O105  GLUCOSE SENSORS AND TRANSPORTERS IN METABOLIC DISEASE: ANALYSIS OF TISSUE FROM OBESE DIABETIC AND NON-DIABETIC HUMANS
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Introduction
The intestine is capable of responding to luminal nutrient quality to help optimize absorption. Intestinal sweet sensing has recently been documented and is thought to be mediated by the sweet taste receptor T1R2/3 which leads to increased intestinal glucose absorption. Whether this nutrient sensing pathway is dysregulated in obesity or type 2 diabetes (T2D) is unknown.

Method
Blood samples and jejunum from obese T2D (n=10) and non-diabetic (n=37) patients undergoing gastric bypass surgery were collected. Plasma glucose, HbA1c and satiety-regulating hormones were measured. Intestinal T1R2, SGLT1 and GLUT2 mRNA was measured using RT-PCR. Functional assessment of the T1R2/3-SLGT1 pathway was made by measuring saccharin-induced glucose uptake in proximal jejunum with the everted sleeves technique. Statistical analyses included Student’s t-test and ANOVA.

Results
Plasma glucose and HbA1c levels were higher in the T2D group. There was no difference in incretin hormones between groups. Intestinal glucose absorptive capacity showed positive correlation with HOMA-IR in all obese patients (r=0.56, p<0.05) Intestinal glucose uptake was however not different between T2D and non-diabetics (3.2±0.3 vs. 2.8±0.3 nmol/mg/min respectively, p=0.2), or between saccharin-exposed intestinal tissue vs. tissue in a control solution (Mammalian Ringer’s) (3.1±0.3 vs. 2.8±0.2 nmol/mg/min respectively, p=0.3). T1R2 mRNA levels were however 2-fold higher in the distal jejunum of T2D patients (p=0.05).

Conclusions
We provide evidence that intestinal glucose absorption capacity is linked to development of insulin resistance. T1R2 is expressed at higher levels in the jejunum of T2D but does not appear to lead to enhanced intestinal glucose absorption in these patients.

Take-home message
Intestinal glucose absorption capacity is linked to development of insulin resistance in obesity. Intestinal sweet taste receptors are expressed at higher levels in the jejunum of diabetics but do not appear to lead to enhanced intestinal glucose absorption in these patients.

O106  THE EPO-DERIVATIVE, ARA-290, ATTENUATES ISCHAEMIA-INDUCED SKELETAL MUSCLE DAMAGE IN CLI MYOBLASTS IN VITRO AND IN A MURINE MODEL OF HINDLIMB ISCHAEMIA
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Introduction
A third of patients with critical limb ischaemia (CLI) eventually require amputation. Inconsistencies between successful revascularisation and functional outcomes exist, and an underlying musculopathy in CLI patients has been identified. Non-haematopoietic EPO-derivatives have been designed to retain only tissue-protective functions of EPO. We hypothesised that ARA-290 (EPO-derivative) may have tissue-protective potential that would represent a novel therapeutic adjunct in patients with CLI.

Method
The effect of ARA-290 in mediating cytoprotection was assessed firstly in vitro in skeletal myoblasts isolated from CLI and control donors. Subsequently, an in vivo murine model of hindlimb ischaemia which recapitulates the muscular pathology observed in CLI patients
was used to assess the potential of ARA-290 to improve functional, histological and perfusion outcomes.

**Results**
Skeletal myoblasts were successfully isolated from CLI patients for the first time. CLI myoblasts and myotubes exhibited increased proliferative capacity but reduced migratory and contractile function and importantly a reduced susceptibility to a second ischaemic- insult compared with control myoblasts and myotubes. ARA-290 treatment led to significant improvements in myoblasts and myotube function and survival via the JAK2/STAT3, PI3k/Akt and NFκB signalling pathways. In vivo, animals treated with ARA-290 demonstrated improved functional, histological and perfusion outcomes compared to vehicle-control treated animals.

**Conclusion**
These studies demonstrate the potential of ARA-290 to protect tissues and cells from ischaemic-injury and encourages the development of novel pharmacological therapies for use in patients with “no option” CLI or severe functional deficit.

**Take-home message**
In combination with the haemodynamic compromise seen in CLI patients there is an important underlying musculopathy which remains untreated despite successful revascularisation. Novel therapies exist which may be able to mediate ischaemia-induced tissue damage.

