Depression and distress in patients with type 2 diabetes: results from ANDA 2016

Natalie Nanayakkara, Anthony Pease, Sanjeeva Ranasinha, Natalie Wischer, Sofianos Andrikopoulos, Barbora de Courten, Sophia Zoungas

1. School of Public Health and Preventive Medicine, Monash University, Clayton, VIC, Australia
2. Diabetes and Vascular Medicine Unit, Monash Health, Clayton, VIC, Australia
3. National Association of Diabetes Centres, Sydney, New South Wales, Australia
4. The George Institute for Global Health, Camperdown, New South Wales, Australia

Introduction
Depression and distress in diabetes is associated with greater morbidity, mortality and healthcare costs. This study explores factors associated with depression and distress in patients with type 2 diabetes.

Methods
Data were analysed from the Australian National Diabetes Audit (ANDA) including 2552 adult patients with type 2 diabetes from 56 diabetes centres across Australia during the 1-month survey period in May/June 2016. Pre-specified demographic and clinical variables were obtained. The Brief Case find for Depression (BCD) and Diabetes Distress Score 17 (DDS17) were administered to screen for likely depression and diabetes-related distress, respectively. Logistic regression was used to examine factors associated with depression and distress.

Results
Mean age of participants was 62.7±12.7 years (mean±SD) and diabetes duration was 12±10 years. Mean HbA1c was 8.3±1.9%. Thirty percent of patients had a BCD score suggesting likely depression and 20% of patients had a DDS 17 score suggesting diabetes distress. Of patients with likely depression, only 35% were on antidepressant medication, 19% were undergoing counselling, and 12% had both. Factors associated with depression on BCD screening were smoking, low medication adherence, lower self-health rating and higher diabetes distress score (all p<0.02 in models adjusting for antidepressant use, age, gender, physical activity and blood glucose monitoring). Factors associated with distress on DDS17 screening were female gender, insulin use, difficulty following the recommended diet, lower self-health rating and depression (all p≤0.03) in models adjusting for antidepressant use, age, physical activity and blood glucose monitoring (Table 1).

Conclusion
Many patients with type 2 diabetes experience depression and distress with a significant proportion remaining untreated. This emphasises the importance of addressing emotional and psychological health in people with diabetes and highlights the need for longitudinal data to confirm the determinants of depression and diabetes distress in type 2 diabetes.
Table 1: Unadjusted and adjusted odds of depression and diabetes distress among patients with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
<th>Distress on Diabetes Distress Score 17 (DDS 17)</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>p value</td>
<td>OR (95%CI)</td>
<td>p value</td>
<td>OR (95%CI)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 year increase</td>
<td>0.97 (0.97-0.98)</td>
<td>&lt;0.001</td>
<td>1.01 (1.00-1.02)</td>
<td>0.117</td>
<td>0.98 (0.97-0.99)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.27 (1.07-1.50)</td>
<td>0.007</td>
<td>0.94 (0.69-1.28)</td>
<td>0.682</td>
<td>1.97 (1.40-2.75)</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year increase</td>
<td>1.00 (0.99-1.01)</td>
<td>0.945</td>
<td></td>
<td></td>
<td>1.00 (0.98-1.02)</td>
</tr>
<tr>
<td><strong>Insulin use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.53 (1.28-1.82)</td>
<td>&lt;0.001</td>
<td>0.87 (0.62-1.21)</td>
<td>0.407</td>
<td>1.61 (1.11-2.35)</td>
</tr>
<tr>
<td><strong>Current smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.97 (1.54-2.51)</td>
<td>&lt;0.001</td>
<td>1.61 (1.09-2.59)</td>
<td>0.020</td>
<td>1.45 (0.94-2.23)</td>
</tr>
<tr>
<td><strong>Interpreter required</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.10 (0.74-1.64)</td>
<td>0.638</td>
<td></td>
<td></td>
<td>3.29 (0.77-14.04)</td>
</tr>
<tr>
<td><strong>Forget medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.28 (1.90-2.74)</td>
<td>&lt;0.001</td>
<td>1.51 (1.11-2.12)</td>
<td>0.010</td>
<td>1.84 (1.32-2.56)</td>
</tr>
<tr>
<td><strong>Diet Difficulty</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.38 (2.00-2.83)</td>
<td>&lt;0.01</td>
<td>1.11 (0.81-1.52)</td>
<td>0.532</td>
<td>2.31 (1.62-3.31)</td>
</tr>
<tr>
<td><strong>Sufficient physical activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.51 (0.42-0.62)</td>
<td>&lt;0.001</td>
<td>0.73 (0.53-1.02)</td>
<td>0.068</td>
<td>0.45 (0.30-0.67)</td>
</tr>
<tr>
<td><strong>Monitors blood glucose as recommended</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.70 (0.58-0.85)</td>
<td>&lt;0.001</td>
<td>1.13 (0.82-1.53)</td>
<td>0.413</td>
<td>0.58 (0.41-0.81)</td>
</tr>
<tr>
<td><strong>Unsure of recommended testing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.90 (0.62-1.31)</td>
<td>0.592</td>
<td>1.11 (0.61-2.29)</td>
<td>0.628</td>
<td>0.47 (0.21-1.04)</td>
</tr>
<tr>
<td><strong>On anti-depressant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.92 (2.40-3.56)</td>
<td>&lt;0.001</td>
<td>1.95 (1.39-2.72)</td>
<td>&lt;0.001</td>
<td>1.60 (1.13-2.25)</td>
</tr>
<tr>
<td><strong>Own health rating (1-100)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For each 1 point increase</td>
<td>0.96 (0.96-0.97)</td>
<td>&lt;0.001</td>
<td>0.91 (0.97-0.99)</td>
<td>&lt;0.001</td>
<td>0.97 (0.96-0.98)</td>
</tr>
<tr>
<td><strong>Total DDS17 Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 point increase</td>
<td>2.35 (1.96-2.83)</td>
<td>&lt;0.001</td>
<td>1.93 (1.58-2.37)</td>
<td>&lt;0.001</td>
<td>0.91 (0.63-1.39)</td>
</tr>
<tr>
<td><strong>Diabetes Specialist</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.14 (0.93-1.38)</td>
<td>0.139</td>
<td></td>
<td></td>
<td>0.81 (0.63-1.29)</td>
</tr>
<tr>
<td><strong>Diabetes Educator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (ref)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.13 (0.93-1.37)</td>
<td>0.22</td>
<td></td>
<td></td>
<td>0.80 (0.56-1.15)</td>
</tr>
</tbody>
</table>

* Sufficient physical activity for health benefit is defined as ≥150 total minutes per week (National Physical Activity Guidelines for Australians)

# Patient indicated that they have difficulties following recommended diet
Anxious depression increases all-cause mortality in type 2 diabetes: The Fremantle Diabetes Study Phase II

Wendy A Davis¹, David G Bruce⁵, Timothy M Davis¹, Sergio E Starkstein¹

1. The University of Western Australia, Fremantle, WA, Australia

Background: Previous research using Latent Class Analysis (LCA) identified classes of patients with type 2 diabetes (T2D) and specific profiles of depression/anxiety. Since LCA-defined anxious depression strongly predicts cardiovascular outcomes and mortality but cannot be applied to individual patients, we developed a validated combined depression-anxiety metric, the Diabetes Anxiety Depression Scale (DADS) for potential clinical application.

Objective: To determine whether DADS-defined anxious depression independently predicts all-cause mortality in people with T2D.

Methods: 1,337 participants with T2D from the Fremantle Diabetes Study Phase II underwent assessment including the Patient Health Questionnaire 9-item version (PHQ-9) and Generalised Anxiety Disorder Scale (GADS) to assess the presence of depression and anxiety symptoms. A single DADS score (0-39) was calculated by adding all PHQ-9 items plus four anxiety items used for the LCA and categorised into major anxious depression (>18), minor anxious depression (8-17), subsyndromal anxiety (3-7), and no anxiety/depression (≤2). All-cause mortality to end-December 2016 was ascertained from WA health data linkage and active follow-up.

Results: At baseline, patients were 66±11 years old, 53% were male, with median diabetes duration 9 years. Based on DADS, 9% had major and 25% minor anxious depression, 33% had subsyndromal anxiety, and 33% had no anxiety/depression. During 9,099 patient-years follow-up, 199 died. In Cox regression with age as timeline, male sex, ethnicity, current smoking, HbA₁c, pulse rate, aspirin use, eGFR<30 and ≥90 ml/min/1.73m², and log₂(N-terminal pro-brain natriuretic peptide) independently predicted all-cause mortality. After adjusting for these, total DADS score added significantly to the model (HR (95% CI): 1.02 (1.002-1.04)/unit. Categories of anxious depression showed a dose-response relationship with minor and major anxious depression reaching statistical significance (1.57 (1.07-2.30) and 1.76 (1.05-2.94), respectively) versus no anxiety/depression.

Conclusion: DADS combines depression and anxiety symptoms in a single score that enhances screening for both mental health and mortality risk in T2D.


Younger patients with type 2 diabetes have worse self-care practices compared with older patients: results from ANDA 2016

Natalie Nanayakkara¹, Anthony Pease²,¹, Sanjeeva Ranasinha¹, Natalie Wischer³, Sofianos Andrikopoulos¹, Barbora de Courten²,¹

Sophia Zoungas²,⁴,¹

1. School of Public Health and Preventive Medicine, Monash University, Clayton, VIC, Australia
2. Diabetes and Vascular Medicine Unit, Monash Health, Clayton, VIC, Australia
3. National Association of Diabetes Centres, Sydney, New South Wales, Australia
4. The George Institute for Global Health, Camperdown, NSW, Australia

Introduction
Type 2 diabetes, traditionally a disease of middle and older age, is increasingly diagnosed among younger people. This study compares the self-care practices of younger and older patients with type 2 diabetes.

Methods
Data were analysed from the Australian National Diabetes Audit (ANDA) that included 2552 adult patients with type 2 diabetes from 56 participating Diabetes Centres across Australia during the 1-month survey period in May/June 2016. Pre-specified demographic and clinical variables were obtained. Self-care variables (physical activity, following the recommended diet, medication adherence and blood glucose monitoring) were compared in patients <60 years and ≥60 years of age.

Results
Mean age of participants was 62.7±12.7 years, 70.5±7.20 for the older group and 49.4±8.25 for the younger group. Mean diabetes duration was 8.0±7.54 years and 14.0±10.08 years for younger and older patients respectively (p<0.01). A greater proportion of younger compared to older patients had HbA1c levels above 7.0% (76% vs 68%, p<0.01). Similar proportions of patients aged<60 years and ≥60 years required insulin therapy (59% vs 57% respectively p=0.168). A greater proportion of younger compared to older patients reported difficulty following the recommended diet (50% vs 32%) and forgetting medications (37% vs 22%) (all p<0.01). A smaller proportion of younger compared to older patients reported checking their blood glucose levels as often as recommended (60% vs 70%, p<0.01). In models adjusting for gender, smoking, insulin therapy, depression and allied health attendance, younger age was associated with a 2-fold increase in the odds of not following the recommended self-care practices (Table 1, all p< 0.01).

Conclusion
Despite shorter diabetes duration, younger age was associated with worse glycaemic control and poorer diabetes self-care practices among patients with type 2 diabetes. Targeted strategies to optimise diabetes self-care practices and resultant glycaemic control are urgently required.
The cost of diabetes and obesity in Australia

Crystal MY Lee¹, ², Brandon Goode³, Emil Nørtoft³, Jonathan Shaw⁴, Dianna J Magliano⁴, Stephen Colagiuri¹

¹. Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, University of Sydney, Sydney, NSW, Australia
². School of Public Health, Curtin University, Perth, WA, Australia
³. Novo Nordisk A/S, Søborg, Denmark
⁴. Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Introduction: Excess body weight is strongly associated with the risk of diabetes. In Australia, the latest data suggests that 11 million adults have overweight or obesity and 1.2 million adults have diabetes. The respective costs of obesity and diabetes were estimated previously, but the cost associated with both diabetes and obesity combined have not been reported in Australia.

Objective: To assess and compare the total direct (healthcare plus non-healthcare) cost and government subsidies by body weight and diabetes status.

Methods: The Australian Diabetes, Obesity and Lifestyle study collected health service utilisation and health related expenditure data at the 2004-05 and 2011-12 follow-up surveys. Costing data were available on 4409 participants aged ≥36 years in 2011-12. Unit costs for 2016-17 were used where available or were otherwise inflated to 2016-17 dollars. Age- and sex-adjusted costs per person were estimated using generalised linear models.

Results: The annual total direct cost ranged from $1998 per person with normal weight to $2501 per person with obesity in participants without diabetes. For those with diabetes, total direct costs ranged from $2353 per person with normal weight to $3131 with obesity.

Additional expenditure as government subsidies ranged from $5681 per person with normal weight and no diabetes to $8067 per person with obesity and diabetes.

Compared to participants with costing data at both surveys, those with data in 2004-05 only were older, more likely to have diabetes and have died by the end of 2012, and had higher direct healthcare cost.

Conclusion: The annual total excess cost was 26% for obesity alone and 46% with the addition of diabetes. Diabetes prevention programs targeting people with excess body weight may potentially reduce the financial burden for both individuals and the government.

Cardiac stress and inflammatory markers as predictors of heart failure in patients with type 2 diabetes: the ADVANCE trial

Toshiaki Ohkuma¹, Min Jun¹, Sophia Zoungas², Paul Welsh³, Naveed Sattar⁴, Mark E. Cooper⁵, Jonathan E. Shaw⁶, John Chalmers¹, Mark Woodward¹, ⁶, ⁷

¹. The George Institute for Global Health, University of Sydney, Camperdown, NSW, Australia
². School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
³. Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
⁴. Diabetic Complications Division, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
⁵. Department of Clinical Diabetes and Epidemiology, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia
⁷. Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA

Background: Heart failure has been noted to be the second most common first presentation of cardiovascular disease in patients with type 2 diabetes, and more common than myocardial infarction. However, few studies have investigated the prognostic ability of circulating biomarkers for heart failure in patients with type 2 diabetes.

Objective: This study examined the individual and combined impact of N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity cardiac troponin T (hs-cTnT), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) on the prediction of heart failure incidence or progression in patients with type 2 diabetes.

Research Design and Methods: A nested case-cohort study was conducted in 3,098 participants with type 2 diabetes in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial.
Results: A higher value of each biomarker was significantly associated with a higher risk of heart failure incidence or progression, after adjustment for major risk factors. The hazard ratios per 1-SD increase were 3.06 (95% CI 2.37-3.96) for NT-proBNP, 1.50 (1.27-1.77) for hs-cTnT, 1.48 (1.27-1.72) for IL-6, and 1.32 (1.12-1.55) for hs-CRP. Addition of NT-proBNP to the model including conventional risk factors meaningfully improved 5-year risk predictive performance (c-statistic 0.8162 to 0.8800; continuous net reclassification improvement [NRI] 73.1%; categorical NRI [<5%, 5-10%, >10% 5-year risk] 24.2%). In contrast, addition of hs-cTnT, IL-6 or hs-CRP did not improve the prediction metrics consistently either in combination or when added to NT-proBNP.

Conclusions: Only NT-proBNP, strongly and consistently improved prediction of heart failure in patients with type 2 diabetes beyond a wide range of clinical risk factors and biomarkers.

Lower Rates of Hospitalization for Heart Failure and All-Cause Death in Patients Newly Initiated on SGLT-2 Inhibitors versus other glucose lowering drugs: The CVD-REAL Study

Maro Williams1, Matthew Cavender2, Anna Norhammar3, John Wilding4, Kamlesh Khunti5, Alex Z Fu6, Reinhard W Holi7, Kare I Birkeland8,9, Marit Eika Jorgensen10,11,12, Niklas Hammar13,14, Johan Bodegard14, Betina Blak15, Eric T Wittbrodt16, Sara Dempster17, Markus Scheerer18, Niki Arya19, Marcus Thuresson20, Peter Fenici21, Mikhail Kosiborod22

1. Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, USA
2. University of North Carolina, Charlotte, North Carolina, USA
3. Karolinska Institutet, Solna, Stockholm, Sweden
4. Institute of Ageing & Chronic Disease, Liverpool, UK
5. Diabetes Research Centre, Leicester, UK
6. Georgetown University Medical Center, Washington, DC, USA
7. Institute for Epidemiology and Medical Biometry, University Ulm, Ulm, Germany
8. University of Oslo, Oslo, Norway, Oslo, Norway
9. Oslo University Hospital, Oslo, Norway
10. Steno Diabetes Center, Copenhagen, Gentofte, Denmark
11. National institute of Public Health, Southern Denmark University, Copenhagen, Denmark
12. National institute of Public Health, Southern Denmark University, Copenhagen, Denmark
13. AstraZeneca Gothenburg, Malmö, Sweden
14. AstraZeneca, Oslo, Norway
15. AstraZeneca, Luton, UK
16. AstraZeneca, Wilmington, Delaware, USA, Wilmington, Delaware, USA
17. AstraZeneca, Waltham, Massachusetts, USA
18. AstraZeneca, Wedel, Germany
19. AstraZeneca, Gaithersburg, Maryland, USA
20. Statisticon AB, Uppsala, Sweden
21. AstraZeneca, Cambridge, UK

Background: Reduction in cardiovascular death and hospitalization for heart failure (HHF) was recently reported with a sodium-glucose cotransporter-2 inhibitor (SGLT-2i) in Type 2 diabetes patients with cardiovascular disease. We compared HHF and death in new users of SGLT-2i versus other glucose lowering drugs (oGLDs) in six countries to determine if these benefits are seen in real-world practice, and across SGLT-2i class.

Methods: Data were collected via medical claims, primary care/hospital records and national registries. Propensity score for SGLT-2i initiation was used to match treatment groups. Hazard ratios (HRs) for HHF, death and a combined endpoint of HHF or death were estimated by country.

Results: After propensity matching, there were 309,056 patients newly initiated on either SGLT-2i or oGLD (154,528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42% and 5% of the total exposure time in the SGLT-2i class, respectively. Baseline characteristics were balanced between the two groups. There were 961 HHF cases among 309,056 patients with 190,164 person-years follow-up (incidence rate [IR] 0.51/100 person-years). Of 215,622 patients in the US, Norway, Denmark, Sweden, and UK, death occurred in 1334 (IR 0.87/100 person-years), and HHF or death in 1983 (IR 1.38/100 person-years). Use of SGLT-2i, versus oGLDs, was associated with significantly lower rates of HHF (HR 0.61; 95% CI 0.51–0.73; p<0.001); death (HR 0.49; 95% CI 0.41–0.57; p<0.001); and HHF or death (HR 0.54; 95% CI 0.48–0.60; p<0.001) with no significant heterogeneity by country.

Conclusions: Treatment with SGLT-2i versus oGLDs in this large international study was associated with a significantly lower risk of HHF and death, suggesting a class effect applicable to a broad population of T2D patients in real-world clinical practice.
Diabetes and higher HbA1c are associated with adverse outcomes following surgery

Priscilla Yong\textsuperscript{2,1}, Laurence Weinberg\textsuperscript{2}, Niloufar Torkamani\textsuperscript{2,1}, Leonid Churilov\textsuperscript{3}, Raymond Robbins\textsuperscript{2}, Ronald Ma\textsuperscript{2}, Rinaldo Bellomo\textsuperscript{2}, Que Lam\textsuperscript{2}, Graeme Hart\textsuperscript{2}, Jeremy Lew\textsuperscript{2,1}, Johan Martensson\textsuperscript{2}, Dave Story\textsuperscript{2}, Andrew Motley\textsuperscript{2}, James Burns\textsuperscript{2}, Doug Johnson\textsuperscript{2}, Jeffrey Zajac\textsuperscript{2,1}, Elif I. Ekinci\textsuperscript{2,1}

1. Medicine, The University of Melbourne, Melbourne, Victoria, Australia
2. Austin Health, Heidelberg, VICTORIA, Australia
3. The Florey Institute of Neuroscience & Mental Health, Melbourne, Victoria, Australia

Introduction: There are limited studies examining the association between diabetes and postoperative outcomes outside of the cardiac surgery setting. Our objective was to investigate the independent association of diabetes defined categorically or using HbA1c as a continuous variable, with outcomes following surgery.

Methods: In this prospective, observational cohort study, all patients ≥54 years admitted to Austin Health between July 2013 to February 2016 had an automated HbA1c measurement as part of the Diabetes Discovery Initiative. Patients were diagnosed with diabetes if they had an HbA1c≥6.5% or a pre-existing diagnosis of diabetes, and prediabetes if they had an HbA1c of 5.7-6.4%. Baseline demographic and clinical data were obtained from hospital records and patients were followed up for 6 months. Random-effect logistic and negative binomial regression models were used for analysis, with surgical units treated as random effects.

Results: 7565 hospital admissions of patients undergoing surgery were studied, with 30% of patients having diabetes and 37% having prediabetes. After adjustment for age, Charlson comorbidity index excluding diabetes, estimated glomerular filtration rate, and length of surgery, diabetes, defined categorically, was associated with increased hospital length of stay (IRR=1.09; 95%CI: 1.05-1.14; p<0.001), 6-month mortality (OR=1.29; 95%CI: 1.05-1.58; p=0.015), intensive care unit (ICU) admission (OR=1.54; 95%CI: 1.32-1.79; p<0.001), mechanical ventilation (OR=1.69; 95%CI:1.35-2.13; p<0.001), and major complications as defined by Clavien-Dindo grade ≥4 (OR=1.38; 95%CI:1.18-1.58; p<0.001) (Table 1). Furthermore, each percentage increase in HbA1c was associated with increased hospital length of stay (IRR=1.05; 95%CI:1.03-1.07; p<0.001), ICU admission (OR=1.14; 95%CI: 1.07-1.21; p<0.001), and major complications (OR=1.08; 95%CI:1.01-1.14; p=0.019) (Table 1). No significant association between prediabetes, defined categorically, and adverse outcomes was observed.

Conclusion: Diabetes and higher HbA1c were independently associated with higher risk of adverse outcomes following surgery. Studies are necessary to examine the role of intensive pre- and postoperative glycemia management of patients with diabetes.

Table 1: Association of diabetes with post-surgical outcomes

<table>
<thead>
<tr>
<th></th>
<th>Diabetes compared to no diabetes</th>
<th>HbA1c (per 1% increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR/IRR</td>
<td>p-value</td>
</tr>
<tr>
<td>Length of stay (days) (IRR)</td>
<td>1.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality (OR)</td>
<td>1.29</td>
<td>0.015</td>
</tr>
<tr>
<td>Intensive care unit admission (OR)</td>
<td>1.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation (OR)</td>
<td>1.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>28-day readmission (OR)</td>
<td>0.93</td>
<td>0.406</td>
</tr>
<tr>
<td>Major complication (OR)</td>
<td>1.37</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adjusted for age (years), Charlson comorbidity index excluding diabetes, Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) estimated glomerular filtration rate (mL/min/1.73m²), and length of operation (minutes), with surgical unit treated as a random effect.
Identifying hospitalised patients at risk of adverse glycaemia: a risk stratification model

Mervyn Kyi1, 2, Jane Reid1, Alex Gorelik1, Shanal Kumar3, Anna Galligan1, Lois M Rowan1, Alison J Nankervis1, Katie A Marley1, David M Russell1, Paul R Wraight1, Peter G Colman1, Spiros Fourlanos1
1. The Royal Melbourne Hospital, Parkville, VIC, Australia
2. Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Melbourne, VIC, Australia

Background: In hospitalised patients, adverse glycaemia (both hypo- and hyperglycaemic extremes) should be avoided. We analysed a cohort of inpatients with diabetes and developed a risk-stratification model to predict those at risk of adverse glycaemia.

Methods: We recruited 643 consecutive inpatients with diabetes or new onset hyperglycaemia (random capillary blood glucose [BG] ≥11.1 mmol/L without known diabetes) with ≥2 day length of stay. Networked BG meters were used to collect capillary BG measures from the time of admission until discharge (or day 14 for long-stayers). Adverse glycaemia was defined as the occurrence of any capillary BG <4 or >15 mmol/L from day 2 onwards after admission.

Multivariable logistical regression analysis was used to investigate the association between adverse glycaemia and patient clinical factors (age, sex, Charlson index, admission creatinine, HbA1c, diabetes type & regimen), hospital treatment factors (surgery, glucocorticoid treatment, duration of hospital stay), and unstable day 1 BG (any BG <4, >15 or two BG >10 mmol/L). A split-sample approach was used for model construction and internal validation.

Results: Patient characteristics were: age 70±14 years; HbA1c: 7.6±1.7%; 33% insulin-treated. Adverse glycaemia occurred in 278 (43%) patients. Factors associated with adverse glycaemia were: Charlson index, HbA1c, duration of hospital stay, sulphonylurea or insulin treatment, and unstable day 1 BG (table). A risk-stratification model using these five factors had sensitivity 84%, specificity 60%, PPV 64%, NPV 82%. A second model using two practical factors easily available on admission (pre-admission insulin treatment or unstable day 1 BG) also predicted adverse glycaemia (sensitivity 83%, specificity 56%, PPV 56%, NPV 83%).

Conclusion: Factors associated with adverse glycaemia include pre-admission insulin or sulphonylurea treatment, unstable BG on day 1, higher HbA1c and greater comorbidities. These factors should be used to risk-stratify patients for concentration of specialist inpatient diabetes management efforts.

Table: Factors associated with adverse glycaemia: Multivariable logistic regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>(95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson index *</td>
<td>1.27</td>
<td>(1.11, 1.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>1.19</td>
<td>(1.09, 1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.26</td>
<td>(1.02, 1.56)</td>
<td>0.036</td>
</tr>
<tr>
<td>Treatment Regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Nil (Diabetes controlled only)</td>
<td>1.00</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>- Medications only not including SU **</td>
<td>2.07</td>
<td>(0.81, 5.29)</td>
<td>0.129</td>
</tr>
<tr>
<td>- Medications only including SU **</td>
<td>4.82</td>
<td>(1.86, 12.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>- Insulin requiring</td>
<td>6.08</td>
<td>(2.35, 15.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unstable day 1 BG (BG &lt;4 or &gt;15 or two BG &gt;10 mmol/L)</td>
<td>3.11</td>
<td>(1.67, 5.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Charlson index was modified and excluded items related to diabetes. ** SU = sulphonylurea

Interferon-gamma released from omental adipose tissue of insulin-resistant humans alters adipocyte phenotype and impairs response to insulin and adiponectin release

John Wentworth1, Leonard Harrison2, Paul O’Brien3
1. Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia
2. WEHI, Parkville, VIC, Australia
3. Monash University Centre for Obesity Research and Education, Prahran, Australia

Background
Inflammatory factors derived from adipose tissue have been implicated in mediating insulin resistance in obesity. We sought to identify these using explanted human adipose tissue exposed to innate and adaptive immune stimuli.

Method
Subcutaneous and omental adipose tissue from obese, insulin-resistant donors was cultured in the presence of macrophage and T-cell stimuli and the conditioned medium tested for its ability to inhibit insulin-stimulated glucose uptake into human Simpson-Golabi-Behmel Syndrome
(SGBS) adipocytes. The nature of the inhibitory factor in conditioned medium was characterized physico-chemically, inferred by gene microarray analysis and confirmed by antibody neutralization.

**Results**

Conditioned medium from omental adipose tissue exposed to a combination of macrophage- and T-cell stimuli inhibited insulin action and adiponectin secretion in SGBS adipocytes. This effect was associated with a pronounced change in adipocyte morphology, characterized by a decreased number of lipid droplets of increased size. The bioactivity of conditioned medium was abolished by trypsin treatment and had a molecular weight of 46kDa by gel filtration. SGBS adipocytes exposed to bioactive medium expressed multiple gene transcripts regulated by interferon-gamma (IFN-g). Recombinant human IFN-g recapitulated the effects of bioactive medium and neutralizing antibody against IFN-g but not other candidate factors abrogated medium bioactivity.

**Conclusion**

IFN-g released from inflamed omental adipose tissue may contribute to the metabolic abnormalities seen in human obesity.

---

### SMOC1 – A new therapeutic target for glycaemic control?

Magdalene K Montgomery^1, Ruth Meex^1, Cheng Huang^2, Ralf B Schittenhelm^2, Matthew J Watt^1

1. Department of Physiology, Monash University, Clayton, VIC, Australia
2. Department of Biochemistry and Molecular Biology, Monash University, Clayton, VIC, Australia

**Introduction:** Current medications for the treatment of type 2 diabetes (T2D) have side effects or are not effective in all patients, necessitating the development of new medications. We have recently identified the protein ‘secreted modular calcium-binding protein 1’ (SMOC1) as a liver-secreted factor whose secretion is increased in non-alcoholic fatty liver disease and is responsive to glucose and insulin, suggesting a role in glycemic control.

**Objective:** This study aimed to further investigate the role of SMOC1 in glucose metabolism and its potential as a therapeutic for T2D.

**Methods:** Lean, obese insulin-resistant C57BL/6 mice and diabetic db/db mice were injected with SMOC1 recombinant protein (2 mg/kg) either acutely (2h before metabolic assessment) or chronically (daily injections for 14d). Additionally, we used adeno-associated virus (AAV) to overexpress SMOC1 in livers of db/db mice with the view to achieving a stable increase in circulating SMOC1. Metabolic outcome measures included oral glucose tolerance, insulin sensitivity (insulin tolerance test and euglycemic hyperinsulinemic clamps) and liver function. Phosphoproteomics and targeted cell signalling analysis were carried out to gain mechanistic insights into the function of SMOC1 in the liver.

**Results:** Acute injection of SMOC1 substantially improved glucose tolerance in all three mouse models. AAV-induced hepatic overexpression increased liver and plasma SMOC1, and improved glucose tolerance and insulin sensitivity. Clamp studies as well as glucose tolerance testing using [6,6-*H]*glucose indicated that the improvements in glycemic control were predominantly due to SMOC1 effects on hepatic glucose output. Phosphoproteomic analysis of SMOC1-mediated signalling in HepG2 hepatocytes as well as targeted functional analysis suggested that SMOC1 decreases glucose output by increasing glycolytic flux acutely and inhibiting gluconeogenesis via a AMPK-HNF4a-Foxo mediated pathway.

**Conclusion:** We have uncovered a striking and previously unknown role for SMOC1 in the regulation of glucose metabolism and are investigating SMOC1 as a possible novel therapeutic for T2D.

---

### Muscle-specific NOX4 deficiency impairs glucose metabolism and mitochondrial function

Chrysovalantou E. Xirouchaki^1, Supreet Kaur^1, Melanie Tran^2, Garron T. Dodd^1, Tony Tiganis^1

1. Metabolic Disease & Obesity Program, Biomedicine Discovery Institute, Department of Biochemistry and Molecular Biology, Monash University, Clayton, 3800, Victoria, Australia
2. Physiology and Neurobiology, University of Connecticut, Storrs, CT 06269, USA

Reactive oxygen species, produced by all living organisms as natural by-products of oxygen metabolism and by specialised enzymes known as NAPDH oxidases (NOXs), have been shown to elicit both deleterious and protective effects in various human diseases, including obesity and type 2 diabetes. The focus of the current study is on skeletal-muscle NOX4 and its role on muscle glucose metabolism and mitochondrial function. Muscle-specific NOX4 knockout mice [Mck-Cre;Nox4^fl/fl] were fed either a standard chow diet or a high-fat diet and were then subjected to insulin and glucose tolerance tests as well as hyperinsulinaemic/euglycaemic clamps. NOX4-deficiency resulted in reduced Nox4 mRNA and NOX4 protein, and was accompanied by glucose intolerance and insulin resistance after high fat feeding. High fat-fed NOX4-deficient mice showed reduced energy expenditure, mitochondrial gene expression and mitochondrial capacity (as assessed by measuring citrate synthase activity) and reduced expression of antioxidant defence genes including Nrf2. These results indicate that muscle-specific NOX4 deficiency promotes insulin resistance, glucose intolerance, as well as impaired mitochondrial function in high-fat-fed mice. Our results highlight the importance of muscle NOX4 on muscle glucose and mitochondrial metabolism.
A hypothalamic phosphatase switch coordinates white adipose tissue browning with feeding

Garron T Dodd1, Zane B Andrews2, Stephanie Simonds2, Jens Bruning3, Natalie J Michael2, Michael de Veer4, David Spanswick2, Michael A Cowley2, Tony Tiganis1

1. Metabolic Disease and Obesity Program, Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia
2. Department of Physiology, Biomedicine Discovery Institute, Monash University, Melbourne, VIC, Australia
3. Max Plank Institute for Metabolism Research, Cologne, Germany
4. Monash Biomedical Imaging, Monash University, Melbourne, VIC, Australia

Obesity is the single most important contributor to the development of type 2 diabetes (T2D) and effective obesity treatments will have profound implications for combating T2D.

The identification of the thermogenic beige adipocyte has opened up new ways in which to treat obesity and T2D. Beige adipocytes can interconvert between a white and beige adipocyte state, a process referred to as white adipose tissue (WAT) browning. This interconversion allows the adipose tissue to switch between an energy storage versus expenditure state. The co-ordination of energy intake with energy expenditure is essential to maintaining energy homeostasis.

To examine the role of WAT browning in this process, we measured WAT browning in the inguinal WAT (ingWAT) of fed versus food-restricted C57BL/6 mice by measuring the expression of beige adipocyte markers and beige fat activity by 18F-FDG-PET. We found that feeding induced the expression of beige adipocyte markers, enhanced beige adipocyte activity and whole-body energy expenditure. These changes in WAT browning and whole-body energy expenditure are dependent upon the hypothalamic-adipose tissue axis as these effects are lost if sympathetic outflow to ingWAT is denervated. Our results indicate that the feeding-induced changes in WAT-browning are mediated by the regulation of insulin signalling within neurons of the arcuate nucleus (ARC) of the hypothalamus. By deleting the insulin receptor phosphatase, TCPTP within ARC neurons we enhanced the neuronal responsivity to insulin which resulted in elevated sympathetic outflow promoting WAT browning. These effects were attenuated by partial insulin receptor deletion within the ARC. Furthermore, TCPTP deletion within the ARC of diet-induced obese mice resulted in significant weight loss, reduced adiposity and improved whole-body insulin sensitivity. Our studies suggest that insulin signalling within neurons of the ARC coordinate WAT browning and energy expenditure with feeding for the maintenance of energy balance.
The effect of ingested glucose dose on the suppression of endogenous glucose production in humans.

Greg Kowalski¹, Samantha Moore¹, Steven Hamley¹, Ahrathy Selathurai¹, Clinton R Bruce¹
1. Deakin University, Burwood, VIC, Australia

Insulin clamp studies have shown that insulin’s suppressive actions on endogenous glucose production (EGP) are markedly more sensitive than that for stimulating glucose disposal. However, clamp conditions do not adequately mimic postprandial physiological responses. Here, in healthy subjects, using the variable infusion dual-tracer approach, we used a 3-fold range of ingested glucose doses (25, 50 and 75 g) to investigate how physiologic changes in plasma insulin influence EGP. Remarkably, the glucose responses were similar for all doses tested, yet there was a dose-dependent increase in insulin secretion and plasma insulin levels. Nonetheless, EGP was suppressed with the same rapidity and magnitude (~55%) across all doses. The progressive hyperinsulinemia, however, caused a dose-dependent increase in the estimated rates of glucose disposal which likely accounts for the lack of a dose-effect on plasma glucose excursions. This suggests that following glucose ingestion, the body preferentially permits a transient and optimal degree of postprandial hyperglycemia so as to efficiently enhance insulin-induced changes in glucose fluxes, thereby minimizing the demand for insulin secretion. This may represent an evolutionarily conserved mechanism that not only reduces the secretory burden on β-cells but also avoids the potential negative consequences of excessive insulin release into the systemic arterial circulation.

Indirect effects of Protein Kinase C epsilon in high fat diet-induced insulin resistance: crosstalk between adipose tissue and liver

Mana Bing Liao¹, Barbara Diakanastasis¹, Sophie McManus¹, Amanda Brandon¹, Carsten Schmitz-Peiffer¹
1. Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

Mice with global deficiency in protein kinase C epsilon (PKCε) are strongly protected against high fat diet (HFD)-induced glucose intolerance. Improved suppression of hepatic glucose output (HGO) has shown to be a major effect, which leads to the proposal that the kinase inhibits proximal insulin signalling in the liver.

To compare the direct and indirect effects of PKCε, we used “floxed” PKCε mice to generate whole body-, liver- and adipose tissue-specific PKCε knockout (KO) mice, and examined glucose tolerance, as well as insulin action during euglycaemic-hyperinsulinaemic clamps, following chow or HFD for up to 16 weeks. Adipose tissue mRNA was analysed by RT-PCR and Affymetrix gene array. The conditioned media proteome from adipose tissue explants, subjected to normoxia or hypoxia, or from mice fed a HFD, was analysed by mass spectrometry.

Surprisingly, liver-specific PKCε KO did not recapitulate the protective effects of global PKCε KO on glucose homeostasis in fat-fed mice. In contrast, adipocyte-specific PKCε KO did improve glucose tolerance and partly improved the suppression of HGO. Further examination showed that despite a lack of alteration in the key enzymes of proteins of lipid metabolism and inflammation of the adipose tissue, there was a widespread upregulation of genes involved in the complement and coagulation cascade in the fat-fed adipose-specific PKCε KO. Conditioned media from adipose tissue explants inhibited insulin signalling in cultured hepatocytes, and proteomic analysis of this media indicated alterations in several proteins of the complement and coagulation cascade.

Collectively, our in vivo and in vitro data suggest a role for PKCε in diet-induced insulin resistance mediated in adipose tissue but not directly in liver, possibly through alterations in the secretion of proteins of the complement and coagulation cascade, which in turn leads to a beneficial crosstalk with the liver.

Adult-onset obesity and insulin resistance is triggered by impaired mitochondrial biogenesis

Nicola Ferreira¹, Kara Perks¹, Tara R Richman¹, Judith A Ermer¹, Irina Kuznetsova¹, Anne-Marie J Shearwood¹, Giulia Rossetti¹,
Richard G Lee¹, Vance Matthews², Helena M Viola³, Victoria Johnstone³, Livia C Hool³, Oliver Rackham¹,²,²,², Aleksandra Filipovska¹,²,²
1. Harry Perkins Institute of Medical Research, Perth, WESTERN AUSTRALIA, Australia
2. School of Medicine and Pharmacology, The University of Western Australia, Perth, Western Australia, Australia
3. School of Anatomy, Physiology and Human Biology, The University of Western Australia, Perth, Western Australia, Australia
4. School of Chemistry and Biochemistry, The University of Western Australia, Perth, Western Australia, Australia

Mitochondria are small sub-cellular organelles often referred to as the powerhouse of cells as they produce more than 95% of the energy required by cells. Mitochondria are essential to our survival and are responsible for many other essential metabolic processes including lipid and carbohydrate metabolism. Mitochondria are unique as they contain their own genome that codes for 13 proteins involved in energy production. The mitochondrial genome is regulated by a family of RNA-binding proteins known as pentatricopeptide repeat (PPR) proteins. Defects in the regulation of mitochondrial gene expression can arise due to mutations and environmental factors such as a high caloric diet and sedentary lifestyle. Such defects lead to mitochondrial dysfunction which can result in diminished energy production and consequently metabolic disease, including insulin resistance, obesity and type 2 diabetes. Little is known about how defects in mitochondrial gene expression can lead to changes in energy metabolism observed in metabolic disease. Here we investigated the link between a specific mitochondrial RNA-binding protein and the development and onset of metabolic disease via the characterization of a unique mouse model. We show that the mitochondrial RNA-binding protein is essential for the regulation of gene expression. Reduction of this protein leads to mitochondrial dysfunction and consequently the development of an age-induced metabolic syndrome. We further show the molecular mechanisms that potentially different cellular pathways which provide insight into the onset and development of disease in this mouse model. We conclude that reduction of the mitochondrial RNA-binding protein is a predisposing factor for the development of a metabolic syndrome and this novel mouse model provides a useful tool for the study of metabolic disease.
Improving skeletal muscle mitochondrial turnover to combat insulin resistance

Emily J King\(^1\), Anna C Calkin\(^1\), Yingying Liu\(^1\), Darren C Henstridge\(^1,2\), Brian G Drew\(^1,2\)
1. Baker Heart and Diabetes Institute, South Yarra, VIC, Australia
2. Monash University, Melbourne, VIC, Australia

**Introduction:** Diabetes is a leading cause of morbidity and mortality, worldwide, and is strongly associated with skeletal muscle mitochondrial dysfunction. Exercise has been recognized to improve diabetic outcomes by enhancing muscle mitochondrial turnover and insulin sensitivity. However, compliance to set exercise regimes is a major hurdle. Our laboratory has identified a novel protein, trim28 (T28), as a potential target for manipulating mitochondrial turnover and improving mitochondrial function.

**Objectives:** This research aimed to characterize the effect of muscle-specific trim28 knockout (T28KO) on mitochondrial function and glucose tolerance in a high fat fed, insulin resistant model.

**Methods:** T28KO mice were developed using the cre/lox system with developmentally expressed MCK-cre. Muscle-specific knockout of trim28 was confirmed via western blot. The effect of T28KO was characterized over a 16 week high fat diet regime by EchoMRI, oral glucose tolerance test (oGTT), intraperitoneal insulin tolerance test (ipITT), the comprehensive laboratory animal monitoring system (CLAMS) and Oroboros O2k analysis.

**Results:** At baseline, 4, 8 and 12 weeks post-diet, there were no significant differences between genotypes in total body, lean or fat mass. Neither glucose nor insulin tolerance was significantly different between the groups at these time points. T28 deletion did not affect whole-body oxygen consumption, energy expenditure or substrate preference at 3 and 7 weeks post-diet, though T28KO animals displayed a significant reduction in daytime activity 7 weeks post-diet (p=0.04). At 16 weeks post-diet, respiratory measurements in red gastrocnemius, as determined by a substrate- uncoupler-inhibitor titration protocol, did not differ between groups.

**Conclusions:** Whilst the current study failed to identify a metabolic consequence of T28 deletion, the possibility exists that this developmental knockout model underwent compensatory mechanisms during development. Hence, the potential for trim28 knockout to improve mitochondrial function and insulin sensitivity will be tested in an inducible cre mouse model, currently breeding in our laboratory.

Improving Biomedical & Psychosocial Outcomes in Young Persons with Type 1 Diabetes

Lori Laffel\(^1\)
1. Joslin Diabetes Centre, Boston, ACT, Australia
Not available at time of printing

Disease modifying therapy in type 1 diabetes; what an endocrinologist needs to know

Carla Greenbaum\(^1\)
1. Benaroya Research Institute, Seattle, WA, United States
We can now identify individuals at very early stages of T1D. This alone can prevent dka. But the real issue is to delay progression to clinical disease. Recent trial results are tantalizing.

Diabetes peer support in Australia: the experience, the evidence and a roadmap for future service provision

Jessica L Browne\(^2,1\), Jane Speight\(^2,1\)
1. School of Psychology, Deakin University, Geelong, VIC, Australia
2. The Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria, Melbourne, VIC, Australia
Peer support may be a beneficial adjunct to the formal healthcare available for people with diabetes. However, only one in ten Australians with diabetes participate in peer support, and the available information about the benefits and impact is often lacking in consistency, depth, and breadth. Thus, there is often confusion around what peer support is and whether or not it is worthwhile. In our symposium, we will take a 360 degree view of diabetes peer support, exploring the issue from the perspective of a consumer (Renza Scibilia, Diabetes Australia), and a clinician-researcher, Prof David Simmons (Western Sydney University). They will examine both the experience of, and the evidence behind, peersupport and identify ways in which they are in synergy and/or in tension with one another. Dr Jessica Browne (ACBRD) will review the current state of diabetes peer support offerings in Australia, and discuss a roadmap for design and delivery of peer support initiatives in the future. Finally, Carolyn Jones (Diabetes Victoria) will discuss Diabetes Victoria’s model for peersupport. The symposium will be of interest to healthcare professionals who are wondering if/how to recommend peer support to people with diabetes, as well as to consumer advocates and those involved in service design and delivery.
Exercise as a synergistic medicine for cancer

Daniel Galvão¹
1. Edith Cowan University, Joondalup, WA, Australia

Since initial reports in the mid-1980s, there has been increasing interest in the application of exercise as medicine for the prevention and management of cancer. A large number of high-quality RCT’s with cancer survivors have confirmed both aerobic and resistance exercise to be highly beneficial for improving body composition, quality of life, mental health and functional capacity, and reducing the risk of cancer recurrence and development of other chronic diseases. Moreover, data from observational studies indicates a 30-60% reduced risk for mortality. As a result, a logical research priority is to conduct clinical trials to confirm the survival advantage that can be achieved through targeted exercise medicine specifically prescribed to address cancer type, disease stage, and treatment side effects. Our hypothesis is that the relative rate of mortality will be even lower for those patients who undertake tailored exercise medicine. INTERVAL – MCRPC is a multicentre, randomised, controlled phase 3 trial evaluating highly specific resistance and aerobic exercise prescription tailored for men with metastatic castrate-resistant prostate cancer with the primary outcome being overall survival. The second research priority is to determine the specific mechanisms by which certain exercise modalities and dosages actually impact tumour biology. For example, Pedersen and co-workers² reported exercise to suppress tumour growth through NK cell mobilization and tumour infiltration in a rodent model. Understanding these mechanisms combined with our existing knowledge of exercise benefits for associated comorbidities is critical for effective and efficient prescription of exercise medicine for cancer management.³ The potential of exercise as a medicine for cancer management working independently and synergistically with other therapies is considerable and should be further pursued so that such interventions become standard care in people with cancer.

