Expanding the View: the Ongoing Conundrum of Diabetes Classification

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DISCLOSURES FOR DR. JAMES R. GAVIN III

- Board Member/Advisory Panel: Abbott Diabetes Care; Janssen Pharmaceuticals; Merck; Novo Nordisk, Inc.; Intarcia Pharmaceuticals
- Consultant: Boehringer Ingelheim/Lilly Alliance; Janssen Pharmaceuticals
- Speaker’s Bureau: AstraZeneca; Boehringer Ingelheim/Lilly Alliance; Janssen Pharmaceuticals; Merck; Novo Nordisk, Inc.

Special Attribution to my colleague, a Clinical-Translator working at the Interface of Patient Care and Basic Science with a focus on

DIAGNOSING DIABETES MELLITUS IN ADULTS: TYPE 1, LADA, TYPE 2

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The Rising Tide of Global Diabetes: the Epidemic of Our Time


Why the Rapid Increase in Prevalence?
Change in Lifestyle in Native Americans

Arizona Pima 1900
Arizona Pima 2000

We have certainly not experienced a massive physiologic shift in the functional capacity of our beta cells in a century. We must look at and beyond the beta cell to account for the explosive increase in DM, and for an appropriate exploration of its heterogeneity. A beta cell focus is necessary but not sufficient to adequately characterize the forms of DM.


Are we “Handcuffed” Clinically by Arcane Notions of what Is Diabetes?

- A state of absolute or relative insulin deficiency,
- Characterized by hyperglycemia
- And the risk of microvascular and macrovascular complications.

WHO, 1999
Classification of Diabetes: Still Sufficient?

- Type 1 diabetes (T1DM)
  - β-cell destruction
  - Usually autoimmune, characterized by insulitis and presence of antibodies to components of islet cell or insulin itself
- Type 2 diabetes (T2DM)
  - Usually characterized by a combination of insulin resistance and an insulin secretory defect
- Gestational diabetes
  - Diabetes diagnosed during pregnancy
- Secondary diabetes – diabetes secondary to other conditions, e.g.
  - Pancreatic disease
  - Acromegaly, Cushing's

Glucose must be the Main Metabolic Driver of Long-term Complications in DM!
(Direct Consequences of Sustained Hyperglycemia)

Diabetic Retinopathy
Leading cause of blindness in working age adults

Diabetic Neuropathy
Leading cause of nontraumatic lower extremity amputations

Cardiovascular Disease
2-fold to 4-fold increase in cardiovascular events and mortality

Diabetic Nephropathy
Leading cause of end-stage renal disease


Our focus on the beta cell as the dominant physiologic defect in diabetes has resulted in perhaps an excessive reliance on the levels of one of its principal regulated substrates, i.e. glucose, to define the presence or absence of DM, its optimal treatment, and the clinical course/severity of the disease.

While the beta cell and the dysglycemia that results from its malfunction are necessary elements for classifying DM, they are not sufficient for determining the prospective clinical course, the treatment required, or the likelihood of complications.

Since the TYPE of DM one has at any given time really matters with respect to treatment and prognosis, we need a better and more precise system of classification.

Glucose Levels a Central Focus of CVD: Metabolic Basis of Increased Atherosclerosis

- Metabolic substrates
  - Glucose
  - Fatty acids
  - Lipoproteins

- Inflammation
  - Oxidation/glycoxidation
  - Endothelial dysfunction

- Prothrombotic state
  - Thrombosis

Michael Brownlee, MD
**Good Glycemic Control (Lower HbA1c) Reduces Incidence of Complications**

<table>
<thead>
<tr>
<th></th>
<th>DCCT</th>
<th>Kumamoto</th>
<th>UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>9→7%</td>
<td>9→7%</td>
<td>8→7%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>63%</td>
<td>69%</td>
<td>17–21%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24–33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>60%</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>–</td>
<td>–</td>
<td>16%</td>
</tr>
</tbody>
</table>


Slide modified from D. Kendall—International Diabetes Center, Minneapolis.

