Diagnosing Diabetes Mellitus in Adults: Type 1, LADA, Type 2:
Rationale and Implications of a β-Cell-Centric Classification of Diabetes

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I was asked how to Diagnose Diabetes Mellitus in Adults: Type 1, Type 2, LADA

or, Since we quickly noted
That Confusion Abounds, Isn’t it

Time for A New Classification Schema for the Diagnosis and Treatment of Diabetes Mellitus (DM)

Get us ready for ‘PRECISION MEDICINE’
Purely Clinical Answer
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 WHATEVER agent(s) necessary to control glycemia
  - Use ‘best clinical guess’; ‘label’ patient; Independent of age
  - (but must work under constraints of current ‘definitions’ for the classification of T2D- per payors/governments)
‘Diagnosis’ Has Many Functions

Need To Be More Than Pragmatic!!

- To plan patient’s care – MORE 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 SINCE THEN

OLD=

- T1DM = Immune destruction of β-cells
- T2DM = Insulin Resistance

This distinction has been used as basis of distinction between T1D, and T2D

- Literature Review
  - Distinction between T1 and T2 – 5 papers (4 in young people)
  - Distinction between diabetes and ‘no diabetes’ – 3 papers
  - Incorrect classification relating to MODY – 4 papers
  - Failure to distinguish diabetes by type (e.g. classification just as ‘diabetes’) – 2 papers
  - Failure to recognise LADA, pancreatic diabetes or persistence of foetal haemoglobin – 1 paper each
  - Diagnosis of AIDS considered in patients later identified as having diabetes – 1 paper

Stone M et al Diabet Med 2009
Current DM Classification Failing

(Certainly appropriate with knowledge available when current classification adopted)

- Diagnosis is often *imprecise/ or overlapping phenotypes*
  - Flatbush DM - present in DKA - ‘turn out to be T2DM’
  - LADA - Adults who look like ‘typical T1DM’
  - Antibody positive patients who look like ‘T2DM’
  - T1DM with Insulin Resistance (like T2DM)

**Literature Review**

- Distinction between T1 and T2 – 5 papers (4 in young people)
- Distinction between diabetes and ‘no diabetes’ – 3 papers
- Incorrect classification relating to MODY – 4 papers
- Failure to distinguish diabetes by type (e.g. classification just as ‘diabetes’) – 2 papers
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- Diagnosis of AIDS considered as having diabetes – 1 paper

(Stone M et al Diabet Med 2009)
Definitions: T1D, ‘LADA’, T2D
May Seem Precise BUT..., Overlapping Phenotypes
In particular:

‘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
# Comparing Definitions for T1D, ‘LADA’, T2D

<table>
<thead>
<tr>
<th></th>
<th>IMMUNITY</th>
<th>AGE</th>
<th>GENES</th>
<th>BMI</th>
<th>INSULIN THERAPY</th>
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<td><strong>T1D</strong></td>
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<td>In children</td>
<td>Strong</td>
<td>child</td>
<td>HLA++</td>
<td>low</td>
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<tr>
<td>In adults</td>
<td>++</td>
<td>adult</td>
<td>HLA+</td>
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<td><strong>LADA</strong></td>
<td>+</td>
<td>adult</td>
<td>HLA</td>
<td>normal</td>
<td>Variable</td>
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<td><strong>T2D</strong></td>
<td>weak</td>
<td>adult</td>
<td>?</td>
<td>high</td>
<td>Infrequent</td>
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</table>

Adapted from Leslie et al. Diabetes Metab Res Rev. 2008 Oct;24(7):511-9
Diabetes is a Continuum OF β-cell FUNCTION

SO ISSUE IS LESS
‘What is LADA?’-

ISSUE IS WHAT ARE MECHANISMS
And RATE OF DESTRUCTION OF β-cells
In ALL PATIENTS WITH DIABETES-
?Improve therapy!!