Targeting metabolic vulnerabilities in obesity-related cancers

Kyle Hoehn¹
1. University of New South Wales, Kensington, NSW, Australia

A hallmark feature of many cancer cells is their increased uptake and metabolism of glucose compared to non-cancerous cells from the same origin. Cancer cells generally use a greater proportion of incoming glucose for non-oxidative purposes including the production of building blocks for cell division (lipid, DNA and protein), rather than oxidative pathways that produce carbon dioxide in mitochondria. This talk will focus on our recent efforts to target potential metabolic vulnerabilities in obesity-related cancers including blocking cancer-specific glucose uptake and the metabolic pathway that converts glucose to lipid (lipogenesis).

Manipulating lipid metabolism as a treatment for prostate cancer

Matthew Watt¹
1. Monash University, Clayton, VIC, Australia

The global epidemic of obesity is closely linked to the development of serious co-morbidities, including many forms of cancer. Epidemiological evidence consistently shows that obesity is not associated with increased incidence of prostate cancer, but rather increased risk for aggressive prostate cancer and prostate cancer-specific mortality. Studies in mice demonstrate that obesity induced by high-fat feeding increases prostate cancer progression; however, the mechanisms underpinning this relationship remain incompletely understood. Adipose tissue expansion in obesity leads to local tissue dysfunction changes in lipolysis that results in increased delivery of fatty acids to tissues of the body. Recent work from our laboratories shows that fatty acid uptake is increased in malignant human prostate tissue and that the influx of fatty acids leads to increased lipid storage. This process is regulated by molecular reprogramming of genes and proteins encoding lipid metabolism in human prostate cancer. Genetic and monoclonal antibody silencing of the major fatty acid transporter, CD36, reduced fatty acid uptake and slowed prostate cancer progression in cancer susceptible mice. Furthermore, increased expression of CD36 correlated with poor survival in prostate cancer patients. This presentation will report on this new data identifying a critical role for fatty acid uptake in prostate cancer progression, suggesting a novel therapeutic avenue for the treatment of this disease.

Common mechanisms of metabolic reprogramming in diabetes and breast cancer

Sean McGee¹
1. Deakin University, Waurn Ponds, Vic, Australia

Reprogramming of cellular metabolism is emerging as a fundamental characteristic of many chronic diseases, including both type 2 diabetes and cancer. In studying metabolic reprogramming of skeletal muscle in type 2 diabetes, we have identified a link between nutrient excess, metabolic reprogramming and cell survival that involves a class Ilia histone deacetylase-p53 signalling axis. Phenotypically, this adaptive response shares many characteristics with cancer. We have used transcriptomic studies to predict a role for this signalling axis in breast cancer. Manipulating class Ilia HDAC expression in breast cancer cell lines has uncovered metabolic vulnerabilities that we are attempting to target with both novel and common diabetes drugs.
NADC activities leading to better diabetes services

Natalie Wischer

1. National Association of Diabetes Centres, Sydney, NSW, Australia

The National Association of Diabetes Centres (NADC) has been focused on improving the standards of care provided to people with diabetes for over 20 years. Under the leadership of ADS, the NADC has continued over the last 12 months to set the standards of diabetes care for services through their accreditation programs as well as provide opportunities for organisations to benchmark their services through the annual ANDA audit.

The NADC continues to innovate and implement projects that support all diabetes services and this session will provide an overview of the 2016/2017 program achievements and provide a summary on future projects that continue to support the implementation of many elements of the National Diabetes Strategy.

The Australian National Diabetes Audit (ANDA): Lessons from the 2016 Australian Quality Self-Management Audit

Anthony Pease

1. Diabetes and Vascular Medicine Unit, Monash Health, Clayton, VIC, 3168
2. School of Public Health and Preventive Medicine, Monash University, Clayton, VIC, 3168

The Australian National Diabetes Audit-Australian Quality Self-Management Audit (ANDA-AQSMA) is facilitated by the National Association of Diabetes Centres (NADC). In 2016 the ANDA-AQSMA has built on the successful, well-established ANDIAB2 initiative, and provided data on people attending services in diabetes care across Australia. Participating diabetes centres, endocrinologists and diabetes health care professionals are able to evaluate their data against their peers, enabling them to identify and implement mechanisms to improve outcomes for their patients.

In 2016, 56 diabetes centres (members of the NADC) responded to an expression of interest invitation. Of these, 50 provided de-identified data on 3930 individuals all aged over 18 years seen mainly during the one-month survey period of May or June 2016. A total of 6 sites were unable to participate in the audit due to shortage of staff or not being able to meet the minimum requirement of patients. The ANDA-AQSMA dataset is derived from the ANDIAB2 data set developed for the ANDIAB2 2005 Pilot, and revised for 2010 and the following biennial collections. It contains demographic, clinical, self-management and wellbeing data items that have standardised definitions, and has been promulgated for collection in all clinical practice settings.

The key findings from ANDA-AQSMA 2016 were:

- The majority of patients reported the correct use of insulin or other injectable medications as well as good adherence to their prescribed medication.
- One third of patients do not monitor their blood glucose level as often as is recommended.
- 54% of patients with diabetes do not engage in sufficient physical activity.
- One third of patients have trouble following their recommended diet, but only half of all patients audited had attended a dietitian in the last 12 months.
- Of the 13% of patients who are current smokers, three-quarters had tried to quit smoking.
- Reduced wellbeing and diabetes distress was identified in a considerable number of people (37%).
- 27% of patients with diabetes were found to have ‘likely depression’.
- 45% of patients had not seen a podiatrist in the last year.

ANDA’s 2017 and beyond

Sophia Zoungas, Eleanor Danek

1. Monash University, Clayton, VIC, Australia

Not available at time of printing
Delay in insulin secretion following an oral glucose load after islet transplantation in human type 1 diabetes

Glenn M Ward1, 2, 3, Jacqueline M Walters1, 4, Judith L Gooley1, 4, Shireene R Vethakkan1, Margaret Krishnapillai1, 4, Raymond C Boston1, 5, Alicia J Jenkins1, 4, Richard J MacIsaac1, 4, Kathy Howe1, 6, David Goodman1, D. Jane Holmes-Walker7, Philip O’Connell1, Thomas WH Kay18

1. Endocrinology and Diabetes, St. Vincent’s Hospital, Melbourne, Australia
2. Clinical Biochemistry, St. Vincent’s Hospital, Melbourne, Australia
3. Pathology, University of Melbourne, Melbourne, Australia
4. University of Melbourne Department of Medicine, St. Vincent’s Hospital, Melbourne, Australia
5. Department of Medicine (Endocrinology), University of Malaysia, Kuala Lumpur, Malaysia
6. University of Pennsylvania, Philadelphia, USA
7. NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia
8. Nephrology, St. Vincent’s Hospital, Melbourne, Australia
9. Westmead Hospital, Sydney, Australia
10. St. Vincent’s Institute of Medical Research, Melbourne, Australia

Introduction: Islet cell transplantation (ICT) is a highly effective therapy for Type 1 diabetes (T1D) with impaired awareness of hypoglycaemia (IAH) (1). We detected after ICT a deficiency of early insulin secretion by intravenous glucose tolerance tests (IVGTT)(2), despite transplantation of healthy islets.

Aims: The study aim was to further investigate this deficiency of early insulin secretion in ICT using oral glucose tolerance tests (OGTT). OGTTs have incretin effects(IE) boosting insulin secretion, though we found IE reduced by 40% of normal following ICT(3).

Methods: Seven insulin-independent T1D ICT recipients (Mean±SE Age=56±4yr, BMI=19.8±1.0kg/m2, T1D-duration=46±10yr) had frequently-sampled 75-grm OGTTs, compared to nine similar non-diabetic controls (ND) (53±4yr, BMI=24.8±1.9).

Results: Total insulin secretion in ICT-recipients was 21% of ND (Median[IQR] glucose-corrected incremental-AUC-insulin, ICTvsND=6.4[3.9-7.5] vs 29.5[17.2-37.1], mU/mmol, p<0.01 Wilcoxon). However, the 30-minute Insulinogenic Index (Δinsulin[0-30]/Δglucose[0-30]), in ICT was 15% of the ND (ICTvsND =2.3[0.7-6.7] vs 15.1[8.0-28.0]). Despite the reduced secretion, average ICT glucose levels were near-normal (HBA1c%, ICTvsND =5.7±0.3 vs 5.5±0.1, NS), and 2-hour OGTT glucose was non-diabetic in 2 ICT-recipients. Although the mean ICT-recipients’ 2-hour glucose was elevated (13.8±1.7 mmol/L) it returned to baseline by 4-hours (5.8±1.2). The good glycaemic control may be related not only to a trend to higher mean insulin sensitivity (HOMA2-%S) in ICTvsND (117±28% vs 83±8%, NS); but also, to the portal route of ICT causing suppression of hepatic glucose production via high intrahepatic insulin concentrations.

Conclusions: Selective measurement of early insulin release by OGTT in ICT could underestimate later secretion by ~30%, confirming our previous IVGTT report (2). The defect of early insulin secretion may reflect beta-cell overdrive causing depletion of readily-releasable insulin stores, but with good control of glycaemia due to the portal route of transplantation. Our results indicate OGTT evaluation of beta-cell function or incretin effects in ICT should measure both early and later insulin secretion.

Sustained improvement in diabetes-specific quality of life in adults with long-standing type 1 diabetes and problematic hypoglycaemia: 2-year results from the HypoCOMPaSS study

Elizabeth Holmes-Truscott1,2, Jane Speight3,1,2, David Kerr4, Daniel Flanagan5, Simon R Heller6, Mark L Evans7, James AM Shaw8
1. School of Psychology, Deakin University, Geelong, Victoria, Australia
2. The Australian Centre for Behavioural Research in Diabetes, Diabetes Victoria, Melbourne, Victoria, Australia
3. AHP Research, Homchurch, Essex, UK
4. William Sansum Diabetes Centre, Santa Barbara, CA, USA
5. Peninsula College of Medicine and Dentistry, Plymouth, UK
6. School of Medicine and Biomedical Science, Sheffield University, Sheffield, UK
7. Wellcome Trust-MRC Institute of Metabolic Science Metabolic Research Laboratories, University of Cambridge, Cambridge, UK
8. Institute of Cellular Medicine, Newcastle University, Newcastle, UK

Aims: The HypoCOMPaSS 24-week randomised controlled trial among adults with long-standing type 1 diabetes demonstrated improved awareness and reduction in severe hypoglycaemia following education and support, with no relative benefit of technology: insulin pump vs multiple daily injections (MDI) and real-time continuous glucose monitoring (RT-CGM) vs conventional finger prick monitoring (SMBG). These improvements were sustained at 2 years. We now examine the impact of diabetes and the role of technology on quality of life among HypoCOMPaSS participants before, during the trial and at 2-year follow-up.

Methods: Participants were 96 adults with type 1 diabetes: 64% women, aged 49±12 years, diabetes duration 29±12 years. The novel ‘Diabetes QoL-Q’ was completed at baseline (n=92), 24 weeks (n=84) and 24 months (n=59). It includes 26 items (scored 1-5) reflecting the impact of diabetes on various aspects of life, e.g. family, work, driving, holidays, independence, spontaneity. Repeated measures t-tests and analysis of variance were conducted on Diabetes QoL-Q items and composite score to examine change over time. At 24 weeks and 24 months, independent groups t-tests were used examine differences in scores by insulin and monitoring allocation (MDI vs. insulin pump and RT-CGM vs. SMBG).

Results: At 24 weeks, 19/26 items significantly improved, contributing to an improved Diabetes QoL-Q composite score (p<0.001, Cohen’s d=0.36). There were no significant between-group differences at 24 weeks or 24 months. Improvement in Diabetes QoL-Q scores was sustained at 2-year follow-up.

Conclusions: Education and 24-week support to reduce problematic hypoglycaemia was associated with significant improvement in overall diabetes-specific quality of life at 24 weeks, which was sustained at 2 years. Benefits were observed for most aspects of life and achieved across all groups, indicating no relative benefit of insulin pump over MDI or RT-CGM over conventional monitoring.

Day-to-day variability of fasting self-measured blood glucose (SMBG) correlates with risk of hypoglycaemia in adults with type 1 (T1D) and type 2 diabetes (T2D)

Timothy S Bailey1, Anuj Bhargava2, J. Hans DeVries2, Gregg Gerety4, Janusz Gumprecht5, Wendy Lane6, Carol Wysham7, Britta Anker8
Bak4, Elise Hackmann-Nielsen9, Athena Philis-Tsimikas5, Sultan Linjawi10
1. AMCR Institute, Escondido, California, USA
2. Iowa Diabetes and Endocrinology Research Center, Des Moines, Iowa, USA
3. Academic Medical Center (AMC), University of Amsterdam, Amsterdam, The Netherlands
4. Albany Medical Center, Albany, New York, USA
5. Medical University of Silesia, Zabrze, Poland
6. Mountain Diabetes and Endocrine Center, Asheville, North Carolina, USA
7. Rockwood Clinic, Spokane, Washington, USA
8. Novo Nordisk A/S, Søborg, Denmark
9. Whittier Diabetes Institute, Scripps Health, San Diego, California, USA
10. Cofts Harbour Diabetes Clinic, Cofts Harbour, New South Wales, Australia

The relationship between hypoglycaemia and day-to-day variability of glycaemic control has not been well established.

A post hoc analysis was performed correlating day-to-day variability of fasting SMBG with hypoglycaemia in two double-blind, treat-to-target, crossover trials that compared insulin degludec once daily (OD) with insulin glargine 100 units/mL OD in adults with T1D (SWITCH 1, n=501) or insulin-experienced adults with T2D (SWITCH 2, n=721). Available SMBG measurements were used to determine a weekly variance for each patient, using the log SMBG values to allow for relative comparisons. For each patient and treatment, the geometric mean of the weekly variance was calculated and these values were categorised into low, medium and high tertiles. Available SMBG measurements were used to determine a weekly variance for each patient, using the log SMBG values to allow for relative comparisons. For each patient and treatment, the geometric mean of the weekly variance was calculated and these values were categorised into low, medium and high tertiles. Available SMBG measurements were used to determine a weekly variance for each patient, using the log SMBG values to allow for relative comparisons. For each patient and treatment, the geometric mean of the weekly variance was calculated and these values were categorised into low, medium and high tertiles. Available SMBG measurements were used to determine a weekly variance for each patient, using the log SMBG values to allow for relative comparisons. For each patient and treatment, the geometric mean of the weekly variance was calculated and these values were categorised into low, medium and high tertiles. Available SMBG measurements were used to determine a weekly variance for each patient, using the log SMBG values to allow for relative comparisons.

At 24 weeks, 19/26 items significantly improved, contributing to an improved Diabetes QoL-Q composite score (p<0.001, Cohen’s d=0.36). There were no significant between-group differences at 24 weeks or 24 months. Improvement in Diabetes QoL-Q scores was sustained at 2-year follow-up.

Conclusions: Education and 24-week support to reduce problematic hypoglycaemia was associated with significant improvement in overall diabetes-specific quality of life at 24 weeks, which was sustained at 2 years. Benefits were observed for most aspects of life and achieved across all groups, indicating no relative benefit of insulin pump over MDI or RT-CGM over conventional monitoring.

Day-to-day variability was a significant predictor for the risk of overall and nocturnal hypoglycaemia in T1D and T2D, and severe hypoglycaemia in T1D (Table).

In conclusion, day-to-day glycaemic variability relates to hypoglycaemia risk.

Table: Effect of fasting SMBG variability on hypoglycaemia in SWITCH 1 and 2: low and high tertiles compared with medium tertiles.
Within-day variability based on 9-point profiles correlates with risk of overall and nocturnal hypoglycaemia in adults with type 1 (T1D) and type 2 diabetes (T2D)

Timothy Bailey¹, Anuj Bhargava², J. Hans De Vries³, Gregg Gerety⁴, Janusz Gumprecht⁵, Wendy Lane⁶, Carol H Wysham⁷, Britta Anker Bak⁸, Charlotte Thim Hansen⁸, Athena Philis-Tsimikas⁹, Roger Chen¹⁰

1. AMCR Institute, Escondido, California, USA
2. Iowa Diabetes and Endocrinology Research Center, Des Moines, Iowa, USA
3. Department of Endocrinology, University of Amsterdam, Amsterdam, The Netherlands
4. Albany Medical Center, Albany, New York, USA
5. Medical University of Silesia, Zabrze, Poland
6. Mountain Diabetes and Endocrine Center, Asheville, North Carolina, USA
7. Rockwood Clinic, Spokane, Washington, USA
8. Novo Nordisk A/S, Søborg, Please Select, Denmark
9. Whittier Diabetes Institute, Scripps Health, San Diego, California, USA
10. Concord Repatriation General Hospital, Concord, NSW, Australia

Higher glycaemic variability has previously been linked to an increased risk of hypoglycaemia. The correlation between within-day variability, based on 9-point profiles, and hypoglycaemia was investigated in two double-blind, treat-to-target, crossover trials comparing insulin degludec once daily (OD) with insulin glargine 100 units/mL OD in adults with T1D (SWITCH 1, n=501) or insulin-experienced adults with T2D (SWITCH 2, n=721). Within-day glycaemic variability was calculated as the relative fluctuation of the 9-point profile, defined through the integrated absolute distance from the mean within-day variability. Variabilities were subsequently categorised into low, medium and high tertiles based on the geometric mean. Hypoglycaemia was defined as overall symptomatic (severe or blood glucose [<3.2 mmol/L confirmed], nocturnal symptomatic (00:01–05:59) and severe (requiring third-party assistance and confirmed by a blinded adjudication committee) events.

This analysis showed that an increase in within-day variability has a significant correlation with an increasing risk of overall and nocturnal hypoglycaemia (Table). However, no correlation was found for severe hypoglycaemia in this dataset.

In conclusion, within-day glycaemic variability is associated with a risk of overall and nocturnal hypoglycaemia.

**Table.** Effect of within-day variability (9-point profile) on hypoglycaemia in SWITCH 1 and 2: low and high tertiles compared with medium tertile.

<table>
<thead>
<tr>
<th>Hypoglycaemia</th>
<th>Variability tertiles</th>
<th>SWITCH 1</th>
<th></th>
<th></th>
<th>SWITCH 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Estimate [95% CI]</td>
<td>p-value</td>
<td>Events</td>
<td>Estimate [95% CI]</td>
<td>p-value</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1113</td>
<td>0.71 [0.62; 0.81]</td>
<td>&lt;0.0001</td>
<td>63</td>
<td>0.32 [0.23; 0.45]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medium</td>
<td>1971</td>
<td>Reference</td>
<td></td>
<td>199</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2790</td>
<td>1.17 [1.05; 1.29]</td>
<td></td>
<td>587</td>
<td>2.25 [1.81; 2.81]</td>
<td></td>
</tr>
<tr>
<td>Nocturnal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>129</td>
<td>0.40 [0.30; 0.54]</td>
<td>&lt;0.0001</td>
<td>16</td>
<td>0.27 [0.15; 0.48]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medium</td>
<td>335</td>
<td>Reference</td>
<td></td>
<td>74</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>428</td>
<td>1.31 [1.04; 1.64]</td>
<td></td>
<td>190</td>
<td>2.15 [1.55; 2.98]</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>39</td>
<td>1.16 [0.68; 1.98]</td>
<td>&lt;0.0001</td>
<td>5</td>
<td>0.74 [0.23; 2.35]</td>
<td>p=0.1835</td>
</tr>
<tr>
<td>Medium</td>
<td>34</td>
<td>Reference</td>
<td></td>
<td>8</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>130</td>
<td>2.52 [1.60; 3.96]</td>
<td></td>
<td>14</td>
<td>1.85 [0.74; 4.61]</td>
<td></td>
</tr>
</tbody>
</table>

Data are estimates [95% CI]; CI, confidence interval; SMBG, self-measured blood glucose.

SWITCH 1: NCT02034513; SWITCH 2: NCT02030600

32
Corneal confocal microscopy assessed nerve structure in Type 1 diabetes adults correlates with non-invasive measures of tissue health (skin autofluorescence and retinal vessel calibres)

Andrzej Januszewski1,2, Acyel Al-Alosi2, Rachel McGrath3, Emma Scott2,3, Gregory Fulcher2, Alicia Jenkins2,1
1. Department of Medicine, University of Melbourne, Fitzroy, VIC, Australia
2. NHMRC Clinical Trials Centre, University of Sydney, Camperdown, NSW, Australia
3. Department of Endocrinology, Royal North Shore Hospital, University of Sydney, St Leonards, NSW, Australia

Introduction: Tools for early detection of neuropathy and other tissue damage in diabetes are of interest. Corneal confocal microscopy (CCM), which assesses corneal structures, is increasingly available. CCM measures have been associated with neuropathy in diabetes, but have not been related to other measures of tissue health, including retinal vessel calibre and skin autofluorescence (SAF, which correlates with AGEs); which are associated with and predictive of chronic complications.

Aims: To determine if CCM measures (1) differ between non-diabetic (CON) and T1D, and by T1D complication (CX) status; and (2) correlate with (a) retinal vascular parameters and (b) SAF.

Methods: Cross-sectional study: T1D subjects (n=33, including 13 CX+); mean±SD age 44±17 yrs; T1D duration 22±14 yrs and n=10 healthy controls (CON). Quantification: CCM HRT-3 (Heidelberg Engineering, Germany): corneal nerve fibre density (NFD), nerve branch density (NBD), nerve fibre length (NFL), endothelial cell density (ECD); Forearm SAF: AGE Reader (Diagnoptics, Netherlands). Retinal posterior pole images (CR-2 camera, Canon, Japan) graded for Central Retinal Arteriolar and Venular Equivalents (CRAE and CRVE) and arterio-venous ratio (AVR)( Vampire software, University of Dundee, Scotland).

Results: CCM differences between groups and correlations: NFD and NFL differences for CON vs. T1D and T1DCX- vs. T1DCX+ remained significant after adjustment for age and T1D duration respectively. SAF: T1D SAF correlated inversely with NFD (r=0.48; p=0.006), NBD (r=0.48; p=0.006) and NFL (r=-0.54; p=0.002). Retinal vessels: CRAE and CRVE (but not AVR) correlated with NFD (r=-0.49; p=0.005, r=-0.41; p=0.02), NBD (r=-0.41; p=0.02, r=-0.43; p=0.01) and NFL (r=-0.47; p=0.007, r=0.41; p=0.02). In T1D CX- AVR and in CX+ CRAE correlated with NFL (r=-0.54, r=0.02, r=0.56; p=0.04 respectively).

Conclusions: Corneal nerve measures and SAF are worse in T1D and in T1D CX+ vs. CX-. Some CCM measures inversely correlate with SAF and retinal vessel calibres. Such tools may facilitate diabetes monitoring.

Table 1. CCM measures, retinal AVR and skin AFL (unadjusted) in T1D vs. CON and in CX- vs. CX+

<table>
<thead>
<tr>
<th>Hypoglycaemia</th>
<th>Variability tertiles</th>
<th>SWITCH 1</th>
<th>SWITCH 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Estimate [95% CI]</td>
<td>p-value</td>
</tr>
<tr>
<td>Overall</td>
<td>Low</td>
<td>1318</td>
<td>0.92 [0.82; 1.03]</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>1675</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>2234</td>
<td>1.15 [1.04; 1.27]</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>Low</td>
<td>166</td>
<td>0.76 [0.59; 0.97]</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>247</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>365</td>
<td>1.45 [1.14; 1.84]</td>
</tr>
<tr>
<td>Severe</td>
<td>Low</td>
<td>54</td>
<td>0.78 [0.49; 1.25]</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>55</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>53</td>
<td>0.81 [0.50; 1.31]</td>
</tr>
</tbody>
</table>

SWITCH 1: NCT02034513; SWITCH 2: NCT02030600
CI, confidence interval
Mitochondrial dysfunction defines a population of young people with type 1 diabetes at risk of kidney disease

Josephine M Forbes1, Nicole Fleming1, Domenica McCarthy1, Kristof Boot2, Neisha D’Silva2, Linda Gallo1, Janelle Nisbett1, Adam Morton1, Stephanie Teasdale1, David Thorburn3, Anthony Russell3, Nicolle Isbel4, David Johnson5, Grant Morahan1, Mark Harris1, Tim Jones8, Jenny Couper2, Kim Donaghey19, Mark Hodson11, Trisha O’Moore-Sullivan2

1. Mater Research Institute - The University of Queensland, Brisbane, QLD, Australia
2. David Serisier Biobank, Mater Health Service, Brisbane, QLD, Australia
3. Mater Young Adult Health Centre, Mater Health Service, Brisbane, QLD, Australia
4. Murdoch Children’s Research Institute, Royal Children’s Hospital, Melbourne, VIC, Australia
5. Diabetes and Endocrinology, Metro South Health, Brisbane, QLD, Australia
6. Metro South and Ipswich Nephrology and Transplant Service, Metro South Health, Brisbane, QLD, Australia
7. Harry Perkins Institute of Medical Research, University of Western Australia, Perth, WA, Australia
8. Telethon Kid’s Institute, Perth, WA, Australia
9. Women’s and Children’s Hospital, Adelaide, SA, Australia
10. Children’s Hospital at Westmead, Sydney, NSW, Australia
11. Metabolomics Australia, The University of Queensland, Brisbane, QLD, Australia

Aim: The objective of this study was to examine the relationships between mitochondrial and renal function in young people with Type 1 diabetes (T1D).

Background: Recent evidence suggests that kidney disease in T1D develops much earlier than previously appreciated. In adolescents with type 1 diabetes (T1D), the highest tertile of urinary albumin-to-creatinine ratio (uACR), predicts renal and cardiovascular disease risk.

Methods: A cross-sectional cohort of young adults with T1D was recruited [n=100; 20.0±2.8 yrs; M:F=54:46; HbA1c=6.1(12.3) mmol/mol; diabetes duration=10.7±5.2 yrs; BMI=24.5(5.3) kg/m²]. Mean uACR tertiles (3 morning urine samples) were used to divide the study population. Lower (uACR=0.66 mg/mmol; n=33) and middle (uACR=0.67-1.16; n=33) tertiles were defined as having low-moderate risk and those in the upper tertile (uACR≥1.17; n=34) as high risk of future DKD. Mitochondrial function in circulating leukocytes and urinary metabolomics were performed.

Results: Participants had hyperfiltration [CKD_eGFR, 135.0(13.8) ml/min/m²] and individuals in the upper tertile of uACR had the highest median eGFR (P<0.031 vs low risk tertile; age, gender and diabetes duration adjusted). In a generalized linear model which included HbA1c, BMI, diabetes duration, sex and age, a significant inverse relationship was identified between eGFR-CKD_eGFR and logACR in the upper tertile, which was not seen in lower risk tertiles (vs middle, P=9.8x10^-6; vs lower, P=2x10^-10). Mitochondrial function (ATP dependent respiration) in circulating leukocytes, was decreased in individuals in the higher uACR tertile (P=0.008). Multivariate modelling of urinary metabolites identified a signature which separated the upper uACR tertile from the lower risk tertiles.

Conclusions: Young individuals with type 1 diabetes and higher risk of DKD have mitochondrial dysfunction and an inverse relationship between GFR and uACR.


Predictors of mortality in Australians with type 1 diabetes

Amy L Harding1, Xinyang Hua2, Leon F Heffer2, Javier Haurat2, Philip M Clarke2, Peter G Colman1, Amy Harding1

1. Department of Diabetes & Endocrinology, Royal Melbourne Hospital, Parkville, Victoria, Australia
2. School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia
3. BioGrid Australia, Melbourne, Victoria, Australia

Background: Several large cohort studies suggest that patients with type 1 diabetes are at increased risk of all-cause and cardiovascular mortality. Despite this, little is known about the clinical predictors for mortality and first cardiovascular event in Australian patients with type 1 diabetes.

Methods: We undertook a retrospective longitudinal cohort study linking clinical data captured from patients with type 1 diabetes attending Royal Melbourne Hospital outpatient clinics from 1998 to November 12 2016 (using the BioGrid diabetes database), with hospital separation data and the Australian National Death Records.

Results: Overall 107 of the 1,420 patients with type 1 diabetes died during the follow-up period, and 85 patients in the cohort suffered their first cardiovascular event. The mean follow-up was 9.6 years and mean age at diagnosis 18.7 years. Multivariate regression analysis demonstrated an adjusted hazard ratio for all-cause mortality of 2.34 (95% CI, 1.08 to 4.98) for patients with HbA1c of <7% and 2.28 (95% CI, 1.42 to 5.42) for patients with HbA1c levels of ≥9% compared with those with levels of 7-8%. Adjusted hazard ratios for all-cause mortality compared to those without albuminuria were 2.24 (95% CI, 1.34 to 3.72) for and 2.67 (95% confidence interval 1.39 to 5.14) for those with microalbuminuria and macroalbuminuria, respectively. Corresponding adjusted hazard ratios for first cardiovascular event were 2.19 (95% CI, 1.06 to 4.53) for patients with macroalbuminuria.
Conclusions: Concordant with other cohort studies, our data demonstrated that in Australians with type 1 diabetes, both HbA1c levels ≥9%, and also those <7% were associated with greater than twice the risk of death. Other clinical predictors for death included both micro- and macroalbuminuria. Furthermore, in our study, macroalbuminuria conveyed the largest risk of developing first cardiovascular event, even following adjustments for other clinical risk factors.

36

Trends in Body Mass Index at Type 1 Diabetes diagnosis in Western Australia from 1999-2012 and its impact on glycaemic control.

Melissa J Simonds1, Smith Grant2, Aveni Haynes3, Elizabeth A Davis2

1. University of Western Australia, Perth, WA, Australia
2. Telethon Kids Institute, Perth, WA, Australia

OBJECTIVE: To investigate trends in BMI z-scores (BMiz) of Western Australian (WA) children at T1D diagnosis over the 1999-2012 period. We aimed to elucidate associations of BMiz with age, sex and socioeconomic status (SES) to determine if an increased BMiz at T1D onset was associated with earlier disease manifestation, and poorer glycaemic control at 3 years post-onset.

DESIGN AND METHODS: The relationships between BMiz at 2-5 months post-diagnosis with demographic variables (age, sex, SES) and mean glycated haemoglobin (HbA1c) calculated from 3 months to 3 years post-diagnosis were examined in children aged 2-14 years at T1D onset residing in WA from 1999-2012. Multivariable linear regression models were used to assess associations, examining for interaction effects and adjusting for potential clinical confounders.

RESULTS: Mean BMiz at T1D diagnosis decreased over 1999-2012 by an average of 0.015 BMiz scores each year [p<0.05, 95% CI(-0.028,-0.002)], with the greatest decrease observed for older children (10-14 yrs). Comparatively, younger children (2-4 years) became progressively heavier whilst incidence in this age group remaining steady. Mean BMiz between age groups (2-4, 5-9, 10-14yrs) were significant (p<0.01), and children from lower SES were likely to be 0.451 BMiz scores heavier than their socioeconomically advantaged counterparts (p<0.01). Finally, there was no evidence for a strong relationship between mean 3-year HbA1c and BMiz category (p=0.11) with little variation over the 13 year study period.

CONCLUSION: The mean BMiz of WA T1D children is decreasing over time comparative to the plateauing overweight/obesity rates in Australian children, but that this trend is observed only for those aged 4-14years at diagnosis, with the youngest age group becoming increasingly heavier at diagnosis. Age group, year-diagnosed and SES were all significant predictors of mean BMiz, with no evidence currently to suggest a greater BMiz at diagnosis is associated with poorer glycaemic control at 3-years.

37

The E3 ubiquitin ligase MARCH5 is a PPARy target gene that regulates mitochondrial function in white adipocytes

Simon T Bond1, Sarah C Moody2, Andrea L Hevener2, Bronwyn A Kingwell1, Mete Civelek2, Darren C Henstridge1, Aldons J Lusis3,

Anna C Calkin1, Brian G Drew1

1. Baker IDI, Melbourne, VIC, Australia
2. University of California, Los Angeles, California, USA

Obesity can lead to lipid accumulation in non-adipose tissues leading to health complications including insulin resistance, T2D and NAFLD. These complications are caused in part by peripheral lipid deposition that occurs in lieu of adipose tissue becoming saturated and unable to store excess lipid. Thus, by redirecting fat from non-adipose tissues back into adipose tissue, complications associated with obesity may be alleviated. Recent studies have shown that activating adipogenesis, or enhancing healthy WAT expansion, can reduce obesity induced complications and results in a metabolically healthy phenotype.

Mitochondria are well known organelles that generate energy in the form of ATP but also play a role in whole body energy homeostasis and cell division. Mitochondrial dynamics is the process of fusion, fission, mitophagy, and biogenesis, which has been shown to be important for maintaining mitochondrial health and recently implicated in healthy WAT expansion. Here, we demonstrate that expression of the E3 ligase March5 is reduced in ob/ob mice, is negatively correlated with fat mass in a panel of genetic diverse mouse strains (HMDP), and reduced with visceral adiposity in men. We also demonstrate in the HMDP, in cells and in ChIP-Seq data, that March5 is a bone fide PPARy target gene in adipocytes. March5 has been shown to ubiquinate and thus act as an upstream regulator of the mitochondrial dynamics proteins mitofusin2 (Mfn2), and Dynamin-1-like protein. Accordingly, we demonstrate that March5 knockdown using shRNA in 3T3-L1 differentiated cells increases Mfn2 protein levels, suggesting a reduction in fission and an increase in fusion, which leads to increased mitochondrial respiration as measured by the Seahorse flux analyser.

Collectively, these data suggest that altering March5 expression could be a potential mechanism to increase mitochondrial activity in WAT, which might subsequently allow for increased adipogenesis and greater capacity to store lipid in the setting of obesity.
Role of the sympathetic nervous system in regulation of the sodium glucose co-transporter 2.

Vance Matthews1,3, Rosemary Elliot1,2, Caroline Rudnicka3,2, Jana Hricova1,3, Lakshini Herat1,2, Markus Schlaich1,2,4
1. The University of Western Australia, Perth, WA, Australia
2. Dobney Hypertension Centre, Perth, Western Australia, Australia
3. Research Centre, Royal Perth Hospital, Perth, WA, Australia
4. Royal Perth Hospital, Perth, Western Australia, Australia

**Background:** Sympathetic nervous system (SNS) activation is a common feature in obesity and type-2 diabetes and regulates glucose metabolism in organs including the kidneys. The sodium glucose co-transporter 2 (SGLT-2) mediates re-absorption of glucose from the renal proximal tubules in the kidney. SGLT-2 inhibitors have garnered attention due to their glucose lowering effects and may improve cardiovascular and renal outcomes.

**Aims:** Firstly, to investigate the hypothesis that SGLT-2 is up-regulated by norepinephrine (NE), the main neurotransmitter of the SNS. Secondly, we also aimed to determine whether SGLT-2 inhibition may limit SNS activity in vivo.

**Methods:** We used the human renal proximal tubule cell line, HK2. Cells were treated with NE at a range of concentrations and time-points. SGLT-2 expression in HK2 cells in response to treatment with NE was determined by immuncytochemistry and western blotting. IL-6 release was also determined by ELISA. We also performed studies to determine the influence of SGLT-2 inhibition on the SNS in vivo. Mice fed a high fat diet were oral gavaged with dapagliflozin (DAPA) and the expression of NE and the sympathetic neuron protein tyrosine hydroxylase was measured in the kidney and heart by immunochemistry.

**Results:** A marked increase in SGLT-2 and IL-6 expression in HK2 cells and translocation of SGLT2 to the cell surface could be demonstrated in response to NE treatment. In vivo, DAPA treatment resulted in marked glucosuria in high fat diet fed mice. Importantly, SGLT-2 inhibition in vivo, significantly reduced high fat diet induced elevations of NE and tyrosine hydroxylase in the kidney and heart.

**Conclusions:** Our in vitro and in vivo studies provide first evidence for an important cross-talk between the SNS and SGLT-2 regulation, which may not only account for SNS-induced alterations of glucose metabolism but may potentially contribute to cardiovascular and renal protection observed with SGLT2 inhibitors.


Reducing VEGF-B signalling ameliorates renal lipotoxicity and protects against diabetic kidney disease

Pierre Scotney1, Annelie Falkevall2, Annika Mehem2, Isolde Palombo2, Benjamin H Sahlgren2, Lwaki Ebara2,3,4, Liqun He3, Jimmy A Ytterberg1,4, Hannes Olauson3, Jonas Axelson3,7, Birgitta Sundelin4, Jaakko Patrakka1, Andrew Nash1, Ulf Eriksson2
1. Research, CSL Limited, Parkville, Victoria, Australia
2. Division of Vascular Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden
3. Department of Immunology, Genetics, and Pathology, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden
4. Division of Renal Medicine, Department of Clinical Sciences, Intervention, and Technology, Karolinska Institutet, Stockholm, Sweden
5. Division of Physiological Chemistry I, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden
6. Rheumatology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden
7. Center for Apheresis and Stem Cell Handling, Karolinska University Hospital, Stockholm, Sweden
8. Department of Oncology-Pathology, Karolinska Institutet and Karolinska University Hospital, Huddinge, Sweden
9. KI/AZ Integrated CardioMetabolic Center (ICMC), Department of Laboratory Medicine, Karolinska Institutet at Karolinska University Hospital, Huddinge, Sweden

Diabetic kidney disease (DKD) is the most common cause of severe renal disease, and few treatment options are available today that prevent the progressive loss of renal function. DKD is characterized by altered glomerular filtration and proteinuria. A common observation in DKD is the presence of renal steatosis, but the mechanisms underlying this observation and to what extent they contribute to disease progression are unknown.

Vascular endothelial growth factor B (VEGF-B) has been shown to control muscle lipid accumulation through regulation of trans-endothelial fatty acid transport (Hagberg et al., 2012). VEGF-B expression is under control of PGC1α, a regulator of mitochondrial energy metabolism and ERRα, the estrogen-related receptor α (Mehem et al., 2016). In experimental mouse models of DKD (db/db mice) renal VEGF-B expression correlates with the severity of disease. Inhibiting VEGF-B signalling in DKD mouse models, either by Vegfb gene deletion in db/db mice or targeting VEGF-B with an antagonist antibody in db/db, high fat diet and streptozotocin treated mice, reduces renal lipotoxicity, re-sensitizes podocytes to insulin signalling, inhibits the development of DKD-associated pathologies (glomerular mesangial expansion, glomerular sclerosis and podocyte loss), and prevents renal dysfunction (Falkevall et al., 2017). Elevated VEGF-B levels are found in the glomeruli of patients with DKD, suggesting that VEGF-B antagonism represents a novel approach to treat DKD.

Differences in matrix synthetic and degradative pathways may contribute to differences in susceptibility to development of renal changes in BALB/c and C57BL/6 mice.

Anh Tao¹, Surya Sutanto¹, Linda Ban¹, Danqing Min¹,², Stephen Twigg¹,³, Susan McLenann¹,²,³
1. Greg Brown Diabetes and Endocrinology Research Laboratories, Sydney Medical School, Charles Perkins Centre and Bosch Institute, University of Sydney, Sydney, NSW, Australia
2. Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, NSW, Australia
3. NSW Health Pathology, Sydney, NSW, Australia

The BALB/c mouse is more prone to development of diabetic nephropathy (DN) than the C57BL/6. Furthermore, the relationship between matrix synthetic and degradative pathways in association with the development of DN in these strains has not been investigated.

Diabetes (DM) was induced in 6-week-old male BALB/c and C57BL/6 mice (STZ: 3x65mg/kg), age-matched non-diabetic mice acted as control. Animals were euthanased 5, 10 and 30wks later. Kidneys were harvested for measurement of markers of inflammation (CXCL10 and MCP-1), profibrotic markers (TGFβ1 and CTGF), and matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) by qRT-PCR. Endogenous kidney MMP activity was measured using a fluorogenic substrate. Renal changes were assessed by histology.

In all DM animals blood glucose level was increased (P<0.01). In BALB/c mice renal changes were evident at 5wks of DM, with increased glomerular size, thickened basement membrane and mesangium expansion prominent by 30wks. In BALB/c, diabetes increased CXCL10 and MCP-1 (5-30wks) and TGFβ1 but not CTGF at 5 and 10wks (all P<0.01). MMPs (MMP-2, -14) and TIMPs -1 and -2 were increased at 5wks of DM (P<0.05), and at 10wks for MMP-14 and TIMP-2 (P<0.01). Kidney MMP activity was also increased at 10wks (P<0.05). The pattern for CXCL10 in C57BL6, was similar, but MCP-1 was increased only at 5wks and TGFβ1 and CTGF were increased at all time points (P<0.05). In C57BL6, the MMP profile was different with increased MMP-3 and -9 at 5 and 10wks as well as increased TIMPs (P<0.05). Interestingly, in BALB/c animals, the mRNA levels of MMPs and TIMPs were all decreased at 30 weeks (P<0.05) but in C57BL6 mice the increased TIMP-1 persisted (P<0.05).

This study suggests that there are subtle differences in response to diabetes in BALB/c and C57BL6 mice which may contribute to the different susceptibility to the development of DN.

Diabetes and hypertension differentially affect renal reactive oxygen species and catecholamine content

Anna MD Watson¹,², Sally Penfold¹, Eleanor AM Gould², Kristy L Jackson², John-Luis Moretti², Putra Riza Pratama², Stephen P Gray²,
Eikelis N², Gavin W Lambert¹,³, Geoffrey A Head¹,³, Karin AM Jandeleit-Dahm¹,²
1. Monash University, Melbourne, VIC, Australia
2. Baker Heart and Diabetes Institute, Melbourne, VIC, Australia
3. Swinburne University of Technology, Melbourne, VIC, Australia

Background: Patients with both diabetes and hypertension develop nephropathy at an accelerated rate. Using the hypertensive Schlager mouse model, we examined changes in renal function, sympathetic nerve status and the oxidative status of the kidney in diabetic mice with and without concomitant hypertension.

Methods: After 10 weeks of study, hypertensive BPH/2J and normotensive BPN/3J Schlager mice with and without concomitant streptozotocin induced diabetes (5x 55 mg/Kg i.p.) were placed in metabolic cages for 24hr and had kidneys harvested. In a separate group of animals BP telemetry probes were implanted.

Results: Induction of diabetes did not change the hypertensive status of BPH mice (MAP 131 ± 4 vs. 129 ± 4 mmHg for non-diabetic vs. diabetic BPH, n=5 &6). Diabetic BPN and BPH mice showed significantly greater albuminuria than non-diabetic controls, with diabetic BPN showing less albuminuria than diabetic BPH (439 ± 73 vs. 1205 ± 196 μg/24hr, n=8, 7). Plasma cystatin C was significantly lower in diabetic animals, with no difference between strains. HPLC measurement of cortical noradrenaline showed significantly greater levels in kidneys from hypertensive mice but interestingly diabetic mice had significantly less renal noradrenaline in both mouse strains. Renal cortical peroxide formation was increased in non-diabetic BPH mice and while activity of the anti-oxidant enzyme catalase was increased in non-diabetic BPH mice it was significantly less in diabetic BPH animals (non-diabetic vs. diabetic BPH 104 ± 8 vs. 63 ± 6 nmol/min/ml, n=8/gp).

