2655-PUB

Optimal Gestational Diabetes Screening Cutoff for Obese and Overweight Women

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Background: A woman's risk of developing gestational diabetes mellitus (GDM) varies by body mass index (BMI), from 5% when normal weight to at least 12% when obese. In the United States, pregnant women are screened for GDM with a 50 g glucose challenge test (GCT) at 24-28 weeks gestation. If they screen-positive, a diagnostic 3 hour 100 g glucose tolerance test is performed. However, studies used to determine screen positive cutoffs were performed years ago when the obstetric population was leaner and GDM prevalence was lower.

Objective: To determine the predictive value of commonly used GDM GCT screening cutoff for women with pre-pregnancy BMI ≥25 kg/m^2.

Method: Retrospective cohort study of obese/overweight women with singleton pregnancies who underwent GDM screening from 2013 to 2016 at one tertiary care hospital which uses 130 mg/dL as its screen positive cutoff. GDM diagnosis was based on the Carpenter Coustan criteria.

Results: 552 women had GCT values ≥ 130 mg/dl, 196 of them had values <140 mg/dl. Ultimately, 149 women were diagnosed with GDM, 22 of these women had values <140 mg/dl (Table).

Conclusion: Among overweight and obese women with a GCT <140 mg/dl, 11% have GDM. This high rate of GDM among women with a GCT <140 suggests that the screening cutoff may need to be different in obese and overweight women compared to their normal weight counterparts, although costs must also be considered in future studies.

Table. Testing Characteristics of GDM Screen Values Based on Different Cutoffs.

GDM Screen Cutoff	Sensitivity	Positive Predictive Value	Negative Predictive Value
>=130 mg/dL	100%	27%	100%
>=135 mg/dL	91.9%	29.8%	87.4%
>=140 mg/dL	85.2%	35.7%	88.9%
>=145 mg/dL	75.2%	40.9%	86.8%

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ISLET BIOLOGY—BETA CELL—DEVELOPMENT AND POSTNATAL GROWTH

2656-PUB

Identification of C-Maf as a Coordination Regulator of Islet β-Cell Development and Function

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V-maf musculoaponeurofic fibrosarcoma oncogene homologue C (c-Maf) is the member of the large macrophage-activating factor, the family contains MafA MafB and c-Maf which play an important role in the secretion of insulin and the development of pancreas islet B-cell. C-Maf was generally found in hematopoietic system, nervous system and lens differentiation. Little is known about the contribution of c-Maf in pancreas. To examine the effects of c-Maf in pancreas endocrine cell development and function, we analyzed c-Maf expression in a wide array of mouse tissues, revealing the highest expression in spleen, and the expression in pancreas. Isolated adult mouse islets, X-gal and insulin double staining of pancreas frozen sections shows c-Maf is related to insulin positive cell. Plasma glucose level of c-Maf+/–: MafA+/– knockout mouse is significantly increased than the MafA+/– group (P<0.01), and both higher than the WT group (P<0.01), whereas c-Maf+/– group not show significantly increased than the MafA+/– group based on glucose tolerance test of gene deficient mice. Additionally, these changes were consist with the in vitro experiment, gene expression analysis of Beta-TC-6 by quantitative RT-PCR revealed decreased levels of insulin genes and β-cell-related genes whose expressions are known could affect the development of islet B-cell when co-transfection siRNA to interrupt the expression of both MafA and c-Maf gene compare to the siRNA MafA group, the insulin level in the co-transfection group is lower than the MafA siRNA group detected by ELISA, the number of islet B-cells is decreased in the co-transfection group. Suggest c-Maf may involve in the development and function of islet B-cell.

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2657-PUB

Regulation of Beta-Cell Insulin Receptor Expression in Prediabetic and Diabetic Mice

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Beta cells express insulin receptors (IR), but their role in regulating beta cell size, function and glucose metabolism is not well described. This study investigated effects of peripheral insulin resistance with and without persistent hyperglycemia on islet IR. The hypothesis was that IR expression would decrease with T2DM in KKA^y mice but would remain steady in euglycemic, insulin-resistant KK mice. Tissue sections from 4-12 wk old mice were immunohistochemically stained for IR. Confocal images were taken of islets. Using image analysis, the sum relative intensity (RI) of IR fluorescence in a region of interest (RoI) outlining the islet and in the exocrine pancreas (nonspecific staining) were determined. The sum RI was normalized to RoI area and nonspecific staining was subtracted from IR staining. Data were log transformed then analyzed by 2-way ANOVA with factors KK/KKA^y and age. For some islets, IR were not detected, and a higher percentage of those islets were from KKA^y mice [% total islets: KK: 4 wk: 28%, 8 wk: 9%, 12 wk: 1%; KKA^y*: 4 wk: 50%, 8 wk: 11%, 12 wk: 10%; Chi distribution *p<0.05]. For islets expressing IR [Interaction: KK/KKA^y *age, F (2,846)=9.539, p<001], IR was decreased in 4 and 12 wk KKA^y mice, with maximum expression at 12 and 8 wks in KK and KKA^y mice [KK: 4 wk (n=120), 208±23; 8 wk (n=118), 238±24; 12 wk (n=154), 334±31†; KKA^y: 4 wk (n=70), 99±15*; 8 wk (n=197), 250±22†; 12 wk (n=193), 149±15*‡; *p<0.05 vs. control; †p<0.05 vs. 4 wks; ‡p<0.05 vs. 8 wks]. At 12 wks, the IR ROI was about double in KKA^y mice [Interaction: KK/KKA^y *age, F (2,846)=13.072, p<001; KK (n=154) 3,076±362; KKA^y (n=193) 6,454±722*; *p<0.05]. Expression of IR was lower prior to onset of T2DM, increased at onset of T2DM, then was suppressed after 4 wks of chronic hyperglycemia. Any feedback regulation on beta cells by secreted insulin acting through IR may diminish with chronic hyperglycemia in T2DM KKA^y mice, which may contribute to beta cell dysfunction.