**Each A1C Percentage Point Is Critical**

Each 1% reduction in A1C is associated with:

- A 14% reduction in macrovascular disease
- A 11% reduction in microvascular endpoints
- A 13% reduction in stroke
- A 12% reduction in stroke
- A 37% reduction in microvascular endpoints
- An 16% reduction in heart failure


**Elements of Weakness in Using Glucose and Its Surrogates as Metrics to Classify DM and Define “DM Control”**

- Poor correlation of intensity of glucose control with full spectrum of morbid outcomes associated with the disease, especially those that account for majority of the death and disability
- Increasing insight into the lack of correlation between “estimated A1C” and “Glucose Time in Range, TIR” as assessed by CGM
- Is the AGP a more “physiologic” assessment of Glucose Tolerance than the oGTT?
- Increased insight into the contributions of other risk factors, i.e. lipids, BF, inflammation, SNS overactivation, sleep deprivation
- Beyond hypos, prospect that agents used to achieve glucose control might have other deleterious effects on CV outcomes
General Considerations for Addressing the Range of Unmet Needs

- Refresh our understanding of diabetes pathophysiology
- Understand implications of its natural history
- Understand implications of its overall heterogeneity
- Understand the urgency for individualization of therapy
- Understand the capabilities of current tools/treatments
- Understand the shortcomings of current treatments— in design, in composition, in timing, in consistency
- Understand the greater urgency of matching therapy to existing pathophysiology than precise classification of DM

Genetic and environmental risk factors impact inflammation, autoimmunity, and metabolic stress.

Hyperglycemia is a Metabolic Defect Common to all Forms of DM: But That's not all There is!
Gene/Environment Interactions with DM and its Complications: some in common to both

Genes related to b-cells and complication risk may be the Same Or Different: Haptoglobin PPAR TCF7L2- acl-5

Greater Biologic Precision Regarding the Underlying Disease Allows for Optimization of the Clinical Impact of the Available Therapies in Diabetes Mellitus

Insulin secretion Diabetes incidence Success of pharmacotherapy

Genetic variation TCF7L2 Reduced incretin action Insulinotropic effects

Genetic variation FFA1 Insulotrop effects

African American white Nordic Hispanic Non-SM Asian Hispanic

Insulin secretion Success of pharmacotherapy

Greater Biologic Precision Regarding the Underlying Disease Allows for Optimization of the Clinical Impact of the Available Therapies in Diabetes Mellitus
**New β-Cell Centric Construct: Implications**

**Genetics 101 for DM**

Phenotype is **DEPENDENT ON** Genotype:

Number of Genes - which genes, their nature, how many different ones, the 'severity/intensity' of expression; epigenetics*

i.e. Genes influence:

- Insulin secretory dynamics, insulin resistance, sites of susceptibility of β-Cell to destruction by endogenous/exogenous triggers
- Immune Modulation/Inflammation
- Insulin Resistance
- Environment

*Int J Biochem Cell Biol. 2015 May 27; pii: S1357-2725(15)00143-0. doi: 10.1016/j.biocel.2015.05.022. [Epub ahead of print]


**Genotyping: Relevance for DM?**

- Genotyping should be used for current research (cost ~$100) and future diagnostic markers on custom chips (even LESS $)
- Use for **Pharmacogenetics** should help guide choice of treatment
- Find Gene action/ Function - Leads to understanding mechanisms
  - e.g.: TCF7L2; Potential Therapy re: PARP-1 Inhibitor, other
  - Other Gene/Mechanism/ Therapy
    - low BMR: results in morbid obesity
    - Asian/Eastern Europeans: store more Visceral Fat at Lower BMI
    - PREVENT T2DM: SLC30A8
    - Increase Risk: TBC1D4 (Greenland)

Trends in Endocrinology and Metabolism. September 2014, Vol. 25, No. 9

**Can picture Molecular Pharmacogenetics Assay for DM as was developed for Breast Cancer**

multi-gene assay applied to paraffin-embedded breast cancer tissue, which allows physicians to predict subgroups of hormone-receptor positive, node negative patients who may benefit from hormonal therapy alone or require adjuvant chemotherapy to attain the best survival outcome

**Molecular Mammoscan**

22 vs Traditional Pharmacogenomic Assay

Could put other * Markers on same chip, eg: mRNA, islet DNA, Metabolomics, IR markers

As/when validated
Pathophysiology of Diabetes Complications
(the same factors that damage our vasculature in CVD of DM also damage our beta cells!)

Diagnosing Diabetes Mellitus in Adults:
Type 1, Type 2, LADA
or
Since Confusion Abounds, Isn’t it Time for A New Classification Schema for the Diagnosis and Treatment of Diabetes Mellitus (DM)?

