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Diabetes and Kidney Disease: Advances and Controversies

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POSTERS

1 P2X7 deficiency attenuates renal inflammation and pancreatic beta cell injury in experimental diabetes.

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Chaired poster session: 1 Science

Introduction: Inflammation is a key pathogenic mechanism in both diabetes and diabetic nephropathy (DN). The P2X7 receptor is an ATP-gated cation channel with roles in inflammation and cell death; it is expressed in immune cells and also in resident renal cells and pancreatic islets. We investigated the role of P2X7 in early DN and pancreatic injury using a mouse model of type 1 diabetes as well as human mesangial cells (HMC) cultured in a diabetic milieu.

Methods: Low dose (50mg/kg) streptozotocin injections (x5) were administered to wild-type (WT) and two strains of P2X7 knockout mice with differing profiles of residual receptor expression: Glaxo (GSK) and Pfizer (PF). Random blood glucose (BG), pancreatic insulin staining and islet Mac-2 (macrophage) staining were assessed at 3 weeks. Renal macrophages (CD68+) were assessed at 12 weeks in persistently diabetic mice. HMCs were grown for 2 days in 4mM or 30mM D-glucose media using metabolically-inactive L-glucose as an osmotic control. Secreted MCP-1 was measured by ELISA, and the effects of the selective P2X7 antagonist A438079 (10µM) and the P2X7 agonist BzATP (0.1M) were tested.

Results: 24/29 (83%) WT and 13/18 (72%) GSK mice achieved a BG >16mM at 3 weeks. In a separate experiment, 6/7 (86%) WT and 1/6 (17%) PF mice achieved this. Islet insulin staining was relatively preserved in PF mice ($p=0.036$ vs WT) and was accompanied by reduced macrophage numbers (46%↓, $p<0.001$ vs WT). In persistently diabetic mice, glomerular macrophage accrual was reduced by 70% at 12 weeks in GSK mice ($p<0.01$ vs WT); urine albumin excretion was not increased at this time. In vitro, hyperglycemia enhanced MCP-1 secretion from HMCs by 31%, independent of osmotic stress, and this was reduced 44% by A438079 ($p=0.057$). BzATP further augmented glucose-induced MCP-1 release by 99% ($p<0.05$).

Conclusions: P2X7 contributes both to early renal inflammation and β-cell injury in experimental diabetes. P2X7 appears to regulate glucose-induced MCP-1 release from HMCs which may, in part, explain the renal findings.

2 Multicentre validation of proteomic classifier for diagnosis of diabetic nephropathy

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Chaired poster session: 1 Science

Background. Current practice uses urinary albumin as a clinical marker of early diabetic nephropathy (DN) but tools for preclinical disease detection are lacking. We have previously established a urinary proteomic classifier of 273 peptides ("CKD273") to successfully predict progression from normo- to macroalbuminuria in diabetic patients 3-5 years before onset of microalbuminuria. In a multicentre cross-sectional study we evaluated the performance of CKD273 in differentiating between normoalbuminuria and DN.

Methods. Spot urine samples were obtained from 165 type 2 diabetic patients (87 with DN, 78 without.) across 9 European centres. Blinded sample analysis was performed using capillary electrophoresis coupled to mass spectrometry (CE-MS). Sensitivity and specificity of CKD273 was calculated using receiver operating characteristic (ROC) curves.

Results. ROC curves for each centre resulted in area under the curve (AUC) values between 0.9 and 1.0 with no significant differences between centres. Taking a classifier score of 0.343 as the cut-off for DN, combined analysis of all samples resulted in AUC of 0.95 (95% CI 0.90-0.98). Logistic regression confirmed no influence of age or gender on CKD273 classifier score (p=0.269 for age, p=0.312 for gender).

Conclusion. These data suggest that the CKD273 classifier is accurate and reproducible in differentiating between patients with and without DN. Its utility for prediction of DN in normoalbuminuric diabetic patients with normal renal function and subsequent impact on therapeutic decisions will now be evaluated in a multicentre trial (PRIORITY study).