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**O107 MESENTERIC VASCULAR TRANSIT TIME, AS ASSESSED BY CONTRAST-ENHANCED ULTRASOUND; ITS RELATIONSHIP TO CARDIAC OUTPUT AND VOLUME STATUS.**

**Introduction**
Current point-of-care volume assessment tools address systemic rather than mesenteric circulation. Anastomotic healing and mucosal barrier function demand adequate mesenteric bloodflow. We describe a novel contrast-enhanced ultrasound (CEUS) technique that calculates transit times across the mesenteric vascular bed by simultaneous registration of intravenous contrast arrival at kidney (systemic arterial) and liver (portal blood).

**Method**
With ethical committee approval, after 15h nil-by-mouth, 8 healthy men (~63y) had cardiac output (CO) assessment by oesophageal Doppler (OD). With synchronous CEUS recording of liver and kidney, after Sonovue™ contrast injection via antebrachial vein, time-to-50% contrast peak was measured in both organs, the difference representing mesenteric vascular transit (MVT). After rapid intravenous infusion of 1000mL 0.9%NaCl, OD/CEUS were repeated, allowing estimation of change in CO(ΔCO) and MVT(ΔMVT).

**Results**
Fluid increased CO (+1.0L, range -0.26 to +2.5L, P=0.02, paired t-test) but not mean MVT (range -17 to +8s). However, there was strong negative correlation between ΔCO and ΔMVT (R² = 0.87, P=0.008, least squares).

**Conclusion**
The variable impact of 1L fluid on CO is mirrored by ΔMVT. Large ΔCO (>+1L) reflects correction of hypovolaemia; the associated faster MVT (ΔMVT < -2s) likely reflects physiologically significant improvements in gut perfusion. Small ΔCO (<+1L) is seen in volume replete subjects; concomitant slower MVT (ΔMVT > +2s) may reflect more blood pooling in the splanchnic reservoir. This clinically acceptable technique may facilitate development of a point-of-care volume assessment that is truly orientated to gastrointestinal perfusion. Contrast-enhanced ultrasound (CEUS), cardiac output (CO), oesophageal Doppler (OD), mesenteric vascular transit (MVT).

**Take-home message**
This clinically acceptable, minimally invasive contrast-enhanced ultrasound technique provides a volume assessment tool that is truly orientated to changes in gastrointestinal perfusion. It has potential for use at the point-of-care.
ASSOCIATION BETWEEN GENE EXPRESSION BIOMARKERS OF IMMUNOSUPPRESSION AND BLOOD TRANSFUSION IN SEVERELY INJURED POLYTRAUMA PATIENTS

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Introduction
Blood transfusion is known to induce an immunosuppressive phenotype. However, the key inflammatory pathways activated by the transfusion of blood products in polytrauma, and the influence it has on the incidence of nosocomial infection are unclear.

Method
101 ventilated polytrauma patients were recruited. mRNA was extracted from PaxGene tubes collected within 2hrs of the trauma (baseline), at 24hrs and 72hrs. T-helper cell subtype specific cytokines and transcription factors were quantified using real-time polymerase chain reaction.

Results
Immediate blood transfusion was administered to 23 (23%) patients prior to the baseline blood sample and was associated with a greater immediate rise in IL-10 (p=0.007) and IL-27 (p=0.04) mRNA levels. Blood products were transfused in 70 (69%) patients during the first 24hrs. There was an association between transfusion within the first 24hrs and higher IL-10 (p=0.0002), lower Foxp3 (p=0.02) and lower RORγt (p=0.02) mRNA levels at 24hrs. There were greater reductions in T-bet (p=0.02) and RORγt (p=0.04) mRNA levels and lesser increases in TNFα (p=0.01) over 24hrs and IFNγ mRNA over the first 72hrs in those transfused in the first 24hrs. Multiple regression models confirmed that transfusion was independently associated with these early changes in gene expression. Bacteraemia was seen in 13 (18.6%) patients who received transfusions in the first 24hrs, compared to 1 (3.2%) patient not transfused (OR 6.8 (0.85-55) p=0.058).

Conclusion
Polytrauma is associated with a primarily immunosuppressive response; this was increased in magnitude in patients receiving blood products. This may have important clinical consequences such as an increased susceptibility to develop serious nosocomial infections.

Take-home message
Polytrauma provokes a primarily immunosuppressive response. Blood product transfusion contributes to this phenotype, potentially increasing the susceptibility to develop late nosocomial infections in the critical care environment.