Leif Groop, Can genetics improve precision of therapy in diabetes?
The β-Cell Centric Classification of DM

*Intuitively obvious approach...*

ANSWERS THE CALL TO ACTION

ALL DM = Hyperglycemia

*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* aimed at

all possible mediating pathways of hyperglycemia

The ‘β-Cell Centric’ Classification will help improve diagnosis and treatment,

especially as our knowledge-base expands
β-Cell Centric Classification of Diabetes: Implications for Classification, Diagnosis, Prevention, Therapy, Research

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

Insulin Resistance

Environment

Inflammation/Immune Regulation

β-Cell secretion/mass

Final Common Denominator
β-Cell Centric Classification of Diabetes:

*Implications for Classification, Diagnosis, Prevention, Therapy, Research*

- **Environment**
  - Genetic susceptibility to: viruses, endocrine disruptors, food AGEs, Gut Biome

- **Inflammation/Immune Regulation**
  - Insulin Resistance (IR): Centrally Induced IR, Peripheral IR, Stress Hormones, Gut Biome

- **β-Cell secretion/mass**
  - FINAL COMMON DENOMINATOR

**GENE**

Polygenic
Monogenic

Epigenetics
Pushback

- What about ‘pure’ Insulin Resistance Syndromes?
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

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 exposed as phenotypic hyperglycemia
Phenotypic Presentation is defined by:

* D>isease Modification: B-Cell Function/ Mass
  1. Avoid Agents that destroy Beta Cells
  2. Use agents that preserve Beta-cells
  3. Newer / Future Agents to Increase Beta-Cells

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**Increasing Age**

- **Pre-Diabetes** = FBS ≥100, PPG ≥140
- **All DM** = FBS ≥126, PPG ≥200
The β-cell centric classification allows for individualized care by identifying and treating patient-specific etiologies and mediating pathways of hyperglycemia.

**EGREGIOUS ELEVEN**

1. One CORE 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
   - ↓ Insulin

2. ↓ Incretin effect
   - ↓ Amylin

3. α-cell defect
   - ↑ Glucagon

**HYPERGLYCEMIA**

4. Adipose
   - Increased lipolysis

5. Muscle
   - Decreased peripheral muscle uptake

6. Liver
   - Increased glucose production

7. Brain
   - Increased appetite
   - Decreased morning dopamine surge
   - Increased sympathetic tone

8. Colon/Biome
   - Abnormal-microbiota; possible decreased GLP-1 secretion

9. Immune Dysregulation/Inflammation
   - Decreased morning dopamine surge

10. Stomach/Small intestine
    - Increased rate of glucose absorption

11. Kidney
    - Increased glucose re-absorption

**INSULIN RESISTANCE**
Brief Discussions

- Genetics
- Beta-Cell
- Immune Modulation/Inflammation
- Insulin Resistance
- Environment
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:**

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

*(AND some address **susceptibility to DM COMPLICATIONS*)

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*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]*

Epigenetic dynamics in immunity and autoimmunity. Zhao M1, Wang Z1, Yung S2, Lu Q. ;


Acta Diabetol. 2015 Apr 5.*
Gene/ Environment Interactions with DM and it Complications: some in common to both

Genes related to b-cells and complication risk may be the Same Or Different:

Haptoglobin
PPAR
TCF7L2- acls-5
Pharmacogenetics:

Which agents most likely to be effective in a given patient

Fig. 1 Summary of the pharmacokinetic, pharmacodynamic and regulatory genes involved in significant gene–drug interaction in response to antidiabetic medication (adapted from Maruthur et al. [10]).
Can picture Genomics CHIP for DM as 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

*Ex Vivo Functional Pharmacogenomic Assay*

Could put other ‘Markers on same chip, eg:

Proteinomics, Metabolomics, miRNAs, islet DNA, IR markers, inflam., Immune markers

As/when validated
Genetics of ‘LADA’

**Typical age of onset**

- **SPIDDM**: Antibody + T2DM
- **40 yrs**
- **~25-40 yrs**
- **<10 yrs**

**Type 1 Diabetes**

- ~60 genes

**‘LADA’**

- Late onset type 1 diabetes?

**Type 2 Diabetes**

- ~60 genes

We are looking for LADA-Specific Genes

No genes in common

**HLA**

And Same Genes (or other T1DM –associated genes)

May be over-represented/ present in ‘T2DM- Like’ LADA patients

**TCF7L2**

We have found ‘typical’ T1DM genes,
(Whose defects destroy b-cells)
Whose ABSENSE may result in delay of T1DM,
Thus = ‘Type 1-Like’ LADA

Slow Destruction of B-Cells in T1DM-like LADA; Fast Destruction of B-Cells in T2DM-Like LADA
New β-Cell Centric Construct: Implications

β-cell Issues

- Usual use of Glycemic Criteria - HgA1c, FBS, PPG
- Markers-Usual/Classic = 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-Generic Causes