Conclusion: Kidneys of non-diabetic hypertensive mice show greater renal oxidative stress than normotensive mice. While diabetic hypertensive animals have greater oxidative stress they had lower catalase activity, indicating compromised ability to deal with hypertensive lead increases in oxidative stress. This could contribute to greater renal neuropathy, further compromising renal function. This mechanism may underlie the poor outcome for patients with hypertensive diabetic nephropathy.
Three dimensional glomerular reconstruction: A novel approach to evaluate renal microanatomy in diabetic kidney disease

Niloufar Torkamani\textsuperscript{1,2}, George Jerums\textsuperscript{3}, Paul Crammer\textsuperscript{3}, Alison Skene\textsuperscript{1,4}, David Power\textsuperscript{1,5}, Sianna Panagiotopoulos\textsuperscript{1}, Michele Clarke\textsuperscript{3}, Richard MacIsaac\textsuperscript{6}, Elif I. Ekinci\textsuperscript{1,2,7}

1. Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia
2. Department of Endocrinology, Austin Health, Melbourne, VIC, Australia
3. Anatomical Pathology, Monash Medical Centre, Melbourne, VIC, Australia
4. Department of Pathology, Austin Hospital, Melbourne, VIC, Australia
5. Department of Nephrology, Austin Health, Melbourne, VIC, Australia
6. Department of Endocrinology and Diabetes, St. Vincent’s Hospital Melbourne, Fitzroy, VIC, Australia
7. Menzies School of Health Research, Darwin, Northern Territory, Australia

Background

Mesangial volumes are important metrics reflecting glomerular filtration surface area in diabetes. The point-sampled intercept (PSI) method is the conventional method used to calculate these parameters. However, this is time-consuming and is subject to underestimation. We introduce a novel technique to measure mesangial volumes using three-dimensional (3D) imaging.

Methods

Renal tissue from 22 patients with type 2 diabetes and estimated glomerular filtration rate of <60mL/min/1.73m\textsuperscript{2} were obtained. Patients were classified into normo-, micro-, or macroalbuminuria categories according to their 24h urine albumin excretion rate. Six ultra-thin serial sections were cut for Periodic acid–Schiff–diastase and Haematoxylin-Eosin staining. Up to five glomerular units from each section were photographed (x40). Three methods were used to quantify total glomerular area, mesangial volume, and mesangial/total area ratio. These included a transmission electron microscopy (TEM) based method (using computer-assisted measurement), the PSI method and our new 3D imaging method. A 3D representation was reconstructed from all glomeruli (320 glomeruli) using “Reconstruct” software for our new method. The correlation coefficient between results from the three methods was calculated using images from 8 patients with the TEM method being the gold-standard reference method.

Results

The correlation coefficient between TEM/3D, TEM/PSI and 3D/PSI methods was 0.98, 0.93, and 0.96 respectively. Our 3D method demonstrated that mesangial area increased progressively in normo- to macroalbuminuric patients. Significantly higher levels of mesangial proliferation were also seen in macroalbuminuric > normo and > microalbuminuric groups (p<0.05).

Conclusions

3D reconstruction was demonstrated to be a reliable method to calculate mesangial area and is more accurate than PSI. Moreover, this technique is less time consuming and is not dependent on electron microscopy. Due to its ease of use, 3D reconstruction may prove to be useful for studying renal biopsies and in clinical practice to quantify the glomerular changes in diabetic kidney disease.
Expression of miR-146a and miR-378a in wound fluid: A possible biomarker for poor wound healing in diabetes

Carla Cannizzo1, Luisa Olaya Agudo1, Maryam Abdollahi1, Taria Ng1, Surya Sutanto1, Susan McLennan1,2,3
1. Greg Brown Diabetes and Endocrinology Research Laboratory, Sydney Medical School, Charles Perkins Centre, Bosch Institute, University of Sydney, Camperdown, NSW, Australia
2. Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, NSW, Australia
3. NSW Health Pathology, Sydney, NSW, Australia

Increasing evidence suggests that micro-RNAs (miRs) may serve as potential biomarkers of healing. miR-146a and miR-378a are involved in inflammation and fibroblast migration respectively and are thus associated with poor wound closure. Whether these miRs are detectable in wound fluid (WF) and are altered in diabetes has not been investigated.

Male Sprague–Dawley rats were injected intraperitoneally with streptozotocin (STZ: 65mg/kg) to induce diabetes (D: n=11) and were maintained for 6 weeks with Insulin (2-6U Humalog® 25). After 6wks diabetic and age-matched non-diabetic rats (C: n=8) were anesthetized and 4x1cm² PVC sponges were implanted subcutaneously. On day 6 post-surgery, animals were euthanized and plasma (P) as well as WF from harvested sponges were obtained. miRs were extracted (P: 400µl and WF: 200µl) and their expression measured by qRT-PCR using Taqman probes. Results were normalized to exogenous Caenorhabditis elegans miR-39 and reported as mean ±SD.

**Figure 2** Total mesangial area calculated by TEM, 3D and PSI methods

**Figure 3** Mesangial area to total glomerular area ratio grouped by albuminuria status
Diabetic animals had significantly higher blood glucose levels and lower body weight compared to controls (each \( P < 0.05 \)). In controls there was an increase in WF miR-146a (P: 64.53 ± 38.91 vs WF: 3131 ± 1598, \( P < 0.001 \)) and miR-378a (P: 2.603 ± 1.981 vs WF: 19 ± 5.002, \( P < 0.001 \)) when compared to plasma, this pattern was also seen in diabetic animals: miR-146a (P: 88.53 ± 55.92 vs WF: 21728 ± 25762, \( P < 0.0001 \)) and miR-378a (P: 7.398 ± 2.608 vs WF: 27.86 ± 6.03, \( P < 0.005 \)). In addition miR-146a was significantly increased in the WF of diabetic rats when compared to control (C: 3131 ± 1598 vs D: 21728 ± 25762, \( P < 0.05 \)).

These results indicate for the first time that miR-146a and miR-378a are present in WF in this model. The increase in miR-146a in diabetic WF suggests its utility as a potential biomarker for poor wound healing. Whether these changes are observed in human WFs and their levels are altered in association with wound healing rate remains to be investigated.

**Statin therapy causes gut dysbiosis in mice**

Ricky R Lareu\(^1,2\), Jose A Caparros-Martin\(^3,2\), Josh Ramsey\(^3,2\), Jorg Peplies\(^4\), F. Jerry Reen\(^5\), Henrietta A Headlam\(^6\), Natalie C Ward\(^1,2,6\), Kevin D Croft\(^6\), Philip Newsholme\(^3,2\), Jeff Hughes\(^1\), Fergal O’Gara\(^3,2\)

1. School of Pharmacy, Curtin University, Bentley, WESTERN AUSTRALIA, Australia
2. Curtin Health Innovation Research Institute, Curtin University, Bentley, Western Australia, Australia
3. School of Biomedical Sciences, Curtin University, Bentley, Western Australia, Australia
4. Ribocon, Bremen, Germany
5. BIOMERIT Research Centre, School of Microbiology, University College Cork, Cork, Ireland
6. School of Medicine and Pharmacology, The University of Western Australia, Perth, Western Australia, Australia

Statins, as a group, are amongst the most prescribed drugs in recourse-rich countries: prescribed to lower circulating cholesterol and reduce the risk of cardiovascular disease. However their consumption is associated with a number of secondary side effects that have raised concerns about their safety. This has made statins a controversial therapeutic option, and some question whether long-term benefits outweigh the risks. One recurrent side-effect associated with statin intolerance is an increased risk of developing type-2 diabetes mellitus (T2DM). Up to now the aetiology of these unintended effects is not well understood and it has been hypothesised that the physiological state of the patient plays an important role in its development. However, despite the increasing awareness of the importance of a healthy gut microbiota in health and wellness and the knowledge of gut dysbiosis in the pathogenesis of T2DM, the possible impact of chronic statin therapy on this microbial community has not been investigated. Using a murine model we describe, for the first time, profound changes in the bacterial composition of the gut following statin treatment. This remodelling affected the diversity and metabolic profile of the gut microbiota, and was associated with reduced production of butyrate. Furthermore, statins altered the size and composition of the bile acid pool in the intestine, tentatively explaining the observed gut dysbiosis. Using gene knockout mice we demonstrated that the observed effects were mediated through the pregnane X receptor. Our study suggests that statin therapy affects the intestinal microbiota by deregulating bile acid metabolism and thus unhinging the gut–liver axis. Since the demonstrated importance of the gut microbiota in host well-being, our work expands on the knowledge of the potential physiological consequences of taking statins and provides a new perspective to prevent their inadvertent metabolic effects.

**Getting the diagnosis right in the diabetes clinic.**

Andrew Hattersley\(^1\)

1. University of Exeter, Exeter, DEVON, United Kingdom

Not available at time of printing

**Antihyperglycemic agents and cardiorenal protection**

David Cherney\(^1\)

1. University Health Network, Toronto, Canada

Not available at time of printing

**Transitions in Care for Emerging Adults with Type 1 Diabetes**

Lori Laffel\(^1\)

1. Joslin Diabetes Centre, Boston, ACT, Australia

Not available at time of printing
FlexIT Training for Health Professionals: One year on, a National Perspective

Marisa Nastasi\textsuperscript{1}, Maggie Stewart\textsuperscript{1}, Sonia Middleton\textsuperscript{1}

1. Baker Heart and Diabetes Institute, Melbourne, VIC, Australia

The FlexIT Health Professional Training Program was launched by the Education Service at Baker Heart and Diabetes Institute (Baker) in 2016. The face-to-face two or three day is designed to upskill knowledge and expertise in teaching flexible insulin adjustment principles along with other topics including carbohydrate counting, exercise, alcohol and sick day management.

Completion of the 3 day program is required to become an accredited FlexIT client program provider. Accredited providers are given lesson plans, resources and evaluation procedures to deliver the Baker client program in their health service.

The FlexIT client program is now being facilitated by accredited providers in Perth WA, Black Swan District WA, Bendigo VIC, South Gippsland VIC and Warragul VIC alongside the current program delivered at Baker, Melbourne VIC.

Participants are evaluated at four time points; pre, post, 3 and 12 months after completion. Questionnaires assess diabetes knowledge (adapted MDRTC Diabetes Knowledge Test), self-management behaviours (Self Care Inventory-Revised Version), self-efficacy and confidence (Confidence in Diabetes Self Care Scale), diabetes distress (Problem Areas In Diabetes Questionnaire) and carbohydrate counting (adapted PedCarbQuiz).

A total of 68 participants have completed the program. Mean age 45 years, 52% male and mean duration of type 1 diabetes was 18 years. 14 of these participants have completed the questionnaire at 3 time points (pre, post and 3 months post program) to date. Improvements in self-efficacy and confidence have been demonstrated 3 months post program with mean confidence score 66.25 improving to 77.40 which was significant (p=0.0145). Feelings of distress have also significantly reduced with values reducing by 11 points from a mean average score of 22.59 to 10.57 (p= 0.0101), 3 months post program.

In conclusion the FlexIT client program has positively demonstrated improvements in self-efficacy and reductions in diabetes distress. Further evaluation and follow-up will be required to determine the long-term impact of this program on type 1 diabetes management.

Ambulatory insulin dose adjustment clinic redesign project

Penny E Morris\textsuperscript{1}, Katherine T Tonks\textsuperscript{2}, Joanne E Taylor\textsuperscript{3}, Cecile A Eigenmann\textsuperscript{1}

1. Diabetes Centre, St Vincent's Hospital, Darlinghurst, NSW, Australia
2. Department of Endocrinology, St Vincent's Hospital, Sydney, NSW, Australia

Background: The Diabetes Centre at St Vincent's Hospital Sydney (SVHS) has delivered a Diabetes Nurse Educator (DNE)-led Insulin Stabilisation Program since 1979 with the primary goal of improving patients' blood glucose control without hospital admission. The Insulin Stabilisation protocol was last reviewed in 2006. Clinical care advances and program inefficiencies led to a redesign project.

Aim: To redesign the Insulin Stabilisation Program and establish evaluation measures to assess program efficacy.

Method: In 2016 a literature search and review of other tertiary Diabetes Centres programs identified insulin stabilisation studies, position statements, clinical guidelines and service procedures. Clinical practice improvement methodology was utilised to conduct brainstorming and multi-voting exercises with the SVHS diabetes team. Process flow-diagrams, cause and effect diagrams and Pareto chart analysis were used to prioritise redesign goals. Plan, Do Study, Act cycles were undertaken in identified priority areas. A Working Party was established and met fortnightly.

Results: The program was renamed the Insulin Dose Adjustment (IDA) Clinic. A dedicated database, mobile phone and daily DNE roster was established. Patient demographics, diabetes type, date of enrollment and discharge, clinic completion/non-completion, reason for non-completion and HbA\textsubscript{1c} pre and post enrollment were recorded. A clinic procedure and accompanying forms were drafted, trialed and revised. In contrast to prior practice, the DNE was primarily responsibility for making and maintaining contact with patients. Insulin titration prescription and target blood glucose levels were added to clinic referral forms. An initial insulin assessment checklist, patient information sheet, documentation chart, patient experience questionnaire and IDA Clinic procedure audit tool were developed.

Conclusion: The redesign of the IDA clinic and associated procedure has standardised care delivery. Evaluation measures have been established and will be used to assess efficacy of the clinic in the future.

Supporting people with type 1 diabetes on insulin pump therapy

Marlene Payk\textsuperscript{1}, Deborah Davis\textsuperscript{2}, Tracy Robinson\textsuperscript{3}, Marjorie Atchan\textsuperscript{2}

1. Westmead Hospital, Westmead, NSW, Australia
2. University of Canberra, Canberra, ACT, Australia
3. School of Public Health, Monash Centre for Health Research & Implementation (MCHRI), Melbourne, Victoria, Australia

Aims and Rationale

The aim of this study was to explore the clinical and psychosocial support Australian diabetes nurse educators’ provide to people with type 1 diabetes on insulin pump therapy, with a view to improving clinical practice and, ultimately, outcomes for people using pumps.

Methods
Interpretive Description methodology was used to guide this study which drew on semi structured interviews with diabetes nurse educators and people with type 1 diabetes on insulin pumps. Thematic analysis was used for analysis of the data.

Findings
Twenty participants were interviewed for this study including 9 diabetes nurse educators and 11 people with type 1 diabetes on insulin pump therapy.
The 4 main themes identified from the diabetes nurse educators were; the learning phase, meeting consumer needs and own expectations, reframing professional practice and challenging the role.
Four themes identified from the consumers experiences of receiving pump support from diabetes nurse educators were; support needs, support provided, challenges and enablers, and overlapping roles between diabetes nurse educators, endocrinologists and pump company representatives.

Conclusions
There is a need for diabetes nurse educators to have structured education on insulin pump therapy that includes a mentoring component and consumer participation. Despite having significant support needs consumers of insulin pump therapy receive varying levels of support from diabetes nurse educators, endocrinologists and pump company representatives. Clarification is required on the role of the diabetes nurse educator, endocrinologist and insulin pump company representative to avoid consumer confusion.

Comprehensive sequential diabetes prevalence surveys amongst inpatients at St Vincent’s Hospital Sydney
Joanne E Taylor¹, Lesley V Campbell², Lulu Zhang³, Jerry R Greenfield²
1. St Vincent’s Hospital Sydney Diabetes Centre, Darlinghurst, NSW, Australia
2. Department of Endocrinology, St Vincent’s Hospital, Sydney, NSW, Australia
3. St Vincent’s Public Hospital, Sydney, NSW, Australia

Introduction
Patients with diabetes are hospitalised more frequently than those without. Hyperglycaemia is associated with increased adverse outcomes and length of stay (LOS). Insulin is among the top 5 high-risk medications used in hospitals.

Objectives
To compare: (i) Diabetes prevalence at a Sydney Teaching Hospital between 2013, 2014 and 2016. (ii) Inpatient diabetes management to plan service delivery.

Methods
We conducted 3 single-day point prevalence surveys of all inpatient records in November 2013, 2014 and 2016. Twelve teams completed an 18-item survey on all admitted patients (n=394 2013, n=381 2014, n=368 2016). Diabetes diagnosis was ascertained if: (i) diabetes documented in medical record; or (ii) patient prescribed diabetes medication/s; or (iii) fasting glucose ≥7mmol/L; or (iv) random glucose ≥11.1mmol/L; or (v) HbA1c ≥6.5%.

Results
Diabetes prevalence was 20-25%. In 2016, highest prevalence was found in Heart/Lung Transplant (59%) and Heart Failure (50%). As outlined in the Table, the majority were male and had type 2 diabetes. Half received subcutaneous insulin during admission and many experienced at least one insulin prescription/administration error. In the 7-days preceding the survey, hyperglycaemia occurred on >10 occasions in one quarter of patients and hypoglycaemia occurred on ≥1 occasion in 11-13% of patients. Of the diabetes patients who met referral criteria, only half-to-two-thirds were referred.

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2014</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Prevalence %</td>
<td>25 (n=98)</td>
<td>20 (n=75)</td>
<td>25 (n=93)</td>
</tr>
<tr>
<td>% male</td>
<td>66.3</td>
<td>66.7</td>
<td>57</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>70</td>
<td>75</td>
<td>64</td>
</tr>
<tr>
<td>Subcutaneous insulin in hospital (%)</td>
<td>42</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>≥1 insulin prescription/administration error (%)</td>
<td>41</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>Mean glucose 24h preceding survey (mmol/L)</td>
<td>9.3</td>
<td>9.2</td>
<td>9.1</td>
</tr>
<tr>
<td>Glucose&gt;11mmol/L ≥10 occasions (%)</td>
<td>23</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Glucose&gt;4mmol/L ≥1 occasion (%)</td>
<td>11</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>% referred to Diabetes Team (who met criteria)</td>
<td>41</td>
<td>77</td>
<td>49</td>
</tr>
</tbody>
</table>

Conclusions
One-quarter of hospital patients have diabetes. Half are treated with insulin during admission. Insulin errors are common. Diabetes inpatient teams are underutilised.
Glycaemic outcomes of nurse led insulin dose adjustment clinic

Katherine A Worton1, Cecile A Eigenmann2, Penny E Morris1, Hayley K Patterson1, Leanne C Gregory1, Liam J Collins1, Jerry R Greenfield2, Joanne E Taylor1

1. St. Vincent’s Hospital Diabetes Centre, Darlinghurst, NSW, Australia
2. Department of Endocrinology, St. Vincent’s Hospital, Sydney, NSW, Australia

Introduction: St Vincent’s Hospital (Sydney) Diabetes Centre has delivered an insulin dose titration program since 1979. The IDA Clinic is a core part of the Diabetes Centre’s activity operated by a Diabetes Nurse Educator (DNE) Monday to Friday from 8am to 12 midday. The benefit of this clinic to patient glycaemic outcomes had not been established.

Objective: To determine whether participation in the IDA clinic improves glycaemic outcomes.

Methods: All patients enrolled in the IDA Clinic from 13 April to 12 October 2016 (26 weeks) were audited. The following data was collected on all enrolled patients: age, diabetes type, enrolment date, discharge date, HbA1c pre-enrolment and ≤ 6 months post-discharge and whether patient achieved target BGLs.

Results: We enrolled 172 patients. Mean age was 59 y (range 18-91). Seventy-two percent (n=123) had type 2 diabetes, 22% (n=38) had type 1 diabetes, 4% (n=7) had steroid-induced diabetes and 2% (n=4) had other diabetes. Average length of stay in the clinic was 9 weeks (range 0-28). Of those enrolled, 109 had pre- and post-clinic HbA1c data available. Of these, 69% (n = 75) completed the programme (determined by achieving target blood glucose levels).

As shown in the table, there was a significant improvement in glycaemic control (1.3% reduction in HbA1c) after participation in the IDA Clinic (P<0.001). There was a significantly greater improvement in HbA1c in completers versus non-completers (P=0.02).

<table>
<thead>
<tr>
<th></th>
<th>Mean HbA1c % (mmol/mol) pre-enrolment</th>
<th>Range</th>
<th>Mean HbA1c % (mmol/mol) post-discharge</th>
<th>Range</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>9.4</td>
<td>6.3-16.7 (45-159)</td>
<td>8.1</td>
<td>5.0-11.3 (31-100)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>(n=109)</td>
<td>(79)</td>
<td></td>
<td>(65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completers</td>
<td>9.5</td>
<td>6.3-15.6 (45-147)</td>
<td>7.9</td>
<td>5.0-11.3 (31-100)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>(n=75)</td>
<td>(80)</td>
<td></td>
<td>(63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-completers</td>
<td>9.2</td>
<td>6.8-16.7 (51-159)</td>
<td>8.5</td>
<td>5.9-11.1 (41-98)</td>
<td>P=0.05</td>
</tr>
<tr>
<td>(n=34)</td>
<td>(77)</td>
<td></td>
<td>(69)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Enrolment in an insulin dose adjustment program improves glycaemic control in the short-term. Future analysis will determine whether this benefit is maintained.

What Does Person Centred Care Really Look Like in Practice (and what it doesn't)?

Sophie McGough1, Timothy Skinner2, Ingrid Willaing3, Nana Folmann-Hempler3, Annemarie Varming3, Dan Grabowski3, Kylie Mahony1, 2, Sue Stockdale4, Helen Mitchell4

1. Diabetes WA, Subiaco, WA, Australia
2. School of Psychological and Clinical Sciences, Charles Darwin University, Darwin, Northern Territory, Australia
3. Patient Education Research, Steno Diabetes Center, Copenhagen, DENMARK
4. DESMOND Australia, Perth, WA, Australia

Despite there being no universally accepted definition of person centred care, increasingly there are common themes or principles included in quality frameworks that address this area. These include respectful, responsive health care, informed choice, shared decision making, effective communication and consumers being valued as equal partners in health with their own beliefs and life experience being recognised.

The Australian Diabetes Educator Association released a Person Centred Care Toolkit for diabetes educators in 2015. This included a CDE Quality Improvement Tool to provide guidance in delivery of person centred care in their practice. The experience of DESMOND Australia and the Danish STENO centre has been that educators need tools and resources to assist with delivery of person centred care as part of this quality improvement process.

The aim of this workshop is to empower educators to recognise what person centred care does and doesn’t looks like in practice and to engage with, trial or explore tools to support the development of person centred skill. The combined experience from DESMOND Australia and the STENO centre will address both group and individual education settings. The workshop will focus on self-reflection, peer review and educational tools that support educators to have person centred conversations.
Diagnosis and Treatment of Painful Diabetic Neuropathy

BIN LU
1. Huashan Hospital, Fudan University, Shanghai Shi, China

Diabetic neuropathy (DN) is prevalent in diabetic patient all over the world including China. Pain is one of its most serious symptoms. New horizon in the diagnosis of painful DN is associated with small fiber nerves (C type). Corneal confocal microscopy was conducted in Chinese cohort to identify the normal reference range and distinguish pre-clinical small fiber neuropathy. Current perception threshold (CPT) was also used for detecting injury in different nerves in community cohort. Beyond these new technology, several serum markers were found in DN patients to be associated with the progression and symptoms of DN, like neurofilament heavy chain, C-peptide and other inflammation markers, like neutrophil-to-lymphocyte ratio. On the other hand, Sudoscan was found in Chinese people not only to reflect the function of autonomic nerves system, but also the indicator of diabetic microvascular complications, including DN. Despite of the progression of early diagnosis of DN, we are still lack of effective methods for its treatment because of the ambiguity recognition to its mechanism. Central nerve system is found to play an important role in DN, especially in pain. Our results showed that microglia in both cortex and thalamus were significantly activated in STZ induced T1D rats’ brain in vivo. Glucagon like peptide 1 could improve the inappropriate activation of microglia, induced by both LPS and high glucose, and re-balance its M1/M2 polarization in vitro. Other than glucose control, exercises were believed to be another way for the improvement of DN. Continuous resistive exercises for 6 months had shown its power in Chinese old community diabetic population. With the deepening of the understanding of DN, new techniques and methods will emerge in the diagnosis and control.

Alteration of Olfactory Network in Type 2 Diabetes

YAN BI
1. Xuzhou City Hospital of Traditional Chinese Medicine, XuZhou, JIANGSU, China

Type 2 diabetes mellitus (T2DM) is associated with increased risk of cognitive impairment. Individuals with T2DM have 1.5-2.5 folds increased risk of dementia compared with those without diabetes. Even in prediabetic stage, there is a gradual progression of subtle cognitive impairments involving memory, attention, processing speed, and executive functioning. Previous magnetic resonance imaging (MRI) studies demonstrated that patients with T2DM exhibited increased global brain atrophy and vascular lesions, with reduced cerebral blood flow than those without diabetes. Decreased regional spontaneous neural activation and disrupted functional connectivity in brains regions involving global cognitive processing were observed in T2DM patients in functional MRI (fMRI) studies. In addition, olfactory behavior dysfunction, characterized by increased odor thresholds and impaired odor discrimination and recognition, is considered as one of the earliest manifestations of neurodegenerative diseases and a potential preclinical biomarker of future cognitive decline. Noteworthy, lower scores in olfactory behavior test were also shown in T2DM patients compared with nondiabetic subjects and were significantly correlated with poor cognitive performance. This study firstly evaluated olfactory behavior and olfactory-induced brain activation in T2DM patients with normal cognitive status, providing new insights into the role of olfactory circuit alterations in the development of cognitive decline. Significantly altered olfactory-induced brain activations and disrupted functional connectivity were shown before both brain structural changes and clinical cognitive decrements in patients with T2DM. Such functional alterations in the olfactory network could probably constitute a potential marker for early cognitive decline in T2DM.

Current state of Diabetic Ketoacidosis in China: Still an issue of concern

XIAOHONG WU
1. First Affiliated Hospital with Nanjing Medical University(NMU), China

With increased emphasis on integrated care management for patients with diabetes, rates of diabetes-related complications have declined substantially in the past two decades. However, diabetic ketoacidosis (DKA), one of the most serious acute complications of diabetes, remains a significant cause of morbidity and mortality in clinical practice. China has the largest number of diabetes cases, however, there has been little research on the clinical profiles of patients with DKA episodes in the Chinese population. From a multicentre, clinic-based study between 2010 and 2012 in 15 tertiary medical centres around China, patients with Type 1, Type 2 and atypical diabetes were all at risk of being hospitalized with DKA. Type 2 and Type 1 diabetes contribute to a similar proportion of cases presenting with DKA. Although guidelines on the diagnosis and therapy of DKA have been launched, significant gaps remain in translating the current knowledge to the bedside, especially in relation to the classification of diabetes, fluid supplementation and bicarbonate therapy. Admissions with DKA in China were still associated with significant mortality and prolonged hospitalization. In another multicentre registration study of patients with established type 1 diabetes from 16 centres in Guangdong Province, China, the incidence of secondary DKA was 26.4/100 patient-years. Significant risk factors for secondary DKA were female gender, medical reimbursement rate <50%, uncontrolled diet, smoking and poor glycaemic control. Overweight/obesity was a protective factor. Additionally, 34.4% of secondary DKA occurred in 3.8% patients with recurrent events. The results indicate that secondary DKA occur at high rates in Chinese patients with established T1DM and that recurrence is likely to occur in high-risk patients. The efficiency of DKA management needs to be improved by implementing the updated guidelines.
Clinical features and molecular genetics of Beta-cell related monogenic diabetes

Miao Yu
1. Xuzhou City Hospital of Traditional Chinese Medicine, XuZhou, JIANGSU, China

Optimization of Short-term Intensive Insulin Treatment in Patients with Type 2 Diabetes Mellitus

Yanbing Li
1. First Affiliated Hospital of Sun Yat-sen University, China

Intermittent energy restriction: friend or foe for diabetes and cardio metabolic disease management?

Amanda Salis1, Nuala Byrne2, Leonie Heilbronn3, Jencia Wong4, Jane Overland4, Sharayah Carter4
1. The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, Sydney Medical School, Charles Perkins Centre, The University of Sydney, Camperdown, NSW, Australia

Vitamin D deficiency in early pregnancy is associated with increased cardiometabolic risk and gestational diabetes

Aya Mousa1, Sally K Abell1, Soulmaz Shorakae1, Negar Naderpoor1, Cheryce L Harrison1, Danielle Hiam2, Alba Moreno-Asso2, Nigel K Stepto2, Robert Scragg3, Helena J Teede1, Barbora de Courten1
1. Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

BACKGROUND: Maternal vitamin D deficiency has been associated with cardiometabolic risk factors during pregnancy and adverse pregnancy outcomes including gestational diabetes mellitus (GDM). Vitamin D has well-established anti-inflammatory properties, yet the association between vitamin D and inflammation, particularly adipokines, remains unexplored in pregnancy. We investigated whether maternal 25-hydroxyvitamin D (25(OH)D) concentrations were related to cardiometabolic risk factors during pregnancy and pregnancy outcomes, and whether these relationships may be mediated by circulating adipokines.

METHODS: Serum samples were collected from 102 overweight or obese pregnant women at 12-15 weeks gestation for measurement of 25(OH)D, fasting lipids, interleukin-6, monocyte chemoattractant protein-1, and novel adipokines omentin-1, visfatin, and high-molecular-weight (HMW)-adiponectin. Fasting, 1-, and 2-hour glucose levels were measured by oral glucose tolerance tests (OGTT) at 28-weeks gestation. Pregnancy outcomes were recorded at delivery. All analyses were adjusted for maternal factors: age, BMI, parity, smoking status, and ethnicity.
RESULTS: In 102 pregnant women (age=31.9±4.5 years; BMI=30.6±6.6 kg/m\(^2\) [mean±SD]), mean 25(OH)D concentration at 12-15 weeks was 47.9±16.0 nmol/l. After adjustment for maternal factors, 25(OH)D concentrations were negatively associated with total cholesterol (p=0.02), triglycerides (p=0.01), fasting glucose (p=0.006) and 1-hour post-OGTT glucose (p=0.045), and positively associated with HMW-adiponectin (p=0.008). Higher 25(OH)D concentrations were associated with increased length of gestation (p=0.006) and reduced risk of GDM (OR(95%CI)=0.97(0.94-0.99),p=0.04). After additional adjustment for C-sections, higher 25(OH)D concentrations were associated with reduced risk of preterm birth (OR(95%CI)=0.89(0.80-0.99),p=0.03). Adding HMW-adiponectin to the models attenuated all associations except fasting glucose (p=0.03) and length of gestation (p=0.03).

CONCLUSIONS: Low first-trimester 25(OH)D concentrations were associated with increased cardiometabolic risk factors and adverse pregnancy outcomes, and most associations appeared to be mediated by HMW-adiponectin. Intervention and mechanistic studies are needed to further explore the effects of vitamin D in pregnancy, and to elucidate whether these effects are independent or modulated by circulating adipokines.

Prevalence of pre-existing dysglycaemia among inpatients with acute coronary syndrome and associations with outcomes.

Dinesh Mahendran\(^1\), Garry Hamilton\(^2\), Jeremy Weiss\(^1\), Jeremy Lew\(^1\), Leonid Churilov\(^2\), Kaylyn Khoo\(^3\), Que Lam\(^4\), Raymond Robbins\(^5\), David L. Hare\(^6\), Omar Farouque\(^2,6\), Jeffrey Zajac\(^1,6\), Elif I. Ekinci\(^1,6\)

1. Endocrinology and Diabetes, Austin Health, Heidelberg, Victoria, Australia
2. Cardiology, Austin Health, Heidelberg, Victoria, Australia
3. The Florey Institute of Neuroscience and Mental Health, Heidelberg, Victoria, Australia
4. Department of Pathology, Austin Health, Heidelberg, Victoria, Australia
5. Austin centre for applied clinical informatics, Austin Health, Heidelberg, Victoria, Australia
6. Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia

Introduction
Routine HbA1c testing on admission of inpatients presenting with acute coronary syndrome (ACS) presents a unique opportunity for diagnosing pre-existing dysglycaemia without the limitations of stress-induced hyperglycaemia.

Objectives
We aimed to determine the prevalence of pre-existing dysglycaemia in inpatients presenting with ACS and its association with clinical outcomes, including acute pulmonary oedema (APO), recurrent ACS and, all-cause mortality at 12 months.

Methods
As part of the Austin Health Diabetes Discovery Initiative, routine HbA1c testing was undertaken on all inpatients aged ≥54 years admitted with ACS if none was available within the preceding 90 days. Patients were categorised into those with diabetes (prior diagnosis or HbA1c ≥ 6.5%, ≥48mmol/mol), pre-diabetes (HbA1c 5.7-6.4%, 39-46mmol/mol) and no diabetes (HbA1c <5.6%, <38mmol/mol).

Results
Between July 2013 and July 2015, 847 consecutive patients were admitted with ACS. 313 (37%) inpatients had diabetes, 312 (37%) had pre-diabetes and 222 (25%) had no diabetes. After adjusting for age, sex, smoking status and previous myocardial infarction, diabetes, as opposed to no diabetes, was associated with a higher risk of APO (OR 2.60, P<0.01), longer length of stay (LOS) (IRR 1.18, P=0.02) and, higher risk of 12-month ACS recurrence (OR 1.86, P<0.05). Pre-diabetes was not a statistically significant marker of adverse clinical outcomes. However, analysed as a continuous variable, HbA1c was associated with an increased risk of APO (OR 1.28, P=0.002) and, longer LOS (IRR 1.05, P=0.03).

Conclusions
In our study, three-quarters of all inpatients aged ≥54 years admitted with ACS had pre-existing dysglycaemia. Inpatients with diabetes were at increased risk of developing APO and subsequent 12-month ACS recurrence. Increases in HbA1c, even in the pre-diabetic range, was associated with a higher risk of APO and longer LOS. Randomised studies would be necessary to determine if improving dysglycaemia in ACS patients improves longer term outcomes.
Determinants of incident intraocular lens implantation in type 2 diabetes: The Fremantle Diabetes Study Phase 2

Jocelyn J Drinkwater¹, Wendy A Davis¹, David G Bruce¹, Timothy M E Davis¹
1. School of Medicine, University of Western Australia, Fremantle, WA, Australia

People with type 2 diabetes (T2D) are at increased risk of cataracts and subsequent intraocular lens (IOL) implantation but there are few diabetes-specific data relating to the underlying risk factors. The aim was to investigate variables associated with incident IOL implantation in a large community-based sample of Australians with T2D. The Fremantle Diabetes Study Phase II (FDS2) recruited 1,551 T2D participants (mean±SD age 65.7±11.6 years, 51.9% males, median [IQR] diabetes duration 9.0 [3.0-15.8] years) from a postcode-defined population of 157,000 between 2008 and 2011. Detailed biochemical, physical, questionnaire and interview assessments were conducted at entry and then biennially. Cataract and IOL status was ascertained by the Western Australian Data Linkage System using relevant ICD codes and hospitalisation for IOL implantation was ascertained to end-June 2013. Cox regression analysis with age as timescale was used to identify predictors of IOL implantation. Participants with a prior IOL implantation at study entry (20.1%, n=322) were excluded. Of the remaining 1,229, 14.1% (n=173) had IOL implantation during 4,120 person-years of follow up. These patients were significantly older (70.2±8.8 vs 61.8±10.7 years, P<0.001) and had longer diabetes duration (13.0±4.0 vs 6.2±2.0 years, P<0.001) at study entry than those without any IOL implantation. Independent predictors of incident IOL implantation are shown in the table.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR ≥ 90ml/min/1.73m²</td>
<td>3.54</td>
<td>2.16-5.81</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR 60-89ml/min/1.73m²</td>
<td>1.93</td>
<td>1.27-2.93</td>
<td>0.002</td>
</tr>
<tr>
<td>Asian ethnic background</td>
<td>2.67</td>
<td>1.32-5.4</td>
<td>0.007</td>
</tr>
<tr>
<td>Severe hypoglycaemic episode in last year</td>
<td>2.28</td>
<td>1.19-4.34</td>
<td>0.013</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.03</td>
<td>1.01-1.06</td>
<td>0.020</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/L)</td>
<td>0.60</td>
<td>0.37-0.95</td>
<td>0.030</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>1.14</td>
<td>1.01-1.29</td>
<td>0.039</td>
</tr>
<tr>
<td>Hormone replacement therapy</td>
<td>2.12</td>
<td>1.02-4.40</td>
<td>0.044</td>
</tr>
</tbody>
</table>

The multiple predictors of incident IOL implantation included those reported previously for cataract development (glycaemic control, body mass index, hormone replacement and Asian ethnicity (1)). The relationship with relatively high eGFR categories may reflect hyperfiltration, a precursor for rapid decline in renal function leading to chronic renal disease which is itself a risk factor for cataract. Novel predictors comprised severe hypoglycaemia and low HDL cholesterol which have been associated with cataract development in animal studies (2, 3). These findings suggest there are modifiable risk factors for IOL implantation which could be targeted as part of usual care in T2D.


Microvascular complications in type 2 diabetes: increased retinopathy in the young adult onset subgroup

Timothy Middleton³, Maria Constantine³, Lynda Molyneaux¹, Stephen M Twigg³, Ted Wu¹, Jencia Wong³
1. Diabetes Centre, Royal Prince Alfred Hospital, Sydney
2. Discipline of Medicine, The University of Sydney, Sydney

It is increasingly recognised that type 2 diabetes (T2D) with onset in young adulthood is an aggressive condition. However, reliable data on long term complication outcomes in comparison to later onset T2D are lacking. A cross sectional study of T2D patients attending the RPA Diabetes Centre (1990-2016) was undertaken. Data relating to 4,457 clinical encounters were abstracted from the Diabetes Centre Database and outcomes by age of T2D onset analysed. To account for increasing risk of complications by T2D duration, data were stratified into duration bands: 10-15, 15-20 and 20-25 years. Binary logistic regression analysis was performed to compare microvascular complication rates (retinopathy, microalbuminuria and peripheral neuropathy) in age of diagnosis bands (15-29, 30-39, 40-49, 50-59 and 60-69 years). Adjusted odds ratios after accounting for current age, gender, smoking, BMI, updated HbA1c, systolic blood pressure and cholesterol are presented. The odds of any detectable retinopathy after 10-15 years of T2D were greatest in those with T2D onset 15-30 years (OR 4.7, p=0.005). Similar results were seen 15-20 and 20-25 year duration bands, a pattern not observed in models of albuminuria or peripheral neuropathy. Early onset T2D appears to be
a particularly aggressive disease with respect to the microvascular complication of retinopathy, even accounting for duration of disease and traditional risk factors, including HbA1c exposure. Whether factors such as greater growth hormone bioactivity in youth may account for this relationship remains to be determined.
Patient-centred factors associated with poor glycaemic and blood pressure control in co-morbid diabetes and chronic kidney disease.

Clement Lo1, Edward Zimbudzi1, Helen J Teede1, Peter Kerr1, Sanjeeva Ranasinha2, Alan Cass3, Gregory Fulcher4, Martin Gallagher5, 6

Kevan Polkinghorne1, Grant Russell1, Timothy Usherwood6, 4, Rowan Walker9, Sophia Youngs4, 1

1. Monash University and Monash Health, Clayton, VIC, Australia
2. Monash Centre for Health Research and Implementation, Monash University, Clayton, Victoria, Australia
3. Menzies School of Health Research, Charles Darwin University, Casuarina, Northern Territory, Australia
4. Department of Diabetes and Endocrinology, The Royal North Shore Hospital, Sydney, New South Wales, Australia
5. Concord Clinical School, University of Sydney, Sydney, New South Wales, Australia
6. The George Institute of Global Health, Sydney, New South Wales, Australia
7. School of Primary Health Care, Monash University, Melbourne, Victoria, Australia
8. Department of General Practice, Westmead Clinical School, University of Sydney, Sydney, New South Wales, Australia
9. Department of Renal Medicine, Alfred Health, Melbourne, Victoria, Australia

Background and aims: The extent to which patient-centred factors affect treatment target attainment in co-morbid diabetes and chronic kidney disease (CKD) is unclear. Here, we explore the association between patient-reported barriers to health-care, patient activation, quality of life and diabetes self-care, with attainment of glycaemic and blood pressure (BP) targets.

Materials and methods: This cross-sectional multi-centre study recruited adults with diabetes and CKD (eGFR between 20 and 60 ml/min/1.73m²). All completed a questionnaire exploring patient-reported barriers to care (elicited from focus groups), the Patient Activation Measure (PAM), 12-item Short Form Survey (SF-12), the Summary of Diabetes Self-Care Activity (SDSCA) surveys, and had demographic and clinical data collected. Poor glycaemic and BP control were defined as an HbA1c ≥ 8% and systolic BP ≥ 140 mmHg respectively. Multivariable logistic regression was used to identify the most parsimonious models inclusive of age, gender and diabetes duration for poor control, using STATA v13.1.

Results: 199 patients, mean age 68.7 (SD 9.6) were studied. Most were male (70.4%) and had type 2 diabetes (90.0%). There were no differences in the proportion of patients with poor glycaemic and BP control across age groups, gender, smoking status, eGFR, diabetes duration and activation levels. Poor glycaemic control was associated with an increased odds of “poor family support” (OR 4.90; 95% CI 1.80 to 13.32, p ≤ 0.002), Poor BP control was associated with an increased odds of “not having a good GP” (OR 6.01; 2.42 to 14.95, p < 0.001). Poor glycaemic or BP control was not associated with lower PAM, SDSCA and SF-12 scores (all p > 0.05).

Conclusions: Lack of patient perceived family and GP support were associated with increased odds of poor glycemic and blood pressure control. Models of care addressing these issues may improve patient outcomes in co-morbid diabetes and CKD.

Can salt supplementation alter sympathetic nervous system activity and endothelial function in people with Type Two Diabetes?

Sara Baqar1, 2, Yee Wen Kong1, Angela X Chen1, Christopher O’Callaghan3, Richard J MacIsaac1, 4, Maree Buterakos1, George Jerums1, 2, Elisabeth Lambert1, Elif I Ekinci1, 2

1. Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia
2. Department of Endocrinology, Austin Health, Heidelberg, Victoria, Australia
3. Department of Clinical Pharmacology, Austin Health, Heidelberg, Victoria, Australia
4. Department of Endocrinology & Diabetes, St Vincent’s Hospital, Melbourne, Victoria, Australia
5. Faculty of Health, Arts and Design, Iverson Health Innovations Research Centre, Swinburne University of Technology, Hawthorn, Victoria, Australia

Publish consent withheld

A Randomised trial of a Proactive Inpatient Diabetes Service (RAPIDS) demonstrates decreased adverse glycaemia and hospital-acquired infections

Mervyn Kyi1, 3, Peter G Colman4, Paul R Wraith1, Jane Reid1, Anna Galligan1, Shanal Kumar1, Lois M Rowan1, Alison J Nankervis1, Alex Gorelik1, Katie Marley1, David M Russell1, Spiros Fourlanos1

1. The Royal Melbourne Hospital, Parkville, VIC, Australia
2. Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Melbourne, VIC, Australia

Background: In hospitalised patients, both hypoglycaemia and significant hyperglycaemia are associated with adverse outcomes. We hypothesised that a proactive inpatient diabetes service (IDS), which electronically identifies inpatients with diabetes and provides immediate management, will decrease the incidence of adverse glycaemia & hospital complications.

Methods: RAPIDS (ACTRN1261600265471) was a cluster-randomised trial on 8 wards of a tertiary hospital. Consecutive inpatients with diabetes or new-onset hyperglycaemia (random blood glucose [BG] ≥11.1 mmol/L without known diabetes) were recruited. Networked glucose meters recorded capillary BG measures from admission until discharge, or day 14 for long-stayers. There was a 10-week baseline observational phase followed by a 12-week active phase, where the wards were cluster-randomised into 4 intervention and 4 control wards. Intervention wards
received proactive IDS (early consultation by endocrinologist or nurse practitioner without referral), while control wards continued usual care (a referral-based consultation service). Primary outcome was the incidence of adverse glycaemic days (AGD) (patient-day with any BG <4.0 or >15.0 mmol/L) and secondary outcomes were mean glucose, hospital-acquired infections and length of stay.

Results: We investigated 1002 patients (87% type 2 diabetes; 29% insulin-treated; HbA1c: 7.5±1.7%) totalling 5447 patient-days & 19062 BG measures. Incidence of AGD decreased in the intervention wards (243 vs. 186 per 1000 patient-days [23% decrease], p<0.001), but there was no change in the control wards. On multivariable analysis, proactive IDS was independently associated with 24% decrease in AGD (p=0.005). Proactive IDS decreased patient-day mean glucose (mean [SD]: 9.0 [2.7] vs. 9.5 [3.2] mmol/L, p<0.001), and the incidence of hospital-acquired infections (7% vs. 3%, p=0.02; adjusted OR: 0.24, 95% CI: 0.08-0.67, p=0.007). There was no difference in length of stay.

Conclusion: This randomised trial of a proactive diabetes service decreased the incidence of adverse glycaemia and hospital-acquired infections and may change the approach to inpatient diabetes care.

