferred by patients and staff, and levels of perceived understanding were higher in this group compared with usual practice.

Conclusions: Near-patient testing of HbA1c with immediate feedback of results improves glycaemic control in young people with type 1 diabetes over a 12-month period, correlates well with laboratory methods and is tolerated well by patients, families and staff.

G17 WHAT ARE THE LEVERS AND BARRIERS TO INTRODUCING MULTIPLE DAILY INJECTIONS OF INSULIN TO PRIMARY SCHOOLS?

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Background: The paediatric incidence of type 1 diabetes (T1DM) is increasing by 3–5% each year, with the steepest rise in children under 5 years. As children spend on average a quarter of their waking lives at school, it is important that school staff are trained to implement the child's diabetes plan effectively.

Aims: The aim was to determine the levers and barriers to introducing multiple daily injections of insulin in primary schools with pupils who have diabetes from the perspective of schools and parents, and what supporting measures are required by schools.

Methods: This was a qualitative study using interviews and questionnaires. Twenty-nine children with T1DM and the 24 primary schools they attended during the academic year September 2007–8 were identified. Structured interviews were carried out with all head teachers. A diabetes information pack with an accompanying feedback questionnaire was given to each school to complete. The parents of the children with T1DM who attended these schools were also interviewed.

Results: All of the schools were interested in having training and receiving a diabetes information pack, and had staff who considered themselves aware of how to care for children with diabetes. Eighty-eight per cent would consider administering insulin injections, and reasons given for not administering them included wanting a disclaimer and procedures to safeguard staff from allegations, concerns regarding accepting responsibility especially in very young children or those newly diagnosed with diabetes and limited time and resources. Seventy-six per cent of parents would allow school staff to give their child an insulin injection if they had appropriate training and understanding, and the same amount thought their child's school provided enough support. Reasons cited for not allowing injections were concerns with staff training and lack of knowledge, and reluctance by either the child or the parent to allow anyone else to administer injections.

Conclusions: Education and training were highlighted as areas for improvement by both school staff and parents if progress is to be made in implementing intensive insulin regimens such as multiple daily injections of insulin. Future studies using pre and post-intervention assessments of staff knowledge may yield more information about the type of education and training they would find most helpful.

G18 CONTINUOUS SUBCUTANEOUS INFUSION OF INSULIN IN CHILDREN WITH TYPE 1 DIABETES: FACTORS ASSOCIATED WITH IMPROVED GLYCAEMIC CONTROL

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Aim: To describe the demographic characteristics of children with type 1 diabetes on continuous subcutaneous infusion of insulin (CSII) over the previous 5 years and to determine the factors associated with improved glycaemic control.

Methods: We collected retrospective data on 46 children on CSII by visiting six different paediatric centres in our region. The data were collected from the diagnosis onwards for growth, glycosylated haemoglobin (HbA1c), estimated insulin dose, the presence of chronic complications, demographics and indication for starting CSII.

Results: The mean age at diagnosis of type 1 diabetes was 5.2 years. The mean duration on CSII was 1.6 years and the mean HbA1c before CSII was 8.8% (SD 1.1). 43% of children were started on CSII based on patient choice or quality of life indications. On average, 7.2% of patients at each of the clinics were on CSII. After an initial phase of fall in HbA1c in the first 6 months, there was a subsequent deterioration in glycaemic control. However, not all patients on CSII deteriorated and therefore we did a subgroup analysis by comparing patients who improved on CSII with those who did not show improved glycaemic control in the first year of CSII. This revealed that higher HbA1c before the commencement of CSII (9.1% vs 8.3%) was significantly associated with improved glycaemic control. When the variables were analysed using a regression model, patient choice or quality of life indications for starting CSII (odds ratio (OR) 15.1) and a structured education

pathway (OR 9.9) were significantly associated with improved glycaemic control. Other factors, such as age, sex, body mass index, social deprivation, education and normal saline priming, were not significantly associated with improved glycaemic control.

Conclusion: Higher HbA1c levels before the start of CSII were associated with improved glycaemic control in the first year of CSII therapy. The other predictors of improved glycaemic control on CSII were patient choice and quality of life indications and structured CSII education pathway. The indices of social deprivation and education should not be barriers to starting CSII.

G19 POSITIVE ANTI-GLUTAMIC ACID DECARBOXYLASE ANTIBODIES IN SUBJECTS WITH REFRACTORY EPILEPSY AND TYPE 1 DIABETES

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Introduction: Glutamic acid decarboxylase (GAD) catalyses the production of gamma aminobutyric acid (GABA) from glutamic acid, the main inhibitory neurotransmitter in the central nervous system (CNS). GAD is found abundantly in the innervation of pancreatic islets. Antibodies to glutamic acid decarboxylase are found in Stiff–Person syndrome, type 1 diabetes, cerebellar ataxia and other neurological disorders (such as epilepsy and myoclonus) involving the GABAergic pathways. In type 1 diabetes a variety of circulating antibodies such as anti-GAD, islet cell antibodies and islet cell-associated phosphatase are found. Like islet cell antibodies, anti-GAD antibodies decline over time. Following a single case report1 of refractory epilepsy in a child with type 1 diabetes responsive to plasmapheresis, we assessed the GAD antibody status of children with refractory epilepsy and diabetes.

Methods: More than 400 children under the age of 19 years with type 1 diabetes are managed at Norfolk and Norwich University Hospital. GAD antibodies were measured in four patients, aged 8.9–18.1 years (one male) with refractory epilepsy, (three of whom (one male) also had hypothyroidism).

Results: All four children were positive for GAD antibodies and three were positive for antithyroid peroxidase antibodies. Two of them required thyroxine replacement therapy. All four patients had epilepsy refractory to treatment with multiple anticonvulsants. The titre of anti-GAD antibodies was high (9.2–200 μ/ml) in three patients; all had frequent breakthrough seizures. One child had a dramatic improvement with high-dose steroid therapy. Immune-directed therapy has not been attempted in the remaining patients.

Discussion: Anti-GAD antibodies in patients with type 1 diabetes may be associated with refractory epilepsy. The observed association of refractory epilepsy and type 1 diabetes needs corroboration in larger epidemiological studies. Such children may benefit from immune-directed therapy to control their epilepsy.

1. **Olson JA,** Olson DM, Sandborg C, *et al*. Type 1 diabetes mellitus and epilepsia partialis continua in a 6-year-old boy with elevated anti-GAD65 antibodies. *Pediatrics* 2002;**109**:E50.