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

STOP USING SU’s, GLINIDES; Minimize INSULIN THERAPY
Be aware of all the Secretory Dynamic Pathways involved, AND GENES INVOLVED
New β-Cell Centric Construct: **Implications**

Inflammation/Immune Dysregulation Issues-ALL DM

β Cells are Destroyed by Innate (macrophages/cytokines) and Adaptive (T-cell/antibody) Immune Reactions

- Pancreas

**Phase 1:** β-cell death, APC activation
- β-cells are destroyed via multiple interactions between macrophages, dendritic cells, natural killer cells, and lymphocytes

**Phase 2:** Expansion of selfAg specific T cells

**Phase 3:** Immune cell cross talk, inducing or preventing β-cell death

Cytokines, Inflammation, and Metabolic Stress May Play a Role in β-cell Apoptosis in T2DM

- Initiation of a broad inflammatory response involves increased β-cell apoptosis

Gut Microbiota Trigger Inflammation/Immune destruction of B-Cell in ‘T1DM’

Haptoglobin Gene Variant Associated with leaky gut

Fig. 1. The role of gut microbiota in the development of T1D. Gut flora can affect islet autoimmunity through mechanisms: (1) expression of autoantigen mimicry to activate autoreactive T cells by antigen-presenting cells to destruct islet beta cells. (2) Generating metabolites, such as acetate, butyrate etc., to induce the differentiation or migration of regulatory T cells to control autoreactivity through GPCR signaling pathway (such as Gpr43). (3) Gut bacteria-derived pathogen-associated molecular patterns (PAMP) activate TLR signaling pathway to initiate the inflammation, which activates autoreactive T cells and/or directly cause injury to beta cells through inflammatory cytokines. (4) Gut bacteria can penetrate the leaky gut and cause inflammation to destruct beta cells.
Pathogenesis and biological interventions in T1DM- LIKE autoimmune diabetes- Insulitis

The class I MHC molecules are hyperexpressed on the β-cell surface in T1D patients making β-cells more susceptible to cytotoxic lymphocyte (CTL)-mediated destruction.

Novel diagnostic and therapeutic approaches for autoimmune diabetes — A prime time to treat insulitis as a disease

http://dx.doi.org/10.1016/j.clim.2014.11.007  Clinical Immunology, 2014

Juha Grönhoml, Michael J. Lenardo
Efficacy of Immunotherapy in T1DM: Some Can Delay Decline in C-peptide

Figure 2. Heterogeneity in efficacy of immunotherapies in Type 1 diabetes. Treatment efficacy is determined by the impact of immunotherapy on decline in stimulated β-cell function as defined by C-peptide production in response to glucose. A positive effect implies delayed decline of C-peptide production upon a given immunotherapy (green). Lack of effect (white) denotes immunotherapy not changing the course of decline in β-cell function compared to placebo-treated subjects, whereas a (tendency of) negative effect (orange) implies an accelerated loss in β-cell function in response to intervention therapy (orange). GADA: Glutamic acid decarboxylase autoantibodies; T1D: Type 1 diabetes.
Insulin Resistance within the β-Cell Centric Construct

- Insulin Resistance is understood to expose and exacerbate the core β-cell defect

**Insulin Resistance Impairs β-Cell Function by:**

- Lipo- and gluco-toxicity
- Inflammatory mechanisms
- Adipocytokines effect on β-cell

- Genetically-Based
- Exacerbated by Environmental issues: Diet, Activity, Biome
- Includes Multiple Causes of Insulin Resistance
Potential Causes of Insulin Resistance and Their Interplay

Central IR
- Loss of dopamine surge in SCN
- Increased appetite
- Increased sympathetic tone

Weight Reduction Agents
- Bromocriptine-QR

Biome IR
- Pro-Biotics
- Pre-Biotics
- Antibiotics

Peripheral IR
- TZD (Pio-), Metformin

Hyperinsulinemia

Inflammation IR
- Anti-Inflammatories
- Immune modulators
Metabolic Derangement, and Insulin Resistance Associated with Microbiome

Lipopolysaccharides (LPS)

Fasting-induced adipocyte factor

Pioglitazone Treats Secondary Adverse Effects of Abnormal Biome
New β-Cell Centric Construct: Implications

Environmental Risk Factors in T1D/T2D, ? ‘LADA’

**T1D**
- Seasonality at diagnosis
- Migrants assume risk of host country
- Risk factors from case-control studies
  - Hormones
  - Stress
  - Improved Hygiene
  - Infant/childhood diet
  - Viruses – exposures as early as in utero

**T2D**
- Obesity-Diet
- Lack of Physical Activity
- AGE ingestion

**LADA**
- Coffee
- More Educated
Can Keep Current Terminology
Incorporate the β-Cell Centric Approach with each to determine issues in individual patient or a New Terminology?