Mortality amongst people with severe unstable type 1 diabetes referred for islet cell transplantation

1. St Vincent's Hospital, Fitzroy, VIC, Australia
2. Westmead Hospital, Sydney, New South Wales, Australia
3. Royal Adelaide Hospital, Adelaide, South Australia, Australia
4. St Vincent's Institute, Melbourne, Victoria, Australia

Introduction: Islet cell transplantation (ICT) is a treatment option for people with type 1 diabetes (T1D), hypoglycaemia unawareness and recurrent hypoglycaemia. Those referred for consideration of ICT need to fulfil stringent inclusion/exclusion criteria.

Aims: We describe a cohort of individuals who died following referral to the Islet Transplant Clinic but prior to ICT.

Methods: We retrospectively collected data on people referred for consideration of ICT at three Australian centres from 2005 to 2016. Medical records were reviewed for severity of hypoglycaemia and hypoglycaemia unawareness; medical comorbidities and cause of death if documented or if a coroner’s report was available.

Results: Of the 325 people referred for ICT, 9 deaths (8 females, 1 male) were reported (2.8%). The mean age of the deceased was 44 years (27-55). Duration of diabetes was >14 years and all Edmonton HYPO scores were >1500. Only 1 person fulfilled the criteria for ICT. Reasons for ineligibility for ICT included renal impairment (eGFR<80ml/min) (2), gastroparesis affecting ability to take medications (1), depression (1), kidney transplant (1) and smoker (1). Cause of deaths was hypoglycaemia (5), diabetic ketoacidosis (1), sepsis (1), and unknown, presumed “dead-in-bed” (2). One death attributed to hypoglycaemia was due to deliberate insulin overdose. There were no deaths in the 39 people who received ≥1 ICT.

Conclusions: ICT can be a life-saving procedure for people with unstable T1D. Our cohort demographics are different from the classical “dead-in-bed” syndrome, typically affecting younger males. Our mortality rate of 2.8% may be an underestimate as follow-up of all referrals has not been completed. The data suggests that severe recurrent hypoglycaemia is a serious complication for those living with T1D, and supports the view that these high-risk individuals should be managed in specialised clinics.

A new approach to hepatic insulin sensitzers

Domenico Accili
1. Columbia University, New York, United States

Not available at time of printing

Fatty liver disease: mouse models and potential therapies

Mark Gorrell
1. Centenary Institute, Sydney, NSW, Australia

Not available at time of printing

The role of the liver microcirculation in insulin metabolism

Victoria Cogger
1. ANZAC Research Institute/CERA, Concord Hospital, NSW, Australia

The liver carries out numerous separate metabolic and detoxification functions which are essential for maintaining human health. Supporting these functions are the dense networks of blood vessels called sinusoids and the highly specialised liver sinusoidal endothelial cells (LSEC) that line these vessels.
The LSEC occupies a strategic position in the liver, separating blood in the sinusoid from the surrounding liver cells. It has long been recognized that LSECs have a role facilitating, and perhaps regulating, the transfer of substrates between the blood and the liver parenchyma, forming a blood-liver cell barrier. LSECs have a unique morphology compared to other endothelial cells, which underpin their physiological role in substrate transfer. The cytoplasmic extensions of LSECs are very thin and perforated with transcellular holes called fenestrations that are true discontinuities in the endothelium. These fenestrations permit the bidirectional transfer of a wide range of substrates between the blood and underlying liver cells for further processing. These substrates include plasma and substances within plasma, such as medications, toxins, albumin, smaller lipoproteins, colloidal particles and importantly insulin. The fenestrated LSEC acts as a filter for larger particles and hence has been termed ‘the liver sieve’.

We have recently explored the role of the LSEC in hepatic insulin metabolism and found the initial transfer through the fenestrations to be critical in liver insulin signalling and metabolism. This key step is especially important in the context of the numerous diseases and pathological processes that influence fenestrations, including: liver disease, exposure to liver toxins and most significantly, ageing.

---

Its reticulated: The liver at the heart of atherosclerosis

Man KS Lee¹, Michael J Kraakman², Michelle C Flynn¹, Helene L Kammoun¹, Ira J Goldberg³, Prabhakara R Nagareddy⁴, Andrew J Murphy⁵

1. Baker Heart and Diabetes Institute, St Kilda Road Central, VIC, Australia
2. Columbia University, New York, USA
3. New York University, New York, USA
4. Nutrition Science, University of Alabama at Birmingham, Birmingham, AL, USA

Platelets play a critical role in atherogenesis and thrombosis-mediated myocardial ischemia, processes that are accelerated in diabetes. It remains unknown if hyperglycemia promotes platelet production and whether this contributes to enhanced atherothrombosis. Here we show that in response to hyperglycemia, neutrophil-derived S100A8/A9 interacts with the receptor for advanced glycosylation end-products (RAGE) on hepatic Kupffer cells resulting in increased production of interleukin-6 (IL-6), a pleiotropic cytokine implicated in inflammatory thrombocytosis. IL-6 acts on hepatocytes to enhance the production of thrombopoietin, which in turn interacts with its cognate receptor, c-MPL on megakaryocytes and bone marrow progenitor cells to promote their expansion and proliferation resulting in reticulated thrombocytosis. Lowering blood glucose using a sodium-glucose co-transporter 2 inhibitor (dapagliflozin), depleting neutrophils/Kupffer cells or inhibiting S100A8/A9 binding to RAGE (paquinimod) all reduced diabetes-induced thrombocytosis. Inhibiting S100A8/A9 also decreased atherogenesis in diabetic mice. These studies provide novel insights into the communication between innate immune cells, the liver and the bone marrow to regulate platelet production. These findings contribute to our understanding of the disease process and may help to develop strategies to improve on current antiplatelet therapies and to reduce cardiovascular disease risk in diabetes.

---

Sweet Support: e-learning and support for ward based nursing staff

Jane Payne¹, Megan Stephens², Gael Holters²

1. Bankstown-Lidcombe Hospital, Bankstown, NSW, Australia

Background:

At any given time between 20-30% of hospital in-patients have diabetes¹. Most are admitted for other medical conditions rather than for diabetes care, however their diabetes adds to the complexity of their management and length of stay. Despite this, knowledge of appropriate diabetes management is often suboptimal².

Aims:

1. To develop an electronic evidence-based resource regarding in-patient diabetes management for nursing staff
2. To evaluate the effectiveness of the electronic resources on patient nursing care.

Method:

Our team developed diabetes care sheets and an e-learning education package targeted at nursing staff to address common in-patient care issues supported by an intranet site to allow 24/7 access. Education sessions regarding use of ‘Sweet Support’ were held. We then administered pre & post knowledge questionnaires to nurses. A retrospective audit of 50 clinical notes was undertaken to assess the nursing compliance with diabetes related guidelines in use prior to the launch of intranet site. Data were collected at baseline, 3, 6, 9 & 12 months. For the purpose of statistical analysis data at 3 & 6 months and 9 & 12 months were combined.

Results:

Overall 475 questionnaires were completed. We noted an increased knowledge in all aspects of care except ‘How to refer to Diabetes Educator’. This increase in knowledge was statistically significant at 3/6months for ‘when to refer to Medical Officer [MO] in the presence of hyperglycaemia’ [p=0.02].

Clinical notation audit demonstrated statistical significance from baseline at 9/12months in treating an episode of hypoglycaemia appropriately and referring a patient with hyperglycaemia to MO [p=0.02, p=0.01]. There was a significant increase in the incidence of diabetes medication only being withheld with an instruction from MO reached at 3/6month and 9/12months [p=0.0008 & p=0.0001]

Conclusion:

These findings support the concept that accessible diabetes information may improve clinical care.

Co-creating and piloting a new diabetes foot app for people with diabetes

Rajna Ogrin1,2,3,4, Rekha Viswanathan2, Tracy Aylen5, Fiona Wallace4, Janine Scott6, Dinesh K Kumar2
1. Royal District Nursing Service, St. Kilda, VIC, Australia
2. Biosignals, Royal Melbourne Institute of Technology, Melbourne, Victoria, Australia
3. Austin Health Clinical School, University of Melbourne, Heidelberg, Victoria, Australia
4. Physical Therapy, University of Western Ontario, London, Ontario, Canada
5. Royal District Nursing Service Institute, St. Kilda, Vic, Australia
6. IDEAS, Carrington Health, Box Hill, Victoria, Australia
7. Primary Health care, Carrington Health, Box Hill, Victoria, Australia

Background:
Diabetes is the most common cause of non-traumatic amputations in the world. Seeking early intervention is key, however there is no standard, validated interactive education on foot health available in Australia to support people with diabetes to prevent amputation.

Methods:
A diabetes foot App was co-created with people with diabetes. The app was provided for 12 weeks to a convenience sample of adults with diabetes from one community health service in metropolitan Melbourne. Pre and post intervention data was collected on foot health, footcare knowledge and self-care practices and interviews and focus groups were undertaken post intervention. We report the qualitative findings here.

Preliminary results:
Forty participants with a mean age 66.9±17.1 years, average diabetes duration 17.1±10.3 years. Amputation risk, based on International Working Group of the Diabetic Foot Guidelines, as low (n=4); increased (n=18); and high (n=18). 7 people withdrew due to personal and health related issues.

Qualitative interviews or focus groups were undertaken with 31 participants. Average duration of interviews; 23 minutes (range 5 – 65 minutes). Many participants felt that information would be highly useful for people newly diagnosed with diabetes or who had no previous exposure to footcare education. A number would prefer more guidance regarding what to do once an issue is identified, over and above seeing a healthcare provider. More examples of what to look for were suggested, as were additional features to increase functionality and usefulness of the app.

Discussion/Conclusion
The app was received positively by most participants, with all recommending that an app would be of benefit to people with diabetes to prevent serious foot complications, particularly those who are newly diagnosed. Further work involving refining the diabetes foot app is warranted.

Acknowledgements
This project was funded by Eldon & Anne Foote Trust and Pam & Alfred Lavey Trust.

Diabetes Telehealth: Bridging gaps in diabetes services in rural Western Australia through innovative technology

Amanda AL Lee7, Gill GD Denny1, Carole CR Rainsford2, Jennifer JT Thompson2, Christine CC Carne1, Deborah DS Schofield1, Helen HM Mitchell1
1. Diabetes WA, Subiaco, WA, Australia
2. WA Country Health Service, Perth

2008-2012 ‘diabetes complications’ was the leading cause of potentially preventable hospitalisations across all seven regions; with a non-Aboriginal rate significantly higher than the state average. Limited regional capacity for diabetes education and long travel distances greatly limits access, resulting in poor health outcomes.

Service gap locations were identified through data analysis and regional consultation. Partnering with Diabetes WA, in March 2015 the Diabetes Telehealth for Country WA Service commenced. The service is delivered via videoconference (or phone if required), and addresses gaps in diabetes education and clinical support for consumers and increases regional capacity through provision of professional development for health professionals in the management of diabetes.

Delivering timely triaged, assessed and individualised education sessions, referral to other services and direct links to local diabetes educators, the service can be provided at home and outside of traditional business hours to support consumer needs. Professional development sessions are delivered in the workplace.

Lessons learned have been applied to subsequent telehealth service development. Flexibility to support tailoring of the service to the specific and unique requirements of each region is integral. Working closely with health professionals and private practices to demonstrate the triage process with referral back to existing services on the ground, ensuring private business models are supported, has been key to service acceptance. Building trust and establishing shared care roles via a virtual multidisciplinary team has resulted in GP and health professional acceptance – with 56% of referrals coming from GPs.

The service is now available across all seven WACHS regions. Since commencement there have been over 1315 occasions of service, with 68 referrals for Aboriginal people. Over 43 hours of health professional upskilling has been delivered. An external evaluation is being finalised. Initial indications are $120,000+ service delivery savings for WACHS whilst saving consumers over 113,000 travel kilometres, with over 90% of consumers saying that using telehealth saved them time and money.
Evaluating the use of mHealth to support young adults with T1DM during life transitions

Ashley Ng1, Bodil Rasmussen1, Tim Crowe2, Kylie Ball2
1. School of Nursing and Midwifery, Deakin University, Burwood, Vic, Australia
2. School of Exercise and Nutrition Sciences, Deakin University, Burwood, VIC, Australia

Introduction
As young adults with T1DM progress through life transitions, they must adapt the way they live with the condition while managing competing commitments. Currently, there are limited diabetes education programs and services that address the needs of young adults with T1DM as they progress through these life transitions.

Objectives
To pilot and evaluate the Diabetes Youth, Empowerment and Support (Diabetes YES) mHealth program developed to address the diabetes education program and service needs of Australian young adults aged between 18 and 35 years with T1DM.

Methods
Over 12 weeks, participants were provided access to the Diabetes YES program, which consisted of a website and a moderated Facebook peer support group. Common themes were identified and categorised from open-ended responses from the evaluation survey.

Results
Evaluation findings from 34 participants found that the overall Diabetes YES program helped participants to navigate through life transitions. Through shared experiences on the Facebook group, participants felt emotionally validated and gained practical insight around various diabetes management options. The Facebook group also allowed participants to gain real-time responses to diabetes-related questions. In turn, participants felt emotionally supported; less isolated and gained motivation towards their self-management. Participants valued the website for its credible, easy to understand and up-to-date diabetes-related information, which supplemented knowledge obtained from healthcare professionals. However, participants were less likely to return to the website after initial visits as they forgot about the site or had no reason to access it. In contrast, the Facebook group provided notifications for new posts and weekly discussion topics to encourage member engagement.

Conclusions
The Diabetes YES program provided ongoing emotional support and informational resources specific to young adults with T1DM as they progressed through life transitions. mHealth tools have potential to be valuable resources for young adults with T1DM when used in conjunction with clinical support.

Rural Nurse Practitioner telehealth model Improving access to metropolitan specialist services for children with diabetes

Barbie Sawyer1, Alison Aston1, Elaine Tham2, Jane Giles3, Kylie Bailey1
1. South East Regional Community Health Services, Mount Gambier, SA, Australia
2. Endocrine, Women's and Children's Hospital, Adelaide, South Australia, Australia
3. Diabetes Service, Country Health SA, Adelaide, South Australia, Australia

Introduction
Children with type 1 diabetes and their families living in rural SA have historically travelled to Adelaide 4 times a year to access their specialist service. The tyranny of distance and travel expectations is a significant barrier for some families and has seen children go without the timely access to specialist services currently outlined in the clinical practice guidelines.

Objective
To develop a model of care that improves access for rural children with type 1 diabetes and their families to metropolitan based specialist services

Method
3 monthly telehealth video-conferencing clinics are undertaken with the paediatric endocrinologist from the Women’s and Children’s Hospital endocrine unit. All pre consultation work up is undertaken locally and securely transmitted to the specialist. Follow up medication adjustments are undertaken locally with the diabetes nurse practitioner. Local support from Paediatrician is integrated into the service

Results
More than 180 videoconferencing consultations have been conducted since commencing the service in October 2013. The service has successfully facilitated and improved access to metropolitan based endocrinology services. Evaluation undertaken with the families has been very positive with high level of satisfaction. For example; there is strong support for continuation of service, families also identified significant financial and time savings.

Continuous Glucose Monitoring: A useful tool in diabetes patients with hypoglycaemia?

Catherine Finneran¹, Gael Holters¹, Megan Stephens¹, Michelle Griffiths¹, Jane Payne¹, Sarah Abdo¹,²,³, Tang Wong¹,²,⁴
1. Department of Diabetes and Endocrinology, Bankstown-Lidcombe Hospital, Sydney, NSW, Australia
2. University of NSW, Sydney, NSW, Australia
3. Western Sydney University, Sydney, NSW, Australia
4. University of Sydney, Sydney, Australia

Background: Continuous Glucose Monitoring (CGM) is a useful adjunct to the assessment of glucose profiles in people with problematic diabetes management on insulin therapy. It has been published that the use of CGM can have positive effects on diabetes management and can help identify periods of hypoglycaemia and hypoglycaemia unawareness (1). Hypoglycaemia can considerably increase the risk of falls, cardiac arrhythmia and has significant adverse psychosocial effects, including a reduction in quality of life.

Aims: To evaluate the utility of CGM in the identification and management of hypoglycaemia.

Methods: In a retrospective analysis of 86 consecutive CGMs performed between 2013 and 2017, using blinded–CGM (i-Pro2 Medtronic™), 45 (52.3%) were referred for the indication of hypoglycaemia and/or hypoglycaemia unawareness. We assessed: (a) whether there was a treatment change following CGM, (b) whether there was a decrease or cessation of periods of hypoglycaemia and (c) whether hypoglycaemia awareness was restored.

Results: Hypoglycaemic events were confirmed in 32 of 45 (71.1%) of CGMs. Average HbA1c results prior to and post CGM were 8.0% and 7.7% respectively (p=0.24). The outcomes following CGM are summarised in Table 1.

<table>
<thead>
<tr>
<th>Outcome achieved following CGM</th>
<th>Cases (% of CGMs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteration of treatment regimen</td>
<td>22 (68.8)</td>
</tr>
<tr>
<td>Cessation of hypoglycaemia</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Decrease in episodes of hypoglycaemia</td>
<td>7 (21.9)</td>
</tr>
<tr>
<td>Resumption of hypoglycaemia awareness</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Persistent hypoglycaemia</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>Persistent hypoglycaemia unawareness</td>
<td>1 (3.1)</td>
</tr>
</tbody>
</table>

Conclusion: CGM is effective at identifying hypoglycaemia where self-monitoring of blood glucose (SMBG) fails to demonstrate hypoglycaemia. In two-thirds of patients found to have hypoglycaemia a change of therapy ensued. Cessation of hypoglycaemia and restoration of hypoglycaemia awareness was often achieved in our cohort of patients.

Identification of occult hypoglycaemia through CGM is a useful platform in providing both patients and clinicians insight not otherwise appreciated by SMBG and allows targeted patient education.


Person Centred Diabetes Management Goal Setting Using a Smartphone App: Do people make the "right" choice

Timothy C Skinner¹, Isabelle K Kathleen¹
1. Charles Darwin University, Cassurine, NT, Australia

Background. We developed the EmojiFit Diabetes iPhone app to enable person centred goal setting for diabetes self-management.

Aim: To determine (i) which complication individuals with type 2 diabetes are most concerned about; (ii) which risk factor individuals with type 2 diabetes choose to target for change; (iii) what diabetes management plan individuals with type 2 diabetes choose, when not supported by a health care professional.

Method: Individuals with type 2 diabetes were given free access to EmojiFit Diabetes, an iPhones app, that supports individuals with type 2 diabetes to make informed decisions about their goals for their diabetes management. We recorded the complication of diabetes that individuals decided they were most concerned about, the risk factor that they wanted to target for change, and the diabetes action they choose to build their self-management plan around. Individuals also completed the WHO5 Well-Being questionnaire.

Results: 319 individuals from 27 countries, downloaded and trialled the app. 27% scored below clinical cut-off for possible depression. Primary concern was Heart Disease, 64% of users, Stroke 9%, Eye Disease 9%, Foot Problems 9%, Sexual Functioning 7% and Kidney Disease in 3%. 30% chose to focus on weight reduction, 26% cholesterol, 22% blood pressure, 15% HbA1c, 15% emotional well-being and 3% to quit smoking. Most individuals, 42%, chose to increase their physical activity, 17% taking medication, 15% eating less and 11% on fruit and veg. For
all individuals who chose Blood Pressure, Depression, Smoking, this was their highest risk factor for complications. For waist reduction 90% this was their highest risk in 90% of individuals.

Discussion: The EmojiFit Diabetes app appears to support individuals in setting appropriate diabetes management plans, that would be considered as “right” by most health professionals most of the time.

79

Understanding Flash Glucose Monitoring in the real world

Michelle Robins¹, Marg McGill¹, Bruce Passingham¹, Neale Cohen¹, Joey Kaye
1. Northern Health, Broadmeadows, VIC, Australia
2. Department of Diabetes, RPA, Sydney, NSW, Australia
3. Abbott, Melbourne, Victoria, Australia
4. Baker International Diabetes Institute, Melbourne, Victoria, Australia

New technology brings many benefits to assist people with their self-management of diabetes. The FreeStyle Libre is designed to replace routine blood glucose testing in people treated with insulin which includes on demand glucose readings, trend arrows and the capacity to hold the last 8 hours of data. However, exposure to large amounts of data can generate additional challenges for the individual and health care professional. The ability to understand the science behind the technology, interpret data and identify glycaemic trends is crucial when using this new technology with the outcome of achievement of HbA1c targets and reduction of incidence of hypoglycaemia. Through practical strategies and case studies, incorporating Ambulatory Glucose Profiling (AGP), developed by Dr Roger Mazze, CDE’s and Endocrinologists will increase their understanding and confidence in supporting and educating of clients to maximise this new technology and use the data to their advantage. The masterclass will also cover troubleshooting, device setup and insertion and optimal wear time. Practical application and thorough understanding of this technology will be the major focus of this forum.

80

Molecular biomarkers of diabetes progression

Mugdha Joglekar¹
1. University of Sydney, Camperdown, NSW, Australia

The prevalence of diabetes and associated complications is increasing and accounts for much of Australia’s healthcare burden. Current clinical biomarkers do not allow efficient prediction of diabetes progression. There is, therefore, a need to obtain an improved understanding of molecular signatures of diabetes onset and vascular damage. In order to understand the potential of microRNAs as circulating biomarkers of diabetes progression, we carried out discovery analyses using an OpenArray platform for profiling of 754 microRNAs followed by validation in well-characterized clinical samples. microRNAs are short, non-coding RNA molecules that are important regulators of several pathophysiological functions. In the past few years, circulating microRNAs have been looked upon as important biomarkers of disease progression. Although such mRNA biomarkers are well described in cancer progression, the understanding of similar biomarkers in diabetes research is lacking. Using systematic approaches in sample processing, assaying and data analyses, we identified microRNA signatures that are highly associated with insulin expression, pancreatic beta cell death (in vitro and in vivo), presented at increasing abundance during human pancreas development or dysregulated in individuals with/without diabetes. I will present our new findings on the analysis of these miRNAs in >600 individuals from multiple cohorts/groups with and without diabetes, followed by independent validation in other clinical study samples. I will also present our data on derivation and validation of RNA-based signature of endothelial damage/vascular complications in diabetes. These data demonstrate that our microRNA signatures not only facilitate the potential prediction of diabetes progression, but also help in understanding treatment efficacies in trials aiming to retard beta-cell death. Hopefully, our study results will provide basic scientists with a tool for selecting treatments to selectively block beta-cell death and inform medical researchers/clinicians as to how to predict the development of diabetes and monitor response to interventions.

81

An Arp2/3 complex-mediated contractile actin coat on insulin granules facilitates secretion in beta cells

Wei Ma¹, Jason Tong¹, Peter Thorn¹
1. University of Sydney, Sydney, NSW, Australia

Actin has long been known to be involved with exocytosis in a variety of cell systems. However, the mechanisms of actin remodelling remain unclear. To better understand actin dynamics, we used live-cell two-photon imaging of mouse beta cells isolated from transgenic mouse expressing Lifeact-eGFP; a fluorescent probe that has a low affinity for filamentous (F-actin). Simultaneously we recorded glucose-induced insulin granule fusion using the entry of Sulforhodamine B (SRB) extracellular dye into each granule as it fused with the cell membrane. Our data showed that each granule fusion event was associated with a transient increase in F-actin at the site of fusion. Application of 100μM Latrunculin B, which sequesters actin monomers, enhanced the number of glucose-induced fusion events but abolished the F-actin increase. This suggests F-actin remodelling, at the sites of fusion, is by nucleation rather than movement. Inhibition of actin nucleator Arp2/3-complex with 100μM CK666 blocked F-actin changes at the sites of insulin granule fusion and slowed the decay time of SRB fluorescence, indicating altered granule fusion kinetics. The secretory phenotype was further examined using insulin secretion assay. CK666 treated primary mouse beta cells showed a significantly reduced glucose stimulated insulin secretion compared with control conditions. The data suggests Arp2/3-mediated actin nucleation plays important role in facilitating insulin granule fusion. Western blot and qPCR data confirmed Arp2/3 is present in mouse pancreatic islets and MIN6
Physiological levels of IL-1B increase islet amyloid deposition in vitro

Thinn Thinn Khine¹ ², Mahnaz Mellati³, Daniel T. Meier¹, Andrew T. Templin¹, Meghan F. Hogan¹, Sakeneh Zraika¹, Rebecca L. Hull¹

Steven E. Kahn¹

¹. Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, KING, United States
². Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Victoria, Australia
³. Deakin University, Geelong, VICTORIA, Australia

In human type 2 diabetes islet amyloid deposition is associated with B-cell loss and increased B-cell apoptosis. Islet amyloid polypeptide (IAPP), a normal secretory product of the B-cell, is the unique peptide component of these amyloid deposits. Amyloid-laden islets in humans and human IAPP (hIAPP) transgenic mice contain increased numbers of macrophages. Further, incubation of macrophages with hIAPP results in increased IL-1B production. Whether this production of IL-1B then feeds back to further increase islet amyloid deposition has not previously been determined. Thus, we sought to determine whether exposure of islets to physiological levels of IL-1B exacerbates islet amyloid deposition.

Isolated islets from hIAPP transgenic and wild-type mice were cultured for 48 hours in 16.7 mmol/l glucose with or without a physiological concentration of IL-1B (4 pg/ml), after which islet amyloid deposition and mRNA levels of lapp and Ins2 were quantified by histomorphometric analysis and qRT-PCR, respectively.

As expected, in the absence of IL-1B, hIAPP transgenic islets developed amyloid, while wild-type mice did not. Exposure of hIAPP transgenic mouse islets to IL-1B resulted in an increase in amyloid severity (% islet area occupied by amyloid; 3.85±0.9 vs. 0.6±0.23%; p=0.02, n=5). IL-1B did not change lapp mRNA expression in hIAPP transgenic islets (0.58±0.02 vs. 0.72±0.17; n=7). In contrast, IL-1B decreased Ins2 mRNA expression in these islets (0.60±0.04 vs. 1.11±0.17, p=0.01; n=7), so that the ratio of lapp/Ins2 mRNA was increased (1.59±0.11 vs. 1±0.12, p=0.003; n=7).

We conclude that physiological levels of IL-1B increase islet amyloid formation. Further, IL-1B reduces insulin but not IAPP gene expression, thus producing an imbalance in the normal ratio of lapp:Ins2, and an islet environment which could favor islet amyloid formation. Thus, antagonizing the effects of islet IL-1B may be beneficial to improve B-cell function and reduce B-cell mass in type 2 diabetes.

Abrogation of adenosine receptor A₁R signalling potentiates VCP746 dependent beta-cell proliferation

Tharan B Mysore¹, Sarah White¹, Lauren T May², Karen M Dwyer¹

¹. Deakin University, Geelong, VICTORIA, Australia
². Monash Institute of Pharmaceutical Sciences, Monash University, Melbourne, Victoria, Australia

Background

Adenosine receptor signalling is implicated in β-cell survival, insulin production and proliferation. The non-specific adenosine receptor agonist NECA promotes β-cell regeneration in zebrafish¹. The novel adenosinergic compound VCP746 activate adenosine receptor (AR) subtypes A₁R, A₂BR and A₃R with similar potency to adenosine but with minimal side effects on heart rate or systolic blood pressure². VCP746 utilises the unique pharmacological property of biased agonism, a new paradigm of G-protein coupled receptor (GPCR) drug action to examine its efficacy in the regeneration of β-cells.

Aim

To investigate the effect of VCP746 on β-cell viability in vitro and development in vivo using Tg(ins:CFP-NTR);Tg(ins:Kaede) (NTR) zebrafish regeneration model.

Methods

INS-1 cells were cultured in serum-free DMEM media for 24h, and β-cells ablated NTR fish embryos in fish water for 48h, with either buffer only (DMSO) or with VCP746 ± 25nM SLV320 (A₁R specific antagonist). In vitro INS-1 viability/proliferation was quantified by MTT assay and in vivo β-cell development by measuring relative area of insulin (RAI) expression in the embryos using whole mount in situ hybridisation (WISH).

Results
VCP746 inhibited INS-1 cell proliferation at all concentrations tested, which was ameliorated with A1R antagonist, SLV320 in a dose dependent manner. (B) RAI following ablation and treatment was reduced significantly with VCP746 treatment and increased with NECA in NTR fish embryos.

Conclusions

VCP746 increased INS-1 cells proliferation, but only when treated with SLV320 to block A1R receptor signalling in vitro. The preliminary data suggests possible involvement of A2AR and A2BR signalling in proliferation. Further in vivo studies to decipher VCP746 role in β-cell proliferation including, receptor signalling pathways and gene expression is underway.

References


Development of an Interleukin-22 based immunocytokine as a novel therapeutic approach in type 2 diabetes

Sahar Keshvari1, Christian Fercher2, Ross T Barnard2, John B Prins1, Sumaira Z Hasnain1, Michael A McGuckin1

1. Mater Research Institute - University of Queensland, Woolloongabba, QLD, Australia
2. School of Chemistry & Molecular Biosciences, The University of Queensland, Brisbane, QLD, Australia

In Type 2 diabetes β-cell dysfunction is accompanied by adverse cellular responses to high concentration of lipids and glucose, oxidative stress, endoplasmic reticulum (ER) stress and local inflammation. Cellular stress activates an inflammatory response in the cell, stimulating local innate islet inflammation, which in turn exacerbates β-cell further decreasing the ability to synthesise efficacious insulin. Previously we demonstrated a novel role for Interleukin-22 (IL-22) as a natural regulator of β-cell insulin biosynthesis and secretion, which protects the β-cell from stress, prevents hypersecretion of poor quality insulin, and suppresses innate islet inflammation1. However, due to the pleiotropic nature of cytokines, prolonged administration of high IL-22 doses in human patients might potentially lead to deleterious off-target effects in other tissues such as increased and uncontrolled cell proliferation in the gut and skin2. Thus, fusion protein candidates were created using human IL-22 and a single-chain variable fragment composed of a single-chain antibody domain specific to rodent and human pancreatic islets (IL22-ScFv).

In the current study we tested the hypothesis that IL22-ScFv fusion proteins target pancreatic islets and would restore metabolic function in preclinical murine models of diabetes by IL-22 receptor-mediated suppression of oxidative/ER stress in pancreatic islets. In high fat diet induced obese (HFDIO) mice IL22-ScFv (i) increased the activation of downstream signalling effectors in pancreas compared to other responsive tissues, (ii) induced ~5% of weight loss in the HFDIO mice over the 2 weeks of treatment, (iii) protected pancreatic islets from oxidative and ER stress and (iii) effectively restored glycaemic control within 10 days of commencement of treatment.

Collectively these results demonstrate that IL-22-based biologics can be effectively targeted to the pancreas and retain its biological activity, providing proof of principle that IL-22 targeting can be used to reduce side effects on other tissues while retaining beneficial metabolic effects.

Islet β-cell hyper-responsiveness to nutrient-induced stress may underlie β-cell failure in the NOD\textsuperscript{k} mouse

Matthew Waters\textsuperscript{1}, Viviane Delgingharo-Augusto\textsuperscript{1}, Christopher Nolan\textsuperscript{1}

1. Endocrinology and Diabetes Research Unit, Australian National University, Acton, ACT, Australia

Introduction: NOD\textsuperscript{\textdagger} mice, derived from the non-obese diabetic (NOD) mouse, are type 1 diabetes resistant, but develop marked hyperinsulinaemia followed by a severe type 2 diabetes phenotype when fed >10 weeks on a high fat (HF) diet. We hypothesized that islet β-cell hyper-responsiveness of the NOD\textsuperscript{\textdagger} mouse underpins its diabetes susceptibility.

Objectives: To determine the effects of a 5-day HF diet challenge (HFDC) on insulin secretion in the NOD\textsuperscript{\textdagger} mouse and two-comparator stains, C57Bl10 (B10) and Balb/c.

Methods: The effects of the 5-day HFDC compared to remaining on chow diet on male NOD\textsuperscript{\textdagger}, B10 and Balb/c mice at 8 weeks of age were studied. Morning body weight (BW), fed-state blood glucose and plasma insulin were measured on day-0 and day-5. An intra-peritoneal glucose tolerance test (ipGTT) with plasma insulin measurements was performed on day 5 after a 6h fast. Insulin responsiveness was assessed by analysis of the ipGTT ratio of the insulin area under the curve (AUC), to the glucose AUC (insAUC/glucAUC).

Results: The HFDC increased BW in NOD\textsuperscript{\textdagger} and Balb/c mice only. Fed-state and ipGTT glycaemia was best in chow-fed NOD\textsuperscript{\textdagger} mice (fed-glucose (mM): 6.4±0.1, 7.6±0.2, 7.5±0.2; ANOVA p<0.001; NOD\textsuperscript{\textdagger}, B10, Balb/c). The 5-day HFDC had little effect on glucose levels within strains. The HFDC, however, caused marked hyperinsulinaemia in NOD\textsuperscript{\textdagger} mice only (fed-insulin (ng/mL): 3.8±0.6, 0.5±0.8, 0.8±0.13; p<0.001). The insAUC/glucAUC showed much greater insulin responsiveness in NOD\textsuperscript{\textdagger} compared to the B10 and Balb/c strains on both chow diet (ng/mL×mM: 0.14±0.01, 0.03±0.1, 0.06±0.01; p<0.001) and after the 5 day HFDC (0.31±0.06, 0.04±0.01, 0.08±0.01; p<0.001).

Conclusions: The results support the hypothesis that NOD\textsuperscript{\textdagger} mice have hyper-responsive b-cells that is evident even on chow-diet. This hyper-responsiveness may drive excessive weight gain and later b-cell failure in NOD\textsuperscript{\textdagger} mice. The converse of insulin hypo-responsiveness was seen in diabetes resistant B10 mice.

Issues with engineered ex vivo expanded murine mesenchymal stem cells as a cell replacement therapy for type 1 diabetes

Ann M Simpson\textsuperscript{1}, Dario Gerace\textsuperscript{1}, Rosetta Martiniello-Wilks\textsuperscript{1}, Binhai Ren\textsuperscript{1}, Najah Nassif\textsuperscript{1}

1. School of Life Sciences and The Centre for Technology Universities, University of Technology Sydney, Sydney, NSW, Australia

Gene therapy as a means of generating “artificial” insulin-producing cells is being considered as a potential cure for type 1 diabetes (T1D). The aim of this study was to evaluate the utility of ex vivo expanded murine mesenchymal stem cells (MSCs) as targets for gene therapy and the development of a cell replacement therapy. CD45/Ly6\textsuperscript{−} murine MSCs were isolated from the bone marrow of non-obese diabetic (NOD) mice and nucleofected to express the bioluminescent protein Firefly luciferase (Luc2). The persistence of a subcutaneous (s.c) transplant of Luc2-expressing MSCs was assessed in immune-competent (NOD) (n=4) and immune-deficient (NOD/Scid) (n=4) animal models of diabetes. Ex vivo culture-expanded MSCs were subsequently transduced with the HMD lentiviral vector (MOI=10) to express furin-cleavable human insulin (INS-FUR), murine NeuroD1 and Pdx1; followed by characterisation of pancreatic transdifferentiation via reverse transcriptase polymerase chain reaction (RT-PCR), and acute and chronic insulin secretion assays. A s.c transplant of 1x10\textsuperscript{7} and 5x10\textsuperscript{7} INS-FUR-expressing MSCs in NOD/Scid mice (n=5) was assessed for their ability to reverse diabetes. Luc2-expressing MSCs persisted for 2 weeks and 12 weeks respectively in NOD and NOD/Scid mice. INS-FUR-expressing MSCs lacked glucose-responsiveness and secreted human insulin chronically, whereas NeuroD1 and Pdx1-expressing MSCs lacked glucose-responsiveness and insulin secretion capabilities. Transduced MSCs did not undergo pancreatic transdifferentiation as determined by RT-PCR analysis, and upon transplantation did not reverse diabetes. The data suggests that ex vivo expanded MSCs lose their multipotent differentiation potential and may be more useful as gene therapy targets prior to expansion. This correlates with other studies where ex vivo expansion of MSCs is associated with a loss of MSC function and negative T1D clinical outcomes.

Neuropeptide Y1 receptor antagonism improves islet transplant outcome

Kim Loh\textsuperscript{1}, Yan-Chuan Shi\textsuperscript{2}, Stacey Walters\textsuperscript{1}, Shane Grey\textsuperscript{1}, Herbert Herzog\textsuperscript{1}

1. St. Vincent's Institute of Medical Research, Fitzroy, VIC, Australia
2. Neuroscience Division, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia
3. Immunology Division, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

Failure to secrete sufficient quantities of insulin is a pathological feature of type-1 and type-2 diabetes, and also reduces the success of islet cell transplantation. Here we demonstrate in a number of models that Y1 receptor signaling inhibits insulin release in b-cells, and show that this can be pharmacologically manipulated to boost insulin secretion. Importantly, transplanting islets with Y1 receptor deficiency accelerates the normalization of hyperglycemia in chemically induced diabetic recipient mice, which can also be achieved by short-term pharmacological blockade of Y1 receptors in transplanted mouse and human islets. Furthermore, treatment of NOD mice with a Y1 receptor antagonist delays the onset of diabetes. Mechanistically, Y1 receptor signaling in islets inhibits the production of cAMP, which via CREB mediated pathways results in the down-regulation of several key enzymes in glycolysis and ATP production. Thus, manipulating Y1 receptor signaling in β-cells offers a unique therapeutic opportunity for correcting insulin deficiency as it occurs in the pathological state of type-1 diabetes as well as during islet transplantation.
The Power of New technologies in diabetes care - 5 e’s, 2 B’s and a Journey

Petra Wilson
1. Digital Health & Care Institute, Scotland, United Kingdom
Not available at time of printing

Uric acid lowering therapies, physiological mechanisms and clinical trials: the potential for cardiorenal protection in diabetes

David Cherney
1. University Health Network, Toronto, Canada
Not available at time of printing

The Eye: The Window to Diabetic Pathology

Andrew Symons
1. The Royal Melbourne Hospital, Melbourne, VIC, Australia
The audience will be update on advances in the following areas:
- Epidemiology: especially the rising prevalence of diabetic macular oedema and the declining prevalence of diabetes induced blindness
- Imaging: the critical importance of OCT imaging of the retina; new technologies to examine retinal blood flow, especially OCT angiography and adaptive optics
- Retinal non-perfusion and diabetic retinopathy are associated, even in non-proliferative diabetic retinopathy
- Modifiable pathways in diabetic retinopathy - especially VEGF; discussion of the role of fenofibrate
- Update on screening: new item numbers; DCCT/EDIC results on stratifying screening intervals by HbA1c; artificial intelligence approaches
- New results in treating diabetic retinopathy: anti-VEGF as an alternative to laser for both proliferative diabetic retinopathy and macular oedema
- Role of surgery for diabetic retinopathy

Cardiovascular Disease and Lipids in Diabetes

Alicia Jenkins
1. The University of Sydney, Sydney, NSW, Australia
Background: Lipids are implicated in the pathogenesis of accelerated atherosclerosis and in microvascular damage in diabetes. Many trials demonstrate vascular benefit of lipid lowering and of some glucose and BP drugs and insulin pumps. Statin intolerance can limit statin use. Vascular memory exists for vascular risk factors and some drugs.
Aims: To summarise (a) results of trials and observational studies of clinically available drugs that can improve clinical outcomes in people with diabetes; (b) current treatment guidelines; (c) a clinical approach to statin intolerance.
Methods: Review of (i) trials of statins, ezetimibe, fenofibrate and PCSK9 inhibitors in diabetes, and (ii) BP and glucose control trials with cardiovascular end-points; (iii) current guidelines for cardiovascular risk assessment and management including (iv) statin intolerance.
Results: A general assessment of cardiovascular risk is favoured by many guidelines and is used to guide drug use and the intensity of (if appropriate) statin therapy. Various cardiovascular risk calculators exist to assess vascular risk in diabetic patients without clear-cut evidence for pharmacologic lipid control. Statins, ezetimibe and PCSK9 inhibitors, which predominantly lower LDL-C, have macrovascular disease benefit. Guidelines for statin intolerance are available. Fenofibrate has proven benefit against microvascular complications and for some cardiovascular complications in adults with Type 2 diabetes. Updated lipid guidelines by ADS will soon be released. There are guidelines to diagnose and manage statin intolerance. Glucose control SGLT2 inhibitors also have trial-proven cardiovascular benefit in diabetes. In Type 1 diabetes large observational studies support vasoprotection with insulin delivery by pumps rather than multiple daily injections. Metabolic memory has been shown for vascular risk factors and related drugs, including fenofibrate and metformin.
Conclusions: Many clinical trials show vascular benefit of an increasing range of existent lipid (and non-lipid) drugs and devices in people with diabetes. Updated guidelines exist, including for statin intolerance.
Recent advances in our understanding and management of diabetic kidney disease

Elif I. Ekinci
1. The University of Melbourne, Heidelberg West, VIC, Australia

Diabetes is the leading cause of renal failure and need for dialysis. In diabetes, early renal function loss is characterised by a long, clinically silent period, which typically occurs prior to the development of either chronic renal failure, or premature death from cardiovascular disease. Current estimates of glomerular filtration rate (GFR) are inaccurate in patients with diabetes who have hyperfiltration or early renal function loss. Lack of availability of simple and accurate methods of assessing renal function has lead to inability to optimally identify those with early renal function loss, until almost half of renal function has already been lost.

There is a need to accurately identify early decline in renal function in people with diabetes because unlike other forms of chronic kidney disease, improved methods to detect early deterioration in GFR will allow targeting of novel therapies at an earlier stage when progressive renal injury may be slowed or even reversed. These therapies include SGLT2 inhibitors (including canagliflozin and empagliflozin), GLP1 agonists (including liraglutide, semaglutide and dulaglutide), anti-inflammatory and anti-fibrotic agents.

Youth-onset type 2 diabetes: increasing incidence and high prevalence of complications at diagnosis

Aveni Haynes
1. Princess Margaret Hospital for Children, Subiaco, WA, Australia

An increase in the number of children and adolescents being diagnosed with Type 2 diabetes (T2D) continues to be reported in many populations worldwide. Although not as prevalent in childhood as Type 1 diabetes (T1D), early onset T2D is associated with an increased risk of complications of diabetes, comorbidities and mortality early in life when compared to youth diagnosed with T1D. This talk will focus on the epidemiology of youth-onset T2D, showcasing evidence of its increasing incidence and/or prevalence in different populations worldwide. Data describing the demographic characteristics of youth diagnosed with T2D as well as the high prevalence of comorbidities and diabetes related complications at the time of diagnosis will also be presented. T2D is a relatively new disease in pediatrics and its diagnosis in youth with risk factors for this significant disease needs to be considered even in pre-pubertal children. Early diagnosis and targeted management of their diabetes, with regular screening to minimise the risk of chronic complications is critical to reduce the current and future burden of this disease, including the potential trans-generational effects of youth-onset T2D to future generations.

Developmental overnutrition and pediatric obesity and type 2 diabetes

Dana Dabelea
1. University of Colorado, Colorado, ACT, Australia

Not available at time of printing

Epigenetics of Childhood Obesity and Diabetes Risk

Rae-Chi Huang
1. Telethon Kids Institute, Perth, WA, Australia

Epigenetic changes are associated with the development of non-communicable diseases, including obesity related disease and type 2 diabetes. Experimental studies have suggested that the early life environment makes a significant contribution to an individual's risk of developing obesity, through the altered epigenetic regulation of genes.

In human populations, progressive identification of DNA methylation loci associated with obesity and related phenotypes is occurring. However, despite this, the role of the methylome in mediating early life environmental exposures on obesity and related diseases remains challenging. Gaps in knowledge include uncertainty as to variability of the methylome after birth, the relative contribution of genetic and epigenetic influences on fetal programming and contribution of cell heterogeneity.

In this talk, we discuss within the context of longitudinal birth cohorts (Raine Study, Southampton Women's Survey, Singapore GUSTO cohort, Epigenetics Consortia), studies identifying DNA methylation loci associated with obesity and diabetes-related phenotypes.

The Western Australia Pregnancy Cohort (RAINE) study (www.rainestudy.org.au) recruited 2900 pregnant women between 1989 and 1992. The offspring born to these women have longitudinal exposure data, and adiposity phenotypes. Follow-up of the offspring has been undertaken at birth, 1, 2, 3, 5, 8, 10, 14, 17 and 24 years. Fasting samples, including insulin and glucose were measured at 8, 14, 17 and 24 years. During adolescence, all subjects have datasets derived from Illumina Infinium HumanMethylation450 BeadChips and mass spectrometry based
metabolomics. Early life environmental exposures (maternal BMI, gestational weight gain, maternal smoking in pregnancy, maternal stress, breast feeding) have been prospectively recorded in this cohort.

