2454-PUB

WITHDRAWN

IMMUNOLOGY

2455-PUB

Individuals with a First-Degree Relative with Type 2 Diabetes Manifest Adverse Inflammatory Responses following a Meal Rich in Carbohydrate

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We have previously found that obese individuals with insulin resistance manifest adverse immune-metabolic responses that can be magnified after consuming a meal rich in carbohydrate. Here, we studied normoglycemic men with (n=9) or without (n=9) a first degree relative with type 2 diabetes (FDRT), matched for body mass index, waist circumference, age, and insulin sensitivity (homeostasis model assessment) during fasting, and after consuming a 600-kcal liquid, carbohydrate rich meal (57% of energy from carbohydrate). We assessed plasma glucose, insulin, triglycerides, non-esterified fatty acids (NEFA), cytokines (IL6 and TNFα), and gene expression levels of NFκB complex (i.e., RelA, p105, IκBα, IκBβ), IL6, TNFα, IL1β, IL10, TGFβ, TLR4, and MCP1 in circulating mononuclear cells (MNC). Postprandial glucose excursion and NEFA suppression were not different between groups, but FDRT subjects had greater postprandial insulin and triglyceride concentrations during the first 2 h after the meal. Postprandial expression of TNFα and IL10 in MNC was greater in FDRT. There were also trends for increased expression of key pro-inflammatory transcription factor (NFkB complex) genes and its target genes (i.e., MCP1 and IL6); and decreased expression of anti-inflammatory genes (i.e., TGFβ) in MNC of FDRT subjects. Despite higher basal plasma IL6 concentrations in the FDRT, the postprandial IL6 response in plasma was similar between two groups. TNFα concentrations in plasma were too low to be detected in the majority of the samples. MNC gene expression (i.e., MCP1, IL10, and TGFβ) correlated positively with the 2 h postprandial rise in insulin concentrations. These results suggest that heredity of type 2 diabetes is associated with a pro-inflammatory immune-metabolic response in the postprandial period. This may predispose FDRT individuals to greater cardio-metabolic risk.

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2456-PUB

WITHDRAWN

TRANSPLANTATION

2457-PUB

Peak Insulin Drip Rate Associated with Decreased Infections Post-Liver Transplant

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Hyperglycemia is associated with infection and rejection in post-liver transplant (LTX) patients (pts), but little is known about peak insulin requirements and morbidity.

This retrospective cohort study (N=207) was conducted to evaluate peak insulin requirements and subsequent morbidity in post-LTX pts (2011-2012). Pts were further separated into quartiles (Q) by peak insulin drip (gtt) rate [U/hr].

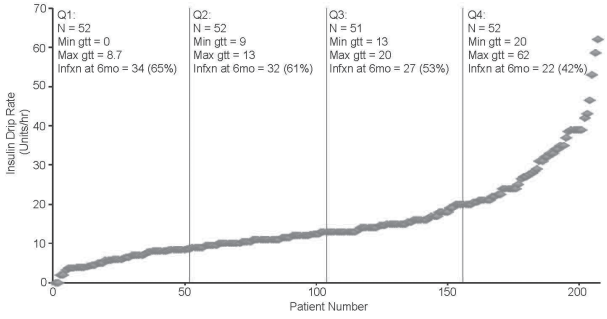
Peak gtt rate ranged 0-62 (mean 15.65 ± 11) and Qs are shown in Figure 1. Comparisons were made between Q4 and Q1-3. Q4 pts were similar in age and BMI, but more had DM (Table). Q4 pts had significantly fewer infections up to 6 mos and borderline lower rejection. Peak insulin gtt was associated with decrease odds of infection up to 6 mos following adjustment for BMI, MELD score, and DM status (OR: 0.50, p = 0.046 95% CI 0.25-0.99).

Table. Patient Characteristics.