<table>
<thead>
<tr>
<th></th>
<th>Younger</th>
<th>Older</th>
<th>‘LADA’</th>
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<tbody>
<tr>
<td>Genes</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>- mono</td>
<td>T2D</td>
<td>MODY, monogenic</td>
<td>T1D</td>
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<tr>
<td>- poly</td>
<td>+,which</td>
<td>+,which</td>
<td>+,which</td>
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<tr>
<td>Inflammation</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Resistance</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Environment</td>
<td>+,which</td>
<td>+,which</td>
<td>+,which</td>
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</tbody>
</table>

Easier to get buy-in from many different stakeholders, MDs, etc
Or New Terminology Should Reflect the **β-Cell Centric Approach**;

**Disease = DIABETES; Phenotype= Hyperglycemia**

<table>
<thead>
<tr>
<th>Genes</th>
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<tbody>
<tr>
<td>- mono</td>
<td>+,which</td>
<td></td>
</tr>
<tr>
<td>- poly</td>
<td>+,which</td>
<td></td>
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</table>

**Inflammation** | +/- |

**Resistance** | +/- |

**Environment** | +,which |

Implications for Therapy: Use whatever logically sensible/necessary based on cause of hyperglycemia in each patient.
New approach is commensurate with Natural History of ALL DM

<table>
<thead>
<tr>
<th>Age</th>
<th>0-15</th>
<th>15-40+</th>
<th>15-50+</th>
<th>25-70+</th>
</tr>
</thead>
</table>

- **Macrovascular Complications**
  - Disability
  - MI
  - CVA
  - Amp

- **Microvascular Complications**
  - Blindness
  - Amputation
  - CRF
  - Disability
  - Risk of Dev. Complications

- **ALL DM**
  - IGT
  - ETOH
  - BP
  - Smoking
  - Eye
  - Nerve
  - Kidney

- **Insulin Resistance**
  - IR Phenotype
  - β-Cell secretion/mass
  - Final common denominator

- **Environment**
  - Inflammation/Immune Regulation
  - Epigenetics
  - Polygenic Monogenic
ANOTHER INSIGHT:

WHAT ABOUT COMPLICATIONS OF DIABETES?

We noticed 2 ‘old’ general principles:
Pathophysiology of Diabetic Complications: Old Conundrum: why similar HgA1c in different folk give different risks

I Metabolic Disorder
Glucose, insulin hormones, enzymes, metabolites, etc. (i.e., control)

II Individual Susceptibility
Genetic/ethnic
?Acquired

III Modulating Factors
Hypertension, diet, smoking, etc.

IV Early
Delayed Complications
Retinal, renal neural, cardiovascular, cutaneous, etc.

V Late

Point of metabolic “no return”

Factors Contributing to Cardiometabolic Risk

ARE THE SAME AS THOSE THAT DAMAGE THE Beta-Cell

- Genetics
- Age
- Overweight/Obesity

Insulin Resistance Syndrome
- Lipids
- BP
- Glucose

Cardiometabolic Risk
- Global Diabetes/CVD Risk

- Abnormal Lipid Metabolism
  - LDL↑
  - ApoB↑
  - HDL↓
  - Triglycerides↑

- Smoking, Physical Inactivity
- Hypertension
- Inflammation, Hypercoagulation
- Age, Race, Gender, Family History

diabetes.org/CMR
A Unifying Pathophysiologic Approach to The Complications of Diabetes in the Context of the Beta-cell Classification of Diabetes

Genes
Some in common/ Some different

Epigenetics

Inflam./ Immune Mech.

Environment

Susceptibility to abnormal metab. envir.