ACUTE ENDOTOXAEMIA BLUNTS NUTRIENT MEDIATED PHOSPHORYLATION OF MUSCLE AKT/MTOR SIGNALLING AND MUSCLE PROTEIN SYNTHESIS IN HUMANS.

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Introduction
Controversy exists concerning the time-course and direction of change in muscle protein synthesis (MPS) during sepsis in humans and the underlying mechanisms involved. We therefore determined the effects of LPS infusion on MPS and muscle anabolic signalling in healthy volunteers.

Method
Seven healthy males (age 21.9±0.6 yrs, BMI 23.4±1.2 kg.m2) participated in this ethically approved study. On 2 occasions separated by >2 weeks, subjects underwent a 4h hyperinsulinaemic (40 mU.m-2min-1) euglycaemic (4.5 mmol.l-1) clamp combined with a primed mixed amino-acid (6 g.h-1; to create a ‘fed-state’) infusion, immediately following bolus saline (control) or LPS (4 ng.kg-1 body weight) infusion (order randomized). A primed constant infusion of [1-13C] leucine (1.0mg.kg-1.h-1) was used throughout to determine muscle protein fractional synthetic rates (FSR) in vastus lateralis muscle biopsy samples obtained at baseline, 120 and 240min. Anabolic signaling protein phosphorylation...
was determined using Western blotting. Statistical analyses were performed using Wilcoxon’s rank test.

Results
Myofibrillar FSR was similar in both groups between 0 to 120 min, but was 36% lower from 120 to 240 min following LPS infusion (Control 0.105±0.015%/h Vs. LPS 0.067±0.014%/h; P<0.05). In control, the ‘fed state’ clamp increased mTOR Ser2448 phosphorylation 5 fold from basal by 120 min (P<0.05). However, LPS infusion caused marked blunting of ‘fed-state’ induced mTOR Ser2448 phosphorylation (P<0.05 vs control), such that there was little change from baseline throughout.

Conclusion
Acute endotoxaemia reduced the normal nutrient-mediated increase in MPS after 120 min, and was preceded by marked and sustained blunting of muscle anabolic signalling.

Take-home message
This study using human model of endotoxaemia revealed suppression of normal nutrient mediated increase in muscle protein synthesis as a possible mechanism involved in muscle loss associated with sepsis.

O110 ROLE OF TOLL-LIKE RECEPTOR 4 (TLR4) INHIBITION IN ISCHAEMIA-INDUCED SYSTEMIC INFLAMMATORY RESPONSE AND SKELETAL MUSCLE DAMAGE
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Introduction
The innate immune response plays an important role in skeletal muscle damage in hind-limb ischaemia, however the mechanism is not fully understood. Previously, we showed less apoptotic changes in cultured human myotubes in simulated ischaemia when TLR4, a pattern recognition receptor, was inhibited. Herein, we investigated whether TLR4 inhibition reduces the ischaemia-induced skeletal muscle damage, via a mechanism that involves systemic IL6 and TNF-α, in vivo.

Method
Hind-limb ischaemia was induced by excision of femoral artery in 12-week-old wild-type (WT) and TLR4−/− mice. Further, a group of CL57/BL6 mice received the TLR4 antagonist, LPS-RS (n=18 per group plus 9 sham operated per group). Laser Doppler was used to measure haemodynamic changes. Tissue collection and serum samples were obtained at day 3, 7 and 21. Systemic levels of IL-6 & TNF-α, cleaved caspase-3 (marker of apoptosis) and inflammatory damage were examined by ELISA, Fluorescent IHC-P and H&E staining, respectively.

Results
TLR4−/− mice and mice given LPS-RS, demonstrated reduced systemic IL6 & TNFα levels (P<0.05). This was associated with significant improved blood flow recovery (P<0.05), diminished apoptosis and attenuated inflammatory cell infiltration (P<0.05) in the skeletal muscle following hind-limb ischaemia as compared to WT mice at day 3, 7 and 21.

Conclusion
Endogenous deletion and exogenous inhibition of TLR4 were associated with reduced systemic IL6 & TNF-α levels and skeletal muscle damage following hind-limb ischaemia. Here we report an intimate link between ischaemia-induced systemic inflammatory cytokine production and TLR4 inhibition.