We need to get ready for ‘PRECISION MEDICINE’

Purely Clinical Answer---
Adopt Empiric, Pragmatic Approach

It doesn’t matter which label is applied

- Insulin-Dependent
  - DKA: ketosis prone; insulin needed for survival
- OR NOT- Everyone else
  - Use ‘best clinical guess’; ‘label’ patient; Independent of age
  - Treat ‘as needed’ to get metabolic control,
  - (but must work under constraints of current ‘definitions’ for the classification of T2D- per payers/governments)
‘Diagnosis’ Has Many Functions
Need To Be More Than Pragmatic!!
- To plan patient’s care – MONI tailored patient-centric therapy
- To prevent – disease development and progression
- To predict – risk of DM
- To proliferate – and stimulate new scientific knowledge about DM
AND NEED TO CLASSIFY ACCURATELY

Current DM Classification Failing
(Certainly appropriate with knowledge available when current classification adopted)

BUT WE’VE LEARNED SO MUCH MORE
- Immune destruction of β-cells / and Insulin Resistance is used as basis of distinction between T1D, and T2D and all other sub-types of DM
- Diagnosis is often imprecise
  - Flatbush DM- present in DKA- “turn out to be T2DM”
  - LADA- Adults who look like ‘typical T1DM’
  - Antibody positive who look like “T2DM”
  - T1DM with Insulin Resistance (like T2DM)
Complicated by extensive overlap yet distinct differences in etiology and phenotype

Are we “Handcuffed” Clinically by Arcane Notions of what Is Diabetes?
- A prevailing view that for each case of DM there is a “cause” for which there is an agreed-upon approach to treatment—forexample of BG!
- While beta cell dysfunction gives rise to the hallmark of hyperglycemia, it is to be regarded as a “Herald” of the presence of DM (much like growing cell masses or unregulated, proliferating cell expansion herald the presence of cancer, without specifying the type)
- We engage a forced focus on reducing the “signal” of the disease, without adequately addressing its cause(s)
- Thus, we miss opportunities for disease modification and for attenuation of the risk of both microvascular and macrovascular complications.
Definitions: T1D, ‘LADA’, T2D
May Seem Precise BUT..., Overlapping Phenotypes

T1D (Formerly: IDDM, juvenile diabetes)
- Hyperglycemia resulting from autoimmune destruction of insulin-producing beta cells in the pancreas
- Insulin therapy is necessary for survival = insulin-dependent
  - Insurers/gov’t don’t permit ‘adjunctive’ therapy

T2D (Formerly: NIDDM; adult-onset diabetes)
- Hyperglycemia resulting from inadequate insulin/insulin-effect, usually in the context of insulin resistance
- Insulin may be ‘needed’ for good control, but not for survival
- Reduction/improvement of dysglycemia may be one of the minor targeted outcomes

‘LADA’- Ambiguous classification
- Later age, SPiDDM, ‘slowly progressive T1D’
  - ‘Slower’ destruction of β-cells than T1D
- Antibody positive T2D = ‘T1.5D’
  - ‘Faster’ destruction of β-cells than in T2D
- T-cell abnormal SPiDDM
  - Antibody negative
- Insulin commonly considered the ‘go to’ drug, even in patients with LADA with retained β-cell function
- May be timely to revisit the “goal” of therapy in these cases, given the wealth of new treatment tools available.

Comparing Definitions for T1D, ‘LADA’, T2D

<table>
<thead>
<tr>
<th>IMMUNITY</th>
<th>AGE</th>
<th>GENES</th>
<th>BMI</th>
<th>INSULIN THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1D</td>
<td>Strong</td>
<td>child</td>
<td>HLA++</td>
<td>low immediate</td>
</tr>
<tr>
<td>T1D</td>
<td>++</td>
<td>adult</td>
<td>HLA+</td>
<td>normal immediate</td>
</tr>
<tr>
<td>LADA</td>
<td>+</td>
<td>adult</td>
<td>HLA</td>
<td>normal variable</td>
</tr>
<tr>
<td>T2D</td>
<td>weak</td>
<td>adult</td>
<td>?</td>
<td>high infrequent</td>
</tr>
</tbody>
</table>

Adapted from Leslie et al. Diabetes Metab Res Rev. 2008 Oct;24(7):511-9
Distinct Etiologies and Characteristics