Circulating master metabolic REDOX regulators (L/P, β/A, SH/SS, ROS)

miRNA, DNA methylation

ALL COMPLICATIONS (Micro/MacroVascular Damage)

Endogenous Fuel Excess (glucose/lipids) (Brownlee’s Unified Theory of Complications)

Glucotoxicity/ lipotoxicity

MOST MECHANISMS OF B-cell Damage Overlap with Causes of ALL Complications:
[ describe in 2 ways]
BTW: In Same Context of changing classification of DM, need to Change Classification/ Nomenclature of the Complications of Diabetes

- In order to reflect:
  - ‘Microvascular/ Macrovascular ‘ terminology have lost their meaning given new understanding of Causes of Complications
  - it’s CELLS/TISSUES affected by the pathophysio logic mechanisms
  - Complications of ‘T1DM’ and T2DM’ are the same, not different
A Unifying Pathophysiologic Approach to The Complications of Diabetes in the Context of the Beta-cell Classification of Diabetes

Defines Logic for Varied Risk of Complications in Individual Patients with similar (poor)HgA1: Likely Genetically based

Susceptibility to abnormal metab. envir.

Endogenous Fuel Excess (glucose/ lipids) (Brownlee's Unified Theory of Complications)

Glucotoxicity/ lipotoxicity

Circulating master metabolic REDOX regulators (L/P, β/A, SH/SS, ROS)

miRNA, DNA methylation

β-Cell secretion/mass

FINAL COMMON DENOMINATOR

ALL COMPLICATIONS (Micro/MacroVascular Damage)

ALL COMPLICATIONS (Micro/MacroVascular Damage)

Inflam./ Immune Mech.

Environ ment

Insulin Resistance

Epigenetics

Genes

Some in common/ Some different

Cause or permit susceptibility to damage

Define Logic for Varied Risk of Complications in Similar Patients: Likely Genetically based
Phenotypic Presentation of Each Complication is defined by:

\[ \text{Slope} = \text{‘Natural History’ over time,} \]

i.e. \( \text{RATE OF Development of Comp.} \) Slope is not linear, and may be intermittently relapsing, remitting, stabilized, and improved, until ‘point of no return’ when presence and damage irreversible

For All DM

\[ \begin{align*} 
\text{Severity of Complication} & \\
\text{end Stage} & \\
\text{DEPENDENT on} & \\
\text{Genes} - \text{which, how many} & \\
\text{Environmental Factors} - \text{which/how many} & \\
\text{Inflammatory/ Immune - which factors/how many} & \\
\text{IR/ Cardiometabolic Syndrome} & 
\end{align*} \]

\[ \text{Increasing Age/ Duration} \]

\[ \text{Age at presentation = tipping point when the combined pathophysiological processes are exposed as phenotypic functional/structural abnormalities} \]
A Unifying Pathophysiologic Approach to The Complications of Diabetes in the Context of the Beta-cell Classification of Diabetes

Endogenous Fuel Excess (glucose/lipids) (Brownlee’s Unified Theory of Complications)

Susceptibility to abnormal metab. envir.

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Environment

Circulating master metabolic REDOX regulators (L/P, β/A, SH/SS, ROS)

miRNA, DNA methylation

Glucotoxicity/lipotoxicity

Explains why some newer meds for DM decrease adverse outcomes without major drops in HgA1c

ALL COMPLICATIONS (Micro/MacroVascular Damage)

Explain why some newer meds for DM decrease adverse outcomes without major drops in HgA1c
## Inferences on Value of Glycemic Control and Other Mechanisms of DM meds in Reducing Complications of Diabetes

### CV Benefits of DM Meds Driven By Other Mechanisms!!

<table>
<thead>
<tr>
<th>Study</th>
<th>HgA1c Drop</th>
<th>Eye Nerve</th>
<th>Kidney</th>
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<td>Glycemic Hypothesis Proven in Primary</td>
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<td>Prevention despite ‘wrong meds’</td>
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<td>ACCORD</td>
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<td></td>
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<td>Wrong drugs, wrong process of care</td>
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<td><strong>PRE</strong></td>
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<td>BROMO-QR</td>
<td>(pts &lt;7.0)</td>
<td>Reduced</td>
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<td>Benefits primarily driven</td>
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<td><strong>VEN</strong></td>
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<td>EMPA-Reg</td>
<td>0.6 early</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
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<td>By other mechanisms</td>
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<td><strong>TI</strong></td>
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<td></td>
<td>Besides glycemia, eg:</td>
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<tr>
<td>IRIS</td>
<td>IR/pre-DM</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Reduced</td>
<td></td>
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<td></td>
<td>↓ IR, Arterial Stiffness, Inflam., Symp. Tone</td>
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<tr>
<td><strong>ON</strong></td>
<td>0.4</td>
<td>Reduced</td>
<td>Reduced</td>
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</table>
β-Cell (Islet Cell) Classification Model-Implications for Therapy: Targets for Therapies/ New Guidelines