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2658-PUB

Hyperglycemia Induced by High-Fat Diet Was Transient and Gender Dependent in C57BL/6J Mice

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High fat diet has long been used to induce hyperglycemia in mice served as one of the type 2 diabetes mice models. Four to 12 weeks intervention were mostly adopted in previous studies. Yet phenotypes of long term high fat diet induction in C57BL/6J mice has not been described by far. Here we observed that high fat diet feeding induced significant hyperglycemia in male C57BL/6J mice at week 12, which accompanied with increasingly weight gain. However, at week 20, blood glucose level returned to comparable level as control male mice fed with chow diet. And this trend sustained until the end of one year observation period. Pancreas section staining revealed that signals of Notch signaling pathway were upregulated in islets from high fat diet group, which were not detected in control ones. More interestingly, restoration of hyperglycemia was not observed in female mice under the same experimental setup even weight gain between high fat diet and chow diet group was also statistically significant.

In conclusion, long term high fat diet induce restoration of hyperglycemia in male C57BL/6J mice, which may contributed by beta cell compensation mediated through Notch signaling pathway.

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ISLET BIOLOGY—BETA CELL—STIMULUS-SECRETION COUPLING AND METABOLISM

2659-PUB

Beta Cells Communicate with Pancreatic Macrophages via Endogenous Secretion of ATP

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Insulin and glucagon secretion from the pancreatic islet of Langerhans is crucial for regulating glucose metabolism. Dysfunction of the islet leads to diabetes. The islet is composed of endocrine, vascular, and immune cells. In other tissues, resident macrophages are in charge of maintaining tissue integrity and homeostasis. Until now, however, islet resident macrophages have not been investigated in their steady state in situ. To study the physiology of the resident macrophage we are conducting studies on isolated islets,

and living tissue pancreatic slices. Using these technological platforms, we are characterizing their phenotype, Ca2+ response profile to islet stimuli, and dynamic behavior. In these studies, we have found that islet macrophages are activated by ATP released by beta cells during high glucose stimulation. We expect our results to define the role of the islet resident macrophage under normal physiological conditions.

2660-PUB

WITHDRAWN

2662-PUB

WITHDRAWN

ISLET BIOLOGY—SIGNAL TRANSDUCTION

2661-PUB

Effect of Arsenic on Proteomes and Phosphoproteomes in Rat Pancreatic Beta Cells

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Arsenic, a well-known environmental and occupational toxin, has been considered as a risk factor for development of pancreatic beta cell dysfunction and subsequent diabetes. It is critical to understand how arsenic leads to malfunction of protein post translational modifications in beta cells, such as phosphorylation. However, no large scale profiling of proteomes and phosphoproteomes in arsenic induced insulinoma cells have been reported. In this study, we treated rat pancreatic beta cells (INS-1) with or without 1 μM arsenic for 24 hours (n=6), and characterized proteins and phosphorylation sites in the beta cells by proteomics analysis. All the proteins in the cells were extracted and digested into peptides, followed by phosphorylated peptides enrichment using titanium dioxide. The digested and enriched peptides were analyzed by high resolution mass spectrometry using Orbitrap Fusion Lumos, and the bioinformatics analysis was carried out by MaxQuant and David Bioinformatics. We identified 5000 proteins (with at least 2 unique peptides) and 2800 phosphorylation sites (with at least 75% localization probability), which were assigned to >1200 proteins. Furthermore, >200 of proteins and >150 phosphorylation sites changed significantly ($p<0.05$) upon the arsenic stimulation. Interestingly, the pathway analysis of the arsenic-responsive sites showed that multiple pathways crucial to diabetes and arsenic binding were significantly enriched, such as insulin secretion, cellular glucose homeostasis; metal ion binding, calcium ion transport, protein ubiquitination, regulation of MAPK cascade.

In summary, we were have provided one of the largest proteomes and phosphoproteomes in rat INS-1 beta cells, and discovered significantly changed proteins and/or phosphorylation events induced by arsenic treatment, which might provide novel insights of molecular mechanism of arsenic induced beta cell dysfunction and diabetes.

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