3 Safety and efficacy of bariatric surgery in obese patients with CKD: the London Renal Obesity Network (LonRON) experience

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Chaired poster session: 1 Science

Bariatric surgery is currently the most effective treatment for obesity, yet recent evidence suggests the rate of complications may be higher in patients with CKD, than in non-CKD obese patients. A retrospective study of all obese patients with CKD - with an eGFR <60ml/min, or an eGFR >60ml/min with evidence of kidney damage & were under the care of a Nephrologist - who underwent laparoscopic bariatric surgery in 3 major London teaching hospitals from 2007-2012 was undertaken. Patient demographics, type of surgery, length of stay, weight change, adverse events, & mortality, were extracted from medical records between October 2012 & March 2013. 74 patients (33M; 31F), aged (mean, ±SD) 52 (±10) years with an eGFR of 48 (±19) ml/min, & a baseline body mass index (BMI) of 44.5 (±5.7) kg/m2, underwent Roux-en-Y bypass (RYGB) (38%), sleeve gastectomy (SG) (57%), or adjustable gastric banding (AGB) (5%). The majority of patients were in CKD stage 3; 11% were classified as CKD stages 1-2, 59% CKD stage 3, 12% CHD stage 4 or stage 5-non dialysis, & 18% were undergoing haemodialysis, at the time of surgery. Mean length of stay was longest for SG at 6 days (5, 7), then RYGB 4 days (3, 5), & was shortest for AGB 3 days (0, 6). Across all forms of surgery, mean (95% CI) excess BMI loss (>25kg/m2) was 49.7% (44.0, 55.4) at 6 months & 61.3% (54.5, 68.0) at 12 months, & mean BMI was

33.2 kg/m2 (31.5, 34.8) 12 months after surgery. There were 16 adverse events (16/74, 22%), including 2 deaths (3%) related to complications of the surgery. Acute kidney injury was the most frequent event (3/74, 4%), followed by leak (3%), acidosis & hyperkalaemia (3%), post operative chest infection (3%), B12/Fe deficiency (3%), fistula/graft failure (3%), & myocardial infarction (1%). A further 4 patients died during the study period, with 2 of these deaths attributed to cancer. Bariatric surgery is effective for weight loss in obese patients with CKD, yet the adverse event and mortality rate may be high, and investigation of non-surgical alternatives remains a priority.

Summary of the data:
No patients n=74 2007-2012
Male 33M; 31F
Mean (SD) age 51.9 (10.1)
Type of surgery 57% sleeves, 38% roux-en Y bypass and 5% adj gastric band
eGFR at baseline 48 (19) ml/min 59% stage 3CKD, 18% HD, 11% stage 1-2 and 12% stage 4 and 5 (non-dialysis)
mean BMI at baseline 44.5 (5.7)

excess BMI loss at 6 and 12 months mean and 95% CI 12 months 61.3 (54.5,68); 6 months 49.7 (44, 55.4)
mean BMI at 12 months 33.2 (31.5, 34.8)
length of stay for each type of surgery mean and 95% CI sleeve los 2 days longer, Roux en Y 4.2 (3, 5.3); sleeve 6.2 (5.2, 7.1); band 3 (0, 6.4)
post op bed 44% surg, 46% HDU or ITU, 10% renal

complications and adverse events and type of surg
deaths and type of surg 6 deaths, 2 directly related to surgery

4/74 gained wt between 6 and 12 months, 2 bypass, 1 sleeve, 1 band, older and longer work up time, lower baseline eGFR, wt loss at 6 months 28.2% vs 48% in whole group

4 Is lipid lowering therapy in diabetic nephropathy systematic and efficacious?

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Chaired poster session: 2 Therapy & Care

Introduction
Dyslipidaemia is common in diabetic nephropathy (DN), which dramatically increases the risk of CVD. NICE guidelines recommend a therauptic goal of total cholesterol 4 mmol/l and LDL concentration of below 2 mmol/l in Type2 Diabetes (1). The SHARP study of simvastatin and ezetimibe in chronic kidney disease included over 2000 diabetes patients and was associated with a significant reduction in major atherosclerotic events, without progression of kidney disease nor major adverse effects. However, the target of level of 4.0/2.0 mmol/l (TC-/LDL-C) was not attained in almost 50% of cases. (2).
To our knowledge, attainment of lipid targets in the routine care of DN has not been specifically examined.

Study design
We collected data from diabetes clinics in East and North Hertfordshire NHS Trust during a twelve month period from June 2012 to June 2013. All diabetic patients with eGFR≤ 90 with total cholesterol l ≥ 5 mmol/l were evaluated with respect to their lipid profiles and drug therapy.