The roles of early environmental exposures in mediating the association between the methylome and adiposity are being investigated. Current focus is on dissecting out the complex interplay between fixed genetic influences, epigenetics and the early life environment on subsequent obesity and type 2 diabetes risk, using higher order –omics data.

---

### Systems based approaches to diabetes and adolescent health in Aboriginal communities

**Sandra Eades**

1. Baker International Diabetes Institute, Melbourne, VIC, Australia

Not available at time of printing

---

### Liver-Specific deletion of UBL-5 associated mitochondrial stress is associated with liver failure that is improved by ACE2 expression or pioglitazone administration

**Viktoria Ntouma**

1. The University of Melbourne, Melbourne, VIC, Australia

Liver fat accumulation correlates with the metabolic syndrome, increases risk of type 2 diabetes (T2D), advanced liver disease & other metabolic complications. There are no simple/wide effective solutions for fat-induced liver failure & further studies are required for clarification of mechanisms. Mitochondrial dysfunction has been implicated in insulin resistance & is associated with hepatic fat accumulation & T2D. Subsequently it has been shown in C. Elegans that UBL-5 is involved in mitochondrial unfolded response (UPRmt) to ensure chaperone proteins are transcribed & available to relieve stress. To explore the role of UBL-5 in UPRmt, we generated inducible & liver-specific UBL-5 KO mice. Liver-specific deletion of UBL-5 caused gross steatosis, increased hepatic enzymes indicating liver failure (Table 1). Death occurred within 12 days following induction. CHOP & UPRmt genes were downregulated while mtHSP70 was upregulated. PGC1a gene (inducer of mitochondrial biogenesis) was reduced in UBL-5 KO mice. Interestingly, angiotensin-converting enzyme 2 (ACE2) expression was also reduced in KO livers. Mice were then treated with the thiazolidinedione pioglitazone, or an ACE2-containing virus to determine if such treatments provide benefit. ACE2 expression was increased with both ACE2 virus & pioglitazone treatment. Liver enzymes showed significant improvement after treatment with both pioglitazone & ACE2 (Table 1). Furthermore, CHOP expression was normalized with pioglitazone treatment.

**Table 1: Liver enzymes.**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>UBL-5&lt;sup&gt;−/−&lt;/sup&gt; (Vehicle)</th>
<th>AAV UBL-5&lt;sup&gt;−/−&lt;/sup&gt; virus</th>
<th>ACE2 UBL-5&lt;sup&gt;−/−&lt;/sup&gt; Vehicle</th>
<th>UBL-5&lt;sup&gt;−/−&lt;/sup&gt; Pioglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilirubin</strong></td>
<td>1 ± 0</td>
<td>39.6 ± 8.9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>1.2 ± 0.2&lt;sup&gt;##&lt;/sup&gt;</td>
<td>41.3 ± 5.9&lt;sup&gt;**&lt;/sup&gt;</td>
<td>15.8 ± 2.2&lt;sup&gt;##&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Alanine transaminase</strong></td>
<td>37.1 ± 8.7</td>
<td>1974 ± 424.4&lt;sup&gt;##&lt;/sup&gt;</td>
<td>43.6 ± 14.9&lt;sup&gt;##&lt;/sup&gt;</td>
<td>2171.16 ± 436.3&lt;sup&gt;##&lt;/sup&gt;</td>
<td>754.83 ± 150.2&lt;sup&gt;##&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Aspartate aminotransferase</strong></td>
<td>189.8 ± 44.8</td>
<td>2084 ± 780&lt;sup&gt;##&lt;/sup&gt;</td>
<td>107 ± 38.3&lt;sup&gt;##&lt;/sup&gt;</td>
<td>4094.5 ± 1172.6&lt;sup&gt;##&lt;/sup&gt;</td>
<td>1112 ± 215.8&lt;sup&gt;##&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase</strong></td>
<td>133.1 ± 7.9</td>
<td>694 ± 75&lt;sup&gt;##&lt;/sup&gt;</td>
<td>169.8 ± 29.5&lt;sup&gt;##&lt;/sup&gt;</td>
<td>838 ± 39.8&lt;sup&gt;##&lt;/sup&gt;</td>
<td>570 ± 40.2&lt;sup&gt;##&amp;##&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

n=4-6

#P<0.05, ##P<0.005 UBL-5<sup>−/−</sup> AAV (Vehicle) vs UBL-5<sup>−/−</sup> ACE2 virus

*P<0.05, **P<0.005 UBL-5<sup>−/−</sup> AAV (Vehicle) or UBL-5<sup>−/−</sup> Vehicle vs Control

&P<0.05, &P<0.005 UBL-5<sup>−/−</sup> Vehicle vs UBL-5<sup>−/−</sup> Pioglitazone

In conclusion, we have generated a model that develops severe fatty liver disease & have shown that both genetic & pharmacological therapies may diminish this disease process.
Understanding AMPK regulation of exercise adaptation and metabolism

Marin E. Healy¹, James G. Burchfield¹, Nolan J. Hoffman², Benjamin L. Parker³, Jacqueline Stoeckli¹, Essi Havula¹, Kristen Thomas¹, David E. James¹

1. Charles Perkins Centre, University of Sydney, Sydney, NSW, AU
2. Centre for Exercise and Nutrition, Mary MacKillop Institute for Health Research, Melbourne, VIC, AU

Exercise is an effective intervention for lifestyle-related diseases with clear benefits in type 2 diabetes (T2D)¹. Exercise causes extensive molecular perturbations which initiate protein phosphorylation events that lead to acute and long-term adaptations. Fortuitously, these adaptations improve processes that are defective in T2D including insulin sensitivity, glucose uptake, mitochondrial biogenesis and defence against a range of intracellular stresses. Unfortunately, many individuals affected by T2D are not capable of meeting exercise recommendations due to comorbidities such as cardiovascular disease and sarcopenia. Tapping into the benefits of exercise at a molecular level could be of major utility for combating T2D.

The most well-characterised exercise-responsive kinase is AMP-activated protein kinase (AMPK). Mice lacking AMPK in skeletal muscle are exercise intolerant² and prone to developing insulin resistance³. However, the full repertoire of downstream AMPK phosphotargets is not known. We have recently used mass spectrometry to expand the signalling network in exercised human skeletal muscle, including several novel AMPK phosphotargets. Among these novel AMPK phosphotargets is stromal interaction molecule 1 (STIM1), which is required for store-operated Ca²⁺ entry (SOCE), the process of refilling the sarcoplasmic reticulum with Ca²⁺ following muscle contraction. We demonstrate that phosphorylation of this site on STIM1 is dependent on AMPK in AMPK knockout cells. Using an in vitro kinase assay, we confirm that AMPK directly phosphorylates STIM1 at this site. Furthermore, using site-directed mutagenesis and fluorescence lifetime imaging microscopy, we show this phosphorylation affects STIM1 activation.

This discovery is intriguing in light of the role of Ca²⁺ as a potent signalling molecule which regulates diverse processes including muscle contraction, nutrient metabolism, and antioxidant defence⁴. Dysregulated Ca²⁺ in skeletal muscle is one of the most consistent features of T2D and is proposed to underlie many of the disease pathologies⁴. This project makes possible development of new targeted therapies to recapitulate exercise benefits.

Genetic deletion of the Set7 lysine methyltransferase attenuates renal damage in a mouse model of diabetic nephropathy

Hanah Rodriguez²,¹, Haloom Rafiehi¹, Mark Ziemann¹, Jun Okabe¹, Bryna Chow², Mrinal Bhave², Mark Cooper⁴, Assam El-Osta¹,¹

1. Epigenetics in Human Health and Disease Laboratory, Department of Diabetes, Monash University, Melbourne, VIC, Australia
2. Faculty of Science, Engineering and Technology, Swinburne University of Technology, Melbourne, VIC
3. Diabetic Complications Laboratory, Department of Diabetes, Monash University, Melbourne, VIC
4. Department of Diabetes, Monash University, Melbourne, VIC, Australia
5. Department of Pathology, The University of Melbourne, Melbourne

Chronic hyperglycaemia promotes the production of pro-inflammatory and pro-fibrotic mediators that lead to the development of chronic kidney disease. Increasing evidence implicates the Set7 lysine mono-methyltransferase in this pathological process in various models of chronic kidney disease. This study aims to define the role of Set7 in the development of diabetic nephropathy and evaluate it as a target for therapeutic intervention. For this purpose, diabetes-induced renal damage, as defined by histological and molecular changes, was studied in ApoE⁻/⁻ and Set7⁻/⁻ ApoE⁻/⁻ male mice compared to non-diabetic controls 10 weeks after the induction of diabetes. Set7 deletion conferred renal protection as evidenced by attenuated albuminuria, mesangial expansion and glomerular deposition of collagen I and IV in diabetic Set7⁻/⁻ ApoE⁻/⁻ mice. RNA profiling by sequencing revealed that diabetes causes widespread gene expression changes in the kidney that are attenuated by Set7 knock-out. We confirmed gene expression changes associated with Set7 using qRT-PCR. Furthermore, treatment of cultured human podocytes and mesangial cells with (R)-PFI-2, a selective Set7 inhibitor, attenuated high glucose and TGFβ1-mediated increases in pro-inflammatory and pro-fibrotic gene expression. Additionally, Gene Set Enrichment Analysis (GSEA) of the RNA-seq data revealed that many diabetes-induced, Set7-dependent genes are associated with the transcription factor Tcf21, a key mediator of kidney development and podocyte function. We performed protein interaction studies and confirmed that Set7 interacts with Tcf21. We hypothesise that Tcf21 represents a novel Set7 methylation target and our results implicate this transcription factor in the pathology of diabetic nephropathy. Collectively, our results suggest that Set7 may represent a target for developing therapies aimed at reducing the burden of diabetic nephropathy.

Deletion of the mitochondrial stress gene UBL-5 results in pancreatic β-cell dysfunction/death and diabetes in mice

Christian Haralambous¹, Viktoria Ntouma¹, Ben Lamont, Sof Andrikopoulos⁵

1. Medicine, University of Melbourne, Melbourne, Victoria, Australia

Type 2 diabetes (T2D) is characterised by hyperglycaemia due to the inability of pancreatic β-cells to secrete enough insulin to compensate for insulin resistance. Hyperglycaemia has been shown to cause oxidative stress in pancreatic β-cells, leading to activation of stress responses such as the mitochondrial unfolded protein response (UPR⁰⁻). Failure of these responses to adapt to or repair damage from stress results in dysfunction and death of β-cells. Ubiquitin-like protein 5 (UBL-5) is a protein thought to regulate post-translational modification of proteins and has a role in the UPR⁰⁻ in both mammalian cells and invertebrates. The aim of this study was to determine whether UBL-5 has a role in maintaining β-cell mass and function, by generating and characterising tamoxifen-inducible islet β-cell specific UBL-5 knockout mice.
Homozygous β-cell UBL-5 knockout mice (UBL5−/−) showed glucose intolerance and lower plasma insulin levels during the OGTT & significantly reduced plasma insulin levels during IVGTT compared to control. β-cell mass was also significantly reduced in UBL5−/−, with most showing signs of frank diabetes (blood glucose >20 mM), polyuria & polydipsia. One week post UBL5 deletion, UBL5−/− mice had significantly increased blood glucose levels & islet cleaved caspase-3 levels compared to controls despite no difference in β-cell mass. In addition, islets taken from UBL5−/− mice 1 week post UBL5 gene deletion showed significant decrease in insulin secretion, suggesting that β-cell dysfunction precedes the decrease in β-cell mass. Real time PCR data showed a decrease in UPR genes (Clpx, Clpp, CHOP, Lomt1, HSP10, HSP70, ATF5) with HSP60 showing increased expression in the UBL5−/− mice one week after gene deletion.

In conclusion, deletion of UBL5 leads to β-cell dysfunction, which precedes β-cell death and diabetes in mice. This is the first demonstration that the UPR and UBL5 are involved in cell function and survival in a mammalian system.
Impact of dietary carbohydrate composition on metabolic benefits of low protein-high carbohydrate diets.

Jibran A Wahl1,2, Tamara Pulpitel1, Melkam Kebede1, Timothy Dodgson1, Gabriela Pinget1, Belinda Yau1, Ian Matthews1, Devin Wahl1, Glen Lockwood2, Samantha M Solon-Biet3, Gregory J Cooney1, Victoria C Cogger1,3, David G Le Couteur1,3, Stephen J Simpson1

1. Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia
2. Biogerontology Laboratory, Ageing and Alzheimer's Institute and ANZAC Research Institute, Concord Hospital, Sydney, NSW, Australia
3. School of Life and Environmental Sciences, University of Sydney, Sydney, New South Wales, Australia
4. Faculty of Veterinary Science, University of Sydney, Sydney, New South Wales, Australia
5. School of Life and Environmental Sciences, University of Sydney, Sydney, New South Wales, Australia
6. Biogerontology Laboratory, Ageing and Alzheimer's Institute and ANZAC Research Institute, Concord Hospital, Sydney, NSW, Australia
7. School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, New South Wales, Australia
8. Cargill Aqua Nutrition, Sandnes, Norway

Nutrition is the major modifiable factor that influences health-span. Recent research using Geometric Framework (GF), a state-space nutritional modelling method, showed that ‘low protein-high carbohydrate’ (LPHC) diets generate the best cardio-metabolic health and lifespan. This seems at odds with advice to reduce intake of simple carbohydrates because there is evidence that they promote metabolic disease. Therefore, we aimed to evaluate which types of carbohydrate contribute to the benefits of LPHC diets.

Male C57BL/6 mice (n=300) were fed ad-libitum one of 15 isocaloric LPHC diets for 18 weeks composed of differing percentages of low protein (5-15%), high carbohydrate (65-75% with five different sucrose-starch ratios), and 20% fat. This array allows examination of the impact of each individual food component (protein, sucrose and starch) and their interactions using GF methodology. Metabolic health was assessed after 5-6 and 13-14 weeks on diets.

GF analysis showed that mouse weights and adiposity were markedly affected by protein intake and peaked on a combination of increased protein-high carbohydrate consumption, but high sucrose ingestion reduced fat mass. In contrast, energy intake increased on lower protein-high starch diets and declined with an increase in dietary protein and sucrose content. Similarly, lower protein consumption increased energy expenditure and circulating FGF-21, and lower protein-high carbohydrate ingestion yielded peak FGF-21 levels. Glucose tolerance and insulin concentrations were adversely affected by protein intake, but surprisingly, moderate sucrose intake did not impair glucose homeostasis, while extreme consumption paradoxically improved insulin sensitivity due at least in part to decreased food intake. Triglyceride levels increased while liver fat decreased with increasing protein consumption, but increased sucrose intake did not induce dyslipidaemia or hepatic steatosis.

Overall, in the setting of LPHC diets, protein intake is the major determinant of the metabolic phenotype, while compared to starch, very high sucrose intake paradoxically improves parameters of metabolic health.

Using the geometric framework to explore the longitudinal effects of dietary macronutrient consumption on markers of diabetic kidney disease

Amelia K Fotheringham1,2, Samantha M Solon-Biet3,4, Aisling C McMahon2,6,4, Bill O Ballard1, Kari Ruohonen4, Danielle J Borg1,2, David Raubenheimer3,9, David G Le Couteur3,6,4, Stephen J Simpson3,5, Josephine M Forbes1,2

1. Mater Research-UQ, Woolloongabba, QLD, Australia
2. Faculty of Science, University of Queensland, Brisbane, Queensland, Australia
3. Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia
4. Centre for Education and Research on Aging, and Aging and Alzheimer’s Institute, Concord Hospital, Sydney, Queensland, Australia
5. School of Life and Environmental Sciences, University of Sydney, Sydney, Queensland, Australia
6. ANZAC Research Institute, Concord Hospital, University of Sydney, Sydney, New South Wales, Australia
7. School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, New South Wales, Australia
8. Cargill Aqua Nutrition, Sandnes, Norway
9. Faculty of Veterinary Science, University of Sydney, Sydney, New South Wales, Australia

Background: Diabetic kidney disease (DKD), a progressive disorder characterised by changes in glomerular filtration rate (GFR) and structural abnormalities such as tubulointerstitial fibrosis (TIF) and glomerulosclerosis (GS), is one of which predict disease progression. Here, we use the geometric framework [1] to assess the effects of 25 macronutrient and caloric combinations on markers of DKD.

Methods: C57BL/6J mice (♂/♀; N=4/group) were given 15 months ad-libitum access to 1 of 25 diets representing a spectrum of macronutrient combinations (protein, carbohydrate (20-75%) and fat (20-75%)), stratified by energy content (low, medium or high). Serum cystatin C (a surrogate for GFR) and DKD risk factors (TIF and GS) were assessed histologically. Three-dimensional models were used to visualise and quantify the impacts of macronutrients, as main effects and interactions using the mgcv package for R. This data was considered in conjunction with existing data for body composition, glucose tolerance, blood pressure, and lipids [1].

Results: Serum cystatin C (126 - 1006 ng/ml) was significantly influenced by dietary protein intake, whereby GFR increased with protein intake (P<0.001). TIF (0.5 - 9%) was influenced by protein consumption in conjunction with either a high fat, or high carbohydrate intake (P<0.0005, P<0.016; respectively). Overall, lower protein intake in conjunction with higher fat consumption, and therefore calories, resulted in a phenotype with the lowest GFR and the most structural damage, as assessed by TIF and GS. Surprisingly, macronutrient combinations which elevated blood pressure or lipids, or induced glucose intolerance did not associate with adverse kidney outcomes.

Conclusions: Macronutrients, individually and in combination influence risk factors for DKD, seemingly independent of other known risk factors.
Temporal changes in glycaemic thresholds for treatment intensification in type 2 diabetes: The Fremantle Diabetes Study

Timothy ME Davis¹, Stephen AP Chubb², Wendy A Davis³

1. University of Western Australia, Fremantle, WA, Australia
2. Biochemistry Department, Fremantle Hospital, Fremantle, W.A., Australia

Background: In a study of 531 participants with type 2 diabetes (mean age 62.4 years, 54% males, median diabetes duration 3.0 years) in Phase 1 of the community-based Fremantle Diabetes Study (FDS1) conducted between 1993 and 2001 and representing 2,893 patient-years of follow-up [1], the median HbA1c triggering progression from diet to oral hypoglycaemic agents (OHAs) was 7.7% (63 mmol/mol; n=97) and from diet/OHA to insulin was 9.4% (79 mmol/mol; n=45), with reductions to 7.4% (57 mmol/mol) and 7.9% (63 mmol/mol), respectively (P<0.001) and no increase in hypoglycaemia during up to one year of follow-up. The aim of the present study was to repeat the analysis in 930 Phase 2 (FDS2) participants (mean age 65.7 years, 52% males, median duration 9.0 years) with valid data from baseline and two biennial reviews between 2008 and 2015.

Results: During 3,922 patient-years, 84 FDS2 participants progressed from diet to OHAs and 85 from diet/OHAs to insulin. Median HbA1c levels before OHAs or insulin were started were 6.9% (52 mmol/mol) and 7.8% (62 mmol/mol), respectively. At next biennial review, HbA1c levels were 6.8% (51 mmol/mol) and 7.6% (60 mmol/mol), respectively (P=0.83 and P=0.34 vs baseline). Insulin initiation was associated with an increase in minor but not major hypoglycaemia in the previous year.

Conclusions: Reflecting factors such as the greater range of OHAs and more reliably absorbed basal insulins, as well as care plans, there has been a reduction in the glycaemic thresholds triggering treatment intensification between FDS Phases. However, the glycaemic effect of treatment intensification in FDS2 was much less than in FDS1 and, in the case of insulin, there was an increase in non-severe hypoglycaemia. Notwithstanding individualisation of glycaemic targets, more Australians with type 2 diabetes have been achieving optimal control (HbA1c ≤7.0% or 53 mmol/mol) over the 15 years between FDS Phases.

SWITCH 2: reduced hypoglycaemia with insulin degludec vs. insulin glargine, both U100, in patients with type 2 diabetes at high risk of hypoglycaemia – a randomised, double-blind, crossover trial

Carol H Wysham¹, Anuj Bhargava², Louis B Chaykin³, Raymond de la Rosa⁴, Yehuda Handelsman⁴, Lone Nørgård Troelsen⁵, Kajsa Kvist⁶, Paul Norwood⁷, Gregory Fulcher⁸

1. Rockwood Clinic, Spokane, Washington, USA
2. Iowa Diabetes and Endocrinology Research Center, Des Moines, Iowa, USA
3. Meridien Research, Bradenton, Florida, USA
4. Paducah Endocrinology, Paducah, Kentucky, USA
5. Metabolic Institute of America, Tarzana, California, USA
6. Novo Nordisk A/S, Søborg, Denmark
7. Valley Research, Fresno, California, USA
8. Royal North Shore Hospital, The University of Sydney, St Leonards, New South Wales, Australia

In this 2x 32-week, double-blind, treat-to-target crossover trial, adults (n=721) with type 2 diabetes (T2D) were randomised 1:1 to receive once-daily insulin degludec (IDeg)/insulin glargine (IGlar) U100, followed by crossover to IGlar/IDeg. Each treatment period comprised a 16-week titration and 16-week maintenance period. Patients included were previously treated with basal insulin ± oral antidiabetic drugs excluding sulphonylureas/meglitinides, and at increased risk of developing hypoglycaemia based on pre-trial risk factors. The primary endpoint was the number of severe (requiring third-party assistance and external adjudication) or blood glucose-confirmed (<3.1 mmol/L) symptomatic hypoglycaemic events in the maintenance periods.

Treatment with IDeg resulted in significantly lower rates of severe or confirmed symptomatic hypoglycaemia and severe or confirmed symptomatic nocturnal hypoglycaemia (occurring 00:01–05:59) versus IGlar (Figure). The proportion of patients experiencing severe hypoglycaemia in the maintenance periods was 1.6% for IDeg versus 2.4% for IGlar (p=not significant). Severe hypoglycaemia rates were significantly lower with IDeg versus IGlar in the total treatment period. HbA1c reductions with IDeg were non-inferior to IGlar. Adverse event rates were similar.

Compared with IGlar, IDeg resulted in a consistent reduction in hypoglycaemia in T2D patients at high risk of hypoglycaemia.

Figure. Rate ratios of hypoglycaemia in patients with type 2 diabetes at high risk of hypoglycaemia.
Achieving fasting plasma glucose (FPG) target without hypoglycaemia: a meta-analysis of insulin degludec versus insulin glargine

Luigi Meneghin¹, Stephen Atkin², Chantal Mathieu³, Athena Philis-Tsimikas⁴, Lars Bardtrum⁵, Deniz Tutkunkardas⁵, Bernard Zinman⁶, Sultan Linjawi⁷

¹. University of Texas Southwestern Medical Center, Dallas, Texas, USA
². Weill Cornell Medicine - Qatar, Doha, Qatar
³. UZ Leuven, Leuven, Belgium
⁴. Whittier Diabetes Institute, Scripps Health, San Diego, California, USA
⁵. Novo Nordisk A/S, Søborg, Denmark
⁶. Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
⁷. Coffs Harbour Diabetes Clinic, Coffs Harbour, New South Wales, Australia

Insulin degludec (IDeg) is a basal insulin with a long and stable glucose-lowering effect and low day-to-day intra-patient variability compared with insulin glargine U100 (IGlar). This meta-analysis investigated the proportion of patients meeting the laboratory-measured FPG target of <7.2 mmol/L, defined as the upper limit of the recommended pre-meal plasma glucose goal based on the 2015 ADA Standards of Medical Care in Diabetes, at each visit during the maintenance period, as well as doing so without experiencing nocturnal hypoglycaemia. The maintenance period is defined as all visits from week 16 onwards. Nocturnal hypoglycaemia was defined as any confirmed (blood glucose <3.1 mmol/L) self-monitored event occurring between 00:01 and 05:59, inclusive. Patients (type 1 [T1D] or type 2 diabetes [T2D]) from seven open-label, randomised, treat-to-target trials treated with either IDeg (n=2501) or IGlar (n=1256) were included. Use of IDeg resulted in significantly more patients reaching the FPG target at each visit throughout the maintenance period, as well as doing so without experiencing nocturnal confirmed hypoglycaemia, compared with IGlar (Figure). These results were similar across the three patient populations; T1D, T2D insulin-treated and T2D insulin-naïve. In conclusion, more patients treated with IDeg can achieve target FPG without nocturnal confirmed hypoglycaemia compared with IGlar.

Figure: Odds ratios for patients meeting FPG target (<7.2 mmol/L) and without experiencing nocturnal hypoglycaemia.
Meeting FPG target (<7.2 mmol/L) at each visit in maintenance period

- BB T1 LONG: 3.19 [1.48; 6.84]
- FLEX T1: 2.68 [1.55; 4.63]
- T1D trials: 2.82 [1.82; 4.36]
- ONCE LONG (IN): 1.67 [1.19; 2.32]
- LOW VOLUME (IN): 1.50 [0.95; 2.36]
- ONCE ASIA (IN): 1.37 [0.81; 2.32]
- T2D IN trials: 1.55 [1.22; 1.96]
- FLEX T2: 1.77 [1.10; 2.84]
- BB: 1.34 [0.94; 1.92]
- T2D trials: 1.51 [1.26; 1.81]

Meeting FPG target (<7.2 mmol/L) at each visit without nocturnal hypoglycaemia in maintenance period

- BB T1 LONG: 2.43 [0.83; 7.10]
- FLEX T1: 1.83 [0.79; 4.22]
- T1D trials: 2.06 [1.08; 3.93]
- ONCE LONG (IN): 1.57 [1.11; 2.23]
- LOW VOLUME (IN): 1.44 [0.96; 2.16]
- ONCE ASIA (IN): 1.44 [0.94; 2.20]
- T2D IN trials: 1.47 [1.18; 1.84]
- FLEX T2: 1.75 [1.17; 2.64]
- BB: 1.39 [0.86; 2.27]
- T2D trials: 1.49 [1.24; 1.78]

BB, basal-bolus; CI, confidence interval; FPG, fasting plasma glucose; IDeg, insulin degludec; IGlar, insulin glargine U100; IN, insulin-naïve; T1D, type 1 diabetes; T2D, type 2 diabetes. Responder for FPG: patient meeting the FPG target of <7.2 mmol/L for all visits (≥2) from week 16 onwards. For the FLEX T2 and FLEX T1 trials, the IDeg Flexible arm is excluded from the statistical analyses. For the LOW VOLUME trial, IDeg U200 is considered as the IDeg arm. For the BB T1 LONG, BB and ONCE LONG trials, patients who do not have at least three valid FPG measurements (at week 16 or later) are not considered. For ONCE ASIA, FLEX T2, LOW VOLUME and FLEX T1 trials, patients who do not have at least two valid FPG measurements (at week 16 or later) are not considered.
Safety and efficacy of ertugliflozin plus sitagliptin vs either treatment alone after 52 wks in patients with T2DM poorly controlled on metformin: VERTIS FACTORIAL extension

Richard Pratley1, Annaswamy Raji2, Roy Eldor2, Sheila Sunga2, Yanping Qiu3, Jeremy Johnson4, Susan Huyck2, Gregory Golm2, Steven Terra4, James Mancuso3, Samuel Engel1, Brett Lauring2, Joao Conceicao (to present on behalf of the authors)6

1. Florida Hospital Translational Research Institute, Orlando, FL, USA
2. Merck & Co., Inc., Kenilworth, NJ, USA
3. MSD R&D (China) Co., Ltd, Beijing, China
4. Pfizer, Inc., Andover, MA, USA
5. Pfizer, Inc., Groton, CT, USA
6. MSD International, Singapore

Background and Aims: Ertugliflozin (ERTU) is an oral sodium/glucose cotransporter 2 (SGLT2) inhibitor in development for treatment of type 2 diabetes mellitus (T2DM). This study compared the safety and efficacy of co-administration of ERTU 5 mg or 15 mg plus sitagliptin (SITA) 100 mg compared with either treatment alone over 52 weeks.

Methods: In a double-blind Phase 3 trial, 1233 patients with HbA1c 7.5–11.0% on stable metformin monotherapy ≥1500 mg/day were randomised into 5 groups (Table). ERTU + SITA combinations were compared with corresponding ERTU doses (5 or 15 mg) or SITA alone. The primary outcome was at Week 26; treatment was continued in a double-blind 26-week extension phase.

Results: Mean HbA1c at baseline was 8.6%. After 52 weeks in the ERTU+SITA groups, greater reductions in HbA1c, fasting plasma glucose (FPG) (vs ERTU or SITA alone), body weight and systolic BP (vs SITA alone) were observed (Table). The odds of having an HbA1c <7.0% were greater for ERTU+SITA versus ERTU or SITA alone. Administration of ERTU alone or with SITA was well tolerated overall. Rates of genital mycotic infections with ERTU+SITA were similar to those observed with ERTU alone, and significantly higher than those observed with SITA alone (p<0.05, except ERTU 5 mg+SITA in females). Symptomatic hypoglycaemia rates were not significantly different among groups but were highest in the ERTU 15 mg+SITA group. Overall the incidences of urinary tract infection and hypovolaemia were similar across groups.

Conclusion: Co-administration of ERTU+SITA resulted in effective glycaemic control sustained over 52 weeks and was generally well-tolerated.

Table. Summary of key efficacy endpoints at Week 52 (excluding rescue approach)

<table>
<thead>
<tr>
<th></th>
<th>ERTU 5 mg (n=280)</th>
<th>ERTU 15 mg (n=248)</th>
<th>SITA 100 mg (n=247)</th>
<th>ERTU 5 mg + SITA 100 mg (n=243)</th>
<th>ERTU 15 mg + SITA 100 mg (n=244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c, %</td>
<td>-0.9 (−1.0, −0.8)</td>
<td>-0.9 (−1.1, −0.8)</td>
<td>-0.8 (−1.0, −0.7)</td>
<td>-1.4 (−1.5, −1.2)</td>
<td>-1.4 (−1.5, −1.3)</td>
</tr>
<tr>
<td>FPG, mmol/L</td>
<td>-1.6 (−1.9, −1.3)</td>
<td>-1.7 (−2.0, −1.4)</td>
<td>-0.8 (−1.0, −0.7)</td>
<td>-2.2 (−2.5, −1.9)</td>
<td>-2.3 (−2.6, −2.0)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>-2.4 (−2.9, −1.8)</td>
<td>-3.2 (−3.8, −2.7)</td>
<td>-0.1 (−0.7, 0.5)</td>
<td>-2.4 (−3.0, −1.8)</td>
<td>-2.8 (−3.4, −2.2)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>-2.7 (−4.2, −1.2)</td>
<td>-1.6 (−3.1, 0.0)</td>
<td>-0.2 (−1.8, 1.5)</td>
<td>-2.3 (−3.8, −0.8)</td>
<td>-2.3 (−3.7, −0.7)</td>
</tr>
<tr>
<td>Patients with an HbA1c &lt;7.0%, n (%)</td>
<td>64 (25.6)</td>
<td>66 (26.7)</td>
<td>97 (39.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SGLT2 inhibitors versus GLP-1 analogues – comparison of efficacy and sustainability; an Australian DINGO (Diabetes Informatics Group) multicentre study of over 1,000 class initiations in private endocrine practice

David M Hoffman1, 2, N Wah Cheung1, Tony Roberts3, David Darnelle4, Anthony F Morrow1, Jerry R Greenfield1, Ash Gargya1, Tien Ming Hng1, Kerri-Ann Chow1, Danijela Dravec1, Katherine Tonks1, Sam Martin2, Tim Freeman2, Jim Stankovich5

1. Endocrinologist, Australian Diabetes Informatics Group (DINGO), Sydney, NSW, Australia
2. Data Management and Analysis, Software 4 Specialists, Hobart, Tas, Australia
3. Endocrinologist, Australian Diabetes Informatics Group (DINGO), Adelaiade, SA, Australia
4. Endocrinologist, Australian Diabetes Informatics Group (DINGO), Gosford, NSW, Australia
5. Health Statistics, Faculty of Health, University of Tasmania, Hobart, Tasmania, Australia

Background: the recent lessening of PBS restrictions on prescribing GLP-1 analogues (GLP1an) and SGLT-2 inhibitors (SGLT2i) in type 2 diabetes (T2D) has seen a proliferation of use of these relatively new players as add on therapies; clinicians are confronted daily with the conundrum of deciding which of the 2 classes to add first, to maximise patient benefit

Aim: To compare the efficacy and durability of SGLT2i with GLP1an
Method: De-identified data of patients with T2D seen in the 4 year period May 2013 - May 2017 were aggregated from the electronic medical record of endocrinologists using Audit4 (Software 4 Specialists, Australia & NZ). We compared responses to initiation of the 2 classes in respect of HbA1c and weight, and drug duration (start to cease) using Kaplan Meier analysis.

Results: Out of a cohort of 5101 patients, 10.8% had ever started a GLP1an and 15.7% an SGLT2i.

<table>
<thead>
<tr>
<th>Class initiations &amp; baseline parameters (1): Change in weight and HbA1c (mean ± SEM) over time (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
</tr>
<tr>
<td>GLP1an</td>
</tr>
<tr>
<td>SGLT2i</td>
</tr>
</tbody>
</table>

| (2) | 3m | 6m | 12m | 18m | 24m |
|----------------------------------|
| Δ Weight kg | | | | | |
| GLP1an | -0.6 ± 1.7 | -2.6 ± 0.6* | -2.5 ± 0.6* | -1.9 ± 1.2* | Insuff. data |
| SGLT2i | -2.3 ± 0.3**† | -3.0 ± 0.3* | -3.4 ± 0.5* | -4.3 ± 1.6*† | Insuff. data |
| Δ HbA1c % | | | | | |
| GLP1an | -0.7 ± 0.2* | -0.9 ± 0.2* | -0.5 ± 0.2* | -1.0 ± 0.3* | -1.0 ± 0.3* |
| SGLT2i | -0.8 ± 0.1* | -0.6 ± 0.1* | -0.7 ± 0.1* | -1.0 ± 0.3* | -0.4 ± 0.3 |

*p<0.05 vs baseline, †p<0.05 SGLT2i vs GLP1an

Summary: SGLT2i and GLP1an both significantly reduced weight and HbA1c, SGLT2i having superior weight loss efficacy in the first 18 months, but comparable HbA1c effects; median duration of use of GLP1an was 1.5 years, 0.6 years shorter than SGLT2i.

Conclusion: Our data suggests that in real-life conditions, addition of an SGLT2 inhibitor may be an overall more effective and durable treatment than addition of a GLP-1 analogue.

Severe hypoglycaemia, cardiovascular outcomes and death – the LEADER experience

Timothy Davis¹, Bernard Zinman², Steven P Marso³, Erik Christiansen⁴, Salvatore Calanna⁴, Søren Rasmussen⁴, John B Buse⁵
1. University of Western Australia, Fremantle, WA, Australia
2. Lumenfeld–Tanenbaum Research Institute, Mt Sinai Hospital, University of Toronto, Toronto, ON, Canada
3. Research Medical Center, Kansas City, MO, USA
4. Novo Nordisk A/S, Sæborg, Denmark
5. University of North Carolina School of Medicine, Chapel Hill, NC, USA
In the LEADER cardiovascular outcomes trial (N=9340; NCT01179048), the risk of cardiovascular and hypoglycaemia events was reduced with liraglutide treatment versus placebo, when added to standard of care, in patients with type 2 diabetes and at high risk for cardiovascular disease. This post hoc analysis examines the associations between severe hypoglycaemia and cardiovascular events and death in LEADER.

We analysed the time to first major adverse cardiovascular event (MACE; cardiovascular death, non-fatal myocardial infarction or non-fatal stroke), cardiovascular death and all-cause death among patients with/without severe hypoglycaemia, and adjusted for different periods of follow-up and randomised treatment.

During the trial, 267 patients experienced severe hypoglycaemia (liraglutide n=114, placebo n=153; rate ratio, 0.69; 95% CI: 0.51; 0.93). These patients were more likely than those without severe hypoglycaemia to experience MACE, CV death and all-cause death, with a considerably higher risk up to 60 days after the hypoglycaemic episode (Table) irrespective of treatment group. The protective effect of liraglutide on risk of MACE was unchanged when patients with severe hypoglycaemia were excluded from the analysis (patients with severe hypoglycaemia accounted for 5% of all MACE in LEADER).

Patients experiencing severe hypoglycaemia in LEADER were at greater risk of cardiovascular events and death, particularly early after the hypoglycaemic episode. Reducing severe hypoglycaemia remains a cornerstone of diabetes management.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Risk of outcome in patients with versus without severe hypoglycaemia, hazard ratio [95% CI], p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time-dependent: event after severe hypoglycaemia*</td>
</tr>
<tr>
<td>MACE</td>
<td>1.9 [1.5; 2.5], p&lt;0.0001</td>
</tr>
<tr>
<td>CV death</td>
<td>2.2 [1.5; 3.2], p&lt;0.0001</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2.2 [1.7; 3.0], p&lt;0.0001</td>
</tr>
</tbody>
</table>

*Time to first MACE, CV death or all-cause death, using Cox regression with severe hypoglycaemia (yes/no) at any time as a factor. †Severe hypoglycaemic episodes leading to MACE, CV death or all-cause death, using a time-dependent covariate Cox regression: all events (follow-up until last contact date), follow-up within 15, 30 and 60 days.

GLP-1 agonism alters peripheral nerve function in patients with type 2 diabetes

Tushar Issar1, Martin Tran1, Natalie Kwai2 1, Ann Poynten3, Kerry-Lee Milner3, Arun Krishnan1

1. Prince of Wales Clinical School, UNSW Sydney, Australia
2. Department of Exercise Physiology, UNSW Sydney, Australia
3. Department of Endocrinology, Prince of Wales Hospital, Sydney, Australia

Introduction: Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes. Currently, treatment primarily involves alleviation of painful symptoms. Animal studies have demonstrated that glucagon-like-peptide-1 (GLP-1) receptors exist on nerves and that GLP-1 agonism (GLP-1A) is neuroprotective in models of type 2 diabetes (T2DM). Nerve excitability is a novel neurophysiological technique that provides information about the axonal ion channel activity underlying peripheral nerve function and may be used to assess the effect of GLP-1A.

Objective: To investigate the effect of GLP-1A treatment on peripheral nerve function in patients with T2DM.

Methods: 80 patients with T2DM either receiving (n=40) or not receiving (n=40) GLP-1A treatment underwent comprehensive clinical screening, neurophysiological studies and functional assessments. Nerve excitability studies were conducted at the median nerve to assess the activity of sodium and potassium ion channels at different regions of the axon. Maximal walking speed was measured using a 6-metre timed walk. Groups were matched for age, sex, BMI, HbA1c%, duration of diabetes, eGFR and neuropathy severity. An additional 10 patients were assessed before commencement of GLP-1A treatment and retested 3 months post-commencement.

Results: Patients receiving GLP-1A treatment demonstrated significant differences in nerve function compared to patients not receiving GLP-1A treatment despite being matched for neuropathy severity and other variables. These differences in ion channel activity were observed in the internodal (P<0.05) and nodal regions (P<0.005) of the axon and suggest healthier nerve function. Patients receiving GLP-1A treatment also exhibited higher maximal walking speeds (P<0.05). Patients that commenced GLP-1A treatment demonstrated a significant improvement in ion
In conclusion, insulin stimulates betatrophin secretion through PI3K/Akt pathway and IR may play an opposite role. In humans, compared with those without insulin treatment, serum betatrophin expression was suppressed by PI3K/Akt inhibitors and IR, suggesting that insulin upregulates and IR decreases betatrophin expression. In the meantime, PI3K/Akt pathway was activated by insulin and suppressed by above agents that caused IR. Insulin upregulated betatrophin expression was suppressed by PI3K/Akt inhibitors and IR, suggesting that insulin upregulates and IR decreases betatrophin production through PI3K/Akt pathway. Consistently, the treatment of insulin in mice dose-dependently upregulated betatrophin levels, and the administration of metformin in IR mice also stimulated betatrophin production since published study showed metformin improved PI3K/Akt pathway and IR. In humans, compared with those without insulin treatment, serum betatrophin levels were increased in type 2 diabetic patients with insulin treatment.

In conclusion, insulin stimulates betatrophin secretion through PI3K/Akt pathway and IR may play an opposite role.

Acute effects of lixisenatide on gastric emptying, glycaemic and blood pressure responses to oral glucose in health and type 2 diabetes

Karen L Jones¹, Rachael S Rigda¹, Madeline D Butfield², Seva Hatzinikolas¹, Hung Pham¹, Chinmay S Marathe¹, Tongzhi Wu¹, Kylie Lange¹, Laurence G Trahair¹, Chris K Rayner¹, Michael Horowitz¹

1. The University of Adelaide, Adelaide, SA, Australia
2. School of Health Sciences, University of South Australia, Adelaide, SA, Australia

Introduction: Postprandial hypotension (PPH), a fall in systolic blood pressure (SBP) of >20mmHg after a meal, occurs frequently in older people and type 2 diabetes (T2DM). Current management of PPH is suboptimal. The magnitude of the postprandial fall in BP is greater when gastric emptying (GE) is relatively more rapid (1). Intravenous administration of glucagon-like peptide-1 (GLP-1) slows GE and attenuates the postprandial fall in BP and rise in splanchnic blood flow in T2DM (2).

Objectives: We evaluated the effects of the prandial GLP-1RA, lixisenatide (LIXI), on GE and the BP, superior mesenteric artery (SMA) blood flow, and glycaemic responses to a 75g oral glucose load in healthy and T2DM subjects.

Methods: 15 healthy subjects (9M, 6F; age: 67.2 ± 2.3yr) and 15 T2DM patients (9M, 6F; age: 61.9 ± 2.3yr) had measurements of GE, BP, SMA blood flow and plasma glucose for 180min after a radio-labelled 75g glucose drink on 2 separate days. All subjects received LIXI (10mcg sc) or placebo (PLAC) in a randomised, double-blind, crossover fashion 30min before the drink.

Results: LIXI slowed GE (Retention at 120min) (P<0.01) and attenuated the fall in SBP (AUC 0-120min) (P<0.001) compared to PLAC in healthy subjects and T2DM, with no difference between the groups. The maximum rise in SMA flow was attenuated by LIXI in both the healthy subjects and T2DM (P<0.01), but was greater in the healthy subjects than T2DM on both PLAC and LIXI days (P<0.001). Plasma glucose (AUC 0-120min) was greater in T2DM (P<0.005) than healthy subjects, and reduced by LIXI in both groups (P<0.001).

Conclusions: In health and T2DM, the marked slowing of GE and consequent reduction in glycaemia induced by lixisenatide are associated with attenuation of the rise of SMA flow and fall in SBP. Accordingly, lixisenatide may be useful in the management of PPH.

Circulating Betatrophin Levels Are Increased in Patients with Type 2 Diabetes and Associated with Insulin Resistance: Mechanism for Regulation of Betatrophin Expression

Xuefeng Yu¹

1. Division of Endocrinology, Department of Internal Medicine, Tongji Hospital, WUHAN, Hubei, China

Betatrophin was identified as a new hormone that could specifically increase b-cell mass in a novel pharmacological marine model of insulin resistance (IR). To explore the clinical relevance of betatrophin in humans, serum betatrophin levels were measured in age-, sex-, BMI- and blood lipids- matched subjects with normal glucose tolerance (n=137), isolated impaired fasting glucose (n=69), isolated impaired glucose tolerance (n=120) and newly diagnosed T2D (n=112). The results showed that circulating betatrophin levels are increased in patients with T2D and associated with indexes of IR (positively correlated with HOMA-IR; inversely correlated with QUICKI, ISLc and ISLu). Betatrophin was, therefore, considered as a biomarker for IR. However, it remains largely unknown how betatrophin expression was regulated in IR condition. To study whether IR could regulate betatrophin expression and the corresponding molecular mechanisms, betatrophin expression were studied in 6 in vitro IR models which were established successfully using human hepatocytes L02 being treated with different agents, including tumor necrosis factor-a, interleukin-1β, dexamethasone, palmitate, high glucose and insulin. Although the IR was detected in all 6 models as showed that glucose uptake was dramatically decreased, betatrophin levels were elevated only in the insulin-treated cells. These results suggest that it is insulin, not IR that promotes betatrophin expression. In the meantime, PI3K/Akt pathway was activated by insulin and suppressed by above agents that caused IR. Insulin-upregulated betatrophin expression was suppressed by PI3K/Akt inhibitors and IR, suggesting that insulin upregulates and IR decreases betatrophin production through PI3K/Akt pathway. Consistently, the treatment of insulin in mice dose-dependently upregulated betatrophin levels, and the administration of metformin in IR mice also stimulated betatrophin production since published study showed metformin improved PI3K/Akt pathway and IR. In humans, compared with those without insulin treatment, serum betatrophin levels were increased in type 2 diabetic patients with insulin treatment.