Medication Choice Based on

1. Glycemic Efficacy
   BUT ALSO
2. Number of Targets of Therapy each drug addresses
   (combo therapy efficacy likely depends on number of overlapping mechanisms- treat with least # of agents that treat most # mechanisms of Hyperglycemia)
3. Weight loss
4. Proven Reduction in Risk Factors/ CV outcomes-Synergies–eg: SGLT-2, pioglitazone, brompcritpine-QR, metformin, GLP-1 RA)
**Precision Medicine Approach to DM/ CV Therapy: Algorithms should Assess not only Glycemic benefits of agents/classes but CV/weight benefits**

***Implications for New Guidelines***

1. **Pancreatic β-cells**
   - ↓Insulin
     - **FINAL COMMON DENOMINATOR**
       - Dpp-4 Inhibitors *
       - GLP-1 RAs **WR**
       - Metformin **WR**

2. **↓Incretin effect**
   - Dpp-4 Inhibitors *
   - GLP-1 RAs **WR**

3. **α-cell defect**
   - ↑Glucagon
   - Dpp-4 Inhibitors *
   - GLP-1 RAs **WR**
   - Pramlintide*

**HYPERGLYCEMIA**

8. **Colon/Biome**
   - Probiotics/Prebiotics *
   - Dpp-4 Inhibitors *
   - GLP-1 RAs **WR**

9. **Immune Dysregulation/Inflammation**
   - Dpp-4 Inhibitors *
   - GLP-1 RAs **WR**
   - Anti-Inflammatories Immune modulators

10. **Stomach/Small intestine**
    - GLP-1 RAs **WR**
    - Pramlintide*
    - AGI**

11. **Kidney**
    - SGLT2 inhibitors**WR**

7. **Brain**
   - GLP-1 RAs **WR**
   - Dopamine agonist-QR**WR**
   - Appetite Suppressants **WR**

6. **Liver**
   - Metformin **WR**
   - TZDs**

**INSULIN RESISTANCE**

**Assessment includes recent prospective trial benefits of SGLT-2 inh, pio, and liraglutide**
Practical Implementation of the

THE COMMON ORIGINS OF DIABETES
AND ITS COMPLICATIONS CONSTRUCT
New β-Cell Centric Construct: *Implications*

Diagnosis Markers

By Virtue of Family History ‘DM”, Physiogomy, hyperglycemia, in prediabetic and diabetic range *

- **Genes**
  - Family History
  - Genotype- HLA, *TCF7L2*, etc

- **β-Cell**
  - FBS, 2hr ppg, HgA1c, ? C-peptide, ?other- β-Cell mass measures

- **Inflammation**
  - Antibodies, Inflammatory Markers, T-Cell function, ?other

- **Insulin Resistance**
  - BMI, Adiponectin, Adipocytokines, ? Other

* Individualized and reliant on cost, insurance coverage, formulary, government
Patient-Centric Diagnosis & Process of Care/Therapy

At Risk Individuals

Traditional Labs/Testing
FBS, RBS, HgA1c

Etiologic Diagnostic Markers:
β-Cell, Insulin resistance,
Inflammation, Environment, Genes

Specific Therapy addressing Genotype

Genes

Least Number of Meds that Rx most Number of Mechanisms of Hyperglycemia

1. Pancreatic β-cells
↓ Insulin

FINAL COMMON DENOMINATOR
Dpp-4 Inhibitors *
GLP-1 RAs * *WR
Metformin*

2. ↓Incretin effect
Dpp-4 Inhibitors *
GLP-1 RAs * **WR

3. α-cell defect
↑ Glucagon
Dpp-4 Inhibitors *
GLP-1 RAs * **WR
Pramlintide*

HYPERGLYCEMIA

8. Colon/Biome
Probiotics/Prebiotics *
Dpp-4 Inhibitors *
GLP-1 RAs * *WR
Metformin *

9. Immune Dysregulation/Inflammation
Dpp-4 Inhibitors *
GLP-1 RAs * *WR
(Anti-inflammatory Immune modulators)

↓Amylin

10. Stomach/Small intestine
GLP-1 RAs **WR
Pramlintide*
AGI**

11. Kidney
SGLT2 inhibitors ***WR

7. Brain
GLP-1 RAs**WR
Dopamine agonist-QR**
Appetite Suppressants**WR

6. Liver
5. Muscle
4. Adipose
Metformin**
TZDs** *

Assessment includes recent prospective trial benefits of SGLT-2 inh, pio, and liraglutide

