Example abstracts

Basic science

Acetyl-CoA carboxylase-1 is a critical regulator of beta cell size and proliferation

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Aims: An adequate, functional beta cell mass is essential to maintain glucose homeostasis. Beta cells sense glucose and trigger insulin secretion using oxidative mitochondrial pathways. A distinctive feature of beta cells is the relatively high proportion of glucose-derived pyruvate entering mitochondrial anaplerotic pathways (non-oxidative) and driving citrate export and cytosolic acetyl-CoA production, supporting the concept of an alternative glucose-sensing pathway. Acetyl-CoA carboxylase-1 (ACC1) is the cytosolic, citrate-activated enzyme, coupling glucose metabolism to lipid biosynthesis by catalysing malonyl-CoA production from acetyl-CoA. We sought to test the role of this ACC1-coupled pathway *in vivo*.

Methods: Beta cell ACC1 activity was ablated in mice using Cre/loxP mediated gene deletion.

Results: Constitutive ACC1 ablation in beta cells using Ins2-cre (bACC1KO) caused impaired *in vivo* glucose-stimulated insulin secretion (GSIS) and glucose intolerance (blood glucose excursion after 2g/kg bolus: cre-control 2023 ±76, bACC1KO 2470 ± 64mmol/l 120/min; $p < 0.0001$; n =17/29), with no effect on insulin action nor adiposity. Surprisingly, *in vitro* GSIS from sized-matched isolated islets was normal. Histological analysis revealed a marked reduction in beta cell mass in bACC1KO pancreata (cre-control 2.203 ± 0.169, bACC1KO 1.042 ± 0.107mg; $p < 0.01$; n = 3), due to a reduction in both beta cell size and proliferation. Finally, we utilised a tamoxifeninducible system to delete ACC1 in the beta cells of adult mice: this caused glucose intolerance four weeks post-ACC1 ablation, indicating that ACC1 plays an active role in maintaining a functional beta cell mass.

Summary: Our data reveal a critical role for ACC1, and potentially glucose-driven lipid synthesis, in regulating beta cell size and proliferation.

Clinical science

Patients with longstanding type 1 diabetes show improved self awareness of hypoglycaemia measured during clamped hypoglycaemic challenges after a six month intensive treatment period in the HypoCOMPASS Study: comparison of optimised multiple daily injections (MDI) and continuous insulin infusion therapy (CSII) with or without adjunctive real-time continuous glucose monitoring (RTCGM)

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Aim: To investigate objectively the restoration of awareness of hypoglycaemia before and after an intensive treatment strategy aimed at rigorous avoidance of biochemical hypoglycaemia (<4mmol/l) in subjects with Type 1 diabetes and impaired awareness of hypoglycaemia (IAH).

Methods: Eighteen subjects with Type 1 diabetes and IAH (Gold questionnaire score ≥4) (age 50± 9 years, duration of diabetes 35±10 years, HbA1c 65 ±11mmol/mol) participating in the UK based multicentre HypoCOMPASS study underwent stepped hyperinsulinaemic hypoglycaemic clamp studies before and after a 6-month study intervention (HypoCOMPASS educational intervention with either optimised MDI with a bolus calculator ± RTCGM or CSII ± RTCGM). Symptoms, cognitive function and counter-regulatory hormones were measured at each glucose plateau (5.0, 3.8, 3.4, 2.8 and 2.4mmol/l) each step lasting 40min with subjects kept blinded to their actual glucose value throughout clamp studies.

Results: Results shown are mean ± SEM, pooled for all treatment groups. Thresholds for deterioration of cognitive function were unchanged in pre- and post-clamps (2.7±0.1 vs 2.7± 0.1mmol/l). In contrast, symptom responses during post-intervention clamp studies were significantly higher than pre-intervention (area under the curve 104±250 vs 653±108, $p =0.04$). In keeping with this, the glucose concentration at which subjects first felt hypoglycaemic increased from 2.6 ± 0.1 to 3.1 ±0.2mmol/l ($p =0.02$).