Findings
Among 1145 diabetic patients with eGFR ≤90, 221 (19%) were found to have total cholesterol ≥5mmol. 124 patients (11%) had LDL-c ≥ 2mmol/l. Selecting the target of total cholesterol ≤ 5 mmol/l, 156 patients did not achieve this goal despite lipid lowering treatment. 122 and 10 patients were on statins and ezetimibe therapy, respectively. 18 patients were on fibrates and 6 patients had dual therapy; statin and ezetimibe. 62 patients were not on any lipid lowering therapy, of whom 58 had eGF30-90.

Table

eGFR	Total	On treatment	Not on treatment	Not sure
<30	23	17	4	2
30-59	67	51	16	-
60-90	131	88	42	1

Summary
Despite a very high CVD risk (diabetes, CKD and total cholesterol ≥5 mmol/l) , a sizeable proportion were not on hypolipidaemic treatment. Although the majority were on statin therapy, total cholesterol ≥5 mmol/l remained a common finding.
CVD risk reduction of these patients is vital yet current treatment appears not to be efficacious. The use of combination statin-ezetimibe or other therapeutic combinations may need more active consideration, whilst recognising safety concerns in the use of combination lipid lowering therapies.

References
1. NICE . Management of type2 Diabetes NICE CG 66
2. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial, Lancet 2011; 377: 2181–92

5 Influencing proactive foot assessment on the inpatient ward at the Lister Hospital

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Chaired poster session: 2 Therapy & Care

Introduction:
The incidence of diabetes related complications including diabetic foot disease is increasing.
As part of a CQUIN for the improvement of diabetes related in-patient care, we have implemented a simple foot assessment tool .
Given the well known association between renal disease and diabetic foot disease (Margolis et al, 2008) we chose the renal ward as the pilot ward for our intervention.
Our aim was to raise general awareness amongst the staff of the need for foot assessment, to assist in the early identification of any issues and to promote prompt referral where necessary.

Methods:
Our pilot revealed that foot assessment was happening intermittently, and was not being routinely documented.
Staff were therefore trained to use the Touch the Toes Test, and it was integrated into the overall admission process for all diabetic patients. Feet are then inspected daily in order to identify any visual changes. Any problems identified are referred to the Diabetes Outreach Team.

Results:
Feedback from the ward staff has been very positive.
Since implementation we have carried out 2 spot audits which have shown that 100% of patients with diabetes are being assessed on admission.

Conclusion:
The Touch the Toes Test has proved simple to implement and has been taken up enthusiastically by staff. This will be extended to include our dialysis unit, and ultimately, rolled out to include all the in-patient areas within the trust.

6 Treatment choices and targets in Type 2 diabetes and Chronic Kidney Disease

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Chaired poster session: 2 Therapy & Care

Aims: Guidelines recommend that metformin is avoided in patients with a creatinine>150 mol/L (eGFR<40ml). Cardiovascular disease (CVD) has a high mortality in patients with diabetes and chronic kidney disease. NICE guidance for CVD targets in diabetes are:- cholesterol<4.0mmol/l, LDL<2.0mmol/l, SBP<140mmHg, DBP<80mmHg. Our aim was to:- (i) Examine treatment choices for glucose control in our clinic for patients with an eGFR<40 (ii) Examine the relationship between the treatment groups and targets for CVD risk factors.

Methods: Using the electronic database at Morriston Hospital we identified 1341 patients seen in the diabetes clinic between 1/9/10-31/8/11.

Results: Of the 1341 patients, 128 (10%) had an eGFR<40. Of these 8 received no treatment, 15 sulphonylurea alone, 81 insulin alone and 24 metformin (alone or with insulin/ sulphonylurea). We observed a significant difference in BMI between these groups (34.9 ±8.6 v 34.7 ±7.5 v 33.0 ±5.5 v 39.3 ±18.8kg/m2, p=0.03); DBP (65.9 ±11.5, v 74.1 ±9.7 v 69.3 ±9.1 v 77.6 ±19.1mmHg, p=0.01) and creatinine (215 [IQR 177-489] v 192 [167-238] v 188 [151-166] v 159 [151-166] mol/L, p=0.001). No differences were seen for SBP and lipids. The proportion reaching the target were:- cholesterol 60%; LDL 60%; SBP 59%. These did not differ across treatment groups. The proportion reaching the diastolic target was lower in the metformin treated group (38%).