Take-home message
TLR4 plays an important role in ischaemia induced skeletal muscle damage

O111 SMALL BOWEL SEROSA, A NOVEL SOURCE OF PROINFLAMMATORY CYTOKINES IN GUT INJURY AND INFLAMMATION
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Introduction
Injury to the parietal peritoneum results in an inflammatory process, which can lead to adhesion formation, a major cause of postoperative morbidity. The underlying mechanisms remain incompletely understood and the role of the visceral peritoneum (serosa) has not previously been investigated. The aim of this study was to test the hypothesis that gut serosa contributes to local inflammatory responses that lead to intra-abdominal inflammation.
Method
Patients undergoing elective small intestinal resection were studied (n=9). Apparently healthy intestine from the resection margin was harvested and the serosa stripped from the underlying muscularis under direct vision. This tissue was weighed, divided in two and incubated for 18hrs at 37°C in either sterile DMEM (control), or DMEM with (200ng/ml) endotoxin (LPS). Secretion of IL-1β, IL-6, IL-10 and TNF-α into the medium was assessed by ELISA, using commercially available antibodies. Wilcoxon Matched Pairs test was used to compare cytokine concentrations in control and LPS groups. Data are presented as medians (IQR) and P<0.05 as statistically significant.

Results
There was a significant secretion of all cytokines into supernatant during incubation. Exposure to LPS resulted in significantly increased concentrations of IL-1 (416.12 vs. 2271.11pg/ml, P=0.008), IL-6 (28,012.57 vs. 66,884.19pg/ml, P=0.003) & IL-10 (435.95 vs. 1179.35pg/ml, P=0.017). TNFα concentration was unaffected by LPS exposure (57.88pg/ml vs. 48.93pg/ml P= 0.889)

Conclusions
Intestinal serosa is capable of producing pro-inflammatory cytokines. Although the cell types and regulatory mechanisms are unclear, these novel findings have important implications for the pathophysiology of adhesion formation.

Take-home message
Our study has demonstrated that intestinal serosa is capable of producing pro-inflammatory cytokines. Although the cell types and regulatory mechanisms are unclear, these novel findings have important implications for the pathophysiology of adhesion formation, a major factor in post-operative morbidity.

O112 THE LOX-1 SCAVENGER RECEPTOR PLAYS A DUAL ROLE IN ATHEROSCLEROSIS AND REGULATES GLUCOSE METABOLISM
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Introduction
The LOX-1 scavenger receptor mediates lipid particle uptake and atherosclerosis. LOX-1 deletion in LDL-R null mice is atheroprotective but only after a sustained 4% cholesterol-rich diet. The link between LOX-1 and glucose homeostasis in this process is unknown. We tested the hypothesis that LOX-1 deletion in ApoE-null mice fed a 0.2% cholesterol-rich diet produces pathophysiological dysfunction.

Method
LOX-1-null and ApoE-null mice were crossed to create a double null line (LOX-1/ApoE). ApoE-null and LOX-1/ApoE-double null mice were fed a 0.2% cholesterol diet for 12 weeks. Aortas were harvested at age 18 weeks and stained for lipid plaques. Glucose tolerance tests were performed at age 16 weeks.

Results
Total aortic atherosclerotic plaque coverage was 5.5% in ApoE-null mice and 7.2% in LOX-1/ApoE-double null mice (p<0.05). Further analysis showed similar plaque volume in the aortic arch (ApoE-null 19.1% vs. LOX-1/ApoE-double null 19.0%) and thoracic aorta (1.4% vs. 1.8% respectively). Differences were predominantly observed in the abdominal aorta (3.7% vs. 6.4% respectively). ApoE/LOX-1-double null mice displayed glucose intolerance compared to ApoE-null mice (30 minute blood sugar 16.6 vs 12.5 mmol/l; p<0.05). This was maintained throughout the challenge (26.9 vs 19.1 arbitrary units; p<0.05), resembling a pre-diabetic phenotype.

Conclusion
The LOX-1 scavenger receptor has a dual role in lipid particle metabolism, with LOX-1 deletion paradoxically increasing plaque volume in ApoE-null mice. This may be due to dysfunctional glucose metabolism and the creation of a glucose intolerant phenotype. Our findings suggest LOX-1 carries both atheroprotective and pro-atherogenic properties dependent on the environmental stimulus. LDL-R - Low-density lipoprotein receptor ApoE - Apolipoprotein E.

