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Pharmacokinetic properties of once-weekly insulin icodec in individuals with renal impairment vs normal renal function

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Poster Abstracts
Basic and clinical science posters: adipocyte function

P1

Mendelian randomisation studies do not support a causal role for reduced circulating adiponectin levels in fasting based measures of insulin resistance and Type 2 diabetes

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Aims: Adiponectin is strongly inversely associated with insulin resistance and Type 2 diabetes but its causal role remains controversial. We undertook Mendelian randomisation analysis to investigate the causal nature of the association between adiponectin, insulin resistance and Type 2 diabetes.

Methods: First, we used genetic variants, including a low frequency large effect variant, at the *ADIPOQ* gene in a multivariable regression analysis to find a set of single-nucleotide polymorphisms (SNPs) that explained the most variance in adiponectin levels. Second, we used the genetic variants as instruments to calculate a regression slope between adiponectin levels and fasting insulin and risk of Type 2 diabetes.

Results: In analyses of up to 33,671 individuals of European descent from 13 studies we identified four SNPs at the *ADIPOQ* gene which together explain 4% of the variance in adiponectin levels. In multivariable models each SNP was associated with adiponectin levels ($p < 5 \times 10^{-8}$). The instrumental variable analysis revealed no causal association with fasting insulin amongst 29,771 individuals without diabetes (0.02 SD, 95% confidence interval −0.07, 0.11, p = 0.60). We observed no causal association between reduced adiponectin levels and increased risk of Type 2 diabetes (odds ratio 0.94; 95% confidence interval 0.75, 1.19, p = 0.61; 3,604 cases vs 14,116 controls) in instrumental variable analyses.

Conclusions: Our results provide no evidence that genetic mechanisms that reduce adiponectin levels increase the risk of insulin resistance (using the surrogate measure of fasting insulin) and Type 2 diabetes. These results challenge the beneficial role of pharmaceutical and lifestyle interventions aimed at increasing adiponectin levels in order to improve insulin resistance or risk of Type 2 diabetes.

Basic and clinical science posters: beta cells, islets and stem cells

P2

Co-encapsulation of islets with mesenchymal stem cells improves graft outcome in mice

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Refer to Oral number A25

P3

Maintaining islet morphology is beneficial for transplantation outcome in diabetic mice

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Aims: We have previously shown that co-transplantation of islets and mesenchymal stem cells improves islet graft function and revascularisation, which was associated with the maintenance of normal islet morphology. The aims of the current study were to determine whether maintaining islet morphology in the absence of additional islet-helper cells would improve transplantation outcome in diabetic mice.

Methods: Islets were isolated from C57BL/6 mice. Recipient streptozotocin-diabetic C57BL/6 mice were transplanted with a minimal mass of 150 islets as a single pellet or islets that were either manually dispersed or dispersed within a matrigel plug beneath the kidney capsule. Blood glucose concentrations were monitored for one month. Islet graft morphology and endothelial number were analysed by histology.

Results: Islets dispersed both alone or within matrigel plugs maintained near normal morphology, in contrast to pelleted islets where individual islets fused to form large endocrine aggregates. Islet vascularisation was increased in mice transplanted with dispersed islets compared with pelleted islets (631 ± 44 vs 1155 ± 207 endothelial cells/mm^2, n = 4, p < 0.05, t test). The vascularisation of islets dispersed in matrigel was elevated compared with pelleted islets (961 ± 10 vs 620 ± 21 endothelial cells/mm^2, n = 4, p < 0.05, t test). After one month 1/6 mice transplanted with pelleted islets were cured compared with 5/6 mice transplanted with dispersed islets. The curative capacity of islets dispersed in matrigel was also better than that of pelleted islets (5/8 islet-matrigel implanted mice vs 1/7 mice transplanted with pelleted islets cured by one month).

compared with healthy subjects ($9.5\mu m^2 \pm 1.7$ vs $2.7\mu m^2 \pm 0.4$, p = 0.027). The addition of anti-TNF-α led to a marked decrease in the area of the disc erosion only in Charcot patients (from $9.5\mu m^2 \pm 1.7$ to $4.7\mu m^2 \pm 1.1$, p = 0.031) but not in patients with diabetes (from $5.2\mu m^2 \pm 0.9$ to $3.7\mu m^2 \pm 0.6$, p = 0.353) nor in healthy subjects (from $2.7\mu m^2 \pm 0.4$ to $3.3\mu m^2 \pm 0.3$, p = 0.704).