Conclusions: Within our routine practice 19% of patients with an eGFR<40 were treated with metformin. This group had significantly lower creatinine, a higher BMI and DBP. Only 60% of patients reached the recommended cardiovascular targets.

7 The effect of Roux-en-Y gastric bypass on diabetic kidney disease in the Zucker diabetic fatty rat model

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Chaired poster session: 1 Science

Background
Roux-en-Y gastric bypass (RYGB) improves the diabetic milieu in humans, and may have effects on diabetic complications. The aim of this study was to determine the effect of RYGB on diabetic kidney disease (DKD).

Methods
18 week old Zucker diabetic fatty (ZDF) rats (n = 21) were randomly assigned to RYGB or sham surgery. Proteinuria was evaluated post-operatively and the animals were renal tissue was evaluated for glomerulosclerosis. Both glomerular size and prevalence were measured. Immunohistochemistry for collagen subtypes (I, III, IV) and the macrophage marker ED-1 (CD68) was performed. Immunostained sections were quantitatively analysed using Imagescope™ and findings were correlated with gene expression and immunoblotting for molecular markers of DKD.

Results
RYGB was associated with significant weight loss (mean final weight 380 versus 480g, P = 0.02) and improved glycaemic control (glucose AUC, P < 0.001). RYGB resulted in significantly less glomerulosclerosis (17% versus 30%, P = 0.01), more glomeruli per unit area (P = 0.02), reduced glomerular hypertrophy (P = 0.001) and a trend towards reduced macrophage infiltration (P = 0.057) compared with the sham-operated group.

Conclusion
This study confirms that RYGB can improve histopathological changes associated with DKD in the ZDF model. Further investigation is required to characterise the functional improvements associated with pathological disease regression and to determine mechanisms that may contribute to improvement in DKD after RYGB.

8 The outcome of Dapagliflozin use in District General Hosiptal

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Chaired poster session: 2 Therapy & Care

Introduction
Dapagliflozin has recently been licensed to be used as a hypoglycaemic agent in patients with Diabetes Mellitus Type 2 (T2DM). It is recommended to be used as a monotherapy in patients for whom metformin is considered inappropriate and as an add-on combination therapy with other glucose-lowering agents.

Methods and Results
Data was collected and analysed for patients on Dapagliflozin seen by the Diabetes team in a district general hospital. Weight and HbA1c were measured at the beginning of treatment with Dapagliflozin and then at 12 weeks.

14 patients were identified as being on Dapagliflozin. From these 7 had been on it for 12 weeks or more. There was an average of 3.64kg reduction in weight and 3.47% reduction in HbA1c.

Conclusion
Randomised control trials have shown that Dapagliflozin has an average of 0.39%-0.96% HbA1c reduction and an average of 1.67kg-3.22kg weight reduction. In our hospital patients in Dapagliflozin have had a significant HbA1c and weight reduction after 12 weeks of treatment.

9 The Ipswich Touch Test: a novel method to detect "at risk" feet in patients receiving renal replacement therapy

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Chaired poster session: 2 Therapy & Care

Aims: Peripheral neuropathy is a common but relatively unrecognised complication of renal failure. Reports suggest that it and can affect up to 65% of patients starting renal replacement therapy (RRT). Patients in renal units are at increased risk of foot ulcers and amputation often starting as pressure related heel ulceration contributed to by sensory loss and prolonged recumbency during dialysis. The Ipswich Touch Test (IpTT) is a simple, safe and quick method to detect loss of foot sensation people with diabetes. It is easy to perform and teach; and is highly correlated with other tests for neuropathy including vibration perception thresholds and 10-gm monofilament (MF). This study determines whether IpTT can be effectively used in patients on RRT to identify those with sensory loss to whom preventative measures can be targeted.

Methods: The IpTT involves lightly and briefly (1-2 seconds) touching the tips of the first, third and fifth toes of both feet with the index finger: an abnormal test indicated by ≥2 insensate areas. We used the 10gm monofilament in the same toes as the comparison test; again reduced foot sensation was defined as ≥2 insensate areas. Both diabetic (DM) and non-diabetic (NDM) patients on hemodialysis (HD) and peritoneal dialysis (PD) at the Ipswich hospital's renal unit were consented for the study. Patients with history of amputation or active ulceration were excluded.