In conclusion, insulin stimulates betatrophin secretion through PI3K/Akt pathway and IR may play an opposite role.
Epigenetics and Diabetes

Xiaoying Li

1. Xuzhou City Hospital of Traditional Chinese Medicine, XuZhou, JIANGSU, China

Diabetes is abruptly increased in the past decades in China. Both genetic and environmental risk factors play major roles in the development of diabetes. People's Lifestyle has dramatically changed in China. The mean body mass index in population has been increase by 1.8 kg/m2 and obesity prevalence increased by 8 folds in the past 30 years. In general, the environmental risk factors, including overnutrition and less physical exercise contributes to the rapid increase of diabetes in China.

Epigenetic modifications, including DNA methylation, histone modification and non-coding RNA can respond to environmental change and further regulate gene expression and function. Thus, epigenetic modifications sense and respond to the change of nutrition, stress, and further regulate those critical gene expression and function in metabolism.

Psychological stress is prevalent in modern society. Both epidemiologic and experimental animal studies demonstrate that chronic psychological stress exerts adverse effects on the initiation and/or progression of diabetes. However, transgenerational effects of this environmental information remains poorly understood. Here, using a mouse model of restraint stress, we show that paternal stress exposure reprograms hepatic gluconeogenesis in the resulting offspring. Relative to controls, adult offspring fathered by stressed males exhibit hyperglycemia as a result of enhanced hepatic gluconeogenesis. At the molecular level, we identify an epigenetic alteration in the Sfmbt2 gene promoter from sperm of stressed fathers and liver of their offspring, which results in a reduced expression of microRNA-466b-3p. Gain- and loss-of-function studies demonstrate that down-regulation of microRNA-466b-3p leads to an elevated PEPCK protein level, a key enzyme necessary for gluconeogenesis. Therefore, we provide evidence showing the transgenerational effects of paternal psychological stress on the regulation of glucose metabolism in the offspring.

GLP-1 and Cancer, Foe or Friend?

Haipeng Xiao

1. The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Glucagon-like peptide (GLP)-1 promotes proliferation and survival in b-cell; however, whether GLP-1 receptor agonists promote growth of human ovarian cancer and colon cancer cells remain unknown.

We aimed to explore the expression of GLP-1 receptor (GLP-1R) in ovarian cancer and colon cancer tissues and the effects of exendin-4, a GLP-1R agonist, on growth, migration, invasion and apoptosis of ovarian cancer and colon cancer cells in vitro and in vivo, in addition, we further explore the molecular mechanisms involved.

We detected GLP-1R expression in 90 cases of human ovarian cancer and 20 cases of normal ovarian tissue samples, and 30 cases of human colon cancer and 20 cases of normal colon tissue samples by immunohistochemical analysis. The effects of exendin-4 were investigated on proliferation, migration and invasion, apoptosis in vitro and tumor formation in nude mice of ovarian and colon cancer cells. The PI3K/Akt pathway and MAPK-ERK1/2 pathway, which are two classic signaling pathways of GLP-1R activation in pancreatic β-cells, were assessed in the study.

We found that GLP-1R expressed in human ovarian cancer and normal ovarian tissues. Exendin-4 inhibited growth, migration and invasion, and enhanced apoptosis of ovarian cancer cells in vitro through inhibiting Akt activation and, subsequently, up-regulation of E-cadherin and caspase-3 cleavage (c-cas-3). The antitumor effects are GLP-1R dependent. Consistent with the in vitro results, exendin-4 attenuated tumor formation by ovarian cancer cells in nude mice. While the results showed lack of GLP-1R expression in both human colon cancer tissues and colon cancer cell lines. Ex-4 did not modulate the proliferation of these cell lines in vitro, and nor did it inhibit apoptosis after exposure to cytotoxic agent. In addition, Ex-4 did not promote the propagation of colon cancer cells in vivo.

Our study suggests that GLP-1R agonists at least do not promote the growth of ovarian cancer and colon cancer, and they may even have anticancer effects on selected diabetic patients with ovarian cancer.

Managing Eating Disorders and Diabetes

Warren Ward1, Carolyn Uhlmann2, Helen d’Emden2

1. University of Queensland, Brisbane, QLD, Australia
2. Queensland Diabetes and Endocrine Centre, Mater Health, Brisbane, Qld, Australia

Disordered eating and eating disorders occur along a spectrum of severity and occur more frequently in individuals with type 1 diabetes [Pinhas-Hamiel et al. 2015]. Insulin omission is a unique eating disorder behaviour only possible in individuals with type 1 diabetes. Such behaviour has been implicated as the primary cause of recurrent ketoacidosis in adolescents, and eating disorders should be high on the differential diagnosis of these patients [Glasgow et al. 1991].

Eating disorder behaviours in such patients are associated with serious health consequences and premature death [Bryden et al. 2001]. These behaviours are associated with recurrent ketoacidosis, and early onset of microvascular complications, particularly retinopathy, which has been observed within 4 years of disordered eating in such patients. [Rydell et al. 1997, Colas 1991, Nielsen 2002].

Eating disorder behaviours in patients with diabetes present significant challenges for the patient, their family, and clinicians. Multidisciplinary teams need to be upskilled in the prevention, detection and management of such presentations. This interactive workshop will provide attendees with the knowledge, skills and confidence to assess and manage patients with comorbid diabetes and subthreshold and clinical eating disorders. Strategies for effective collaboration between diabetes teams, psychiatry and eating disorders specialist services will also be discussed.
From Jock to Doc: a career long passion to prove exercise is medicine

Mark Febbraio
1. Garvan Institute of Medical Research, Darlinghurst, NSW, Australia

Almost 50 years ago Goldstein proposed the hypothesis that muscle cells possess a “humoral” component that contributes to the maintenance of glucose homeostasis during exercise. Approximately 15 years ago, we identified skeletal muscle as a cytokine-producing organ, demonstrating that the metabolic and physiologic effects of exercise may be mediated by muscle derived humoral factors (for review see 1). We have demonstrated that interleukin-6 (IL-6) was the prototypical “myokine”, up-regulated by muscle contraction and released from contracting skeletal muscle, to play important roles in lipid and glucose metabolism in metabolically active tissues. Other subsequently identified myokines were made serendipitously and the “myokinome” continues to grow (for review see 2,3). It is likely that contracting skeletal muscle produces many unidentified myokines that positively act on the metabolism of other organs, presenting novel targets therapeutics for the treatment of complex metabolic diseases. Accordingly, we have recently adopted the use proteomic screening technologies in an attempt to identify the entire contraction-induced myokinome. We have distinguished a selection of candidate myokines, currently undergoing validation and some of which have led to the development of novel drug candidates in or about to enter Phase I clinical trials. These candidates will be discussed in this lecture.

Private practice marketing: How to conceptualize your ideas into a business model

Julie Adams
1. chemo@home, West Perth, WA, Australia

ADEA Masterclass, Symposia & Workshops » ADS-ADEA ASM 2017

With 25 years’ experience as a certified oncology pharmacist, Julie Adams, founded, and continues to manage, home chemotherapy business, chemo@home. Through the business, Julie and her business partner offer patients the convenience and flexibility of having their cancer treatment in the comfort of their own homes. They also provide home infusions for other conditions such as multiple sclerosis, Crohn's disease and rheumatoid arthritis.

With no business model to follow for this type of health care delivery from either a clinical or business perspective, Julie has needed to innovate, negotiate, collaborate and problem solve to make it a reality. From a clinical perspective, she has utilised her expertise in home-based care and complex therapies to provide leadership, accountability and confidence to the nursing team and health care partners. She recently commenced a PhD, with her research aimed to assist those cancer patients in the community who require oral chemotherapy.

‘I love chemo@home because it allows me to provide my patients with high-quality care and respond rapidly to changes in their care requirements. It’s a privilege to get to help people during their time of need.’

Characterisation of novel sub-phenotypes of human obesity: implications for diabetes prevention and treatment

Jerry Greenfield
1. St Vincent's Hospital, Darlinghurst, NSW, Australia

Not available at time of printing

ADS ASM Meet the Expert: Diabetes Foot Disease and the NADC Foot Network Working Party

Stephen Twigg, Leanne Mullan
1. University of Sydney, Sydney, NSW, Australia
2. Australian Diabetes Society, Australia

Foot ulceration occurs commonly in diabetes mellitus, with up to 20% of people with diabetes developing this complication. Through facilitating co-ordination of the series of the applied skills required in foot care, there is evidence that diabetes multidisciplinary High-Risk Foot Services (HRFS) can help to optimize outcomes in foot ulceration in diabetes. This includes preventing hospital admissions, aiding timely healing of infected ulcers, and when amputation is required, reducing the frequency of major amputation. Yet Australian data for amputation rate in diabetes lag behind the UK, ambulatory care multidisciplinary HRFS have not been standardized throughout Australia, and there have been no established processes to realize and sustain this key process. The National Association of Diabetes Centres (NADC) has recently commenced a Foot Network Working Party (FNWP) which has a trans-national agenda to prioritise foot care in diabetes. A high priority outcome is to develop standards setting in HRFS, to be universally adopted, which will then act as a cornerstone for accreditation, auditing, in Health Care Professional education, and comparative outcomes in care and research. This interactive presentation will describe the rationale for, and process in, setting national standards in diabetes HRFS and more than one stratum, including clinical indicators plus the national organisations feeding into this activity, in the context of the broader agenda of the NADC FNWP. With time, it is envisaged that a national map of HRF services will be consolidated.
The new biology of diabetes

Domenico Accili
1. Columbia University, New York, United States

I will discuss two areas of diabetes treatment that are of great interest to our research: hepatic insulin resistance and pancreatic b cell failure. Hepatic insulin resistance is a hallmark of diabetes and an unmet clinical need. Insulin inhibits hepatic glucose production and promotes lipogenesis by suppressing FOXO1-dependent activation of Glucose-6-phosphatase (G6pc) and inhibition of Glucokinase (Gck), respectively. The tight coupling of these events poses a dual conundrum: mechanistically, as the FOXO1 corepressor of Gck is unknown; and clinically, as inhibition of FOXO-dependent glucose production increases lipogenesis. The FOXO1 corepressor acting on Gck is unknown. We have recently discovered that SIN3a is the FOXO1 corepressor of Gck. Using a variety of cellular and biochemical assays, we have shown that SIN3a recruits FOXO1 to the Gck promoter to inhibit Gck expression. Moreover, genetic ablation of SIN3a in the liver abolishes regulation of Gck by fasting and refeeding, without affecting other FOXO1 target genes, and causes hypoglycemia without concurrent steatosis. Using this knowledge, we undertook to identify selective FOXO1 inhibitors that would suppress FOXO1-dependent glucose production without affecting lipogenesis. We screened small-compound libraries and identified two series of FOXO1 inhibitors: pan-inhibitors with insulin-like effects to suppress G6pc and activate Gck; and selective inhibitors devoid of Gck-activating function. In addition to discovering a pathway for the dual actions of insulin on gene transcription, these data raise the possibility of developing selective modulators of unliganded transcription factors to dial out potential adverse effects of insulin sensitizers. In a second area of research, we sought to identify pathways associated with diabetic b cell failure. We have previously demonstrated a role of b cell dedifferentiation in b cell dysfunction. However, in order to design new treatments for this condition, we needed to identify the key mediators of this process. To this end, we undertook an integrated approach in which we examined gene expression and genome-wide chromatin changes associated with the onset of diabetes. The integration of gene expression and genome-wide histone modification profiles indicates that b cell dysfunction can be explained by a relatively small subset of genes. I will discuss how this small number of genes can cause a global failure to adapt to physiologic stressors, with increased repression of gene expression and failure to activate stress-response programs. We show that as b cells fail, they become more similar to immature progenitor cells and activate a cell-specific genes. We tested the idea that b cell failure entails a progressive acquisition of a cell features. I will illustrate results from human islet single cell RNA sequencing that support this hypothesis to propose a new mechanism of b cell failure.

Political Advocacy for Diabetes

Petra Wilson
1. Digital Health & Care Institute, Scotland, United Kingdom

Not available at time of printing

DESMOND: Delivery of person centred care from the participant perspective

Kylie Mahony1, Sophie McGough1, Natasha Watson1, Sue Stockdale1, Diane Ledger1, Sheryl Moore1, Helen Mitchell1, Deborah Schofield1, Timothy Skinner2
1. Diabetes WA, Subiaco, WA, Australia
2. School of Psychological and Clinical Sciences, Charles Darwin University, Darwin, NT, Australia

Introduction

DESMOND (Diabetes Self-Management for the Ongoing and Newly Diagnosed) is the National Diabetes Services Scheme (NDSS) endorsed one day structured self-management education program designed to support people with type 2 diabetes. The DESMOND program has been developed from extensive research and demonstrates positive outcomes. The positive outcomes for people with diabetes were shown to be influenced by the style of delivery by the Educators. DESMOND Educators undertake two days of training to learn core Educator behaviours which support participants learning in an interactive, non-didactic style.

Objective

The success of the DESMOND program lies not only in its content but crucially in how it is delivered by Educators. A rigorous Quality Development process for Educators guarantees that delivery of the DESMOND program meets the required standard of Educator behaviours to ensure these positive outcomes. Participant perceptions of these Educator behaviours and style are also collected.

Methodology

Measurement of respondents’ perceptions of Educator behaviour occurs at post-session evaluation using questions from the Health Care Climate Questionnaire (HCCQ). A 5-point Likert scale is used with scores summed to provide an overall score the extent to which the Educators supported the respondents’ autonomy in making decisions about their diabetes management.

Results

HCCQ data was collected from 383 evaluation respondents from July 2016 to June 2017. The mean HCCQ score was 55.5 (out of possible maximum score of 60), suggesting respondents felt supported by the facilitators. Additional analyses revealed that HCCQ score was significantly positively correlated with diabetes empowerment at both post-session (r=.41) and three-month follow-up (r=.32), suggesting autonomy-supportive facilitator behaviour increased sense of empowerment both immediately an over time.

Conclusion
Results indicate that participants felt a sense of autonomy in learning about and making decisions relevant to self-management of their diabetes. Moreover, autonomy supportive facilitator behaviour may be an important component in improving people’s empowerment to manage their diabetes. Use of specific DESMOND Educator behaviours which facilitate development of this sense of autonomy is the cornerstone of the success of DESMOND programs in structured person centred education for people with type 2 diabetes.


DESMOND: Self-management planning is the goal

Kylie Mahony1, Sophie McGough1, Natasha Watson1, Sue Stockdale1, Diane Ledger1, Sheryl Moore1, Helen Mitchell1, Deborah Schofield1, Timothy Skinner2
1. Diabetes WA, Subiaco, WA, Australia
2. School of Psychological and Clinical Sciences, Charles Darwin University, Darwin, NT, Australia

Introduction

DESMOND (Diabetes Self-Management for the Ongoing and Newly Diagnosed) is the National Diabetes Services Scheme (NDSS) endorsed one day structured self-management education program designed to support people with type 2 diabetes. The overall aim of the DESMOND program is to engage people to be empowered and proactive in managing their diabetes and to feel less distressed about living with diabetes. This can only happen when people understand their diabetes, understand the importance of and how to self-manage and believe in their ability to achieve set goals.

Objective

People with type 2 diabetes attending DESMOND programs are supported to develop their own diabetes self-management plan and develop general self-management skills such as goal setting, action planning and problem solving.

Methodology

Standardised tools developed through the NDSS National Evaluation Framework to evaluate DESMOND involve pre-session, post-session, and three-month follow-up evaluations. Participants were asked at post-session to record the goal set at the DESMOND program. At three-month follow-up, participants rated their success in achieving their goal on a 10-point scale, and reported other changes made to self-management behaviour since attending DESMOND.

Results

For the period July 2016 to June 2017, 350 respondents provided 457 goals they set for themselves after attending the DESMOND program. Respondents frequently listed more than one goal and up to three areas where they were aiming to make changes. The majority of goals were around increased physical activity (n=132, 37.7%), diet or food intake (n=103, 29.4%), and weight loss/shape change (n=89, 25.4%). Of those participants with matched post-session and follow-up data, 50% of respondents were ‘successful’ and another 30% were ‘moderately successful’ in achieving their goal. Moreover, goal success was significantly positively correlated with diabetes empowerment (r=.47), and significantly negatively correlated with diabetes distress (r=-.62) at three-month follow-up.

Conclusion

The ability to develop self-management skills including goal setting is integral to better health outcomes and can successfully engage people in commencing lifestyle changes.1


Emerging adults with type 1 diabetes in regional Victoria perceptions impact and self-management

Claire R Gatto1, Bodil Rasmussen1, Trisha Dunning2
1. Bass Coast Health, San Remo, VIC, Australia
2. Deakin University, Melbourne, Victoria, Australia

Background: Research indicates the prevalence of inadequate metabolic control, psychological distress and mental issues in emerging adults (Eas) with type 1 diabetes mellitus (T1DM) in their transition from paediatric to adult care. Little is known about how a new diagnosis of T1DM impacts the life transitions of Eas living in regional areas, where access to specialist multidisciplinary services can be limited by geographic, financial and psychological factors.

Aim: To explore the lived experience of young adults diagnosed with T1DM during emerging adulthood in regional Victoria.

Methods: A qualitative phenomenological design was used to address the study aims. Three participants took part in semi-structured interviews, which were transcribed verbatim. The analysis identified initial themes which were subdivided into categories, then regrouped into four main interrelated themes presented as a narrative description.

Findings: Four common themes emerged from the participants’ experiences. (a) sense of isolation; (b) difficulty coping with the transition phase following the diabetes diagnosis; (c) difficulties navigating the health services; (d) importance of support networks in the participants’ diabetes journey.
Conclusions: The participants' sense of isolation and struggle to balance the demands of diabetes management tasks with the transitions of emerging adulthood were consistent with the findings of previous research. The participants added new information that indicated their experience was, in some respects, different from that of their peers with earlier T1DM onset: (a) diabetes as a life-changing event, adding to the multiple transitions experienced by EAs and increasing the risk of mental health issues; (b) limited structured diabetes education in regional health services and potential loss to follow-up after diagnosis; (c) limited practical support from participants' significant others; (d) limited peer support due to geographic dispersion.


Diabetes distress and its relationship with self-care behaviors, self-efficacy, glycemic control and acculturation levels among Arabic-speaking and Caucasian English-speaking patients with diabetes

Hamzah Alzubaidi1, Kevin Mc Namara2, Colette Browning3
1. College of Pharmacy and Sharjah Institute for Medical Research, University of Sharjah, Sharjah, United Arab Emirates
2. School of Medicine, Deaking University, Melbourne, Vic, Australia
3. Research Institute, Royal District Nursing Service, Melbourne, Vic, Australia

Background
Diabetes-related distress (DRD) represents a major problem in diabetes care. DRD is highly prevalent among people with diabetes especially among migrant communities and culturally and linguistically diverse groups. DRD has been associated with lower adherence levels to self-care activities and treatment regimens, poor quality of life and worse health outcomes.

Objective
To compare diabetes-related distress between Arabic-speaking immigrants and Caucasian English-speaking people with diabetes, and to explore the relationships between DRD and various patient-related factors.

Methods
A cross-sectional study was conducted in healthcare settings with large Arabic populations in rural and metropolitan Victoria, Australia. Diabetes-related distress, adherence to self-care activities and medications, self-efficacy, medication underuse, satisfaction with healthcare decisions, and clinical data were recorded.

Results
701 participants were recruited; 392 Arabic-speaking participants (ASPs) and 309 English-speaking participants (ESPs). About 84% of ASPs screened positively for low functional health literacy. 58.8% of ASPs had inadequate glycemic control HbA1c >7% (53mmol/mol) and 13.85% had inadequate blood pressure control (BP ≥140/90mmHg). ASPs were significantly less adherent to all aspects of diabetes self-care compared with ESPs: dietary behaviors (P <0.01, 95% CI = -1.17, -0.84), exercise and physical activity (P = <0.001, 95% CI = -1.14, -0.61), blood glucose testing (P <0.001) and foot-care (P <0.001). ASPs displayed higher levels of diabetes-related distress compared with their counterparts in the ESP group (P = 0.04). Significant associations were found between DRD and age, employment status, medication underuse, self-efficacy, self-care activities, and satisfaction with healthcare decisions.

Conclusions
Arabic-speaking migrants had significantly higher levels of diabetes-related distress, compared with Cascina English-speaking people. Higher distress level was significantly associated with lower self-efficacy, lower adherence levels to prescribed treatment, and lower self-care activities. These findings highlight the need to incorporate assessment of DRD in medical encounters. The tide may be turning in the right direction if suitable interventions are designed to lower DRD aiming at improving diabetes outcomes.
Impact of a Diabetes Educator: Post implementing a Guideline for screening and management of Diabetes with Pancreatic Surgery

Gael Holters¹, Catherine Finneran¹, Megan Stephens¹, Michelle Griffiths¹, Christos Apostolou², Sarah Abdo¹

1. Diabetes Centre, Bankstown-Lidcombe Hospital, Bankstown, NSW, Australia
2. Department of Surgery Bankstown - Lidcombe Hospital, Bankstown - Lidcombe Hospital, BANKSTOWN, NSW, Australia

Background
Pancreatic surgery patients are at increased risk of new onset diabetes or worsening glycaemic control in pre-existing diabetes. Bankstown-Lidcombe hospital has a high turnover of pancreatic resections annually, and we have trialed early collaboration between surgical and diabetes management teams to improve quality of care, and correctly diagnose and manage new-onset diabetes.

Aims
To develop a guideline for the preoperative evaluation by a diabetes educator (DE) of all patients undergoing pancreatic surgery and to ensure all patients are assessed preoperatively for diabetes status with HbA1c.

Methods
A DE referral pathway was developed, however, referrals were inconsistently completed. Subsequently, a DE-CNC joined the Pancreatic Cancer Committee and after collaboration between the surgical team, pre-admission clinic and diabetes centre, all patients were to be referred preoperatively on attendance at pre-admission clinic. The guideline developed was commenced in mid-2016 and provides direction for care for all pancreatic surgery patients, regardless of diabetes status pre-operatively. Data have been collected on HbA1c, diabetes status and diabetes diagnosis at discharge.

Results
Following implementation of the guideline, twelve of thirteen patients were referred preoperatively compared to only one referral prior, and all patients were assessed with preoperative HbA1c compared to nil prior, with three new diabetes cases diagnosed preoperatively (Table 1).

Conclusions
A screening and management guideline for diabetes with early active involvement by a DE enhances the patient journey after pancreatic surgery. In particular, patients with a new diagnosis of diabetes or initiation of insulin therapy had already met a DE prior to surgery and were prepared for potential changes to management. Almost all patients were seen by the DE and had a plan for diabetes screening post-operatively or follow-up arranged for review of diabetes management in their local area. A partnership with another hospital is to commence to implement a similar guideline.

Table 1 Comparison of referrals before and after guideline implementation

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Surgeries</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Referred to DE pre-admission</td>
<td>1 (8%)</td>
<td>12 (92.3%)</td>
</tr>
<tr>
<td>Known diabetes or IGT</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>HbA1c attended pre-admission</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Diabetes diagnosed pre surgery (based on HbA1c)</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>New onset diabetes post-operatively</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Declining consumption of added sugars and sugar-sweetened beverages in Australia: a challenge for obesity prevention

Alan W Barclay¹, Jennie Brand-Miller²

1. Dr Alan Barclay, Padstow Heights, NSW, Australia
2. School of Molecular Bioscience and Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Sydney, NSW, Australia

Background: Reduced intakes of added sugars and sugar sweetened beverages (SSBs) have been the main focus of efforts to stall obesity.

Objective: We investigated recent trends in the availability of sugars and sweeteners and changes in intakes of total sugars, added sugars, and SSBs in Australia by using multiple, independent data sources.

Design: The study was designed to compare relevant data published by the Food and Agriculture Organization of the United Nations [FAO Statistics Division Database (FAOSTAT)], the Australian government, academia, and the food industry.

Results: With the use of the FAOSTAT food balance sheets for Australia, the per capita availability of added or refined sugars and sweeteners was shown to have fallen 16% from 152 g/d in 1980 to 127 g/d in 2011 (P-trend = 0.001). In national dietary surveys in 1995 and 2011–2012, added-sugars intake declined markedly in adult men (from 72 to 59 g/d; 21.8%) but not in women (44–42 g/d; NS). As a proportion of total energy, added-sugars intake fell 10% in adult men but nonsignificantly in adult women. Between 1995 and 2011–2012, the proportion of energy from SSBs (including 100% juice) declined 10% in adult men and 20% in women. More marked changes were observed in children aged 2–18 y. Data
from national grocery sales indicated that per capita added-sugars intakes derived from carbonated soft drinks fell 26% between 1997 and 2011 (from 23 to 17 g/d) with similar trends for noncarbonated beverages. **Conclusions:** In Australia, 4 independent data sets confirmed shorter-and longer-term declines in the availability and intake of added sugars, including those contributed by SSBs. The findings challenge the widespread belief that energy from added sugars or sugars in solution are uniquely linked to the prevalence of obesity.

### 129

**What is the quantity of additional insulin required for meals high in fat and protein?**

Megan Evans¹, Carmel E Smart¹, Barbara Keating¹, Nirubasini Paramalingam¹, Grant Smith¹, Tim W Jones¹, ², Bruce R King³, ⁴, Elizabeth A Davis¹, ²

¹, ² Telethon Kids Institute, University of Western Australia, Perth, WA, Australia

² Department of Endocrinology and Diabetology, Princess Margaret Hospital for Children, Perth, WA, Australia

³, ⁴ Department of Paediatric Endocrinology and Diabetes, John Hunter Children’s Hospital, Newcastle, NSW, Australia

4 Hunter Medical Research Institute, University of Newcastle, Newcastle, NSW, Australia

It is routine clinical practice to calculate mealtime insulin doses for people with type 1 diabetes (T1D) based on the carbohydrate content of the meal. Studies have demonstrated that addition of fat and protein to a meal causes prolonged postprandial hyperglycaemia. We have shown that additional insulin is required for a high protein meal. However, the quantity and distribution of insulin required to cover meals high in both fat and protein remains unclear. The aim of this study was to determine the insulin requirement for a high fat high protein meal (HFHP) compared to a low fat low protein meal (LFLP) controlling for carbohydrate.

Nine subjects with T1D aged 12-21yrs attended fasted on 2 occasions and were randomised to consume a HFHP (40g fat, 60g protein) meal or LFLP (5g fat, 5g protein) meal with identical carbohydrate content (30g). An insulin clamp technique was used to titrate IV insulin infusion to maintain blood glucose levels (BGL) in the euglycaemic range for the 5-hour post prandial period.

There was a significant difference in the mean insulin required for the HFHP meal compared with the LFLP meal of 5.3 ± 2.6 units (11.5 ± 3.0 vs 6.2 units ± 2.0; P<0.01). This represents a mean increase of 85% compared to our earlier findings of 57% for a high protein meal. There was inter-individual variation with a range of difference in insulin requirements of 1.7 units to 9.9 units, representing an increase of 30% to 250%. Postprandial glucose excursions were similar on both study days.

The addition of fat and protein increases the amount of insulin required for a meal. The effect of fat and protein together is greater than the effect of protein alone. Substantial individual differences indicate the need for individualised advice regarding meal boluses for HFHP meals.

### 130

**Women after gestational diabetes (WAGs) experience of running a lifestyle modification program for women post gestational diabetes.**

Rebecca Stiegler¹, Josephine Marshall¹, Sonia Middleton¹

¹ Baker Heart & Diabetes Institute, Melbourne, VIC, Australia

Context: Baker Institute piloted a lifestyle modification program (LMP) for women with prior gestational diabetes (GDM) aimed at addressing the typical barriers to attendance including suitable facilities, time constraints and affordability. Following on from the pilot the WAG program has continued to be run with modifications to the program based on our successes and failures.

 Aim: To determine the success of delivering a tailored LMP through maternal child health (MCH) centres.

Method: A tailored LMP was developed for women post GDM and delivered at local MCH centres. The content, timing and venue were all targeted to best meet the needs of mothers. The five week program involved one hour sessions weekly conducted by a dietitian, psychologist or physiotherapist/exercise physiologist. Women were referred to the program by their local MCH nurse or from Baker Institute.

Health questionnaires were administered pre and post program and collected information on diet, physical activity and diabetes screening. Ongoing support post program was provided by a closed Facebook group moderated by Baker staff. Ethics approval was obtained.

Results: 11 programs have been completed (n=70) with an average of 6 participants each session. Retention to the program has been exceptional with 53% of participants attending all five sessions, and only 7% attending one session. The average attendance across all sessions was 81%. Whilst significance has not been tested, improvements were seen post program. Diabetes screening measured by completion of the post-natal OGGT improved (58% pre program compared to 70% post program). Vegetable consumption improved from 2.6 serves to 3.1 serves post program, and walking time improved from 163 minutes to 195 minutes pre and post program respectively.

Conclusion: Collaborating with MCH centres is a successful strategy to engage women post GDM in a LMP to reduce type 2 diabetes risk.

### 131

**Evaluation of a pilot group education workshop to reduce fear of exercise induced hypoglycaemia in patients with type 1 diabetes mellitus**

Janie A Brown¹, Marian Brennan¹, ²

¹ School of Nursing, Midwifery and Paramedicine, Curtin University, Perth, Western Australia, Australia

² Diabetes WA, Subiaco, WA, Australia

**Context and Aims:** The benefits of physical activity (PA) for people living with type 1 diabetes mellitus (T1D) are vast, however activity rates amongst this population are low.¹ Fear of hypoglycaemia (FoH) is a common barrier to PA for people living with T1D and may be preventing this
population from engaging in adequate activity. The aim of this study was to evaluate a pilot group education workshop designed to reduce fear of exercise induced hypoglycaemia in adults with T1D.

Methods: A pre / post / 6 week post, evaluative program review was conducted using a self-administered 25 item questionnaire developed by the researchers. Data was analysed using simple descriptive statistics including median, interquartile range, frequency and percentage.

Findings: Responses from pre (n=31) and post intervention (n=32) questionnaires were included in the initial analysis. Before the intervention, FoH was listed in the top three barriers to PA 17 times (71%), while after the intervention it appeared 14 times (58%). Median confidence levels to manage blood glucose levels (BGLs) surrounding PA increased from 7 (IQR = 3) to 8 (IQR = 3) out of 10 from pre to post intervention. An increased number of participants indicated they would use insulin adjustment, monitoring BGLs and sprints to manage BGLs from pre to post. Data collected at the 6 week post intervention will be analysed and presented.

Conclusion: In this sample, the self-management, group education intervention under investigation was found to modestly decrease FoH as a barrier to PA, improve confidence to manage BGLs surrounding PA and change participant’s intended strategies to manage BGLs surrounding PA.


Plasma lipidomics are associated with insulin sensitivity and secretion in overweight and obese, non-diabetic adults

Aya Mousa1, Negar Naderpoor1, Estifanos Baye1, Josphin Johnson1, Natalie Mellett2, Peter Meikle2, Barbara de Courten1

1. Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia
2. Metabolomics Laboratory, Baker Heart and Diabetes Institute, Melbourne, VIC, Australia

Background: Dyslipidaemia is a key risk factor for type 2 diabetes and cardiovascular disease. Novel lipidomics methods are providing new insights into the pathophysiology of these diseases; however, data from human studies are limited. We examined whether certain lipid species and/or classes were associated with insulin sensitivity and secretion measured by gold-standard methods, in overweight or obese, non-diabetic adults.

Method: In 65 overweight or obese (mean BMI=31.5±5.2 kg/m2) non-diabetic adults (35M/19F; mean age=31.3±8.5 years), we performed lipid profiling of 459 lipid species across 26 lipid classes (liquid chromatography mass spectrometry). Gold-standard methods were used to assess body composition (%body fat, dual X-ray absorptiometry), insulin sensitivity (hyperinsulinaemic-euglycaemic clamps) and total, first-phase, and second-phase insulin secretory response (area under the curve (AUC) by intravenous glucose tolerance tests). Additional measures included anthropometry (BMI, waist-to-hip ratio) and oral glucose tolerance tests (OGTT) for fasting and 2-hour post-OGTT blood glucose concentrations. Multivariable regression was performed with adjustment for age, sex and % body fat, and all analyses were adjusted for multiple testing using Benjamini-Hochberg correction.

Results: On univariable analyses, fasting glucose, 2-hour post-OGTT glucose, fasting insulin, and insulin sensitivity were not associated with lipid species or classes (all p>0.05). However, total and second-phase insulin AUC were positively associated with the lysophosphatidylinositol (LPI) lipid class (rs = 0.16, p < 0.05), and insulin sensitivity was negatively associated with the dihydroceramide (dhCer) lipid class (r = -0.21, p < 0.05), and several diacylglycerol and triacylglycerol lipid species (all p<0.05).

Conclusion: In overweight or obese non-diabetic adults, we found that increased dhCer and LPI were associated with reduced insulin sensitivity and impaired insulin secretory response, respectively. Our findings suggest that these lipid classes may be involved in the pathophysiology of type 2 diabetes.

3-year efficacy and safety for liraglutide 3.0 mg in adults with obesity/overweight, prediabetes and baseline BMI <35 vs ≥35 kg/m² in the SCALE Obesity and Prediabetes, double-blind, placebo-controlled trial

John Prins1, Frank Greenway2, Carel Le Roux3, Barbara McGowan4, Xavier Pi-Sunyer5, Ana-Paula Cancino5, Luc van Gaal7

1. Mater Research Institute - UQ, South Brisbane, QLD, Australia
2. Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA
3. University College, Dublin, Ireland
4. Guy’s and St Thomas’ NHS Foundation Trust, London, UK
5. Columbia University, New York, NY, USA
6. Novo Nordisk A/S, Sæborg, Denmark
7. Antwerp University Hospital, Antwerp, Belgium

The 3-year SCALE Obesity and Prediabetes trial (NCT01272219) randomized 2254 adults with prediabetes (female 76%; mean: age 48 years; BMI 39 kg/m²) 2:1 to liraglutide 3.0 mg or placebo (PBO) as adjunct to diet+exercise for 160 weeks (W).
Effect of carnosine supplementation on the plasma lipidome in overweight and obese non-diabetic adults: a pilot randomised controlled trial

Estifanos Baye1, Jozef Ukropec2, Maximilian PJ de Courten3, Silvia Vallova4, Patrik Krumpolec2, Timea Kurdiova2, Giancarlo Aldini5, Barbara Ukropcova2,4, Barbora de Courten1,6

1. Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia
2. Institute of Experimental Endocrinology, Biomedical Research Centre, Slovak Academy of Sciences, Bratislava, Slovakia
3. Centre for Chronic Disease, College of Health and Biomedicine, Victoria University, Melbourne, VIC, Australia
4. Institute of Pathological Physiology, Faculty of Medicine, Comenius University, Bratislava, Slovakia
5. Department of Pharmaceutical Sciences, Università degli Studi di Milano, Milan, Italy
6. Diabetes and Vascular Medicine Unit, Monash Health, Melbourne, VIC, Australia

Introduction: We have previously reported that carnosine supplementation, an over-the-counter food supplement, prevented worsening of glucose metabolism in humans but did not change plasma lipid levels. However, studies in rodents indicated that carnosine has been shown to improve dyslipidaemia, reduce oxidation and glycation of low density lipoprotein and reduce development of atherosclerosis. The effect of carnosine on human plasma lipidome has thus far not been investigated.

Objective: To determine whether carnosine supplementation improves the plasma lipidome in overweight and obese otherwise healthy individuals.

Methods: Lipidomic analysis was performed by LC/ES-MS in 24 overweight and obese non-diabetic adults: 13 were randomly assigned to 2g carnosine daily and 11 to placebo and treated for 12 weeks. Insulin sensitivity was calculated using homeostatic model assessment of insulin resistance (HOMA-IR). Triple quadrupole mass spectrometer was used to measure urinary carnosine. Serum carnosinase activity was quantified by fluorometric determination of liberated histidine after carnosine addition.

Results: Carnosine supplementation maintained the levels of trihexosylceramide (mean % change ± SD: 0.7±11 carnosine vs -12.6±16 placebo, p=0.05) and phosphatidylserine (3.2±39 carnosine vs 10±520 placebo, p=0.03) lipid classes compared to placebo. Change in trihexosylceramide was inversely correlated with change in fasting insulin (r=-0.4, p=0.02), HOMA-IR (r=-0.5, p=0.02) and carnosinase 1 (r=-0.3, p=0.05) and positively with urinary carnosine levels (r=0.4, p=0.02), and remained significant after adjustment for age, sex and change in body mass index (all p<0.01) except for urine carnosine. No other cardiometabolic parameters were associated with trihexosylceramide. Phosphatidylserine lipid class did not correlate with any cardiometabolic parameters.

Conclusion: We suggest that carnosine supplementation may have beneficial effects on plasma lipidome and contribute to prevention of T2DM and CVD. Future long term studies with larger sample sizes are highly warranted.

Vitamin D supplementation has no effect on insulin sensitivity or secretion in vitamin D-deficient, overweight or obese adults: a randomized placebo-controlled trial.

Barbora de Courten1, Aya Mousa1, Negar Naderpoor1, Helena J Teede1, Nicole Kellow2, Karen Walker2, Robert Scragg3, Maximilian PJ de Courten1

1. Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia
2. Department of Nutrition and Dietetics, Monash University, Melbourne, VIC, Australia
3. School of Population Health, University of Auckland, Auckland, New Zealand
4. Centre for Chronic Diseases, Victoria University, Melbourne, VIC, Australia

BACKGROUND: Vitamin D supplementation has been proposed as a potential strategy to prevent type 2 diabetes. However, existing clinical trials are limited by short durations, low doses of vitamin D, variability in participants’ vitamin D deficiency status, and use of surrogate measures of body composition, insulin sensitivity, and insulin secretion.

OBJECTIVE: We conducted a double-blind randomised placebo-controlled trial to investigate whether vitamin D supplementation, provided in a sufficient dose and duration to vitamin D-deficient individuals, would improve insulin sensitivity and/or secretion measured by gold-standard methods.
METHODS: Sixty-five overweight or obese (BMI≥25 kg/m²), vitamin D-deficient (25-hydroxyvitamin D (25(OH)D)≤50 nmol/l) adults were randomised to a bolus oral dose of 100,000IU followed by 4,000IU daily of cholecalciferol or matching placebo for 16 weeks. Before and after intervention, participants had gold-standard assessments of body composition (dual X-ray absorptiometry), insulin sensitivity (hyperinsulinenemic-euglycemic clamps) and insulin secretion (intravenous glucose-tolerance tests). Additional measurements included BMI, waist-to-hip ratio, blood pressure, serum lipids (ELISA), and high-sensitivity C-reactive protein (highly-sensitive ELISA).

RESULTS: Fifty-four participants completed the study (35M/19F; age=31.9±8.5 years; BMI=30.9±4.4 kg/m² (means±SD)). Serum 25(OH)D concentrations increased with vitamin D supplementation compared to placebo (57.0±21.3 versus 1.9±15.1 nmol/l, p=0.02). Vitamin D and placebo groups did not differ in change in insulin sensitivity (0.02±2.0 versus -0.03±2.8 mg/kg/min, p=0.9) or total, first- or second-phase insulin secretion (all p>0.1). There were no differences in changes in anthropometry, blood pressure, serum lipids, or hsCRP (all p>0.1). Results remained non-significant after adjustment for age, sex, and %body fat, and after additional adjustment for sun exposure, physical activity, and dietary vitamin D intake.

CONCLUSIONS: Vitamin D supplementation does not improve insulin sensitivity or secretion in vitamin D-deficient, overweight or obese adults, despite using sufficient doses and robust endpoint measures. It is therefore unlikely that vitamin D supplementation would be an effective strategy for reducing diabetes risk in this population.

136

Endogenous glucagon-like peptide-1 mediates the lowering of glycaemia during small intestinal glucose infusion by bile acids in type 2 diabetes

Tongzhi Wu1,2, Michael Horowitz1,2, Karen Jones1,2, Chris Rayner1,2
1. Discipline of Medicine, The University of Adelaide, Adelaide, SA, Australia
2. Centre of Research Excellence in Translating Nutritional Science to Good Health, The University of Adelaide, Adelaide, South Australia, Australia

Background: Bile acids are recognised to play an important role in glucose homeostasis. We have reported that small intestinal administration of taurocholic acid (TCA) reduces the glycaemic response to intrajejunal (IJ) glucose infusion markedly in health, associated with stimulation of glucagon-like peptide-1 (GLP-1) release. Here, we evaluated the effects of TCA, with or without the GLP-1 receptor antagonist, exendin(9-39), during an IJ glucose infusion in type 2 diabetes (T2DM).

Methods: Ten T2DM patients were each studied on four days, when an IJ catheter was positioned and a balloon inflated to exclude endogenous bile. An intravenous exendin(9-39) (600pmol/kg/min) or saline was commenced and maintained during t=0–120min. TCA (2g), or saline, was given via IJ infusion during t=30–0min, followed by 2g TCA or saline, together with 60g glucose, during t=0–120min. Blood glucose and plasma hormones were measured. The insulin secretion rate (ISR)/glucose ratio was calculated. Incremental areas under the curves during t=0–120min were compared using repeated measures ANOVA, with TCA and exendin(9-39) as factors.

Results: TCA reduced blood glucose (P=0.022, treatment effect), and increased plasma insulin (P=0.007) and the ISR/glucose ratio (P=0.022), without affecting plasma glucagon. Exendin(9-39) augmented blood glucose (P=0.003) and plasma glucagon (P=0.011), decreased plasma insulin (P=0.008) and the ISR/glucose ratio (P<0.001). Without exendin(9-39), blood glucose was lower (P=0.004), and plasma insulin (P=0.025) and the ISR/glucose ratio (P=0.039) were greater, with TCA vs. control, without any difference in glucagon. With exendin(9-39), insulin was greater with TCA vs. control (P=0.020), without any difference in blood glucose, the ISR/glucose ratio, or glucagon.

Conclusion: In T2DM, small intestinal TCA reduces the glycaemic response to IJ glucose, associated with increased insulin secretion, and these effects are attenuated by exendin(9-39). These observations support the concept of a “bile acid-GLP-1” axis in the regulation of postprandial glycaemia in T2DM.

137

The impact of variable duodenal glucose load on insulin clearance in health

Chinmay S Marathe1, Michael Horowitz1, Karen L Jones1, Chris K Rayner1
1. University of Adelaide, Adelaide, SA, Australia

Introduction: The incretin effect (IE), which accounts for 50-70% of the postprandial insulin release in health, and is reduced in type 2 diabetes (T2D), reflects a) an amplified insulin secretory response (ISR) and b) reduced insulin clearance to oral, compared with intravenous, glucose. We previously reported, using intraduodenal (ID) glucose infusions as a surrogate, that gastric emptying (which ranges between 1-4 kcal/min in health) is a major determinant of the magnitude of both ISR and IE in health and T2D, such that at higher rates of duodenal glucose delivery, both ISR and IE are substantially greater. The impact on insulin clearance is, however, not known.

Objective: We evaluated the impact of ID glucose infusions at 2 kcal/min (ID2) and 4 kcal/min (ID4) (equating to two rates of gastric emptying within the physiological range) on insulin clearance.

Methods: 10 healthy men (age 47±3 years; BMI 29.3±1 kg/m2) received ID glucose infusions at ID2 or ID4 for 120 min in random order following an overnight fast, on two separate days. Blood glucose, serum insulin and C-peptide were measured at baseline and regular intervals and total areas under the curve (AUC) during 120 min of glucose infusion estimated. Insulin clearance was estimated from molar ratios of C-peptide and insulin and the relative reduction in insulin clearance calculated as: [AUC120min (C-peptide) / AUC120min (insulin)] - (C-peptide baseline / insulin baseline) / [AUC120min (C-peptide) / AUC120min (insulin)] and expressed in %.

Results: There was no difference in the glycaemic responses to ID2 and ID4 but insulin and C-peptide secretory responses to ID4 were much greater (P<0.01 for both). Importantly, there was a greater reduction in insulin clearance to ID4 (-68% for ID4 vs. -52% for ID2, P=0.04).

