Differentiation of Diabetes by Pathophysiology, Natural History and Prognosis

October 9-11, 2015

Issues Discussed & Debated

- Genetic and environmental determinants of type 1 and type 2 diabetes
- Risk and progression
- Complications
- How best to determine appropriate therapeutic approaches based on both the pathophysiology and stage of disease, as well as individual phenotype, needs, resources, and concomitant issues

Themes

- Individualization of preventive and therapeutic strategies is the way forward in medicine
- Modern diabetes care remains far from this ideal
- Guidelines do not apply to all people with diabetes – individualize treatment plan
- Adapt therapeutic targets to the individual patient

Critical Questions

- Do we have sufficient evidence to appropriately differentiate people with diabetes?
- Could careful phenotyping of people diagnosed with diabetes allow more tailored interventions?
- Would more tailored therapeutic targets lead to longer, healthier lives?

Common Features

- Hyperglycemia
- Loss of beta-cell mass and/or function
- Hyperglycemia-induced complications

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

- Jay Skyler
- Disclosed no conflict of interest relevant to this presentation.
Needs

- Better understanding of the pathophysiology of diabetes
- Identification of novel biomarkers
- Development of novel therapeutic interventions

The Diabetes Explosion

Diabetes: A global emergency

The Prevalence of Diabetes is Increasing, Particularly in Adults ≥ 65 Years of Age

T1D incidence is Rising 3-5% per Year
Environmental Factors

• Enteroviral infection
• Other viruses
• Bacteria
• Infant feeding
• Inadequate breastfeeding
• Other environmental “toxins”
• Lack of exposure to pathogens – the “hygiene hypothesis”

Environmental Factors in T1D

• Obesity - clearly important in T2D - may be an accelerator of T1D as well.
• Dietary factors promoting islet inflammation and beta cell damage.
• Endocrine disruptors and other environmental polluters may impact metabolism and immunity.
• Autoimmunity (primary or secondary) may have a role in subtypes of T2D (LADA/insulin deficient subtypes) associated with possible environmental triggers (e.g. diet, infection).
• Gut microbiome composition has been linked to risk for T1D and T2D, as well as obesity.

Genetics

Hereditability

• Heritability ($h^2$) defined as sibling-relative risk
• 15 for type 1 diabetes
• 3 for type 2 diabetes
• 50 (high) for Maturity Onset Diabetes of the Young (MODY)
• Increases with the number of affected family members

Mongenetic Diabetes

Maturity Onset Diabetes of the Young (MODY)
• Mutations in any one of 13 different genes
• Most common: glucokinase (GCK) and transcription factors HNF1A, HNF4A and HNF1B

Neonatal Diabetes
• Permanent or transient
• Genes encoding for potassium channels in the pancreatic islets (SUR1, KCNJ11), insulin, glucokinase, and others can cause neonatal diabetes
Genetics and Type 1 Diabetes

- Most (85-90%) patients lack affected family members
- Approximately 10-15% of cases have an affected relative
- Yet there is familial clustering as shown by the increased risk of T1D in family members

**LIFETIME RISK OF T1D**

- Monozygotic Twins: 30-50%, up to 70%
- Siblings: ~6% (1-20%)
- Offspring of diabetic father: 6-9%
- Offspring of diabetic mother: 1-4%
- Parents of diabetic child: 3%
- General population: 0.4%

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Genetics and Type 2 Diabetes

- The lifetime risk of developing T2D is about 40% if one parent has T2D and even higher if the mother has the disease
- 130 genetic variants associated T2D or glucose/insulin levels
- Explain less than 15% of the heritability
- Most of these variants are in non-coding (likely regulatory) genomic regions
- Strongest effect on T2D risk conferred by an intronic variant in the TCF7L2 gene that encodes a transcription factor – mechanism unclear

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**Genome-wide Associations in Type 1 Diabetes**

Global genomic and transcriptomic analysis of human pancreatic islets reveals novel genes influencing glucose metabolism

Staging
Increased number of Autoantibodies is Associated with Increased Incidence of T1D (DPT-1)

Numbers 1–4 are number of autoantibodies at screening. Curves indicate occurrence of type 1 diabetes over follow-up (n = 29,035). DPT-1 = Diabetes Prevention Trial-Type 1

Children with Multiples Islet Autoantibodies Progress to Symptomatic Diabetes

High Likelihood of Progression to T1D in Genetically At-Risk Infants Who Develop Autoantibodies

Stages of Type 1 Diabetes

Stage 1: Beta Cell Autoimmunity/Normoglycemia/Presymptomatic T1D
Multiple T1D-associated islet autoantibodies with normal glycemic control

Stage 2: Beta Cell Autoimmunity/Dysglycemia/Presymptomatic T1D
Multiple T1D-associated islet autoantibodies with glucose intolerance or dysglycemia

Stage 3: Symptomatic T1D
Typical symptoms of clinical disease (polyuria, polydipsia, weight loss, fatigue, diabetic ketoacidosis, etc.)
Heterogeneity of the T1D Disease Process

- Genetic
- Age
- Type of Autoantibody
- Autoantibody Characteristics
- Gender
- Environment

Impact of Age on Risk for Disease Progression in Antibody-Positive Relatives in TrialNet Pathway to Prevention Study.