Take-home message
The role of LOX-1 in atherosclerosis is more complex than previously understood. Its link with glucose metabolism may provide new insight into the pathophysiology of diabetes.
O113 INTESTINAL NUTRIENT SENSING IN THE ANTI-DIABETIC EFFECTS OF BARIATRIC SURGERY
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Introduction
Roux-en-Y Gastric Bypass (RYGB) is emerging as a therapy for Type 2 Diabetes (T2D), but mechanistic understanding is lacking. We hypothesize that the proximal intestine senses luminal glucose to increase intestinal glucose absorption (IGA) more distally, and that RYGB interrupts this pathway. We measure the effects of acute duodenjejunal exclusion (DJ-E) and RYGB on IGA, and investigate the role of the sodium-glucose transporter (SGLT) family, sweet taste receptor, and vagus nerve in glucose sensing.

Method
In anesthetized rats (with ethics committee approval), portal and systemic blood samples were taken at baseline and during intestinal glucose infusion. The portosystemic glucose gradient was used to calculate IGA during: Pre-RYGB experiments •Whole intestinal glucose infusion (N=5); •DJ-E by jejunal glucose infusion (N=6); •Duodenjejunal stimulation (DJ-S), followed by jejunal glucose infusion, using infusion of: saccharin (sweet taste receptor agonist; N=5), 3-O-methyl-D-glucopyranose (3-OMG; SGLT1 agonist, N=5), or alpha-D-methyl-glucopyranoside (aMG; SGLT1/SGLT3 agonist, N=6); •Vagotomy and DJ-S (N=5); Post-RYGB experiments •Roux limb glucose infusion alone (N=6).

Results
Acute DJ-E lowered IGA compared to whole intestinal infusion (132 vs. 251mg/h; p<0.05). DJ-S with aMG, but not saccharin or 3-OMG, increased IGA (260 vs. 132mg/h; p<0.05); vagotomy abolished this effect (151 vs. 260mg/h; p<0.05). Post-RYGB, IGA was unchanged but the baseline portosystemic glucose gradient (-27 vs. -8mg/dl; p<0.01) indicated higher intestinal glucose use.

Conclusions
Proximal intestinal SGLT3 senses glucose to trigger a vagally-mediated acute increase in IGA. Though RYGB does not reduce IGA, it may increase intestinal glucose disposal and this warrants further investigation.

Take-home message
We demonstrate that though acute duodenjejunal exclusion reduces intestinal glucose absorption, Roux-en-Y Gastric Bypass does not. Its anti-diabetic effects may rely on another mechanism involving increased intestinal glucose disposal.

O114 PERIPHERAL NEUROPATHY AND THE RISK OF CARDIOVASCULAR EVENTS IN DIABETES MELLITUS
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Introduction
Identifying individuals with diabetes mellitus (DM) at high risk of cardiovascular disease (CVD) remains challenging. Information on peripheral neuropathy (PN), obtained in annual primary care foot checks, currently informs risk for foot ulceration and amputation. We hypothesised that PN was an independent predictor of CVD events among patients with DM, and that it could improve CVD risk prediction.

Method
Data for individuals with DM and no prior CVD disease, with complete ascertainment of cardiovascular risk factors and information on the presence of peripheral neuropathy, were obtained from a primary care patient cohort. The association between PN and incident CVD events (MI, coronary revascularization, heart failure or stroke) was evaluated in Cox regression. Improvement in risk prediction was assessed using the integrated discrimination index (IDI) and the net reclassification index (NRI).

Results
We report data on 14 591 patients with 36 478 person years of follow-up and 876 composite events (433 non-fatal CVD events). Cumulative event-free survival after 30 months was 94.6% among participants without PN and 89.6% among those with PN (P<0.001). After multivariate adjustment, PN was associated with increased risk of incident CVD events (HR 1.34; 95% CI, 1.04-1.74; P=0.03). PN improved model fit and discrimination (relative IDI 0.7%); the NRI and clinical NRI were improved by 1.4% (P<0.001) and 4.6% (P<0.001) respectively.

Conclusion
Peripheral neuropathy is an independent risk factor for incident CVD events in individuals with diabetes mellitus without prior history of CVD. It provides additional information on cardiovascular risk over and above conventional risk factors.

**Take-home message**
Assessment of peripheral neuropathy among patients with diabetes is routine and provides additional information on cardiovascular risk to that of conventional risk factors, albeit modestly in the short term. Further research is needed to evaluate whether the inclusion of peripheral neuropathy can improve existing risk scores for CVD events in the longer-term, and whether interventions to aggressively target risk factor control attenuate the excess CV risk among those with peripheral neuropathy.