<table>
<thead>
<tr>
<th></th>
<th>T1D</th>
<th>‘LADA’</th>
<th>T2D</th>
<th>MODY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Age of Onset</td>
<td>All Ages</td>
<td>Mostly &gt;30</td>
<td>Mostly &gt;30</td>
<td>Mostly &gt;30</td>
</tr>
<tr>
<td>Etiology of Onset</td>
<td>Autoimmune</td>
<td>Mostly Inflammatory</td>
<td>Mostly Metabolic</td>
<td>Mostly Inherited</td>
</tr>
<tr>
<td>Progression to Insulin</td>
<td>Fast (days/week)</td>
<td>Latent (months/years)</td>
<td>Usually Normal</td>
<td>Depends on MODY type</td>
</tr>
<tr>
<td>autoimmunity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Depends on MODY type</td>
</tr>
<tr>
<td>Type of Diabetes</td>
<td>Mostly Type 1</td>
<td>Mostly Type 2</td>
<td>Mostly Type 2</td>
<td>Mostly Type 2</td>
</tr>
<tr>
<td>Typical BMI</td>
<td>Mostly Normal or Thin</td>
<td>Mostly Normal or Thin</td>
<td>Mostly Overweight or</td>
<td>Mostly Normal</td>
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<tr>
<td>Presence of Autoantibodies</td>
<td>Yes (ICA, IA2, GAD65)</td>
<td>Yes (mostly GAD65)</td>
<td>Some; others no</td>
<td>Depends on MODY type</td>
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<tr>
<td>T cell Response</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Insulin/ C-peptides Level at Diagnosis</td>
<td>Undetectable or extremely low</td>
<td>Low</td>
<td>Normal to High</td>
<td>Normal</td>
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<tr>
<td>Ketoacidosis</td>
<td>Yes</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Insulin Secretion</td>
<td>Low/null</td>
<td>Varies</td>
<td>Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>Islet Inflammation</td>
<td>Chronic Inflammation</td>
<td>Chronic Inflammation</td>
<td>Chronic Inflammation</td>
<td>None</td>
</tr>
<tr>
<td>HLA Link</td>
<td>High</td>
<td>Low</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>TCF7Link</td>
<td>None</td>
<td>In some populations, stronger link than T2D ?5%</td>
<td>None</td>
<td>In some populations, stronger link than T2D ?5%</td>
</tr>
<tr>
<td>Other Genes Involved</td>
<td>PTPN22; INS; CTLA4; CCR5; FOXP3; CLEC16a</td>
<td>PTPN22; INS; PPARG; JAZF1; KCNJ11; NOTCH2; WFS1; IGF2BP2; FTO; SLC30A8; HHEX</td>
<td>HNF1A; GCK; HNF1B; NEUROD1</td>
<td>HNF4A; GCK; HNF1A; IPF1; HNF1B; NEUROD1</td>
</tr>
</tbody>
</table>

Early Treatment
- Insulin required, diet & exercise helpful
- Non-insulin or insulin, diet & exercise helpful
- Non-insulin, diet & increased activity
- Gene specific

Late Treatment
- Insulin, diet, exercise
- Insulin, pills, diet, exercise
- Insulin, pills, diet, exercise
- Gene specific

Interim Summary
- Current definitions are imprecise and ambiguous
  - Complicated by overlapping characteristics (e.g. T1D with T2D parents, or, T2D with antibodies-no insulin)
  - Don’t take into account newer understandings of causes of DM/ mechanisms of hyperglycemia
- Need to focus on preservation/improvement of β-cell function
  - Insulin may be overused in patients with retained β-cell function
- Multiple mediating contributors to hyperglycemia and dysmetabolism are not taken into account in choice of treatment
- Gov’t & payers limit coverage for therapies based on ‘diagnosis’

Diabetes is a Continuum of β-cell FUNCTION

THE ISSUE IS LESS ‘What is LADA?’ RATHER WHAT ARE THE MECHANISMS and RATE of DESTRUCTION of β-cells in ALL PATIENTS WITH DIABETES? Improve therapy!!