Model-based Estimates of Average Slopes of AUC C-peptide over time According to Age Quartiles
Impact of Age on C-peptide after T1D Diagnosis

Research Gaps

Research Gaps 1
- What is the role of specific environmental factors?
- Does infection play a role in the pathogenesis of type 1 diabetes?
- Do nutritional components impact beta cell autoimmunity?
- How do we prove or negate the multiple hypotheses promulgated?
- What determines the point at which beta cell dysfunction becomes irreversible?
- How do different dietary patterns influence the distribution of body fat and development of ectopic fat?
- Are some dietary factors protective whereas others promote ectopic fat deposition and therefore act as accelerators of diabetes progression?
- Can public health interventions that reduce the levels of consumption of sugar sweetened beverages and other energy dense foods reduce the incidence of type 2 diabetes?
- Can public health interventions, including changes to the built environment, that reduce sedentary time and increase time spent in physical activity reduce diabetes incidence at a population level?

Research Gaps 2
- Why is incidence of type 1 diabetes increasing?
- Why is there dramatic regional variation?
- What are causative factors behind known associations?
- Why is prevalence of type 2 diabetes increasing globally?
- What causes the increased risk for type 2 diabetes associated with race/ethnicity and geography?
- What accounts for increasing prevalence of type 2 diabetes among young people?
- Why does risk for type 2 diabetes increase dramatically with aging?
- What drives the increased risk for individuals with low SES?

Research Gaps 3
- What is the basis for the acceleration in the decline of insulin secretion in T1D?
- Is it caused by changes in immunologic factors or has it already been set in motion from previous beta-cell injury?
- To what extent does the loss of insulin secretion represent a reduction in beta-cell mass, a decrease in function, or both?
- Most data pertaining to the pattern of insulin loss in T1D was derived from adolescents & adults. Do young children have similar patterns?
- Even though the rate of the loss of insulin secretion is more severe in T1D than T2D, there is some commonality in the pattern of abnormal insulin secretion. Are common etiologic factor(s) the basis for this or is it a similar reaction of beta-cells to different etiologic factor(s)?
- To what degree is there heterogeneity in the pattern of the loss of insulin secretion, among those who develop T1D & those who develop T2D?
- A randomized controlled trial to determine the clinical benefits of screening and early treatment to normalize glucose levels in people with prediabetes is needed.

Research Gaps 4
- What precipitates beta-cell-specific immune responses and the relative contribution from perturbations that directly affect the beta-cell and the contribution from non-HLA genetic or environmental factors?
- Does heterogeneity in the initial antigenic targets of the immune response have different prognostic, genetic & environmental correlates that can be used to develop & apply therapeutics to prevent beta-cell autoimmunity?
- How do we develop inexpensive, specific and sensitive assays to identify beta-cell autoimmunity on a population-wide level and beyond the confines of specialized laboratories?
- Can we identify and validate prognostic biomarkers that predict rate of progression to dysglycemia prior to clinical diabetes, as well as in new-onset type 1 diabetes to optimize subject stratification and trial endpoints that allow smaller and shorter clinical trials?
- Biomarkers and imaging are needed to define reversion or stable autoimmunity versus active or flaring autoimmunity, and to detect responses to therapeutic interventions in order to accelerate the clinical development and clinical trial pathway.
Research Gaps 5

- Can we identify features of single antibody positivity associated with progression?
- Can we better understand pathophysiological heterogeneity by merging clinical phenotype, genotype, and immune-phenotype data from large cohorts?
- We need to dissect how factors contributing to susceptibility and progression act at one or both stages in order to develop stage-appropriate personalized therapies.
- We need to determine appropriate immune therapies to be used in combination either sequentially or simultaneously to target the β-cell specific immune response, islet inflammation, and more global defective immunoregulation.
- Immune therapies may need to be used in combination with therapies that promote β-cell survival or function, and therefore, an understanding of how β-cells die or fail in the presence of β-cell autoimmunity will be helpful.

Research Gaps 6

- Does the increased β-cell activity stimulated by insulin resistance enhance or accelerate the β-cell lesion of type 1 diabetes and/or type 2 diabetes?
- To what extent does insulin resistance contribute to glycemia and the complications of type 1 diabetes?
- Does the presence of both β-cell dysfunction and insulin resistance in type 1 diabetes patients suggest that type 1 diabetes and type 2 diabetes have common pathogenic features?
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Research Gaps 7

- Why does a subset of people with T1D develop diabetic nephropathy?
- Do environmental exposures or genetics drive development of diabetic kidney disease?
- Can metabolomics of urine identify better predictors of kidney disease progression? It will be critical to identify patients at different stages of kidney disease to identify markers that answer specific questions, including what is going on at the pathological level.
- How does hypoxia drive progression to kidney disease?
- How do various complications of diabetes affect one another and treatment approaches to each?
- When is albuminuria diabetic nephropathy? Should microalbuminuria be a surrogate for nephropathy progression?
- Is atherosclerosis the same disease in T1D and T2D?
- We need randomized clinical trials to examine aggressive glucose control in various populations with co-morbidities and complications.
- We need to develop the evidence base for modifying lipid targets in T2D.

Research Gaps 8

- Dedicated studies with glucose lowering strategies in special populations, including the elderly, with specific attention to frail elderly, renal impaired patients, and those with high cardiovascular risk.
- Is the process of renal impairment in T2D the same as in T1D?
- More insight in impact of hypoglycemia on CV outcomes
- Insight in specific heart disease in T2D- the diabetic heart
- Insight in heart failure and the impact of different agents on HF
- Does a treatment strategy for hyperglycemia that prioritizes weight loss result in better outcomes than a conventional approach that focuses on treatment of hyperglycemia irrespective of effects on body weight?
- Does including weight loss drugs in the algorithm result in better long-term outcomes?
- Who should be offered bariatric surgery?
- Does treatment of sleep apnea in obese people with T2D provide metabolic clinical benefit beyond that on the sleep disruption that characterizes the condition?