**O115 CARDIOPULMONARY EXERCISE TESTING AS A PREDICTOR OF POSTOPERATIVE CARDIAC AND PULMONARY OUTCOMES, EARLY MORTALITY AND LENGTH OF HOSPITAL STAY IN AAA REPAIR PATIENTS**
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**Introduction**
The aim was to assess whether parameters of aerobic fitness can predict cardiac and pulmonary outcomes, length of hospital stay and thirty-day mortality following AAA repair.

**Method**
Prospective data collection for patients undergoing AAA repair who had preoperative cardiopulmonary exercise testing (CPET) from August 2011 for 2 years. Multivariable analysis was used to study the effect of CPET parameters: Peak oxygen consumption (VO2 peak), anaerobic threshold (AT) and ventilatory equivalent for carbon dioxide (VE/VCO2) on postoperative cardiac and pulmonary complications, 30-day mortality and length of hospital stay.

**Results**
118 patients (106 males, mean age ±SD 74.6 ± 6.9) were included (51 EVAR, 67 OAR). Median (IQR) VO2 peak was 17.2 (14.3-19.9) ml/kg/min, AT 11.7 (10.2-13.6) ml/kg/min and VE/VCO2 34.5 (30.0-38.1). 16 (13.5%) patients developed cardiac complications; increased age (odds ratio (OR) 1.1, 95 per cent confidence interval 1.00 to 1.21; P=0.044), increased VO2 peak (OR 1.26, 1.01 to 1.56; P=0.038) and decreased AT (OR 0.65, 0.47 to 0.91; P=0.011) were associated with higher cardiac complications. 23 (19.5%) patients developed pulmonary complications; increased VE/VCO2 (OR 1.16, 1.01 to 1.28; P=0.002) was associated with higher pulmonary complications and EVAR with less (OR 0.12, 0.03 to 0.53; P=0.005). Decreased age (beta=-0.27; P=0.006) and EVAR (beta=-0.44; P<0.001) were associated with shorter hospital stay. CPET parameters were not associated with 30-day mortality.

**Conclusion**
Different CPET parameters seem to predict different cardiopulmonary complications following AAA repair. However, this study showed no association between CPET and early mortality or length of hospital stay.

**Take-home message**
Parameters of cardiopulmonary exercise test can be predictive of postoperative morbidities following all interventions for AAA

**O116 TOLL-LIKE RECEPTOR 4 ANTAGONISM SIGNIFICANTLY IMPROVES FIBROBLAST MIGRATION IN SIMULATED DIABETIC ISCHAEMIC CONDITIONS**
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**Introduction**
Diabetic foot ulceration is a multifactorial, frequent and challenging complication of diabetes. There is increasing evidence that activation of toll-like receptor 4 (TLR4) is involved in the systemic pathogenesis of diabetes and subsequent impairment of wound healing, however the mechanism remains unclear. We aim to study the role of TLR4 in fibroblast migration, an essential process in wound healing.

**Method**
The migration of human skin fibroblasts was assessed by scratch wound assay. Varying glucose concentrations were tested (5.5 mM, 15mM and 25mM), and simulated ischaemia applied using a hypoxic chamber. The effects of TLR4 inhibition on cellular migration was assessed by the addition of a TLR4 neutralising antibody and a TLR4 antagonist to 25mM...
groups. Cellular migration was quantified using a technique to estimate the percentage coverage of the scratch wound following treatment.

**Results**
High glucose concentrations (15mM and 25mM) led to an apparent increase in fibroblast migration compared to 5.5mM in normoxic conditions (not significant). Ischaemic conditions resulted in impaired fibroblast migration, particularly at high glucose concentrations (25mM, p>0.05). TLR4 inhibition by a neutralising antibody and a selective antagonist attenuated the effects of high glucose and ischaemia.

**Conclusion**
The reduced migration of fibroblasts in ischaemic conditions was greatest in the high glucose treatment groups. The addition of a TLR4 neutralising antibody or antagonist resulted in greater observed cell migration. We conclude that inflammatory processes mediated via TLR4 results in reduced migration of fibroblasts and contributes to impaired wound healing, under conditions commonly found in diabetic patients with concomitant ischaemia.

**Take-home message**
Chronic inflammation mediated via activation of the innate immune system (through TLR4) leads to a significant impairment in wound healing. Inhibition of TLR4 attenuates the combined exaggerated effect of hyperglycaemia and ischaemia on fibroblast migration.