Interim Summary
• Current definitions are imprecise and ambiguous
  – Complicated by overlapping characteristics (e.g. T1D with T2D parents, or, T2D with antibodies-no insulin)
  – Don’t take into account newer understandings of causes of DM/ mechanisms of hyperglycemia
• Need to focus on preservation/improvement of β-cell function
  – Insulin may be overused in patients with retained β-cell function
• Multiple mediating contributors to hyperglycemia and dysmetabolism are not taken into account in choice of treatment
• Gov’t & payers limit coverage for therapies based on ‘diagnosis’

THUS....
Call to Action

- There is a need for a nomenclature for the classification and diagnosis of DM that is in line with up-to-date knowledge of current views on pathophysiology and the newer diabetes therapies,
- That supports individualized (PRECISION) medicine
- That creates and targets regimens that build upon all available treatment options, for the multiple contributing pathways of hyperglycemia and the associated cardiometabolic risks in DM
- Compels, by the logic of the new system, gov’t and insurers to pay for the logical, effective, safe therapies for full spectrum of diabetes/defects
- Can accommodate future developments (i.e. CVOTs, renal protection)

The β-Cell Centric Classification of DM

Constitutes an Intuitively obvious approach and...

ANSWERS THE CALL TO ACTION
ALL DM shares Hyperglycemia (like all cancer shares abnormal cellular proliferation)

Classify each patient by the specific cause(s) of the β-cell dysfunction in the clinical presentation of their disease
Prescribe personalized treatment (patient-centric/PRECISION MEDICINE)
through targeted therapies
directed at all possible contributing dysmetabolic pathways of DM

The ‘β-Cell Centric’ Classification will help improve diagnosis and treatment, especially as our knowledge-base expands regarding the full spectrum of disease contributors

Expected Pushback from the Clinical Community

- What is your view then, about ‘pure’ Insulin Resistance Syndromes?

- Answer: This rare syndrome may represent a form of diabetes at the far end of the spectrum where the beta cell defect is not a core, but rather a contributing defect, and the major thrust of treatment must logically be directed accordingly.
The β-Cell:
The ‘Final Common Denominator’

- Rare Insulin Resistance Syndromes, e.g. leprechaunism, may not have a specific β-cell genetic defect, but β-cells damage may be part of the disease.


FINAL COMMON DENOMINATOR FOR DISEASE DIAGNOSIS

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Pushback-2

If you weaken the core concept of “T1DM”, what about the cure?

Answer: Loss of ‘T1DM’ designation WILL NOT take away from a focus on ‘the CURE’.....Indeed a New Classification system may well FACILITATE SEARCH FOR ‘THE CURE’ (i.e. focusing on mechanisms that slow the injury/destruction of the b-cell in ‘T1-LADA’, or speed destruction in ‘T2-LADA’...etc.)
β-Cell Centric Classification of Diabetes: Implications for Classification, Diagnosis, Prevention, Therapy, Research

- INSULIN RESISTANCE
- Environment
- Inflammation/Immune Regulation
- β-Cell secretion/mass
- FINAL COMMON DENOMINATOR

CLASSIFY PATIENT BY CAUSE(s) of Beta-Cell Dysfunction in EACH Individual

- Polygenic
- Monogenic

*Environment=Genetic susceptibility to many factors...
**Insulin Resistance= Centrally induced, Peripheral, Stress Hormones, Gut Biome

β-Cell Centric Classification of Diabetes: Implications for Classification, Diagnosis, Prevention, Therapy, Research

- INSULIN** RESISTANCE
- Environment*
- Inflammation/Immune Regulation
- β-Cell secretion/mass
- FINAL COMMON DENOMINATOR

*Environment=Genetic susceptibility to many factors...

Phenotypic Presentation is defined by:

- **Slope** = 'Natural History' over time, i.e. RATE OF β-cell LOSS.
  - Slope is not linear in either T1DM or T2DM, and may be intermittently relapsing, remitting, stabilized, and improved. Complete loss of β-cell mass may never be reached, especially if newer agents better preserve β-cells.

- **Severity** = β-cell loss of mass
- **Pre-Diabetes** = FBS ≥ 100, PPG ≥ 140
- **All DM** = FBS ≥ 126, PPG ≥ 200

- **Age at presentation** = tipping point when the combined gene effect / environmental trigger is expressed as phenotypic hyperglycemia
Phenotypic Presentation is defined by:

**Slope** = ‘Natural History’ over time, i.e., RATE of β-cell LOSS

Slope is not linear in either T1DM or T2DM, and may be intermittently relapsing, remitting, stabilized, and improved. Complete loss of β-cell mass may never be reached, especially if newer agents better preserve β-cells.