Conclusion: Even in long-standing Type 1 diabetes, IAH may be improved by an intensive clinical strategy aimed at avoidance of hypoglycaemia.

Patient education and self-management

Substantial savings in emergency treatment costs following structured education in patients with Type 1 diabetes

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Aims/objectives: To determine the cost of emergency treatments prior to and post a structured education course in patients with Type 1 diabetes.

Methods: Using the Dose Adjustment for Normal Eating (DAFNE) research database, records of 939 adults with Type 1 diabetes (51.4% female) were examined (baseline mean ± SD: age 41.0±13.6 years, duration of diabetes 17.4 ± 13.4 years). Biomedical data were collected before and 12 months after patients completed DAFNE education. Emergency treatment costs were calculated for hospital admissions, paramedic assistance, and A&E attendances using NSRC1 NHS Trust reference cost schedule 2010–11. Statistical significance was determined using negative binomial and logistic models.

Results: The number of episodes of severe hypoglycaemia requiring healthcare professional input in the preceding 12 months was greatly reduced from 168 to 53 ($p < 0.001$), and the number of admissions for diabetic ketoacidosis had decreased from 73 to 25 ($p < 0.001$). In the 12 months prior to DAFNE the total cost of emergency treatments for diabetic ketoacidosis and severe hypoglycaemia was £130,952, compared with £44,165 in the 12 months post the DAFNE course, representing a saving of £92 per patient. Furthermore, at one year follow-up HbA1c had decreased from 8.7% ±1.5% to 8.4% ± 1.5% ($p < 0.001$).

Conclusions/summary: The frequency of severe hypoglycaemia requiring healthcare professional assistance and admissions due to diabetic ketoacidosis are significantly decreased following DAFNE skills training. Thus in routine clinical care the benefits of DAFNE include not only improvements in glycaemic control and quality of life but also substantial reductions in emergency treatment costs.

Do genetic diabetes nurses make a difference? A 10 year evaluation of increasing knowledge of monogenic diabetes through a national network

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Background: Key monogenic diabetes genes were identified in the 1990s and a UK-wide NHS genetic testing service was established in 2000. However, widespread lack of knowledge of monogenic diabetes results in approximately 80% of patients initially misdiagnosed and treated. The genetic diabetes nurse (GDN) network was created in 2002 to tackle these issues.

Aims: To increase knowledge of monogenic diabetes amongst healthcare professionals and identify families with monogenic diabetes.

Methods: Experienced diabetes specialist nurses were identified and seconded to the project for 3.5–7h/week. They attend ongoing training (4.5 study days/year), share expertise with professionals through presentations across their regions and discuss differential diagnosis with the Exeter team.

Results: Forty-seven GDNs have been trained and have raised awareness of monogenic diabetes through>500 presentations (99% rated very good/excellent) to >6,000 healthcare professionals.

Both referrals for genetic testing have increased (186 in 2001 to 821 in 2011) and the total number of UK patients with confirmed monogenic diagnosis (343 in 2001 to 2570 in 2012). GDNs have a higher positive pick-up rate than patients referred from elsewhere (245/649, 38% vs 726/3364, 22%, $p < 0.0001$) and increased referrals of family members for genetic testing (157/245, 64% vs 317/733, 43%, $p < 0.0001$). GDNs have initiated eight UK-wide specialist monogenic clinics, reviewing >1,000 individuals from 650 families, and have improved treatment, supporting >100 patients stopping unnecessary insulin.

Conclusions: GDNs have improved quality of diabetes care, enhanced professional relationships and enhanced patient experiences. They have provided local expertise in monogenic diabetes resulting in increased referrals, provision of specialist clinics and improved patient/family support.

Psychological care

Psychological interventions for young people with Type 1 diabetes: a meta-analysis

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Aims: We aimed to determine the efficacy of psychological interventions to improve glycaemic control and psychological outcomes in adolescents with Type 1 diabetes.

Methods: A systematic search of six databases was conducted to identify studies reporting randomised controlled trials utilising psychological interventions for young people (eight–21 years) with Type 1 diabetes.