Characteristic	All Patients (N=207)	Q1-3 (N=155)	Q4 (N=52)	P-value
Mean age (years)	56.6 +/- 10.4	56.1 +/- 11.0	58.02 +/- 8.3	p = 0.255
Pre-Transplant Diabetes	74 (35.7%)	46 (29.7%)	28 (53.8%)	p = 0.0025
BMI	29.6 +/- 6.5	29.6 +/- 6.5	29.8 +/- 6.6	p = 0.84
MELD Score	26.8 +/- 12.2	28 +/- 13.6	23 +/- 5.6	p = 0.64
Any Infection to 6 Months	115 (55.5%)	93 (60%)	22 (42.3%)	p = 0.035
Rejection	75 (36.2%)	62 (40%)	13 (25%)	p = 0.066

Data are expressed as mean +/- SD or n (%) unless otherwise indicated.

Figure 1. Decreased Infection with Increased Insulin Drip Rate in Post-Liver Transplant Patients.



2458-PUB

Attempts to Predict Islet Yield Based on Screening Methods and to Simplify Follow-up Measurements after Islet Autotransplantation

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Decision about timing of total pancreatectomy (TP) for chronic pain and pancreatitis is difficult due to risk of postsurgical diabetes despite islet autotransplantation (IAT). It was found in pediatric population, that islet isolation yield and chance for insulin independence could be predicted based on simple preoperative measurements, so we decided to verify it in our adult population. Next, we checked whether simple fasting blood measurements correlate with more logistically challenging stimulation test in order to simplify follow up procedure. We measured weight, body mass index, A1c, fasting glucose, c-peptide and creatinine, as well as performed mixed meal tolerance test (MMTT) prior to TPIAT in 12 adult patients. Next, we analysed results of MMTT and fasting blood samples on day 75 and 1 year after the transplant looking for correlations. We did not find correlation between isle yield in islet equivalent (IEQ) or IEQ/kg and following factors: time with pancreatitis, age, weight, body mass index, fasting serum glucose, fasting c-peptide to glucose creatinine ratio, peak glucose, c-peptide, insulin, area under the curve (AUC) for c-peptide from MMTT. We found weak correlation between A1c and IEQ/kg (r=-0.57, p=0.049) but not with IEQ (NS). After the transplant, peak glucose in MMTT correlated with SUITO index (rho=-0.68, p=0.001) and with fasting c-peptide/glucose (rho=-0.55, p=0.017); c-peptide AUC correlated with fasting c-peptide/glucose (rho=-0.55, p=0.016) but not with SUITO. We found also correlation between c-peptide AUC in MMTT on day 75 and islet dose (r-=0.89, p=0001) confirming importance of high islet dose for efficient insulin secretion after the transplant. We were unable to identify factors predicting islet yield after TP. Fasting measurements of blood glucose and c-peptide can approximate results of MMTT and can be utilized to simplified patient follow up.

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2459-PUB

WITHDRAWN

2460-PUB

A Functionalized Photo Tunable Hydrogel Promoting Islet Transplant Engraftment and Function

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Islet transplantation is emerging as a promising cell replacement therapy for type 1 diabetes. To date, however, several hurdles remain for the widespread adoption of this approach. First, revascularization of islet transplants remains inefficient leading to substantial tissue loss during the first few days after transplantation. Second, immune recognition of allogeneic histocompatibility antigens and recurrence of autoimmunity requires systemic immunosuppressive regimens that have been shown to negatively impact islet engraftment, survival and function. To overcome these limitations, the identification of biocompatible materials that can be used to encapsulate islet grafts offers new opportunities. Yet, encapsulation materials tested so far have met limited success for the long-term survival, function and protection of islet grafts in vivo.

In this study, we have designed and tested a new generation of biocompatible materials whose properties can be readily tuned to integrate user-defined biophysical and biochemical cues that support islets function, promote interaction with the host vasculature and incorporate immune modulatory moieties capable of mitigating host immune responses. The material is a new poly (ethylene glycol)-based hydrogel whose chemistry render it phototunable, allowing for the dynamic material functionalization of the hydrogel with pro-angiogenic cues and immunoregulatory moieties upon mild exposure to cytocompatible light. Our results demonstrate that this new programmable biomaterial supports islet cell survival and function by providing a tissue-like niche whose three-dimensional architecture and biochemical composition is designed to incorporate extracellular matrix moieties that we previously identified in the human pancreas, support angiogenesis, and promote leukocyte exclusion from the grafts. We anticipate that this new approach will have a significant translational application to human islet transplantation.