**Severity** = β-cell loss of mass

Increasing Age = tipping point when the combined gene effect / environmental trigger is expressed as phenotypic hyperglycemia

Phenotypic presentation of complications defined by:

**Slope** = ‘Natural History’ over time, i.e., RATE of Development of Comp

Slope is not linear in either T1DM or T2DM, and may be intermittently relapsing, remitting, stabilized, and improved, until ‘point of no return’ when presence irreversible

β-Cell Centric Classification of DM:

Implications for Classification, Diagnosis, Prevention, Therapy, Research

A β-cell centric classification allows for individualized care by identifying and treating patient-specific etiologies and contributing pathways of hyperglycemia and associated dysmetabolism leading to CVD

**EGREGIOUS ELEVEN**

1. One CORE diagnostic defect: the β-Cell
2. (at least) 6 treatable Causes of β-Cell Damage / HYPERGLYCEMIA
3. 5 treatable mediators of HYPERGLYCEMIA resulting from β-Cell Damage
A. β-Cell-Centric Construct: Egregious Eleven

The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage

1. Pancreatic β-cells
   - ↓ β-Cell function
   - ↓ β-Cell mass
   - ↓ Amylin

2. ↓ Incretin effect
3. α-cell defect
   - ↑ Glucagon

INSULIN RESISTANCE

6. Liver
   - Increased glucose production

5. Muscle
   - Decreased pan-creatine muscle uptake

4. Adipose
   - Increased lipolysis
   - Decreased morning dopamine surge
   - Increased sympathetic tone

3. α-cell defect
   - ↑ Glucagon

2. ↓ Incretin effect

1. Pancreatic β-cells
   - ↓ β-Cell function
   - ↓ β-Cell mass
   - ↓ Amylin

HYPERGLYCEMIA

Brain

Increased glucose uptake

PPG – HYPERGLYCEMIA

Stomach/Small intestine

Increased rate of glucose absorption

Colon/Biome

Abnormal microbiota; possible decreased GLP-1 secretion

Brain

↑ Appetite

Stomach/Small intestine

Increased rate of glucose absorption

Kidney

Increased glucose re-absorption

Muscle

Increased glucose production

Liver

Increased glucose production

Adipose

Increased lipolysis

β-Cell Issues as evidence of the presence of DM

➢ Usual use of Glycemic Criteria- A1c, FBS, PPG
➢ Markers-Usual/Occasional Use of C-Peptide
➢ New Non-Invasive
   ➢ β-Cell Mass Measures- Nano-particle labeled exendin imaging
   ➢ Circulating DNA Markers of β-Cell Destruction
     Glazer- Hebrew Univ
   ➢ Circulating mRNAs
➢ Try to Determine Mono-Genetic Causes

NO LOGIC FOR USE OF AGENTS THAT MAY CONTRIBUTE TO APOPTOSIS OF β-CELL......

OPT for BETA CELL PRESERVATION/REPAIR in DM: STOP USING SU’s, GLINIDES; Customize INSULIN THERAPY
Illustrative Case of the Need for a New System of Classification

• What is T2DM and how does one arrive at it?
• How many defects must be present to justify making this diagnosis?
• What treatment(s) would be required to Prevent, modify the course, avoid the complications, or otherwise “control” this disease?
• What does “controlling” T2DM really mean?
• What metrics should we monitor? For what should we be paid? What do patients really want as outcomes and is this different for HCS?

Natural History of Type 2 Diabetes
(This is Truly a Progressive Disease!)

<table>
<thead>
<tr>
<th>Age</th>
<th>0-15</th>
<th>15-40+</th>
<th>15-60+</th>
<th>25-70+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>Environmental factors; Other Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Resistance</td>
<td>Fasting Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrovascular Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 DM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvascular Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of Developing Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to need glucose-lowering medication</td>
<td>2-4 years</td>
<td>5-7 years</td>
<td>8-10 years</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity of T2DM Within Populations: the Belfast Diet Study
(This Disease is Likewise Quite Heterogeneous!)