Logics for CV risk/outcome reduction exists
Supporting Studies Exist
Prospective Evidence-Based Data Exists
WR= Weight Reduction
Going Forward: New Focus of Care:  
**Primary Prevention:** ? For All DM in New Classification

- Genetic/antibody screening effort to identify eligible subjects
- Potential **Immune Modulators**
- **Environmental Modulation**
  - Especially as we learn more—vaccination, endocrine disruptors, diet, exercise
- Intervention needs to be extremely safe
- **Defining risk factors** will facilitate primary prevention studies

**APPLY MODEL TO ALL DM**

Atkinson, Eisenbarth, THE LANCET • Vol 358 • July 21, 2001 225
Choice of Therapy

• Based on
  – Treating Causes of β-Cell dysfunction
  – Treating Abnormalities resulting from β-Cell dysfunction
• No Logic for Agents that Decrease β-Cell dysfunction

THUS: SELECT AGENTS THAT CAN PRESERVE β-Cell function/mass

Allows us to Correct a myth

MYTH: “Most Patients with ‘T2DM’ will eventually progress to insulin because of inexorable β-Cell loss”
  - But data obtained on SU=apoptosis; Hyperinsulinism with weight gain
  - Think of bariatric patients – no insulin after 25 years DM/ 20 years insulin
  - Most patients dying with DM have > 20% β-Cell mass- Butler
  - Need to remove >80% pancreas in sub-total pancreatectomies to leave patient with DM post-op
Therapeutic Principles Across Continuum of Care

Right Drug for Right Patient and vice versa

DETERMINE INSULIN DEPENDENCY-(DKA, c-peptide, ?other
DETERMINE Patient Specific Mechanisms of Hyperglycemia

➢ Treat ? For prevention/ pre-diabetes
➢ Treat as many of the Egregious 11 Targets as needed,
   least # of agents, lowest sugars/HgA1c as possible
   without undue weight gain or hypoglycemia
• Early Combination Therapy- Patient Centric-
  even 6.5-7.5 HgA1c
  Efficacy, - CV event reduction, Weight Loss
  (Not first-second-third line; Not competition between
classes)
➢ Can Modify therapy after 1m-not 3m-use Fructosamie
➢ Stabilize, preserve β-cells, the CORE DEFECT
  ➢ ( NO SU/GLINIDES)-
  ➢ Ideally agents will have potential to
    synergistically decrease in CV risk factors / outcomes
Avoid Early Insulin Therapy
(except in Ketosis-prone)
Vicious Circle(s) of Hyperinsulinemia-
Result in Weight Gain and Hypoglycemia

Figure 1

- Patient eats too much
- Or simple sugars

Blood glucose rises

Consumption of more calories, diet high in fat and simple carbohydrates and resultant weight gain

Hypoglycemia
Symptomatic or not!

INCREASED APPETITE

Undue Basal Or bolus Insulin
= Overinsulinized

Increase in basal doses of insulin to control blood glucose
NOTE:
There is NO perfect Exogenous Insulin: All result in HyperInsulinemia and Potential Hypoglycemia

Endogenous Insulin

Exquisitely controlled levels of insulin released into the portal vein

Fine-tuned, physiologically appropriate insulinemia

Exogenous Insulin

‘Obligatory’ excess peripheral insulin to get modicum of reduced hepatic glucose production

Hyperinsulinemia

Insulin Resistance

Obesity

Weight gain

Dyslipidemia

Chronic Inflammation

Type II Diabetes

Hypoglycemia

Atherosclerosis

Hypertension

Cancer

β-cell Dysfunction

Potential 6-cell Exhaustion
1. Delay Need for Insulin
2. No need for Early Insulin
3. If need Insulin, Continue Non-Insulin RX (Avoids need for Meal-Time Insulin) (Decrease Risk Hypoglycemia 85%- Garber)
4. Get Patients off insulin who had been given early Insulin
Hedge your Bets: Incretins for all patients
DPP4 inhibitors, GLP-1 RAs, [other agents that increase GLP-1 eg: metformin, colsevalam, (TGR-5)]