Results: A total of 25 papers were identified and effect sizes calculated for 18 interventions. There was a small to medium overall mean effect [d = 0.28, confidence interval (CI) 0.08–0.34] on glycaemic control. Effect sizes for goal setting (d = 0.33, CI 0.12–0.45) and problem solving (d = 0.27, CI 0.14–0.44) were greater than any other intervention. Theoretically guided interventions had greater effect sizes than all other interventions on glycaemic control (d =0.45, CI 0.23–0.59). Thirteen studies investigating psychological outcomes showed improvements in quality of life (n =6), psychological distress (n =2), conflict (n = 2), self-efficacy (n =2) or anxiety (n =1).

Conclusions: Our findings suggest psychological interventions, especially those involving problem solving or goal setting, can contribute to improved glycaemic control and psychological outcomes. Theoretically guided interventions have greater efficacy than non-theoretically guided interventions at improving glycaemic control.

Clinical care: management

The first prospective study of treatment change in transcription factor maturity onset diabetes of the young (MODY): impact on glycaemic control and quality of life

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Background: Eighty per cent of patients with monogenic diabetes are initially misdiagnosed and inappropriately treated. Most patients with HNF1A/4A MODY can be successfully managed on low dose sulphonylureas; however, there have been no prospective studies of treatment change following genetic testing.

Aims: To determine the impact of treatment change on quality of life and HbA1c following detection of a mutation in HNF1A or HNF4A.

Methods: We studied 20 patients, diagnosed < 30 years, aged <50 years, with confirmed transcription factor MODY (19 HNF1A, 1 HNF4A), who were not on sulphonylureas at time of referral for genetic testing. We studied HbA1c and quality of life: EQ5D and visual analogue score (VAS) on a scale of 0–100, for 12 months post-treatment change.

Results: At genetic testing 17 (85%) were on insulin (16 HNF1A, 1 HNF4A) and three (15%) HNF1A on metformin. All patients transferred to low dose gliclazide with 4/17 (24%) continuing to require once-daily insulin in addition to the sulphonylurea. At a mean of six months' follow-up there was no deterioration in HbA1c (pre 71 vs post 69mmol/mol, p = 0.3), an improvement in quality of life (VAS: pre 83.8, post 77.0, p = 0.04) and a reduction in frequency of home blood glucose monitoring (pre 71/month, post 36/month, p = 0.008).

Discussion: This first prospective study of treatment change in MODY indicates that glycaemic control is maintained in the short term with an improvement in quality of life and reduction in home monitoring. Ensuring correct diagnosis has implications for the treatment/management of individuals with improvement in quality of life whilst reducing NHS costs.

Clinical care: complications

Foot risk in diabetes: is there a graded association with adverse diabetes medical risk or mortality?
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Background and aim: Foot risk stratification in diabetes is recommended by NICE. Whilst the association between foot risk and adverse foot outcomes is well understood, a similar association with adverse medical outcomes including mortality is not as well known.

Methods: The integrated district diabetes register that captures demographic, biochemical and clinical information pertaining to structured diabetes care was utilised. Foot risk status (FRS) was categorised into low, intermediate, high and active foot risk groups. A composite medical risk score (MRS) based on relevant diabetes parameters including HbA1c, systolic blood pressure, smoking, cardiovascular, renal and retinal statuses was utilised. Mortality status was captured from the validated UK NHS Strategic Tracing Service.

Results: The study population consisted of 8,994 of 16,573 alive individuals with up-to-date FRS as of 1 January 2011. Of them, 258 (2.8%) individuals had died in the following 12 months from their last foot assessment. The proportions of patients in the highest tertile group of MRS in low, intermediate, high and active foot risk groups were 9%, 18%, 45% and 54% respectively (χ^2 =2805.6, p < 0.001). The proportion of deaths in low, intermediate, high and active foot risk groups were 1.3%, 2.5%, 4.4% and 12.4% respectively (χ^2 =101.4, p < 0.001). In logistic regression, FRS remained an independent risk factor for mortality.