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INSULIN ACTION—ADIPOCYTE BIOLOGY

2461-PUB

Omics Analysis of Adiponectin in African Americans to Elucidate the Biology Underlying Metabolic Disease

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There is extensive epidemiological literature examining adiponectin in T2D and obesity. Despite higher prevalence, few studies have examined African Americans (AAs) where differences are accentuated, i.e., lower protein levels compounded by higher insulin resistance and cardiometabolic disease risk. Beyond statistical implication, we assessed the biological contribution of adiponectin to cardiometabolic phenotypes using omics technologies. Plasma adiponectin, transcriptional profiling of subcutaneous adipose and muscle, glucose homeostasis (fasting and FSIGT), and genotypes (Omni5+) were assessed in 240 fasting nondiabetic AAs. Plasma adiponectin was negatively correlated with insulin resistance ($HOMA_{IR}$; r=-0.36, P=1.7E-8) and adiposity (BMI; r=-0.25, P=9.3E-5), with similar relationships for the ADIPOQ transcript (r=-0.25, P=4.6E-5 and r=-0.37, 1.2E-9, respectively) in adipose (age, gender, admixture adjusted). The correlation between protein and transcript was weak (r=0.28, P=1.5E-5) suggesting additional modulators. Despite no ADIPOQ muscle expression, correlation of the adipose transcript with downstream targets in muscle, e.g., ADIPOR1 and AKT1, indicates tissue-tissue crosstalk. A positive correlation (r≥0.4) of 247 transcripts (e.g., CS, DLST, ECH1) was enriched for mitochondrial function and oxidative phosphorylation (P=1.2E-22). A negative correlation (r≤-0.4) of 44 transcripts (e.g., CD68) was enriched for immune response (P=2.32E-28). Association analysis of the ADIPOQ locus with transcript level identified rs17846866 (P=1.1E-5), in ADIPOQ which was not associated with plasma adiponectin (P=0.9). These results suggest higher order regulation of protein pathways, e.g., protein multimerization. Analysis is currently underway for high molecular weight adiponectin. These results elucidate the metabolic role of adiponectin in human physiology and reveal novel insights into the regulation of metabolic disease.

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INSULIN ACTION—CELLULAR AND MOLECULAR METABOLISM

2462-PUB

WITHDRAWN

2463-PUB

WITHDRAWN

2464-PUB

WITHDRAWN

2465-PUB

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2466-PUB

Insulin Activated AMPK through Inhibiting Rho Kinase in Insulin-Resistant Skeletal Muscle Cells

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Lipotoxicity has been associated with type 2 diabetes mellitus. Our recent study indicated that SREBP-1c, a transcription factor that controls cellular lipogenesis, participated in fatty acid-induced insulin resistance through a direct effect of suppressing the transcription of insulin receptor substrate-1 in skeletal muscle cells, addressing its potential importance in metabolic disease. The molecular mechanism of insulin reducing SREBP-1c protein level is unclear.L6 myotubes were added with a final concentration of 0.5mM palmitic acid (PA) for 0 h to 48 h and then treated with 100nM insulin for 12 h. L6 myotubes were added with 0-100nM insulin after 0.5mM PA intervention. DN-AMPKα2 lentivirus, siRNA-AMPKα2 and AMPK inhibitor were used for determining the role of AMPK in vivo and in vitro. In order to investigate the specific mechanisms responsible for the insulin-induced AMPK activation, siRNA-ROCK1 and siRNA- LKB1 were transfected into PA-induced L6 myotubes. The protein levels were measured by western blot.We found that insulin increased AMPK phosphorylation and reduced SREBP-1c protein

For author disclosure information, see page A696.