Conclusions: Gastric emptying affects the magnitude of the IE by impacting both insulin secretion and clearance.
Blockade of glucagon-like peptide-1 receptors by exendin(9-39) attenuates the increase in heart rate during small intestinal glucose infusion in type 2 diabetes

**Tongzhi Wu**1,2, **Chris Rayner**1,3, **Michael Horowitz**1,2, **Karen Jones**1,2
1. Discipline of Medicine, The University of Adelaide, Adelaide, SA, Australia
2. Centre of Research Excellence in Translating Nutritional Science to Good Health, The University of Adelaide, Adelaide, South Australia, Australia

**Introduction:** Glucagon-like peptide-1 (GLP-1) and its mimetics have been shown to increase heart rate (HR) in both health and type 2 diabetes (T2DM). However, it remains unclear whether this effect is attributable to GLP-1 receptor signaling and, if so, whether endogenous GLP-1 modulates cardiovascular function through this pathway, particularly during the postprandial phase. Given that postprandial GLP-1 secretion is determined in part by the rate of gastric emptying, which varies substantially between individuals and is also modulated by GLP-1, we evaluated the HR and blood pressure (BP) responses to a standardised jejunal glucose infusion, with and without the GLP-1 receptor antagonist, exendin(9-39), in patients with T2DM.

**Methods:** 10 T2DM patients were each studied on two days, separated by ≥7 days, in a double-blind, randomised fashion. On each day, a nasojejunal catheter was positioned. An intravenous exendin(9-39) (600pmol/kg/min) or saline was commenced 60min before, and maintained during, a 120-min intrajejunal glucose infusion (2kcal/min). HR and BP were measured every 5min, using an automated device. On one day, autonomic function was assessed using standardised cardiovascular reflex tests.

**Results:** None had cardiovascular autonomic dysfunction. Prior to jejunal glucose infusion, neither HR nor BP differed between the two study days. During jejunal glucose infusion, HR increased on both days (time effect: P<0.001), and the magnitude of increase was less with exendin(9-39) compared with saline (treatment effect: P=0.009). Systolic and diastolic BP both decreased slightly (P<0.001 and =0.002 respectively) during jejunal glucose infusion, without any difference between the two study days.

**Conclusion:** In relatively well controlled, normotensive patients with T2DM, without autonomic dysfunction, blockade of GLP-1 receptors by exendin(9-39) attenuates the HR response to small intestinal glucose infusion. These observations are indicative of a physiological role of GLP-1 receptor signalling in the regulation of postprandial cardiovascular function in T2DM.

The effect of a high egg diet on cardiovascular risk factors in people with type 2 diabetes during weight loss and weight maintenance: the randomized DIABEGG study

**Nicholas R Fuller**1, **Amanda Sainsbury**1, **Ian D Caterson**1, **Gareth Denyer**2, **Andrzej Januszewski**2, **Tania P Markovic**4, **Alicia Jenkins**5
1. Endocrinology, Royal Prince Alfred Hospital, Camperdown
2. School of Life and Environmental Sciences, University of Sydney, Sydney
3. NHMRC Clinical Trials Centre, University of Sydney, Sydney
4. Metabolism & Obesity Services, Royal Prince Alfred Hospital, Sydney, NSW, Australia
5. Cancer Epidemiology and Prevention Research, The University of Sydney, Sydney, NSW, Australia

**Background:** Contrary to epidemiological evidence, and some guidelines recommending that people with type 2 diabetes mellitus (T2DM) limit their consumption of eggs and/or dietary cholesterol, our published three-month weight maintenance study (Fuller N et al AJCN 2016) demonstrated that a high egg (HiEgg, ≥12 eggs/week) versus low egg diet (LoEgg, <2 eggs/week), did not have any adverse effects on cardiometabolic risk factors in people with T2DM.

**Objective:** To determine the effects of a high versus low egg diet on cardiometabolic risk factors during a weight loss programme over 9 months, following the 3-month weight maintenance period.

**Design:** 128 subjects with pre-diabetes or T2DM commenced the weight loss phase of the study, attending the clinic monthly from 3 to 6 months. They were prescribed a daily energy restriction of 2.1 MJ and instructed on specific types and quantities of food to be consumed as per their allocated diet. They were reviewed at 9 and 12 months.

**Results:** From 3 to 12 months there was similar weight loss (HiEgg -3.1±6.3 vs LoEgg -3.1±5.2 kg, p=0.48). Cholesterol intake was significantly higher in the HiEgg group, but otherwise nutritional intakes were similar. There were no differences in serum lipids, in particular, LDL cholesterol was marginally reduced from 3 to 12 months in both groups (HiEgg -0.04±0.78, LoEgg -0.01±0.90, p=0.77). The high egg diet did not have any adverse effect on serum levels of inflammatory markers (hsCRP, Interleukin-6, E-selectin), cardiovascular risk factors (including isoprostanes and adiponectin) or glycemic control over 12 months.

**Conclusions:** Individuals with pre-diabetes or T2DM on a high egg diet for 12 months exhibited no adverse changes in cardiometabolic markers compared to participants on a low egg diet. It appears that a diet including more eggs than is recommended by some countries may be consumed by this population while on a healthy diet.

Intergenerational impact of type 2 diabetes on First Nations Families and Communities: Lessons from The Next Generation Canadian birth cohort.

**Brandy Wicklow**1
1. University of Manitoba, Winnipeg, MANITOBA, Canada

T2D in childhood continues to increase worldwide and is associated with significant lifetime morbidity and the early development of complications, including retinopathy, neuropathy, and nephropathy. A disproportionate number of affected children reside in Manitoba, Canada. In 2010-2011,
the annual incidence rate of childhood-onset T2D was 25 per 100,000 children in Manitoba, 20-fold higher than in other provinces across Canada. The First Nation people in Manitoba have the highest reported incidence of T2D in children in the world, with rates up to 400/100,000 children. A private polymorphism in the First Nation population, HNF1α G319S, is an important risk factor found in approximately 42% of the children with T2D in our province. Our community knowledge users, patient and parent advisory committee and stakeholder advisory committee have identified the early detection of children at risk of T2D, the determination of modifiable pathways in the natural history of childhood T2D, and focused community based intervention programming as research health priorities for the DREAM (Diabetes Envisioned and Accomplished in Manitoba) clinical and basic science research group at the Children’s Hospital Research Institute of Manitoba (CHRIM). The Next Generation Cohort is a unique First Nations prospective birth cohort designed to address these research priorities by examining metabolic and anthropometric outcomes of offspring born to mothers or fathers diagnosed in childhood with T2D. To date, 226 children of 78 mothers with T2D and 18 fathers with T2D have been enrolled in the cohort. This talk will describe the Canadian experience of type 2 diabetes in children including findings from the Next Generation birth cohort study.

Population level application of price discounts to promote healthy eating: The SHOP@RIC study

Julie Brimblecombe
1. MENZIES SCHOOL OF HEALTH RESEARCH, CASUARINA, NT, Australia

Globally, diet is the leading risk for burden of disease. Diet is poorer and burden of disease higher for socio-economically disadvantaged populations in high and middle income countries. Strategies are urgently needed to address this inequity. We examined the effectiveness of a 20% price discount on selected purchases with and without nutrition education, delivered in store in remote Indigenous communities in Australia. A stepped-wedge randomised design was used, with 20 communities randomly assigned to 5 sets of 4 communities, spaced eight weeks apart. A 20% price discount on fresh and frozen fruit and vegetables, water and diet soft-drinks was applied for a period of 24 weeks in the community store. Two stores in each set were randomly assigned to receive a combined strategy (discount and education). Intervention effect was measured using mixed models employing weekly point-of-sale data for 131 weeks. The primary outcome was the percent change in fruit and vegetable purchases (grams) per person per day. The effect of applying the price discount was to increase sales of fruit and vegetables combined by 13% (4, 22), fruit 21% (7, 36), vegetables 9% (1, 17), water 18% (1, 37), diet soft drink 5% (-6, 18), other foods 6% (-1, 13), regular soft drinks 6% (-3, 15) and other drinks 5% (-5, 15). The benefit of the in-store consumer nutrition education strategy was a further small increase in vegetable sales. Consistent with other studies, a price discount alone can shift food purchasing in low socio-economic communities.

DESMOND WA – working with communities to adapt educational resources

Helen Mitchell
1. Diabetes WA, Subiaco, WA, Australia

Not available at time of printing

Working with communities Aboriginal community leader’s perspective

Glenn Pearson
1. Telethon Kids Institute, Subiaco, WA, Australia

Not available at time of printing

Diet and diabetes: what have genetic studies taught us about causal effects?

Elina Hypponen
1. UniSA, Adelaide, ACT, Australia

Diet, nutrition and our lifestyles are known to affect both the risk of type 1 and type 2 diabetes but evidence for causality of association remains uncertain for many of the proposed factors. Studies using genetic markers as proxy indicators for modifiable exposures (“Mendelian randomisation”) are increasingly used to test for causality between proposed risk factors and disease risk. This talk examines whether common nutritional factors characteristic to our modern lifestyles appear to be truly diabetogenic, and reviews genetic epidemiological evidence relating to the causal role of obesity, vitamin D, coffee and alcohol in diabetes.
Support for the “common disease-rare variant” hypothesis: a mutation in the ahcy gene causes type 1 diabetes

Grant Morahan¹
1. Harry Perkins Institute of Medical Research, Nedland, WA, Australia

Advances in genetic technologies over the last decade have allowed discovery of over 50 genetic variants that contribute to the risk of type 1 diabetes (T1D). Despite this success, these variants still do not account for the total genetic risk of developing this disease. To account for this “missing heritability”, the “Common Disease-Rare Variant” hypothesis has been proposed. This postulates that diseases may be caused by rare DNA variants which have a higher individual impact on disease risk than the known common variants. However, such rare variants have not yet been discovered because different people with the same common disease have rare variants in different genes.

We investigated an unusual family which has members over five generations that have developed T1D. DNA samples were genotyped from affected and unaffected family members and selected samples from family members from three different generations also had whole-exome sequencing. Linkage studies were inconclusive (due to lack of power) but shared haplotype analyses indicated only one region was shared by all six affected family members.

This region contained six novel genetic variants. One of these is in the gene encoding the enzyme S-adenosyl-homocysteine hydrolase. Characterization of the effects of this mutation will be presented.

Systems methylome approach identifies core pathways implicating MTOR in disease progression to diabetic nephropathy

Assam El-Osta¹
1. Baker IDI Heart & Diabetes Institute, Melbourne, VIC, Australia

There is considerable controversy regarding the epigenetic control of genes implicated in type 1 diabetes and its complications. We show CTCF binding sites are sensitive to loss-of-methylation with gain-of-function in diabetes. This strengthens the evidence base against methylation changes just being an epiphenomenon with the identification of gene targets that contribute to the pathogenesis of diabetic nephropathy.

Insights into the human beta-cell from genetics

Andrew Hattersley¹
1. University of Exeter, Exeter, DEVON, United Kingdom

Not available at time of printing

Opportunities & Challenges with Real World Clinical Clinical Data and the Regulatory Initiative

Sanjoy Paul¹, Jonathan Shaw²
1. QIMR Berghofer Medical Research Institute, Brisbane, Australia, ACT, Australia
2. Baker IDI, Melbourne

Recently FDA has taken initiative encouraging the use of real world data (RWD) for regulatory submissions. High quality RWD may be sufficient for use in premarket and postmarket regulatory decisions, without changing the standards used to make those decisions. This brings in new opportunities and challenges in terms of a new innovative and cost effective approach to design clinical trials and observational studies.

I am proposing to organise a dedicated symposium on the usages and advantage of using large primary and ambulatory care based patient-level RWD to conduct clinical studies including late phase studies. The proposed symposium will include presentation on (1) international scenario in the use of real world primary / ambulatory care data to generate much needed population level evidences; (2) the context and new opportunities with the FDA initiative of using RWD; (3) the opportunities and challenges in designing late phase clinical trials and observational studies with RWD; and (4) the Australian scenario with RWD. We can have a dedicated talk from 2 presenters with opportunities for interactive discussions.

For about a decade now, I have been leading pharmaco-epidemiological studies in diabetes with large patient level RWD from UK and USA, in corroboration with international academic and pharma collaborators.
Tips and tricks to enhance your consultations

Ann Morris¹, Christel Hendrieckx²
1. AMCON Diabetes Management Services, Warrnambool, Vic, Australia
2. School of Psychology, Deakin University, Burwood, Victoria, Australia

Increasingly, diabetes guidelines recommend ‘psychological’ care to be incorporated into diabetes pathways. It has become clear that an approach focused on diabetes treatment and complication screening is not achieving the expected outcomes. However, practical guidance on how to change clinical practice, is limited. The NDSS ‘Diabetes and emotional health’ handbook published in 2016, will be used as a reference for this masterclass.

For who?
Health professionals working in diabetes (e.g. GPs, endocrinologists, diabetes educators, dieticians)

• who are aware that diabetes management and outcomes are intertwined with a person’s emotions, lifestyle and behaviours,
• who believe these psycho-social components should be part of the conversations they have with people with diabetes
• but who struggle to let go of their habits to work through a ‘tick box list’.

What will be the outcome?
Enhanced skills and confidence to make small but significant changes to your clinical practice.

How?
Practical approach making use of case studies of adults with diabetes to demonstrate how to ask and talk about psycho-social issues.

Input of participants?
Health professionals enrolled in this masterclass will be invited to read material, reflect on their practice/skills beforehand and bring case studies they would like to discuss with their colleagues.

Max 50 Health professionals

Statistics in plain English

Helen Barraclough¹
1. Eli Lilly Australia, Sydney, NSW, Australia

This interactive masterclass translates commonly reported statistics into plain English. For example:

• What does a hazard ratio tell us?
• How can superiority be claimed?
• How is a non-inferiority margin determined?
• How do I know which method should be used?
• What’s the difference between efficacy and effectiveness?

Examples of what good looks like, plus common mistakes are also covered. The aim is that you will become more confident in critically reviewing clinical papers, and gain some real-life insight into the challenges of designing and analyzing studies.

Diabetic Kidney and Vascular Disease: Evaluating Novel Biomarkers in Type 2 Diabetes

Richard J MacIsaac¹
1. Department of Endocrinology & Diabetes, St Vincent’s Hospital Melbourne and University of Melbourne, Fitzroy, VIC, Australia

Diabetic Kidney Disease (DKD) is the leading cause of end-stage renal disease (ESRD) in Australia. Furthermore, individuals with DKD are at significant risk of cardiovascular (CV) morbidity and mortality, underscoring the importance of early identification, prevention and treatment. It is therefore imperative that patients with diabetes at the greatest risk for a progressive decline in glomerular filtration rate (GFR) are accurately identified so that the management of their risk factors for worsening renal function are optimized. Current clinical risk markers, such as albuminuria, lack predictive accuracy for determining a patient’s risk for a progressive decline in GFR. Furthermore, a significant number of patients with diabetes are now recognized as following a non-albuminuric pathway to renal impairment. Several promising novel serum and urine biomarkers may help to stratify risk for developing progressive DKD in patients with type 2 diabetes. The overall aims of this study are to determine (i) the temporal relationships between changes in novel risk markers and a decline in GFR and (ii) whether novel risk markers improve risk prediction for renal-related events, CV death and all-cause mortality over and above that of traditional risk markers in patients with diabetes. Our preliminary studies suggest that circulating levels of the type 1 tissue necrosis factor receptor (TNFR1) increase as estimated GFR (eGFR) declines...
independently of albuminuria. Changes in sTNFR1 levels also improved prediction of eGFR decline on top of established risk markers for progression of DKD. Circulating levels of the urokinase plasminogen activator receptor (suPAR) also increase as eGFR declines but whether measuring this biomarker results in an incremental improvement on top of established risk markers for predicting eGFR decline remains to be fully defined. Currently, the potential of uric acid and urinary monocyte chemotactic protein-1 as potential biomarkers for progressive DKD are also being investigated.

Predictors of albumin to creatinine ratio (ACR) among Indigenous Australian participants in the eGFR follow up study

Elif I. Ekinci1, 2, Federica Barzi1, Jaqui Hughes1, 4, Elizabeth Barr3, 5, Paul D Lawton3, Graham R Jones4, Wendy Hoy7, Alan Cass3, Mark Thomas8, George Jerums1, 2, Kerin O’Dea9, Richard Maclsaac10, 11, Louise Maple-Brown3, 4
1. Austin Health, Heidelberg West, VIC, Australia
2. Department of Medicine Austin Health, University of Melbourne, Melbourne, VIC, Australia
3. Menzies School of Health Research, Darwin, Northern Territory, Australia
4. Division of Medicine, Royal Darwin Hospital, Darwin, Northern Territory, Australia
5. Baker Heart and Diabetes Institute, Melbourne
6. SydPath, St Vincents Hospital, Sydney, NSW, Australia
7. University of Queensland, Brisbane, Queensland, Australia
8. Royal Perth Hospital, Perth
9. University of South Australia, Adelaide, South Australia, Australia
10. Department of Endocrinology and Diabetes, St Vincents Hospital, Melbourne, Victoria, Australia
11. University of Melbourne, Melbourne, Australia

Background
Macroalbuminuria is associated with kidney function loss in Indigenous Australians, however, no studies have examined the association of albuminuria at follow up with the presence of hyperfiltration at baseline, based on direct measurements of glomerular filtration rate (GFR) in this population.

Aims
To determine the risk factors (including glomerular hyperfiltration) contributing to an increase of ACR after 3 years follow-up in Indigenous Australians.

Methods
Study participants were grouped into baseline mGFR < 90 mL/min/1.73m², mGFR 90-125 mL/min/1.73m², mGFR > 125 mL/min/1.73m² (hyperfiltration group) categories. Multivariable regression models were used to assess the association between the log of follow-up ACR (FuACR), mGFR levels and other factors after adjusting for age, gender and baseline log ACR. Results were expressed in terms of percent change of ACR from baseline to follow-up.

Results
This analysis included 407 individuals (32.5% male, mean age 47 years) followed up after a median of 3 years. At baseline, 77 individuals had hyperfiltration, 191 had normofiltration (mGFR 90-125mL/min/1.73m²) and 139 had chronic kidney disease (CKD) stage 2 or below (mGFR<90mL/min/1.73m²). Each 10% higher baseline ACR was associated with a 8.5% (95% CI: 7.9-9.1%) increase in FuACR and each 1% increase in HbA1c was associated with a 13% (95% CI: 6-20%) increase in FuACR, whereas presence of hyperfiltration at baseline was not associated with higher FuACR. There was a weak association with DBP showing a 6.7% (p=0.02) increase in FuACR for each 5mmHg lower DBP, this association was not seen on a sensitivity analysis restricted to those not on antihypertensive medications.

Conclusions
Higher baseline ACR, higher baseline HbA1c and lower baseline diastolic blood pressure predicted and baseline hyperfiltration did not predict higher ACR levels in Indigenous Australians after a 3 year follow-up. Longer follow-up is necessary to determine the prognostic value of hyperfiltration in this population.

Validation of models for predicting rapidly declining renal function in type 2 diabetes: the Fremantle Diabetes Study Phase II

Kirsten E Peters1, 2, Wendy A Davis5, Jason Ito3, Kaye Winfield3, Thomas Stoll2, Scott D Bringans3, Richard J Lipscombe3, Timothy ME Davis1
1. Medical School, University of Western Australia, Perth, Western Australia, Australia
2. Proteomics International, Perth, Western Australia, Australia

There is a need for earlier detection of individuals at risk of chronic kidney disease (CKD) to optimise timely intervention and monitoring of disease progression. In a previous study we identified circulating protein biomarkers (APOA4, CD5L, C1QB, and IBP3) that improved clinical models for predicting rapid decline in estimated glomerular filtration rate (eGFR). The aim of the present study was to validate these models in an independent cohort of patients with type 2 diabetes.
A mass spectrometry platform was used to measure baseline biomarkers in 792 participants from the longitudinal observational Fremantle Diabetes Study Phase II. Rapid eGFR decline was defined as i) incident CKD, ii) eGFR decline ≥30% over four years, iii) annual eGFR decline ≥5 mL/min/1.73m², and iv) eGFR declining trajectories. Prediction models were developed using multiple logistic regression in a training cohort (n=345) before validation in an independent cohort (n=447). Model performance was assessed in the validation cohort by comparing model predictions to actual outcomes using indices of discrimination (ROC-AUC) and calibration (Hosmer-Lemeshow goodness-of-fit test).

The development and validation cohorts had similar baseline eGFR (80.6±18.8 vs 82.7±16.9 mL/min/1.73m², respectively), but differed in age and diabetes duration (P=0.05). During 4.2±0.3 years of follow-up, 5-10% of participants experienced rapid eGFR decline. Applied to the validation cohort, the best performing model was for incident CKD (AUC=0.88 (95%CI 0.84-0.93)); calibration chi-square=5.7, P=0.77). At the optimal score cut-off, this model provided 86% sensitivity, 78% specificity, 30% positive predictive value and 98% negative predictive value to predict four year risk of developing CKD.

The present study assessed and validated the prognostic utility of novel plasma biomarkers for prediction of rapidly declining kidney function in type 2 diabetes. These prediction models may be useful for risk stratification in future clinical trials and incorporation into clinical decision making.

---

### Liraglutide and renal outcomes in type 2 diabetes: results of the LEADER trial


1. Endocrinology and Diabetes, St Vincent's Hospital & University of Melbourne, Fitzroy, Victoria, Australia
2. Friedrich Alexander University of Erlangen, Erlangen, Germany
3. Novo Nordisk A/S, Søborg, Denmark
4. Massachusetts General Hospital, Boston, MA, USA
5. St. Josef Hospital, Ruhr University, Bochum, Germany
6. Cleveland Clinic, Cleveland, OH, USA
7. London School of Hygiene and Tropical Medicine, London, UK
8. Imperial College London, London, UK
9. George Washington University Medical Center, Washington DC, USA
10. Lunenfeld–Tanenbaum Research Institute, Mt. Sinai Hospital, University of Toronto, Toronto, ON, Canada
11. International Diabetes Center at Park Nicollet, Minneapolis, MN, USA
12. University of Texas Southwestern Medical Center, Dallas, TX, USA
13. University of North Carolina School of Medicine, Chapel Hill, NC, USA

**LEADER was a randomised, double-blind, placebo-controlled trial comparing the cardiovascular safety of liraglutide versus placebo, both on a background of standard of care, in participants with type 2 diabetes and high cardiovascular risk. This subanalysis of the LEADER trial examined clinically relevant renal outcomes.**

Renal events were key secondary outcomes of the LEADER trial. The primary renal outcome of interest was a composite of incident persistent macroalbuminuria, persistent doubling of serum creatinine, end stage renal disease (ESRD), or death due to renal disease. Risk of renal outcomes was determined using intention-to-treat in time-to-event analyses; competing risk of death was taken into account. Changes in estimated glomerular filtration rate (eGFR) and albuminuria were also analysed.

In total, 9340 patients were randomised; median follow-up: 3.84 years. The primary renal outcome occurred in fewer participants treated with liraglutide (268 of 4668) than with placebo (337 of 4672; hazard ratio [HR] 0.78 [0.67-0.92] p=0.003). The difference was primarily driven by new onset of persistent macroalbuminuria, occurring in fewer liraglutide-treated participants (161 of 4668) than placebo-treated (215 of 4672; HR 0.74 [0.60;0.91]) p=0.004). Doubling of serum creatinine and ESRD tended to be less frequent with liraglutide (although this trend was statistically non-significant); eGFR decreased significantly less and albuminuria increased less with liraglutide than placebo. The difference in change of eGFR was driven exclusively by the subgroup with eGFR 30–59 ml/min at baseline (N=1934). The difference in change of albuminuria was independent of baseline eGFR or albuminuria.

Liraglutide, in addition to standard of care therapy, reduced the progression of diabetic nephropathy.

---

### Associations between glycaemic status and renal function decline over time in inpatients with diabetes


1. Department of Endocrinology, Austin Health, Melbourne, VIC, Australia
2. Department of Medicine, University of Melbourne, Melbourne, VIC, Australia
3. Florey Institute of Neuroscience and Mental Health, University of Melbourne, Melbourne, VIC, Australia
4. Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia
5. Department of Administrative Informatics, Austin Health, Melbourne, VIC, Australia
6. Austin Health, Melbourne, VIC, Australia

---
Introduction:
Diabetes is the leading cause of end-stage kidney disease. We investigated the association between glycaemic status defined categorically or using HbA1c as a continuous variable, with decline in renal function over time in inpatients admitted to Austin Health.

Methods:
In this prospective, observational cohort study, all patients ≥54 years admitted 2013-2016 had an HbA1c measurement as part of the Diabetes Discovery Initiative. Only patients with two or more admissions were included in the current analysis. Baseline clinical and biochemical characteristics were obtained. To define the degree of renal function change, patients were classified into three groups based on the Acute Kidney Injury Network (AKIN) classification which utilises changes in the serum creatinine and estimated glomerular filtration rate (eGFR) over time. Results were analysed using robust and negative binomial regression.

Results:
Following exclusion of episodes with missing data or single admissions (n=22,162), 9300 admissions were identified. 25%, 39% and 36% of the inpatients had diabetes, pre-diabetes and no diabetes respectively. 41% of patients experienced some degree of kidney injury (AKIN1-3). After correcting for age, Charlson comorbidity index (excluding diabetes and age), haemoglobin and number of days between first and last admission, presence of diabetes, categorically and using HbA1c level as a continuous variable were significantly associated with decline in renal function defined as higher creatinine and lower eGFR ratio between first and last admission (p<0.001).

Conclusion:
Presence of diabetes, defined categorically and with higher HbA1c levels was associated with higher risk of long term decline in renal function. While glycaemic control is an important factor associated with renal function decline, interventional studies aimed to prevent further decline in renal function over time are required in inpatients with diabetes.

Table 1 - Incidence of Kidney Injury based on AKIN classification. eGFR: Estimated Glomerular Filtration Rate, AKIN: Acute Kidney Injury Network classification

<table>
<thead>
<tr>
<th>Degree of Kidney Injury</th>
<th>Diabetic</th>
<th>Pre-diabetic</th>
<th>No Diabetes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No injury</td>
<td>54.9%</td>
<td>58.7%</td>
<td>62.9%</td>
<td>59.3%</td>
</tr>
<tr>
<td>AKIN 1 (GFR Ratio 50-75%)</td>
<td>28.9%</td>
<td>27%</td>
<td>23.4%</td>
<td>26.2%</td>
</tr>
<tr>
<td>AKIN 2 (GFR Ratio 25-50%)</td>
<td>13.3%</td>
<td>11.2%</td>
<td>10.2%</td>
<td>11.4%</td>
</tr>
<tr>
<td>AKIN 3 (GFR Ratio&lt;25%)</td>
<td>2.7%</td>
<td>2.9%</td>
<td>3.3%</td>
<td>3%</td>
</tr>
</tbody>
</table>
Effect of angiotensin II receptor blocker (ARB) and dietary sodium chloride (NaCl) on short-term blood pressure variability in patients with type 2 diabetes (T2DM)

Angela X Chen¹, John Moran², Sara Baqar³,⁴, Christopher O'Callaghan⁴,⁵, Richard J Maclissac⁴,⁵, George Jerums⁴, Elif I Ekinci³,⁴,⁷

1. Department of Endocrinology, Austin Health, Melbourne
2. Queen Elizabeth Hospital, Adelaide, SA, Australia
3. Endocrinology, Austin Health, Heidelberg, Victoria, Australia
4. Department of Medicine, University of Melbourne, Melbourne
5. Department of Clinical Pharmacology, Austin Health, Melbourne
6. Department of Endocrinology, St Vincent's Health, Fitzroy
7. Menzies School of Public Health, Darwin

Increased blood pressure variability (BPV) is associated with increased cardiovascular risk [1]. Previous studies have explored the effects of various humoral, environmental and neural factors on BPV in the general population. However, the effect of salt supplementation and renin angiotensin system (RAS) activity on BPV in type 2 diabetes (T2DM) is poorly understood.

We aimed to determine the effect of sodium chloride (NaCl) supplementation on 24-hour mean arterial BPV (24hBPV, i.e. short-term blood pressure variability) in the setting of angiotensin II receptor blocker (ARB), telmisartan use and the effects of age, sex, plasma renin activity (PRA) and serum aldosterone on 24hBPV.

In a randomised, double-blind, crossover study, patients with T2DM (n=28), treated with telmisartan 40 mg for a total four weeks received NaCl (100 mmol/24 hr) or placebo capsules in the final two weeks of ARB use. Following a six-week washout, the protocol was repeated in reverse.

24hBPV was evaluated as a coefficient of variation (CV(%) = [mean/standard deviation] x100). 24 hour urinary sodium excretion (24hUNa), ambulatory blood pressure and biochemical tests were performed at each phase. Results were analysed using a linear mixed model.

24hBPV was higher with telmisartan vs predicted baseline (p=0.01), with a trend towards reduced 24hBPV with NaCl supplementation (predicted BPV telmisartan and placebo 11.69% vs predicted BPV telmisartan and NaCl 10.56%, p=0.052). 24hBPV was lower in females (females vs males -0.537%, p=0.17) with increasing age (-0.020% per year age, 95% CI -0.31 to -0.009, p=0.001) and PRA (-0.015% per unit PRA, 95% CI -0.265 to -0.004, p=0.011). SBP and BPV did not correlate.

In patients with T2DM, 24hBPV was higher with telmisartan use, however there was a trend towards reduced 24hBPV with NaCl supplementation. Of the antihypertensive classes, ARBs may not be as effective at lowering 24hBPV as calcium channel blockers or diuretics.

Determining the diagnostic accuracy of the ankle brachial index for detecting peripheral arterial disease in people with diabetes: A systematic review and meta-analysis.

Vivienne H Chuter¹, Alex L Barwick², Peta E Tehan¹, Angela T Searle¹, Lucy Leigh³, Nathan A Johnson⁴, Stephen M Twigg⁵

¹. Discipline of Podiatry, University of Newcastle, Ourimbah, NSW, Australia
². School of Health and Human Sciences, Southern Cross University, Gold Coast, QLD, Australia
³. Clinical Research Design, IT and Statistical Support, Hunter Medical Research Institute, Newcastle, NSW, Australia
⁴. The Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia
⁵. Faculty of Health Sciences, University of Sydney, Lidcombe, NSW, Australia

Background: In diabetes cohorts, diagnostic accuracy of the ankle-brachial index (ABI) for peripheral arterial disease (PAD) has been reported to be variable. This review systematically evaluated the literature investigating the diagnostic accuracy of the ABI for PAD in people with diabetes including utilising meta-analysis where possible.

Methods: A database search of EBSCO Megafile Premier, EMBASE, and The Cochrane Library was conducted to 30th December, 2016. Prospective and retrospective investigations of diagnostic accuracy of the ABI for PAD in people with diabetes using an imaging reference standard were eligible. Study quality was assessed with the revised Quality Assessment of Diagnostic Accuracy Studies tool.

Results: In total 6249 citations were retrieved, and after serial systematic exclusions, 22 studies included. Ten studies compared ABI to angiography, and 12 studies to colour Doppler ultrasonography (CDU). Six studies were retrospective. Primary sources of bias were: inadequate reporting of blinding and risk of spectrum bias. A meta-analysis (mean sensitivity, specificity and receiver operating characteristic [ROC] curve and area under the curve [AUC]) was performed for studies using CDU. For studies using angiography, a standard summary ROC curve was calculated and the AUC derived from this. For CDU studies, sensitivity was 0.56 (95%CI:0.43 to 0.67), specificity was 0.88 (95%CI:0.77 to 0.94) and the AUROC was 0.66 (95%CI:0.52 to 0.74). For angiography studies, sensitivity ranged from 0.50 to 0.91 and specificity 0.40 to 0.89. The AUROC was 0.79 (95%CI:0.68 - 0.90).

Conclusion: Diagnostic accuracy of the ABI for PAD is better compared to angiography than CDU. This is likely to be due to high incidence of disease in study populations undergoing angiography. These findings suggest the ABI has limited use as a screening tool in community-based diabetes populations especially due to low sensitivity, but, has clinical utility where there is a strong suspicion of disease.

Primary care-based diabetic retinopathy screening identifies early intervention opportunities - on behalf of the TEAMSnets Study Group and the CRE in Diabetic Retinopathy

Laima Brazionis¹, Alicia Jenkins², Tony Keech², Chris Ryan², Sven-Erik Busseit³

¹. The University of Melbourne, Melbourne, VIC, Australia
². Clinical Trials Centre, The University of Sydney, Sydney, NSW, Australia
³. Telehealth Unit, University of Hawaii, Hawaii, USA

Background: Telehealth-based diabetic retinopathy [DR] screening was conducted in a remote Australian [Alice Springs, NT] primary care clinic of an Aboriginal community-controlled health organization [ACCHO] as part of the Telehealth Eye and Associated Medical Services Network [TEAMSnetsn] study. The purpose was to use a telehealth approach to determine DR prevalence and facilitate diabetes care in a remote Aboriginal community.

Methods/Design: Diabetes status was determined clinically. A flexible multi-field, image-based DR screening protocol was undertaken in 2013-2015 in Indigenous Australian adults with type 2 diabetes by trained imagers, locally, and expert graders, remotely, at the Centre for Eye Research Australia, Melbourne. TEAMSnets DR screening was a multi-purpose tool for diabetes education/patient engagement, diabetes risk stratification and detection of ‘any DR’ and ‘treatable DR’.

Results: Among the 301 Indigenous Australians aged 19-86 years (33% male) screened, diabetes duration [median (range)] was 9 (0-24) years. Gradable imaging-study rates [% (n)] were 78.7% (237) for DR and 83.4% (251) for diabetic maculopathy [DM]. The crude prevalence of any DR was 46.4% (110) and of DM was 14.4% (36). Prevalence of sight-threatening DR [STDR] was 16.1%, of which 2.1% (5) [0.4% (1) untreated] was proliferative DR and 14.0% (35) [3.2% (8) untreated] was clinically-significant DM.

Conclusion: Any DR and STDR seem more prevalent in this Aboriginal community than reported in other Indigenous studies [21.0-39.4% and 7.0-15.2%, respectively] and in the broader Australian population [19.8-33.6% and 7.4-11.4%, respectively]; but treatment coverage is comparable with recent national data [75-79%]. Importantly, TEAMSnets implemented an effective DR screening program that not only detected STDR, but also identified clinical and patient-based intervention opportunities via earlier detection of non-STDR using a primary care-centric, multi-field imaging approach. Consequently, consideration of Indigenous-specific primary care guidelines for DR management in remote settings is merited.

Type 1 diabetes: a disease of developmental origins?

Jennifer Couper¹

¹. Women’s and Children’s Hospital, Adelaide, SOUTH AUSTRALIA, Australia

The incidence of type 1 diabetes in children has increased rapidly over the last 50 years. Proposed environmental reasons for this increase mirror our modern lifestyle. Type 1 diabetes can be viewed as part of the non-communicable disease epidemic in our modern society. Meanwhile rapidly evolving new technologies are advancing our understanding of how human microbial communities interface with the immune system and
Lessons from the crime scene: steps towards a cellular biomarker of type 1 diabetes and the response to antigen-specific therapy

Michelle So1, V Pathiraja, E Tresoldi, A Ware, C Elso, JM Wentworth, LC Harrison, D Simpkins, TW Kay, S Mannering

1. St Vincent's Institute of Medical Research, Fitzroy, VIC, Australia

Type 1 diabetes (T1D) is primarily an autoimmune disease of beta cells in the pancreatic islets and secondarily a metabolic disorder of impaired glucose metabolism due to insulin deficiency. Beta cell autoimmunity can be detected many years before the development of hyperglycaemia, providing opportunities for immune therapy to prevent T1D.

To date, islet autoantibodies are the only fully validated and clinically useful immune markers of T1D. Autoantibodies confirm the diagnosis of T1D and are risk markers for the development of T1D. However, autoantibodies are not thought to be pathogenic. In contrast, autoreactive CD4+ T cells, orchestrate autoantibody responses, and are pathogenic. The identification of T-cell biomarkers would therefore improve our understanding of T1D pathogenesis and provide opportunities to monitor responses to investigational immune therapies. Identifying such markers is challenging, however, because autoreactive T cells are rare in the blood and clinically relevant beta cell antigens and epitopes have not been defined.

This presentation will describe the CD4+ T-cell antigens we have identified by studying human islet-infiltrating CD4+ T cells. Analysis of these cells revealed that many recognized epitopes derived from proinsulin presented by HLA-DQ8. The location of these islet-infiltrating CD4+ T cells at the site of autoimmune destruction, “the scene of the crime”, their HLA-DQ8 restriction and specificity for proinsulin all point to these cells having a pathogenic role in human T1D. The application of these findings to T-cell biomarker development and the monitoring of disease progression will be discussed.

Randomised trial of imatinib in recent-onset type 1 diabetes: one-year outcomes

John Wentworth1

1. Walter and Eliza Hall Institute of Medical Research, Parkville, VIC, Australia

Imatinib is a tyrosine kinase inhibitor that is used to treat chronic myeloid leukaemia and has been observed to reduce insulin requirements in patients with diabetes. Subsequent studies showed imatinib normalises glucose in the type 1 diabetes NOD mouse. These observations lead us to perform a randomised controlled trial to determine whether imatinib could improve pancreatic beta-cell function in patients with recent-onset type 1 diabetes. Sixty-seven adult participants were randomised in a 2:1 ratio to imatinib 400mg daily or placebo within 100 days of their diagnosis. The treatment period was six months and the primary outcome was C-peptide response to a mixed meal at 12 months. Forty-three imatinib and 21 placebo participants attended the month 12 visit. When compared to the placebo group, active-arm participants had higher C-peptide at 12 months, used significantly less insulin and had similar HbA1c. There were no differences in the rates of serious side effects although the imatinib participants were more likely to experience mild illnesses, particularly asymptomatic leukopaenia and thrombocytopenia, and GI disturbance. These findings suggest imatinib may be a useful adjunctive therapy for recent-onset type 1 diabetes. Demonstration of ‘prospect of benefit’ will justify similar studies in children.

Can digital health programs really improve diabetes outcomes in populations?

Brian Oldenburg1

1. University of Melbourne, University Of Melbourne, VIC, Australia

Rapid advances in new technology and the widespread use of smart devices and wearables are empowering PWD to manage diabetes in new and exciting ways. Digital health programs can help educate, monitor, coach and provide peer support to PWD in ways that have not been previously possible. The increasing use of artificial intelligence, machine learning, big data and real time blood glucose monitoring and other wearable devices will also fundamentally change the ways in which PWD interact with their health professionals and other PWD in the future. The presentation will discuss the benefits and challenges of such approaches.
Using the technology toolbox to build a better diabetes service

Rebecca Johnson¹
1. Telethon Type 1 Diabetes Family Centre, Stirling, WESTERN AUSTRALIA, Australia
The Telethon Type 1 Diabetes Family Centre utilises technology in a variety of ways to deliver a responsive, agile support service and create a highly connected local diabetes community. This talk gives a snapshot of ways in which diabetes services can embrace and maximise the benefits of technology, and use it to support clinical services, deliver education with better reach, develop an empathetic and informed team, and encourage effective peer support.

Not available at time of printing

John Furler¹
1. University of Melbourne, Carlton, VIC, Australia
Not available at time of printing

The AdDIT trial: cardiorenoprotection in at risk adolescents with type 1 diabetes

M L Marcovitchio¹, D Daneman², S Dawson³, K C Donaghuë⁴, Tim W Jones⁵, F H Mahmud⁶, S M Marshall⁷, R N Dalton⁸, J Deanfield⁹, D B Dunger²
1. Department of Paediatrics, NIHR Cambridge Comprehensive Biomedical Research Centre and the Cambridge Clinical Trial Unit, University of Cambridge, Cambridge, UK
2. Department of Paediatrics, Division of Endocrinology, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada
3. Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK
4. Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, NSW, Australia
5. Princess Margaret Hospital for Children, Telethon Kids Institute & Princess Margaret Hospital for Children, Perth, WA, Australia
6. Department of Diabetes & Metabolism, The Medical School, University of Newcastle, Newcastle upon Tyne, UK
7. WellChild Laboratory, Evelina Children's Hospital, St Thomas' Hospital, London, UK
8. National Centre for Cardiovascular prevention and Outcomes, London, UK
9. University Department of Paediatric, Addenbrooke's Hospital, Cambridge, UK

The Adolescent Type 1 Diabetes Cardio-renal Intervention Trial (AdDIT) was a pragmatic clinical trial designed to explore the benefits and risks of angiotensin-converting–enzyme (ACE) inhibitor and statin treatment in adolescents with type 1 diabetes deemed to be at increased risk for complications of their diabetes, based on high urinary albumin-creatinine ratios. We screened 4407 adolescents (10-16 years), identifying 1000 in the upper tertile for albumin-creatinine ratios; 443 were randomized to a placebo-controlled trial of an ACE inhibitor and a statin using a 2x2 factorial design with minimization for baseline characteristics. The primary outcome for both interventions was change in albumin excretion, assessed by albumin-creatinine ratios in three early morning urine samples collected every 6 months over two to four years, and expressed as area under the curve. Key secondary outcomes included development of microalbuminuria, progression of retinopathy, changes in glomerular filtration rate, lipids and cardiovascular risk measures (carotid intima-media thickness, high-sensitivity C-reactive protein and asymmetric dimethylarginine). At baseline, the upper tertile of albumin excretion, although within the normal range, was associated with early evidence of microvascular and macrovascular disease. Overall drug adherence was 75%, and serious adverse events were similar across groups. Statin therapy resulted in significant reductions in total, LDL-, non-HDL-cholesterol, triglycerides and ApoB-Apo-A1 ratio. Overall drug adherence was 75%, and serious adverse events were similar across groups. Further results of the primary and secondary outcomes will be presented.

Cardiovascular outcomes: Are all SGLT2 inhibitors the same?

Timothy Davis¹
1. University of Western Australia, Fremantle, WA, Australia
There have been two recent placebo-controlled trials that have examined cardiovascular disease outcomes for sodium glucose cotransporter 2 (SGLT2) inhibitor therapy in type 2 diabetes, namely EmpaReg (empagliflozin) and CANVAS (canagliflozin), and more will close out in the next few years. Both EmpaReg and CANVAS showed very similar benefit for the conventional 3-point major adverse cardiovascular events (MACE) endpoint, as well as for heart failure hospitalisations and progression of renal disease, in patients allocated active therapy, but there were also differences. In EmpaReg, empagliflozin was associated with significant reductions in cardiovascular and all-cause mortality while there was no such benefit for canagliflozin-treated patients in CANVAS. There was a significantly increased risk of amputations with canagliflozin that was not seen with empagliflozin in EmpaReg. A numerical excess of non-fatal strokes was observed with active therapy versus placebo in EmpaReg while there were fewer strokes in canagliflozin-treated patients in CANVAS. While the two trials cannot be validly compared because of differences in study design, populations and protocols, the results do raise questions as to whether there are within-class differences between available SGLT2 inhibitors that may have clinical implications.
Constitutive knockout of Gpr21 inhibits the ex vivo migration of mouse immune cells

Darren M Riddy, Stephanie Simonds, Sanja Bosnyak-Gladovic, Stewart Fabb, Patricia Rueda, Patrick M Sexton, Roger J Summers, Michael Cowley, Christopher J Langmead
1. Drug Discovery Biology, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria, Australia
2. Department of Physiology, Faculty of Biomedical and Psychological Sciences, Monash University, Clayton, Victoria, Australia

Through immune cell infiltration into adipose tissue, chronic low-grade inflammation can develop and play a key role in the pathogenesis of obesity-induced insulin resistance. Insight into the mechanistic link between insulin resistance and inflammation has revealed the activation of various inflammatory receptors and signalling pathways. One such receptor is the orphan G protein-coupled receptor (GPCR), GPR21. Two independent studies show Deltagen Gpr21−/− mice have improved glucose tolerance and systemic insulin sensitivity compared with wild-type controls, primarily due to a reduction in tissue inflammation caused by impaired migratory capability of monocytes and macrophages into adipose tissue. However, during this study it was revealed that the Gpr21 gene resides within the intron of the RAB GTPase activating protein 1 (Rabgap1) gene, which is also disrupted in the Deltagen Gpr21−/− mice, making it unclear as to which gene might be responsible for the effects. Due to this controversy we developed a new Gpr21 knockout strain, using clustered regularly interspaced short palindromic repeats (Crispr) technology. Gene expression analysis of metabolic tissues from these Crispr animals, including the liver, adipose and spleen, revealed no effect on the Rabgap1 gene. Using bone marrow monocytes and intraperitoneal macrophages isolated from 8-week old Deltagen Gpr21−/− and Crispr Gpr21−/− animals fed normal chow, we observed the complete loss in the migratory capability of these cell types, compared to wild-type, in response to monocyte chemoattractant protein-1 (MCP-1) and leukotriene B4 (LTB4). These data indicate that GPR21 is involved in the chemotaxis of immune cells, however, the effect of a high fat diet is necessary to fully ascertain the importance of these findings. Targeting this receptor may prove beneficial for the treatment of type 2 diabetes and its complications including non-alcoholic fatty liver disease and steatohepatitis (NAFLD/NASH).