Beta Cell function (%)
Insulin Sensitivity

Years from diagnosis

*β-cell function determines onset and progression of secondary dietary failure in DM2
OMINOUS OCTET
(This is Truly a Complex Disease!)
Decreased Incretin Effect
Increased Lipolysis
HYPERGLYCEMIA
Decreased Glucose Uptake
Increased HGP
Islet–α cell
Decreased Insulin Secretion
Incretin Dysfunction
Diabetes 58:773-795, 2009

β-Cell-Centric Construct: Egregious Eleven
The β-Cell is the FINAL COMMON DENOMINATOR of β-Cell Damage
(This Disease May be Even More Complex)

Metformin Has Its Metabolic Limitations
Progressive Natural History of T2DM Associated With a Dynamic Pathophysiology

- The progressive loss of β-cell function associated with T2DM results in the corresponding need for therapeutic intensification.1,2
- Other organ system contributions are also occurring (i.e., kidney, incretin, adipose tissue, etc.).
- Many patients with T2DM will eventually need insulin therapy.2,3
- Progression to insulin therapy occurs at different rates in different study populations:
  - ORIGIN: 11.4% with IFG, IGT, or early T2DM in standard care arm used insulin within 7 years.4
  - TODAY: 46% of adolescents with newly diagnosed T2DM required rescue with insulin within 1 year.5

Case 1: Clarence
- 52 year old centrally obese male
- 1-year history of type 2 diabetes, also diagnosed with dyslipidemia and hypertension
- Family History: Both Parents had type 2 diabetes, HTN and CAD
- Notes: BMI 37 (yr ago it was 34, 2 yrs ago it was 31)
  - Metformin 1000 mg BID
  - Current A1c 8.3% (7.5% 6 months ago, 7.2% at diagnosis)
  - Creatinine 1.3 mg/dl, eGFR 65
  - LDL 112 mg/dl, triglycerides 256 mg/dl, HDL 29 mg/dl
- The scope of likely underlying pathophysiologic contributors to his T2DM include at least a.) β-cell dysfunction; b.) α-cell dysfunction; c.) incretin dysfunction; d.) adipose tissue contribution to insulin resistance; e.) increased renal glucose reabsorption; f.) HGP excess; g.) neurotransmitter/CNS dysfunction. How many defects covered by metformin? Current treatment is indifferent to pathophysiology.

Multiple Defects Contribute to the Pathophysiology of Type 2 Diabetes Necessitating Targeted Therapy
Current Treatment Algorithms Include A Wide Array of Choices and Combinations to Achieve Glycemic Control—But are we sending the wrong message(s)?


Meta-analysis: CV mortality—clearly it’s not all about glucose control!

<table>
<thead>
<tr>
<th>Study name</th>
<th>DPP-4 Inhibitors</th>
<th>Placebo Group</th>
<th>Hazard ratio and 95% CI</th>
<th>Hazard ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P value</th>
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<td>LEADER</td>
<td>156/3201 (1.07)</td>
<td>156/3201 (1.07)</td>
<td>0.98</td>
<td>0.86-1.12</td>
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<td>SAVOR</td>
<td>274/6169 (1.24)</td>
<td>274/6169 (1.24)</td>
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<td>0.86-1.06</td>
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<td>EXSCEL</td>
<td>989/2055 (1.30)</td>
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<td>0.95</td>
<td>0.92-1.00</td>
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<tr>
<td>Overall</td>
<td>1274/2526 (1.32)</td>
<td>1274/2526 (1.32)</td>
<td>0.97</td>
<td>0.94-1.00</td>
<td>0.079</td>
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</tbody>
</table>

Bethel et al. T2D 2017, in press.

PATHOPHYSIOLOGIC-BASED (DEFRONZO) ALGORITHM—HOW SOON?

Lifestyle + TRIPLE COMBINATION: PIO + Metformin + GLP-1 Receptor Agonist

HbA1c < 6.5%
TIME-RELATED CHANGE IN HbA1c IN TRIPLE AND CONVENTIONAL THERAPY GROUPS AFTER 36 MONTHS (Consider the additional role of the SGLT-2 inhibitors)

![Graph showing HbA1c levels over time for different therapy groups]

**Beta Cell Function ($\Delta CP/\Delta G_0-120 \div IR$) in Triple and Conventional Therapy Groups at Baseline and at 36 Months**

![Bar chart comparing beta cell function between conventional and triple therapy groups]

**Likely Advantages of Precise Diagnosis & Early Combination Therapy**

- Earlier definition of therapeutic targets
- Ability to set individualized treatment goals, including disease modification/delay of progression
- Opportunity to combine antidiabetic drugs with complementary modes of action
- Potential to utilize the full spectrum of available therapies
- Despite advantages, the focus on a linear classification approach to the disease has imposed significant limitations on the use of appropriate combination therapy