Conclusion: Our data confirm a strong and graded relation between level of foot risk and adverse diabetes medical risk including mortality. Patients with increased foot risk need closer attention to their medical risk factors in addition to access to structured foot care.

<u>**Clinical care: healthcare delivery and improvement**</u>

Effectiveness of screening questionnaires to detect HbA1c defined abnormal glycaemia in a UK White population

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Aims: The National Institute of Clinical Excellence (NICE) recommend utilising a two-stage approach to identify those at risk of Type 2 diabetes: a risk score followed by (for those who score highly) HbA1c or fasting glucose testing. HbA1c 42–47mmol/mol identifies high risk of progression to diabetes (HR) and HbA1c ≥ 48mmol/mol identifies diabetes. We assessed the ability of the Leicester and Cambridge Risk Assessment scores (LRA, CRA) to detect HbA1c defined abnormal glycaemia.
Methods: LRA and CRA scores were calculated for 2,266 participants [mean (SD) age 58.4 (10.7) years, body mass index 26.7 (4.4), 99% White, 37% male] from the Exeter Ten Thousand Project and assessed performance in detecting abnormal glycaemia (HR/diabetes) using the suggested cut-offs of LRA ≥ 16 and CRA ≥ 0.128.
Results: Prevalence of abnormal glycaemia was 21.5% (diabetes 3.4%, HR 18.1%). Both tests performed similarly in detecting abnormal glycaemia [area under the receiver operating characteristic curve 0.72 (confidence interval 0.69–0.74) and 0.70 (0.67–0.72) for LRA and CRA: no better than age alone, 0.69 (0.66–0.71)]. Using suggested thresholds LRA was less sensitive and more specific: sensitivity/specificity 62.6%/69.2% LRA and 69.1%/57.1% CRA. Positive/negative predictive values were 35.7%/87.1% for LRA and 30.6%/87.1% for CRA. This two-stage approach using LRA would result in HbA1c testing in 38% of the population and detect 83% of undiagnosed HbA1c defined diabetes and 59% of HR.
Conclusion: Both the LRA and CRA perform similarly in detecting abnormal glycaemia, but appear to have little benefit over age alone. Using this approach with LRA would detect nearly 60% of those with abnormal HbA1c but require nearly 40% of the population to undergo HbA1c testing.

Case reports

One is never enough: a case report of three different diabetes phenotypes in a single family

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A 30 year old Caucasian female (D1) was referred with suspicion of maturity onset diabetes of the young (MODY). She had insulin-treated gestational diabetes, with an uncomplicated delivery at 38 weeks. Insulin was discontinued post-delivery but fasting hyperglycaemia persisted. Family history included Type 1 diabetes in her mother, daughter and one sister. Another sister (D2) had gestational diabetes, and her niece (D3, D2's daughter) had permanent neonatal diabetes (PNDM) presenting at 16 weeks and insulin treated since diagnosis. Mutational screenings of KCNJ11, ABCC8 and INS at diagnosis in D3 were negative. Given the clinical picture in D1, we sequenced the glucokinase (GCK) gene which revealed a heterozygous missense (T206M) mutation, confirming the diagnosis of GCK-MODY. Other family members were reviewed. The three individuals with a clinical history of Type 1 diabetes had features including high HbA1c, diabetic ketoacidosis and diabetic nephropathy, inconsistent with GCK-MODY; c-peptide was undetectable supporting the diagnosis of Type 1 diabetes. D2 had clinical features consistent with GCKMODY and also carried the T206M mutation. GCK was subsequently sequenced in D3 who showed heterozygosity for T206M and a further GCK missense mutation, R43P, confirming a diagnosis of GCK-PNDM. Both mutations have been previously functionally characterised in GCK-MODY and shown to be kinetically inactivating due to decreased affinities for glucose and decreased maximal specific activities compared with wild-type GCK. This is the first report of three different diabetes phenotypes (T1DM, GCK-MODY and GCK-PNDM) in one family and demonstrates the importance of careful review of families after discovering a genetic aetiology for diabetes.

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