The metalloproteinase adam28 promotes metabolic dysfunction in humans and mice

Lakshini Herat, Caroline Rudnicks, Yasunori Okada, Joanne Curran, Matthew Johnson, Eric Moses, Harald Goring, Satsuki Mochizuki, John Blangero, Markus Schlaich, Vance Matthews
1. University of Western Australia, Perth, WA, Australia
2. Royal Perth Hospital, Perth, WA, Australia
3. Juntendo University, Tokyo, Japan
4. University of Texas Rio Grande Valley, Brownsville, Texas, USA
5. National Defense Medical College, Saitama, Japan

Background:
Obesity and diabetes are major causes of morbidity and mortality globally. Metalloproteinases which cleave pro-inflammatory mediators from the cell surface have previously been implicated in the pathogenesis of high fat diet-induced obesity.

Aim(s):
Firstly, we aimed to ascertain whether the metalloproteinase ADAM28 correlates with parameters of the metabolic syndrome in humans and mice. Secondly, we endeavoured to determine the mechanisms by which ADAM28 may contribute to metabolic dysfunction. Thirdly, we assessed the effects of limiting ADAM28 activity on parameters of the metabolic syndrome in mice.

Method(s):
To identify novel metalloproteinases associated with the metabolic syndrome, micro-array studies were conducted in a well characterised human cohort. In vitro studies were performed to ascertain novel substrates of ADAM28. In addition, ADAM28 was knocked down in mice fed a high fat diet and metabolic parameters were assessed. Finally, ADAM28 knock-out mice were metabolically phenotyped.

Result(s):
We found that ADAM28 expression levels in lymphocytes isolated from a large human cohort strongly correlated with parameters of the metabolic syndrome. In in vitro studies, human ADAM28 promoted TNF-alpha shedding. This was significantly reduced when ADAM28 was inhibited by siRNA knock-down. In murine investigations, ADAM28 mRNA and protein expression was markedly increased in the livers of mice with the metabolic syndrome. Downregulation of ADAM28 with siRNA technology resulted in a lack of weight gain, promoted insulin sensitivity and glucose tolerance and decreased liver TNF-alpha levels in our diet-induced obesity mouse model. Additionally, ADAM28 knock-down improved kidney function and reduced liver injury. Similar metabolic benefits were also observed in ADAM28 knock-out mice.

Conclusions:
The results of this study provide important insights into the pathogenic role of the metalloproteinase ADAM28 in the metabolic syndrome and suggests that downregulation of ADAM28 may be a potential therapeutic strategy in the metabolic syndrome.


An NMNAT1 over-expressing mouse model shows altered lipid profile in skeletal muscle, despite tissue specific improvements in glucose disposal

Brenna Osborne1, Sarah E Hancock1, Sanket Joshi1, Azrah F Samsudeen1, Corrine E Fiveash1, Amanda E Brandon2, Toshiyuki Araki3,
Greg J Cooney2, Todd W Mitchell3, Nigel Turner1
1. Mitochondrial Bioenergetics, Department of Pharmacology, UNSW, Kensington, NSW, Australia
2. Sydney Medical School, Charles Perkins Centre, Sydney, NSW, Australia
3. Peripheral Nervous System Research, National Institute of Neuroscience, NCNP, Tokyo, Japan

Nicotinamide mononucleotide adenyllytransferases (NMNATs) are enzymes of the NAD+ salvage pathway that convert nicotinamide mononucleotide (NMN) into NAD+. The nuclear isoenzyme NMNAT1 is thought to control NAD+ salvage in the nuclear compartment and may have important roles in modulating the activity of key NAD+ consuming enzymes such as sirtuins and PARPs. Manipulation of NAD+ levels via administration of NAD-precursors has previously been shown to improve metabolic function2.

We have previously found that transgenic mice that globally overexpress NMNAT1 have a marked skeletal muscle phenotype, showing reduced skeletal muscle mass that is accompanied by a shift towards a more oxidative muscle phenotype. Importantly, when challenged with a high-fat diet (HFD) these mice also show improved glucose tolerance in a glucose tolerance test, and improved glucose-handling in their skeletal muscle when assessed by hyperinsulinenmic-euglycaemic clamp. Intriguingly, this improvement in insulin action occurred despite marked increases in triglyceride accumulation in muscle from NMNAT1Tg mice.

To investigate the lipid profile of skeletal muscle in more detail, we performed lipidomic analysis of skeletal muscle from mice fed a chow or HFD for 8 weeks. This analysis revealed that the difference in triglyceride accumulation in NMNAT1Tg mice was due to significant changes in all detected species of triglyceride. Furthermore, there were also significant increases in C18:0 ceramide and several subspecies of diacylglycerols (DAGs), along with variable changes in a number of phospholipid species. Further investigation of how these changes in lipid metabolism contribute to the metabolic phenotype seen in this model will yield insights into the therapeutic benefits of boosting specific NAD+ pools within skeletal muscle.


Y5 receptor signalling counteracts the anorectic effects of PYY3-36 in diet induced obese mice

Yan-Chuan Shi1, Kenny Ip1, Felicia Reed1, David A Sarruf2, Birgitte S Wulff2, Herbert Herzog1
1. Garvan Institute of Medical Research, Darlinghurst, NSW, Australia
2. Incretin and Obesity Research, Novo Nordisk, Novo Nordisk Park, , Maaloev, Denmark

Peptide YY 3-36 (PYY3-36) is known as a critical satiety factor reducing food intake both in rodents and humans. While the anorexic effect of PYY3-36 is thought to be mediated mainly by the Y2 receptor, the involvement of other Y-receptors in this process has never been conclusively resolved. Amongst them the Y5 receptor (Y5R) is the most likely candidate to also be a target for PYY3-36 which is thought to counteract the anorectic effects of Y2R activation. Here we show that short term treatment of diet induced obese WT and Y5R knockout mice (Y5KO) with PYY3-36 leads to significantly reduced food intake in both genotypes, which is more pronounced in Y5R KO mice. Interestingly, chronic PYY3-36 infusion via minipumps to WT mice causes increased cumulative food intake, which is associated with increased body weight gain. In contrast, lack of Y5R reversed this effect. Consistent with the observed increased body weight and fat mass in WT treated mice, glucose tolerance was also impaired by chronic PYY3-36 treatment. Again this was less affected in Y5KO mice suggestive of a role of Y5R’s in the regulation of glucose homeostasis. Taken together, our data suggests that PYY3-36 mediated signalling via Y5 receptors may counteract the anorectic effects that it mediates via the Y2 receptor (Y2R) consequently lowering bodyweight in the absence of Y5 signalling. These findings open the potential of combination therapy using PYY3-36 and Y5R antagonists to enhance PYY3-36’s food intake reducing effects.
The effects of housing temperature on obesity and insulin resistance in mice

Amanda E Brandon1,2, Lewin Small2, Greg Cooney1,3
1. The University of Sydney, University Of Sydney, NSW, Australia
2. Garvan Institute of Medical Research, Sydney, NSW, Australia

The translatability of studies in rodent models to humans are subject to the differences in physiology between humans and mice, and the experimental conditions used when collecting data. One major factor affecting physiology often overlooked is the effect of ambient temperature. The majority of rodent housing is maintained between 20-22°C, the thermoneutral temperature of lightly clothed humans. However, mice have a much higher thermoneutral zone of ~30°C. Thus, the aim of this project is to investigate the impact of housing temperature on the metabolism of mice fed normal chow or an obesogenic high fat diet.

Male C57Bl6 mice were housed at 22°C or a 29°C and fed either chow or a high fat diet (HFD; 60% calories as fat) for 12 weeks. During this dietary intervention, oral glucose tolerance test (oGTT), EchoMRI, and indirect calorimetry experiments were conducted. 2-way ANOVA was used for statistical analysis.

Body fat mass increased with HFD (effect of diet, p<0.05), and was further increased at thermonutrality (22°C Chow 11.3±1.2, HFD 28.1±1.6%; 29°C Chow 14.0±1.4%, HFD 33.4±1.6% effect of temperature, p<0.05). Lean mass was not different with diet or temperature. During an oGTT, mice fed a HFD were similarly glucose intolerant compared to chow mice regardless of housing temperature. Interestingly, animals housed at 29°C had higher insulin levels at 15 min post glucose load with both diets which reached statistical significance in the HFD mice (p<0.05). Not unexpectedly, indirect calorimetry showed that mice held at 22°C had ~45% higher energy expenditure and higher food intake than mice held at 29°C, regardless of diet.

This data show that animals housed at different temperatures do show differences in whole body energy metabolism and glucose homeostasis that could impact on the translatability of results to human disease.


Role of hepatic NADPH oxidase 4 in the development of obesity and liver disease.

Supreet Kaur1, Melanie Tran1, Garron Dodd1, Junichi Sadoshima1, Matthew Watt1, Tony Tiganis1
1. Monash University, Clayton, VIC, Australia
2. University of Connecticut, Storrs, Connecticut, United States
3. Department of Cell Biology and Molecular Medicine, Rutgers New Jersey Medical School, Newark, New Jersey, United States

Reactive oxygen species (ROS) have long been suspected as detrimental to the progression of various human diseases including type 2 diabetes, liver steatosis, non-alcoholic steatohepatitis (NASH) and liver cirrhosis. An excess of ROS (oxidative stress) caused by an imbalance in metabolism, may be a common underlying pathogenic mechanism in such diseases. NADPH oxidases are multi-subunit transmembrane enzyme complexes that generate superoxide (O$_2^-$) or hydrogen peroxide (H$_2$O$_2$) from molecular oxygen using NADPH as an electron donor (Bedard K et al., 2007). Our aim was to examine the contribution of ROS generated by NADPH oxidase 4 (NOX4) in hepatocytes to liver pathophysiology. We investigated the role of hepatic NOX4 in the regulation of glucose homeostasis and in the progression of obesity-induced steatosis and NASH. Mice with hepatocyte-specific deletion of NOX4 (Alb-Cre;Nox4$^{fl/fl}$) and control mice (Nox4$^{fl/fl}$) were fed 1) a chow diet, 2) a 23% high fat diet (12 weeks) that promotes obesity and NAFLD; 3) a choline-deficient 23% high fat diet (CD-HFD) that promotes obesity and NASH; or 4) a choline deficient amino-acid defined diet (CDDA) that promotes obesity independent NASH; and the overall impact on body weight, oxidative stress, insulin sensitivity, glucose homeostasis and steatosis/NASH assessed. Chow-fed Alb-Cre;Nox4$^{fl/fl}$ mice did not exhibit any alterations in body composition or energy expenditure but showed improved insulin sensitivity. High fat fed Alb-Cre;Nox4$^{fl/fl}$ mice had increased body weight, adiposity, steatosis, liver fibrosis and decreased insulin sensitivity. Alb-Cre;Nox4$^{fl/fl}$ mice also exhibited increased hepatic tri-glycerides, plasma insulin levels and hepatic lipogenic gene expression. NOX4 deficiency showed increased inflammation and fibrosis in CDDA-fed mice. NOX4 deficiency did not alter the development of NASH in CD-HFD fed mice. NOX4 in hepatocytes plays an important role in promoting insulin sensitivity and preventing diet induced obesity and hepatosteatosis. This work highlights the importance of NOX4 derived ROS in liver pathophysiology.
**Background/ Aim:** Fibroblast activation protein (FAP) is a post-proline peptidase that has both endopeptidase and dipeptidyl peptidase (DPP) activities. Its closest relative DPP4, is the target of a successful class of antihyperglycemic drug, the gliptins. Here we studied the role of FAP in a diet induced obesity (DIO) mouse model and in human NASH.

**Methods:** Wild type (WT), FAP gene knockout (gko; lacks FAP) and FAP gene knockin (gki; lacks FAP enzyme activity) mice were in a DIO model. Glucose tolerance, insulin sensitivity, serum insulin, serum cholesterol, liver function test, liver lipids, respiratory exchange ratio (RER) (vCO2/vO2) were measured. Circulating FAP (cFAP) was measured in serum from NASH patients (n=146).

**Results:** FAP gko and FAP gki mice had improved glucose tolerance and insulin sensitivity from 8 weeks of DIO. FAP gko mice were protected from DIO-induced hyperinsulinemia and insulin resistance. FAP gko mice were resistant from DIO-induced fatty liver, as seen by less micro and macro-vesicular inclusions in the liver, less hepatocyte ballooning, less liver lipid, less serum alanine transaminase (ALT) and circulating cholesterol. FAP gko mice had lower RER and increased intrahepatic non-esterified free fatty acids, indicative of increased lipolysis and β-oxidation. Lipogenic genes PPARg and GCK and genes of hepatic triglyceride and fatty acid uptake, APOC3 and CD36, were downregulated in FAP gko livers. Glucagon-like protein, Foxo1 was upregulated in fasting but not in fed FAP gko livers. Analyses of FAP gki are ongoing. In human NASH, cFAP activity correlated with circulating insulin (r_s=0.246; p < 0.01) and HOMA-IR (r_s =0.227; p <0.01).

**Conclusion:** These data show that FAP enzyme activity has important roles in glucose and lipid metabolism. FAP inhibition might become a novel treatment for obesity-induced glucose intolerance, insulin resistance, type 2 diabetes and fatty liver.


**Differential metabolic effects of moderate vs. high intensity interval exercise may be related to muscle adiponectin in high-fed fat mice.**

Sergio F Martinez Huenchullan1, Babu Raja Maharjan1, Charmaine S Tam2, Susan V McLennan1, 3, Stephen M Twigg1, 4

1. Sydney Medical School, and Charles Perkins Centre, University of Sydney, Sydney, New South Wales, Australia
2. Charles Perkins Centre and School of Life and Environmental Sciences, University of Sydney, Sydney, New South Wales, Australia
3. NSW Health Pathology, Sydney, Australia
4. Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

Adiponectin has recently been described as a myokine that regulates insulin sensitivity in an autocrine/paracrine manner. This feature is thought to be one of the mechanisms behind exercise-related metabolic benefits in obesity. However, whether skeletal muscle adiponectin varies between different exercise modalities is unclear. This study investigated effects of 10 weeks endurance(END/moderate intensity) or high intensity interval training (HIIT) on metabolic profiles and muscle adiponectin in a mouse model of diet-induced obesity.

Ten week-old male C57BL/6 mice were fed HFD(45% FAT) ab libitum and underwent either END or HIIT for 10 weeks(3x40min sessions/week). Chow-fed mice acted as controls. Compared with HFD alone, both training programs similarly protected against body weight(BW) gain (final weight (g) HFD=45±2;END=37±2;HIIT=36±2), preserved lean tissue mass(%BW) (HFD=58±2.9;END=72±6.6;HIIT=72±7.3), improved blood glucose during an insulin tolerance test(0.65IU/kg*BW) (HFD=411±54;END=350±57;HIIT=320±66 A.U.), and prevented muscle triglyceride accumulation ((mg/ml per mg tissue) HFD=0.39±0.1;END=0.14±0.1;HIIT=0.13±0.1). Fasting hyperglycaemia, hyperinsulinaemia, and altered AST/ALT ratio (HFD=1.7±0.5;END=3.3±1.3;HIIT=2.2±0.2) were prevented only by END. END, but not HIIT, increased skeletal muscle adiponectin mRNA (14-fold; p<0.05) and increased protein content of high molecular weight (HMW) adiponectin (3.3-fold), whereas HIIT induced a milder increase (2.4-fold). Interestingly, END (irrespective of diet) and HIIT alone induced downregulation in muscle adiponectin receptor 1 (ADIPOR1) protein which was not seen with HIIT (fold change from Chow: HFD=0.50±0.2;END=0.48±0.1;HIIT=0.72±0.3; p<0.05). Furthermore, only END prevented the HFD downregulation in mRNA level of PGC1α (p<0.05), which is downstream of adiponectin signaling. Compared with HFD, neither END or HIIT altered circulating low(LMW) or high(HMW) molecular weight adiponectin forms.

While further investigation is needed, differences between training programs might be related to differential induction of muscle adiponectin, particularly in its isoforms and muscle receptor content. Together these results suggest that END is a more effective regimen to prevent HFD induced metabolic disturbances.

**Diabetes in American Youth- Updates from the SEARCH study**

Dana Dabelea1

1. University of Colorado, Colorado, ACT, Australia

Not available at time of printing

**Precision diabetes: right diagnosis leads to the right treatment**

Andrew Hattersley1
Maternal capillary triglycerides in late pregnancy

Helen L Barrett1,2,3, Marloes Dekker Nitert4, Susan de Jersey1, Leonie K Callaway1,2, Michael D’Emden1, H. David McIntyre5,2
1. University of Exeter, Exeter, DEVON, United Kingdom
2. University of Newcastle, Newcastle, NSW, Australia
3. Lidcombe Hospital diabetes, obstetric and pathology databases, between 2011 and 2015. We compared: Group A; with FPG between 5.1 to 5.4mmol/L and Group B; NGT women excluding Group A. Group A would be re-classified as GDM according to new IADPSG criteria. However both groups were defined as normal glucose tolerance (NGT) according to ADIPS 1998 criteria[2].

Background and Aims
Elevated maternal triglycerides are associated with adverse pregnancy outcomes including an increased risk of preeclampsia and macrosomia. Maternal triglycerides are usually measured in the fasting state and at a single time point during pregnancy. It is known that glucose “flux” is important, but it is not known if and how maternal triglycerides change throughout the day in the home setting. The purpose of these investigations was to examine the feasibility of home monitoring of triglycerides, the daily fluctuations in triglycerides and how triglyceride levels are influenced by high and low fat meals.

Materials and methods
A series of studies have been undertaken. The Roche Accutrend Plus meter with triglyceride strips was validated for use in late pregnancy1. Maternal capillary triglycerides were then examined in the home setting for 4-6 days in the third trimester (4 times a day (fasting and two hours post meals))2. Lastly, a home based mixed breakfast meal test was performed using isocaloric high fat (58%) and low fat (10%) meals on alternate days. Women consumed their normal diet around the meal tests.

Results
Home monitoring was found to be feasible, although requiring education in meter use and phone support. In the meal test, thirteen women, 7 with GDM and 6 normoglycaemic completed the study. Median capillary triglycerides were: fasting 3.3 (95%CI 2.9-3.8) mmol/L, postprandial 3.6 (95%CI 3.2-3.8) mmol/L. There was no significant difference in AUC capillary triglycerides between the meals. There was no influence of GDM status on AUC triglycerides for either meal.

Conclusion
These studies demonstrated capillary triglycerides can be monitored at home in a similar fashion to capillary glucose. There was a trend to higher capillary glucose with low fat meal, but no significant differences in triglycerides. This may be due to limited/small sample size which is being further increased.

Are IADPSG defined GDM women with fasting glucose levels of 5.1 to 5.4mmol/L really at higher risk of adverse pregnancy outcomes?

Tang Wong1,2,3, N Wah Cheung3,4, Glynis P Ross1,3, Robyn A Barnes1,5, Jeff R Flack1,2,6
1. Department of Diabetes and Endocrinology, Bankstown-Lidcombe Hospital, Sydney, NSW, Australia
2. University of NSW, Sydney, NSW, Australia
3. Lidcombe Hospital diabetes, obstetric and pathology databases, between 2011 and 2015. We compared: Group A; with FPG between 5.1 to 5.4mmol/L and Group B; NGT women excluding Group A. Group A would be re-classified as GDM according to new IADPSG criteria. However both groups were defined as normal glucose tolerance (NGT) according to ADIPS 1998 criteria[2], neither receiving treatment for GDM.

Background: The International Association of Diabetes and Pregnancy Study Groups’ (IADPSG) diagnostic criteria for GDM, have a lower fasting plasma glucose (FPG) threshold relative to ADIPS 1998 criteria, (5.5vs5.1mmol/L) and a higher 2 hour post glucose load threshold (8.0vs8.5mmol/L). Some continue to use ADIPS 1998 criteria due to predicted increases in workload[1] and a lack of randomised controlled trial (RCT) evidence to support IADPSG criteria.

Aim: To review whether women with FPG of 5.1 to 5.4mmol/L and normal 2 hr post glucose load are at higher risk of adverse pregnancy outcomes

Methods: We reviewed data from the Bankstown-Lidcombe Hospital diabetes, obstetric and pathology databases, between 2011 and 2015. We compared: Group A; with FPG between 5.1 to 5.4mmol/L and Group B; NGT women excluding Group A. Group A would be re-classified as GDM according to new IADPSG criteria. However both groups were defined as normal glucose tolerance (NGT) according to ADIPS 1998 criteria[2], neither receiving treatment for GDM.

Antenatal maternal characteristics and perinatal outcomes, namely incidence of pre-eclampsia, prematurity (<37 weeks), induction of labour, caesarean section, low birth weight(<2500g ) and macrosomia(>4000g), Apgars and need for neonatal ICU(NICU) admission were compared between groups.
Results: There were 245 women in Group A and 2001 women in Group B. At baseline Group A women had a higher pre-pregnancy BMI (27.9±5.8 vs 25.4±6.0 kg/m², p<0.0001), higher pre-pregnancy to booking visit weight gain (6.6±5.5 vs 5.8±5.4 kg, p<0.05) and greater proportion of Caucasian women (50.2 vs 48.5%, p<0.01).

Significant differences in outcomes are summarised in Table 1.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=245) mean±SD or cases / total (%)</th>
<th>Group B (n=2001) mean±SD or cases / total (%)</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)</td>
<td>3499±592</td>
<td>3377±516</td>
<td>1.9 (1.3 - 2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrosomia &gt;4000g (%)</td>
<td>43/245 (17.6)</td>
<td>200/2001 (10.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion
Lowering FPG for diagnosis of GDM according to IADPSG criteria is justified, as women with FPG 5.1 to 5.4 mmol/L appear to have babies of higher birthweight and the macrosomia rate is higher. It remains to be seen, however, whether treating these women will reduce the incidence of adverse outcomes.


Glycaemic variability is associated with accelerated foetal growth and large for gestational age neonates in women with type 1 diabetes

Rachel T McGrath1, 3, 2, Sarah J Glastras1, 3, 2, Sean K Seeho1, Emma S Scott1, Gregory R Fulcher1, 3, Samantha L Hocking5, 1, 3
1. Department of Endocrinology, Royal North Shore Hospital, St Leonards, NSW, Australia
2. Kolling Institute, St Leonards, NSW, Australia
3. Northern Clinical School, University of Sydney, Sydney, NSW, Australia
4. Clinical and Population Perinatal Health Research, Kolling Institute, St Leonards, NSW, Australia
5. The Boden Institute of Obesity, Nutrition, Exercise & Eating Disorders, University of Sydney, Sydney, NSW, Australia

Introduction: Foetal exposure to hyperglycaemia is a major determinant of large for gestational age (LGA) (birth weight >90th centile for gender) neonates, yet targets for glycaemic control beyond the first trimester in type 1 diabetes (T1D) pregnancy remain controversial.

Objective: To determine the association between HbA1c or glycaemic variability (GV) (using J-index) and excess fetal growth in T1D pregnancy.

Methods: Continuous glucose monitoring (CGM) was performed and HbA1c measured in 21 women at 14-18 (t1), 24-28 (t2) and 32-36 (t3) weeks’ gestation. Abdominal circumference was estimated by ultrasound at 30 weeks’ gestation (AC30). The associations between HbA1c or J-index and AC30 and LGA were determined.

Results: 13 neonates had AC30 >90th centile. Of these, 8 neonates were born LGA. J-index at t2 was significantly more correlated with AC30 >90th centile than HbA1c at t2 (r=0.598, p=0.005 and r=0.444, p=0.043, respectively). The LGA group had significantly greater J-index than the non-LGA group at t2 and higher HbA1c at each time point (Figure 1A&B). Using univariate linear modelling, J-index at t2 maintained a significant independent association with birth weight centile (r²=0.229; p<0.05), whereas HbA1c did not (r²=0.008; p=0.713). Combining J-index and HbA1c at t2 resulted in a stronger association with birth weight centile (r²=0.477; p<0.01) than either measure alone, with mean values of 31.7 and 5.95%, respectively. Furthermore, ROC curve analysis demonstrated that using a cut-off of HbA1c >6% and J-index >30 at t2 identified all neonates that were born LGA (Figure 1C).

Conclusions: Elevated GV at 24-28 weeks’ gestation is more strongly associated with accelerated foetal growth at 30 weeks’ gestation and LGA neonates than HbA1c. Minimising GV in the second trimester may reduce the risk of foetal overgrowth in T1D pregnancy.

Figure 1: Difference in A) J-Index and B) HbA1c for LGA vs. non-LGA neonates. C) ROC curve analysis.
A comparison of pregnancy outcomes in treated GDM women compared to those without GDM

Tang Wong\textsuperscript{1, 1, 2}, Glynis P Ross\textsuperscript{1, 2}, N Wah Cheung\textsuperscript{2, 4}, Robyn A Barnes\textsuperscript{1, 5}, Jeff R Flack\textsuperscript{1, 1, 6}

1. Department of Diabetes and Endocrinology, Bankstown-Lidcombe Hospital, Sydney, NSW, Australia
2. University of Sydney, Sydney, Australia
3. University of NSW, Sydney, Australia
4. Department of Diabetes & Endocrinology, Westmead Hospital, Westmead, NSW, Australia
5. University of Newcastle, Newcastle, NSW, Australia
6. Western Sydney University, Sydney, NSW, Australia

**Background:** The Hyperglycemia and Adverse Pregnancy Outcomes study (HAPO) demonstrated continuous relationships between maternal glycaemia and adverse outcomes\cite{1}. Randomised controlled studies have demonstrated that treatment of gestational diabetes (GDM) reduces this risk.

**Aim:** To compare outcomes of pregnant women treated for GDM with those of normal glucose tolerant (NGT) women.

**Methods:**
We reviewed data from the Bankstown-Lidcombe Hospital diabetes, perinatal and pathology databases between 2011-2015. Women were classified as having GDM or normal glucose tolerance (NGT) according to ADIPS 1998 criteria\cite{2}.
Women diagnosed with GDM were educated on blood glucose monitoring, medical nutrition therapy and exercise. Insulin was commenced if glycaemic targets were not met. Metformin was not used.
Antenatal maternal characteristics and perinatal outcomes, including gestational weight gain (GWG), incidence of pre-eclampsia, prematurity (<37 weeks), induction of labour, caesarean section, low birth weight(LBW<2500g ) and macrosomia(>4000g), Apgars and neonatal ICU(NICU) admission were compared between GDM and NGT women. GWG was calculated as self reported pre-pregnancy weight subtracted from last maternal weight measured after 36 weeks gestation. Independent sample t-tests and chi-square analyses were used to assess for statistical significance.

**Results**
There were 1503 GDM women and 9454 NGT women. At baseline, GDM women were older, had higher pre-pregnancy BMI, increased incidence of chronic hypertension, greater number of prior pregnancies >20 weeks, higher fasting and 2 hour glucose levels on oGTT. There was a greater proportion of non-caucasian ethnicities amongst GDM women.
Treatment of women with GDM reduced GWG and mean birthweight. There was a similar risk of low birthweight and macrosomia. Outcomes of women with GDM compared to those with NGT are summarised in table 1.

<table>
<thead>
<tr>
<th>Table 1 Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>GWG (kg)</strong></td>
</tr>
<tr>
<td>GDM (n=1503) mean±SD or case/total(%)</td>
</tr>
<tr>
<td>12.4±6.3</td>
</tr>
<tr>
<td>Non-GDM (n=9454) mean±SD or cases/total</td>
</tr>
<tr>
<td>15.1±6.9</td>
</tr>
<tr>
<td>Odds Ratio</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>p-value</td>
</tr>
<tr>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Induction due to Hypertensive Disease</strong></td>
</tr>
<tr>
<td>8/591(1.5)</td>
</tr>
<tr>
<td>96/9138(4.6)</td>
</tr>
<tr>
<td>0.3 (0.1-0.6)</td>
</tr>
<tr>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gestational Age at Delivery (wks)</strong></td>
</tr>
<tr>
<td>38.6±1.3</td>
</tr>
<tr>
<td>39.0±2.2</td>
</tr>
<tr>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Prematurity &lt;37 weeks (%)</strong></td>
</tr>
<tr>
<td>211/1503(14.0)</td>
</tr>
<tr>
<td>946/9454(10.0)</td>
</tr>
<tr>
<td>1.5 (1.3 - 1.7)</td>
</tr>
<tr>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Induction of Labour (%)</strong></td>
</tr>
<tr>
<td>572/1503(38.1)</td>
</tr>
<tr>
<td>2137/9454(22.6)</td>
</tr>
<tr>
<td>2.1 (1.9 - 2.4)</td>
</tr>
<tr>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Caesarean Section (%)</strong></td>
</tr>
<tr>
<td>213/895(23.8)</td>
</tr>
<tr>
<td>905/5419(16.7)</td>
</tr>
<tr>
<td>1.6 (1.3 - 1.8)</td>
</tr>
<tr>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Birth Weight (g)</strong></td>
</tr>
<tr>
<td>3332±504</td>
</tr>
<tr>
<td>3354±521</td>
</tr>
<tr>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Low Birth Weight &lt;2500g (%)</strong></td>
</tr>
<tr>
<td>66/1498(4.5)</td>
</tr>
<tr>
<td>376/9416(4.0)</td>
</tr>
<tr>
<td>1.1 (0.9-1.5)</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td><strong>Macrosomia &gt;4000g (%)</strong></td>
</tr>
<tr>
<td>134/1503(8.9)</td>
</tr>
<tr>
<td>1044/9454(9.8)</td>
</tr>
<tr>
<td>0.9 (0.7 - 1.1)</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td><strong>Apgars at 1 minute</strong></td>
</tr>
<tr>
<td>8.5±1.3</td>
</tr>
<tr>
<td>8.6±1.3</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td><strong>Apgars at 5 minutes</strong></td>
</tr>
<tr>
<td>8.9±0.6</td>
</tr>
<tr>
<td>8.9±0.8</td>
</tr>
<tr>
<td>N/A</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td><strong>NICU admission (%)</strong></td>
</tr>
<tr>
<td>215/1503(14.6)</td>
</tr>
<tr>
<td>1044/9454(11.0)</td>
</tr>
<tr>
<td>1.4 (1.2 - 1.6)</td>
</tr>
<tr>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Conclusion**
Treatment of GDM was effective in reducing rates of pre-eclampsia, macrosomia and low birthweight to the background rates observed in women with NGT, but obstetric intervention was more common.
Intergenerational effects of hyperglycaemia in pregnancy the PANDORA Wave 1 study

Angela Titmuss¹, Federica Barzi¹, Alex Brown², Christine Connors³, Jacqueline Boyle¹, Liz Moore⁴, Elizabeth Death¹, Danielle Longmore¹, Kerin O’Dea¹, Jeremy Oats¹, David McIntyre⁶, Paul Zimmet⁷, Jonathan Shaw⁹, Louise Maple-Brown¹

¹. Menzies School of Health Research, Darwin, NT, Australia
². South Australian Health and Medical Research Institute, Adelaide, SA
³. NT Department of Health, Darwin, NT
⁴. Monash University, Melbourne, Vic
⁵. Aboriginal Medical Services Alliance, NT, Alice Springs, NT
⁶. University of South Australia, Adelaide, SA
⁷. Melbourne School of Population and Global Health, Melbourne, Vic
⁸. Mater Medical Research Institute, Brisbane, Qld
⁹. Baker IDI Heart and Diabetes Institute, Melbourne, Vic

The risk of Type 2 diabetes (T2DM) is 20 times higher among Indigenous than non-Indigenous Australian children aged <17 years, with increased complication risk. The PANDORA study is a longitudinal birth cohort (n=1225) recruited from a hyperglycaemia in pregnancy (HIP) register across the Northern Territory, where 38% of children are born to Indigenous mothers, and the prevalence of T2DM in pregnancy is up to 10 times higher than in non-Indigenous mothers.

PANDORA Wave 1 is a sub-study (n=163) of Aboriginal (n=84) and Europid (n=79) mothers with HIP and their children aged 18 to 48 months, focusing on anthropometry and body composition measures. Data were analysed using t-tests, chi-squared tests; multivariable linear regression. Children of Aboriginal and Europid mothers were similar in age at follow up [Aboriginal vs Europid, 33.5 vs 33.6 months, p=0.94], gender (56% vs 47% male, p=0.24) and birth weight z-score for gestation [0.33 (-0.62, 1.42) vs 0.15 (-0.44, 0.62), p=0.12]. However, Aboriginal children had lower current weight z-score (WHO) than Europid infants [-0.38 (-1.06, 0.19) vs 0.31 (-0.22, 1.17), p<0.001]. Aboriginal and Europid mothers were similar in age (30.3 vs 32 years, p=0.056) and BMI (28.7 vs 27.7 kg/m², p=0.35), but Aboriginal mothers were more likely to have T2DM in pregnancy (30% T2DM, 70% GDM vs 1% T2DM, 99% GDM, p=0.001).

On regression analysis, Indigenous ethnicity was negatively associated with child weight z-score [-1.1 (-1.59, -0.63), p<0.001], while maternal BMI [0.04 (0.002, 0.07), p<0.037] and birth weight z-score [0.21 (0.08, 0.4), p=0.04] were positively associated. These data suggesting poorer childhood growth of Aboriginal children may reflect ongoing challenges in Aboriginal health, including socioeconomic disadvantage, food insecurity, infection and malnutrition. Further work will assess adiposity, growth trajectories and other potential contributory factors to early onset T2DM in this population, with prevention or delay of T2DM vital to improve intergenerational outcomes.

A whey/guar “preload” reduces postprandial glycaemia and HbA1c in type 2 diabetes: a 12-week, single-blind, randomised and placebo-controlled trial

Linda E Watson¹, Tongzhi Wu¹, Liza Phillips¹, Michelle J Bound¹, Helen Checklin¹, Jacqueline Grivell¹, Karen L Jones¹, Peter Clifton², Michael Horowitz³, Chris K Rayner¹

¹. Discipline of Medicine, The University of Adelaide, Adelaide, SA, Australia
². University of South Australia, Adelaide

Background/Aims:
We have shown that whey “preloads”, taken before meals for up to 4 weeks, slow gastric emptying (GE) and reduce postprandial glucose (PPG) in type 2 diabetes (T2DM). Guar also slows carbohydrate absorption. We aimed to evaluate the effects of 12 weeks treatment with a whey/guar preload on GE, PPG, and HbA1c, in T2DM.

Methods:
79 patients with T2DM [44 male; age 64±0.7 years; BMI 29.8±0.6 kg/m²; HbA1c 6.6±0.1%; 40 managed by diet alone and 39 by diet and metformin] were randomised, in a single-blind fashion, to receive 150ml flavoured shakes containing either 20g whey protein and 5g guar (WG), or flavoured placebo (P), 15 min before two meals each day for 12 weeks. No other specific dietary advice was given. Patients attended the laboratory at baseline, week 1 and week 12, and consumed WG or P shakes (except at baseline) 15 min before a mashed potato meal labelled with 13CO₂. Venous blood was sampled for PPG, and the gastric 50% emptying time was calculated by measuring breath 13CO₂ over 240min. HbA1c, body weight and body composition (DEXA) were also measured. Data are shown as means ± SEM.

Results:
GE at baseline did not differ between the groups. GE was slower with the WG preload (P<0.01, TxTime interaction). PPG at baseline was similar in both groups, and was lower after the WG than P treatments at both week1 and week 12 (Figure 1). At the end of treatment, the difference in HbA1c between WG and P group was 0.1% (P 6.7±0.05% vs WG 6.6±0.05% P<0.05). No change in body weight, lean mass or fat mass were observed in either group.

Conclusion:
In patients with well controlled T2DM, 12 weeks treatment with a low dose whey/guar preload has sustained effects to slow GE, reduce PPG, and modestly reduce HbA1c.
World-wide Trends In Diabetes Incidence: Is The Epidemic abating?

Dianna Magliano
1. Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia

Over the past several decades, the prevalence of diabetes has risen dramatically in developed and developing countries making diabetes a key health priority globally. The rising prevalence of diabetes is often interpreted as meaning that more people are developing diabetes, and that interventions to prevent diabetes are failing. However, increasing prevalence may also be due to improved survival of people with diabetes, because this increases the length of time that each individual remains within the population. Only incidence (i.e. the annual rate of new cases of diabetes) can measure the risk for the population, as well as indicate the success or otherwise of population-level prevention initiatives. Unfortunately, accurate and up-to-date diabetes incidence data are rare. However, the availability of large registry and administrative databases is starting to change this, and provides a means of analysing trends in diabetes incidence. There is evidence from a few of these data sources showing that the incidence of diabetes may be beginning to stabilise in certain parts of the world. This presentation will provide a review of the current evidence around patterns of diabetes incidence and present some preliminary findings showing that the epidemic may be starting to abate.

Diabetes in older adults

Bu Yeap
1. School of Medicine, University of Western Australia, Perth, WA, Australia

The prevalence of diabetes mellitus is increasing, partly as a result of increasing overweight and obesity predisposing to Type 2 diabetes across ages and also due to demographic change. As the incidence of diabetes predominantly Type 2 is higher in older age groups, the increasing proportion of older adults in countries worldwide will drive the diabetes epidemic. Microvascular and macrovascular complications contribute to the higher morbidity and mortality associated with diabetes. The diabetes-associated reduction in life expectancy is clearly demonstrated in middle-aged adults, as is the cumulative impact of diabetes combined with prevalent cardiovascular disease. Of note the influence of diabetes on cardiovascular events and mortality in the expanding demographic of older adults is less well characterised. In older men, increasing duration of diabetes predicts stable increases in all-cause deaths and deaths related to myocardial infarction (MI) and a progressively higher risk of stroke deaths. Increased longevity does not protect against the higher risk of death, MI and stroke associated with diabetes, once diabetes has been present for longer than five years. By contrast, prior MI is associated with increased risk of subsequent MI, and prior stroke with subsequent stroke, particularly in the 10–20 years following the first event. Thus diabetes represents a duration-dependent risk factor for cardiovascular events which influences outcomes differently from prior vascular disease. Examining the behavioural, physical and biochemical characteristics associated with diabetes in at older ages has been informative. In older men, diabetes is associated with poorer self-perceived health, reduced healthy lifestyle behaviours and physical function, and with injurious falls. The majority of these men with diabetes had good glycaemic control as defined by HbA1c concentrations. Such findings support future interventional studies to encourage healthy lifestyle behaviours and improve physical function in order to benefit quality-of-life and health outcomes in older adults with diabetes.

Diabetes complications – is the burden rising or falling?

Wendy Davis
1. The University of Western Australia, Fremantle, WA, Australia

In this talk, firstly, what we mean by “burden” in the context of diabetes complications and what we need to measure to estimate it will be explained.
In the IDF Diabetes Atlas Seventh Edition 2015, "Estimates of complications were not included due to the lack of comparability of available data". Nevertheless, secondly, the international and national evidence for temporal trends in prevalence and incidence of classical diabetic complications (e.g., cardiovascular disease, renal disease, lower extremity amputations, premature mortality) will be reviewed. Pitfalls in interpreting the data will be highlighted. Finally, evidence that non-classical complications (e.g., dementia, depression, heart failure) are emerging will be presented.

Identification of a novel regulator of lipid metabolism using a trans-omics approach

BG Drew1, BL Parker2, TQ De Aguilar Vallim3, MF Keating1, M Sekdin1, EJ Tarling2, SC Moody1, EJ Zerenkurt1, Y Liu3, K Jayawardana1, NA Mellet1, J Weir1, C Pan1, MA Alameida1, JM Peralta5, JE Curran3, J Blangero4, R Lazarus1, AJ Lusis1, PJ Meikle6, DE James7, Anna Calkin8

1. Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia
2. Charles Perkins Centre, The University of Sydney, Sydney, NSW, Australia
3. University of California Los Angeles (UCLA), Los Angeles, CA, USA
4. University of Texas, Rio Grande Valley, USA
5. Baker IDI Heart & Diabetes Institute, Melbourne, VIC, Australia

Background: The liver controls numerous pathways central to the maintenance of whole body lipid metabolism. Dysregulation of these pathways can lead to increased levels of lipids such as cholesterol, triglycerides and diacylglycerols. This can have pathological consequences, promoting the onset of insulin resistance and the development of cardiovascular disease and hepatic steatosis, common complications of diabetes. However, a greater understanding of the pathways mediating this dysregulation is required.

Aims: We used a trans-omics approach combining genomics, phenomics, lipidomics and proteomics to identify novel pathways associated with the regulation of hepatic lipid metabolism. We utilised our exclusive access to a panel of >100 genetically inbred mouse strains, which to our knowledge is the largest and most diverse of its kind in the world, known as the hybrid mouse diversity panel (HMDP) at UCLA.

Methods: We collected livers (n=3) from male mice of 107 HMDP strains that were housed and fed under the same conditions. We performed deep proteomic analysis on livers by performing 34 separate TMT-10 plex multidimensional LC-MS/MS experiments with SPS-MS3 acquisition on an Orbitrap Fusion. We also performed quantitative lipidomics analysis using LC-MS/MS on an AB Sciex API4000 Q/TRAP system on livers and plasma of the same mice.

Results: Proteomic and lipidomics analysis identified numerous hepatic proteins not previously linked to the regulation of lipid metabolism. In particular, we identified a novel protein associated with short-chain saturated diacylglycerols (SCS-DGs), which have been linked to insulin resistance. Interestingly, in vivo adenoviral expression of this target gene was associated with a significant upregulation of these SCS-DGs in various mouse strains. Moreover, this target was associated with onset as well as duration of diabetes in the San Antonio Family Heart Study.

Conclusion: We have established a high-resolution trans-omics network for the identification of novel regulators of hepatic lipid metabolism.

Ectopic lipids and defective glucose metabolism: cause or association?

Clinton Bruce1

1. Deakin University, Burwood, VIC, Australia

Accumulation of lipids in non-adipose tissues, particularly liver and skeletal muscle, has been associated with the development of insulin resistance and glucose intolerance. However, it is not entirely clear whether ectopic lipid accumulation plays a causal role in the development of insulin resistance and glucose intolerance or whether this is simply an associative relationship. We have conducted a number of studies to explore this relationship. Firstly, to further understand the role of muscle lipids in mediating insulin action, we generated a muscle-specific knockout of a key enzyme in phospholipid synthesis, CTP:phosphoethanolamine cytidylyltransferase (ECT), which resulted in marked (2-3-fold) increases in both diacylglycerol and triacylglycerol content in muscle (Selathurai et al. 2015). Despite this increase in lipid content, whole body and skeletal muscle insulin sensitivity, as determined by euglycemic hyperinsulinemic clamp, was not altered. These findings demonstrate that lipid accumulation in muscle is not always associated with insulin resistance. To examine the role of hepatic lipids, we performed a study where chronically (8 wk) high-fat, high-sucrose fed (HFSD) mice were switched back to a standard chow diet for 7 days (Kowalski et al. 2016). Upon the switch, energy intake was reduced, resulting in reductions of fat mass and hepatic diacylglycerol and triacylglycerol content. However, these parameters were still elevated compared to Chow-fed mice, thus representing an intermediate phenotype. Nonetheless, glucose intolerance and hyperinsulinemia were completely normalized in mice that underwent the 7 day diet switch. This indicates that lipotoxicity per se does not necessarily maintain the glucose intolerant and insulin resistant state in HFSD fed mice. Rather, it appears that persistent over nourishment is likely to be the major factor responsible for causing defects in glucose metabolism. Together, these findings dissociate tissue lipid accumulation from the development of insulin resistance and glucose intolerance.

Understanding lipid mediators of insulin resistance

Nigel Turner¹

1. Department of Pharmacology, University of New South Wales, Kensington, NSW, Australia

Insulin resistance is a major metabolic defect associated with obesity and type 2 diabetes. Although many factors have been proposed to mediate a desensitisation of tissues to the actions of insulin, one key perturbation is aberrant accumulation of lipid. In particular, lipid metabolites such as diacylglycerols and ceramides are considered highly deleterious, however with advancements in analytical techniques it is becoming clear that the effects of these lipids can be varied depending on the specific molecular species present, as well as other factors such as the subcellular distribution. Drawing on work from our group and others I will discuss some of the key issues and controversies in this field.