➢ T1DM: minimize brittle, dawn, unpredictablity, variability, ? CV benefits, Treat those ‘Type 2’ Genes’, ANTI-INFLAMMATORY

➢ LADA = SPIDDM/ Autoimmune T2DM. Same as above - Slow , stabilize disease process, ANTI-INFLAMMATORY

➢ T2DM: Same as above, treats 7 MOA’s of DeFronzo’s Octet, decreases oxidative stress, β-cell inflammation decreases lipo- and gluco-toxicity, ?preserve mass, decreases appetite, treats IR via wt. loss

➢ MODY 3- recent report

FOR ALL DM – potential CV benefit (ANTI-INFLAMMATORY)
A Unifying Pathophysiologic Approach to The Complications of Diabetes in the Context of the Beta-cell Classification of Diabetes

Genes
Some in common/Some different

Epigenetics

Insulin Resistance

Inflam./Immune Mech.

Environment

Susceptibility to abnormal metab. envir.

ALL COMPLICATIONS (Micro/MacroVascular Damage)

Circulating master metabolic REDOX regulators (L/P, β/A, SH/SS, ROS)

miRNA, DNA methylation

Endogenous Fuel Excess (glucose/lipids) (Brownlee’s Unified Theory of Complications)

Glucotoxicity/lipotoxicity

Defines Logic for treating Individual components of the pathophysiologic mechanisms contributing to beta cell damage and the complications of diabetes
## Treating the ABCs Reduces Diabetic Complications

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Complication</th>
<th>Reduction of Complication</th>
</tr>
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<tbody>
<tr>
<td><strong>Blood glucose control</strong></td>
<td>Heart attack</td>
<td>↓ 37%&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Cardiovascular disease</td>
<td>↓ 51%&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Heart failure</td>
<td>↓ 56%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>↓ 44%&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Diabetes-related deaths</td>
<td>↓ 32%&lt;sup&gt;3&lt;/sup&gt;</td>
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<tr>
<td><strong>Blood pressure control</strong></td>
<td></td>
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<tr>
<td></td>
<td>Coronary heart disease mortality</td>
<td>↓ 35%&lt;sup&gt;4&lt;/sup&gt;</td>
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<td></td>
<td>Major coronary heart disease event</td>
<td>↓ 55%&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Any atherosclerotic event</td>
<td>↓ 37%&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease event</td>
<td>↓ 53%&lt;sup&gt;4&lt;/sup&gt;</td>
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</tbody>
</table>

Increased Survival, Decreased Micro- and Macrovascular Disease in Steno-2 Rx’ing glucose, BP, Lipids.
Aggressive medical therapy in diabetes - SUMMARY

Adapted from Beckman JA et al. JAMA. 2002;287:2570-81.

Atherosclerosis, CV Outcomes, CV Risk Factors, Mortality

DM MEDS MAY BE A CARDIOLOGIST’S BEST FRIEND
Conclusion

- Current classifications of DM are inadequate:
- new classification schema - the β-cell as THE CORE DEFECT in ALL DM,
- The various mediators of β-cell dysfunction offer key opportunities for Prevention, Therapy, Research and Education
- Note, Same Mechanisms of β-cell dysfunction are responsible for DM complications (explains why some DM meds can decrease CV outcomes)
Conclusion-2

- Patient care should **shift from** current classifications that limit therapeutic choices to:

- one that **views a given patient’s disease and treatment course based on their individual cause(s) of metabolic dysregulation**, e.g. genes, inflammation, insulin resistance- (including gut biome, central (brain) mechanisms), environmental factors, etc.

- **Defining markers, and Processes of Care permits patient-centric, Precision Medicine Care**
Conclusion-3

• Convene Organizations
  eg: ADA/EASD/WHO/IDF/AACE / JDF to Revise Classification of DM

• More research always needed, but,
• in an evidence-based PRACTICE approach to care, we can START NOW
Presenter Disclosure Information

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

Stanley Schwartz

Research Support: 0
Employee: 0

Board Member/Advisory Panel: Janssen, Merck, AZ-BMS, BI-Lilly, Salix, Novo, Genesis Biotechnology Group

Stock/Shareholder: Saturn EMR Decision Support APP.

Consultant: NIH RO1 DK085212, Struan Grant PI

Other: Speaker’s Bureaus: Janssen, Merck, Novo, Salix, BI-LILLY, Eisai, AZ-Int’l, Amgen