Results: A total of 69 patients (22 DM and 47 NDM) were recruited (88.89% HD). 69.6% (n=48) had ≥2 insensate areas to MF testing. Concordance between the MF and IpTT was 87.3% (p=<0.0001). Compared with the MF, the IpTT had a sensitivity of 81.3% and specificity of 95.3% giving a positive predictive value of detecting 'at-risk' feet of 90.1% and a negative predictive value of 87.2%. The positive likelihood ratio was 16.5 and negative 0.24.

Conclusions: This study demonstrates that the IpTT performs well against the MF in detecting sensory loss in patients on RRT with and without diabetes. Since it costs nothing, is always at hand, and easy to perform and teach, we recommend its use in dialysis units to identify patients with 'at-risk' feet. Further prospective studies are required to determine whether its use together with a protective foot measures prevents foot lesions in this group of patients.

10 The prevalence and effect of chronic kidney disease on HbA1c when being used for diagnosis of type 2 diabetes mellitus in primary care population

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Chaired poster session: 1 Science

Introduction
Glycated haemoglobin (HbA1c) has been adopted for type 2 diabetes mellitus (T2DM) diagnosis. Chronic kidney disease (CKD) may increase HbA1c. The prevalence of CKD and its association with HbA1c in T2DM screening in primary care were studied.

Methods
HbA1c, fructosamine, fasting glucose, haemoglobin, age and gender were compared between those with CKD stage <3 and >3 using chi squared or t-tests. Multivariable linear regression analysis was performed with HbA1c the dependent variable; correlates included age, CKD, gender, haemoglobin, fasting glucose and fructosamine. Data are expressed as mean (standard deviation).
Results
829 (59.6% female) had CKD <3 and 170 (54.7% female) had CKD ≥3, of whom 2 had CKD >4 and were excluded from analyses. Compared with CKD <3, patients with CKD 3 were older [71.5(13.8) vs. 51.4(17.3) years, p<0.001], had higher HbA1c [42.1(8.2) vs. 39.5(6.5) mmol/mol, p<0.001], fasting glucose [5.5(1.8) vs. 5.2(1.1) mmol/L, p<0.001] and fructosamine [237.4(43.2) vs. 225.8(25.1) umol/L, p<0.001] but lower haemoglobin [13.8(1.5) vs. 14.2(1.6) g/L, p=0.004]. After adjustment, HbA1c was associated (p<0.05) with increasing age, fasting glucose and fructosamine (higher HbA1c) and increasing haemoglobin (lower HbA1c) but not with CKD [coefficient -0.67(-1.59-0.26)].

Conclusion
Severe CKD (stage >4) is rare in primary care patients being screened for T2DM and its impact on HbA1c could not be evaluated. Although HbA1c is higher among patients with CKD stage 3, this is due to age and fasting glycaemia rather than CKD. HbA1c is a suitable diagnostic test for T2DM in primary care irrespective of CKD.

11 Charcot neuroarthropathy precipitated by foot ulceration

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Chaired poster session: 2 Therapy & Care

Charcot neuroarthropathy (CN) is an uncommon condition, which usually develops without a specific precipitant in patients with diabetes (DM).
We report the case history of a sixty-seven year old lady with DM who presented to our multidisciplinary DM foot clinic with a necrotic right heel ulcer. She had sensory neuropathy but not peripheral arterial

disease. MRI of the right foot revealed extensive soft tissue inflammation, but not osteomyelitis. The patient required intravenous antibiotics, surgical debridement and skin grafting.

The ulceration healed in 4 months, but a few later months, she developed a deformity of the right mid-foot, with local warmth and bounding pulses. Right foot MRI was done and this was consistent with CN. Off-loading was provided using an air cast walker (ACW). A few months later, our patient developed right mid-foot, plantar boggy swelling which ulcerated leading to osteomyelitis, requiring prolonged intravenous antibiotic treatment. The patient continued to use the ACW and ulceration healed and CN finally settled.

This case report highlights the importance of considering CN as a complication of diabetes foot ulceration and the complexities involved in the management of patients with diabetes foot ulceration.