Conclusion: This study has shown for the first time that TNF-α modifies the resorptive behaviour of newly formed osteoclasts in Charcot osteoarthropathy. These cells demonstrate increased osteoclastic activity resulting in large and deep bony erosions, which may explain the pathogenesis of this condition.

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Bone resorption and inflammation are reduced in the chronic phase of charcot neuro-osteoarthropathy

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Objectives: Treatments of Charcot neuro-osteoarthropathy (CNO) most exclusively rely on off-loading of the affected joint despite a 17% rate of relapse if off-loading is discontinued too early. Although osteoclastogenesis and local inflammation are increased in the acute phase, little is known about the evolution of these two processes during settlement of this complication.

Methods: We studied seven patients with diabetes with recent onset of acute CNO for a follow-up period of six months with a visit at onset and at one, two, four and six months. At onset, the patients were age- and sex-matched with 11 patients with diabetes and six healthy control participants. Serum concentrations of TNF-α and C-telopeptide cross-link of type one collagen (sCTX) were determined by ELISA. The number of circulating CD14 positive cells was determined by flow cytometry. Data were compared using the Kruskall–Wallis test.

Results: In CNO patients, the serum concentration of TNF-α and sCTX significantly declined with time by 52% and 47% at 6 months compared with onset. At four and six months, respectively, circulating levels of TNF-α and sCTX were not significantly different from either patients with diabetes (p = 0.558) or healthy volunteers (p = 0.201). In CNO, the number of $CD14^{high}$ positive cells declined by 15% at six months compared with onset (p = 0.028). At four months, the number of $CD14^{high}$ positive cells was not significantly different in CNO patients compared with either patients with diabetes (p = 0.188) or healthy volunteers (p = 0.584).

Conclusions: Monitoring the circulating levels of TNF-α, sCTX and the number of $CD14^{+}$ cells might represent alternatives in identifying CNO patients at risk of relapse.

Basic and clinical science posters: genetics

P77

Impact of Type 2 diabetes susceptibility loci on variation in multiple cardio-metabolic traits

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Aims: Type 2 diabetes is related to pathophysiological changes in metabolic and cardio-vascular traits. We aimed to uncover the mechanistic basis of Type 2 diabetes associations by exploring the pleiotropic effects of Type 2 diabetes risk variants on multiple cardio-metabolic traits.

Methods: We evaluated the effects of 65 established Type 2 diabetes associated common genetic variants (September 2012) on 22 quantitative anthropometric, glycaemic, lipid, blood pressure, obesity, fat distribution and hypertension traits. We analysed the multi-trait effects using two cluster analysis methods, k-means clustering and complete hierarchical agglomerative clustering. Clustering identified groups of loci with shared genetic effects on cardio-metabolic traits. We compared genetic associations with known epidemiological correlations.

Results: Complete hierarchical cluster analysis grouped 65 Type 2 diabetes loci into five major clusters based on patterns of their associations with 24 cardio-metabolic traits. Type 2 diabetes risk variants near *GCKR* and *CILP2* were associated with lower low density lipoprotein cholesterol, total cholesterol and triglycerides, whilst those at *FTO* and *MC4R* were correlated with obesity-related traits. The group including *ARAP1*, *GCK* and *MTNR1B* were related to hyperglycaemia and decreased beta cell function. K-means clustering distinguished two additional subgroups of loci: (I) *GRB14*, *IRS1*, *PPARG1*, *KLF14* and *ADAMTS9*; and (II) *CDKAL1*, *ADCY5* and *SLC30A8*. In both subgroups, the Type 2 diabetes risk alleles were associated with 'leanness' via an impaired metabolic profile. However, only in the second subgroup were Type 2 diabetes risk alleles also associated with decreased beta cell function. All other loci showed no clear-cut cardio-metabolic trait associations.

Conclusions: Our findings indicate that Type 2 diabetes susceptibility variants exert their effects on ultiple cardio-metabolic traits through a variety of mechanisms.

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Newly identified genetic locus influencing fasting plasma glucose levels in people with Type 2 diabetes: the Edinburgh Type 2 Diabetes Study (ET2DS)

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Aims: To date, over 40 Type 2 diabetes susceptibility loci have been identified, associated with either diabetes onset or glycaemic phenotypes. We explored the association between single-nucleotide polymorphisms (SNPs) on Metabochip, an Illumina custom array, and fasting glucose in a representative cohort of subjects with Type 2 diabetes.

