Beyond Patient-Centered to Personalized Diabetes Care

Jennifer B. Marks, MD, FACP, FACE
Emeritus Professor of Medicine
University of Miami Miller School of Medicine
Diabetes Research Institute
Former Director, Diabetes Management Program &
Former Section Chief, Diabetes, Endocrinology & Metabolism
Miami Veterans Affairs Health System
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• Advisory Panel
  – Novo Nordisk

Beyond Patient-Centered to Personalized Diabetes Care:
Outline

• The case for personalized diabetes care (focus on type 2 diabetes) vs. individualized/patient-centered care
• What the landscape looks like now: individualized/patient-centered care
  – Current framework/algorithms
  – The GRADE Study
  – A step toward personalized care: The Elements of Diabetes Care Scale
• Potential tools to achieve personalized care
  – The PRIBA Study
  – Diabetes reclassification?
  – The ANDIS Study
  – Lessons from cancer care
• The future for personalized diabetes care
  – Filling research gaps
  – Conclusions: moving to personalized diabetes care
The Case for Personalized Diabetes Care

Let’s start with something we all can agree on... (I think)

Not all type 2 diabetes is alike so it shouldn’t all be treated the same...
The Case for Personalized Diabetes Care – The Vision

• Existing algorithms for diabetes care encourage individualization and patient-centered approaches but are limited by the tools for individualization that we currently have, and often do relatively little to expand the “one-size-fits-all” approach
• Current treatment guidelines are limited by the fact that they are largely reactive – to poor metabolic control when it occurs – but cannot predict which patients will need which treatment(s), in a proactive manner

The Case for Personalized Diabetes Care – The Vision

• The challenges to achieve personalized care vs. individualized care are to 1) characterize the multiple pathways that lead to β-cell destruction underlying the development of hyperglycemia, and 2) identify the best therapeutic approaches that target each pathway
• A truly personalized approach to therapy for T2D, with the critical goal of preventing or treating specific complications, could help reduce or eliminate the burden (morbidity/mortality) associated with diabetes

The Case for Personalized Diabetes Care – The Caveats

• A personalized approach adds a higher level of burden to understand the nuances of treatment options, since its goal is to avoid the “one-size fits all” approach
• Many factors need to be considered in personalized diabetes management, some that we understand, some which we do not. For this reason, we can currently achieve some level of “individualized” or “patient-centered” care but not yet truly “personalized” care
### What We Do Now – Individualized Care

- We diagnose diabetes, and classify it largely on available clinical/laboratory evidence.
- For T2D, we provide lifestyle/nutrition advice, and most often prescribe metformin.
- We currently individualize A1c targets (do we?), based on multiple medical and psychosocial factors.
- When A1c targets are not met, we select secondary medication options based on multiple factors in an attempt to individualize care.
- Ideally, we utilize shared decision-making regarding treatment choices with an informed patient.

### Framework to Assist in Determining Glycemic Treatment Targets in T2D

<table>
<thead>
<tr>
<th>Most Intensive</th>
<th>Less Intensive</th>
<th>Least Intensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0%</td>
<td>7.0%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

**Psychosocial/behavioral**
- Highly motivated, adherent, knowledgeable, excellent self-care capacities, and comprehensive support systems
- Less motivated, nonadherent, limited insight, poor self-care capacities, and limited support systems

<table>
<thead>
<tr>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>60</td>
<td>70</td>
<td>80</td>
</tr>
</tbody>
</table>

**Patient age, y**
- <50
- 50-60
- 60-70
- >70

**Duration, y**
- <10
- 10-20
- 20-30
- >30

**Complications**
- None
- Cardiovascular disease
- Early microvascular
- Established advanced microvascular

**Other comorbid conditions**
- None
- Few or mild
- Multiple or severe

### Individualization is Key

**ADA Standards of Medical Care in Diabetes**

<table>
<thead>
<tr>
<th>Tight Targets (&lt;6.5%)</th>
<th>Looser Targets (&lt;8.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short diabetes duration</td>
<td>Severe hypoglycemia history</td>
</tr>
<tr>
<td>Long life expectancy</td>
<td>Limited life expectancy</td>
</tr>
<tr>
<td>No significant CVD</td>
<td>Advanced microvascular and macrovascular complications</td>
</tr>
<tr>
<td>Patient with long-term diabetes in whom general A1c is difficult to obtain</td>
<td>Patient with long-term diabetes in whom general A1c is difficult to obtain</td>
</tr>
</tbody>
</table>

CVD = cardiovascular disease.
Strategies for Initial Management

Stratify treatment based on A1c

**ADA/EASD Position Statement**
- Monotherapy for A1c < 9%
- Dual Therapy for A1c ≥ 9 – 10%
- Triple therapy or insulin for A1c > 10%

**AACE/ACE Algorithm**
- Monotherapy for A1c ≤ 7.5%
- Dual Therapy for A1c > 7.5% - 9%
- Triple therapy or insulin for A1c > 9%
Therapeutic Advancement Following Failed Therapy

Percentage of subjects advancing as soon as, or before, A1C >8%

- Diet + Exercise: 66.6%
- Sulfonylurea: 35.3%
- Metformin: 44.6%
- Combination (Sulfonylurea + metformin): 18.6%


Question: Which 2nd Drug?

GRADE* Study Design

NIH-supported, randomized, open label, parallel group comparative effectiveness clinical trial in T2D comparing 4 drugs added to metformin, with planned >4 year average follow-up (3 to 7 years)

*Glycemic Reduction Approaches in Diabetes: A Comparative Effectiveness Study
Comparative Effectiveness Research – Definition

- The direct comparison of existing health care interventions to determine which work best for which patients and which pose the greatest benefits and harms
- A critical feature of CER is the use of "pragmatic trials" which measure effectiveness - the benefit that the treatment produces in routine clinical practice

GRADE Study Population

- Type 2 diabetes
- Age ≥30 years (≥20 for American Indians)
- Duration diagnosed diabetes <10 years*
- HbA1c 6.8–8.5%
- Treated with metformin or no drug only

*Intended to represent relatively new-onset Type 2 diabetes

GRADE Study Overview

- GRADE is the first comprehensive comparative effectiveness study of major pharmacologic treatments for T2D, and long enough in duration to be clinically relevant
- GRADE will advance understanding of how to better individualize therapy
- Ancillary studies are examining efficacy/effectiveness (including by race/ethnicity/gender), other metabolic outcomes, side effects, CVD risk/protection, cost effectiveness, selected microvascular complications, and patient-centered outcomes such as tolerability, satisfaction, and quality-of-life, providing a comprehensive assessment and comparison
GRADE Study Overview

- GRADE's focus on demographic, clinical and metabolic factors that are associated with response to, and failure of, the different treatments will promote understanding of how to individualize therapy
- Results: 2021

Refining Individualized Care: Elements of Diabetes Care Scale (EDCS)

Current Factors to Consider for Personalized Diabetes Care

- Clinical characteristics
  - Patient age and life expectancy
  - Diabetes duration
  - Glycemic control history
  - Comorbid conditions
  - Vascular complications
  - Risk of hypoglycemia
- Personal characteristics
- Psychosocieoeconomic factors
  - Support system
  - Psychological status
  - Economic issues
  - QOL

Diab Spectrum 2014;2:87-91
EDCS and Setting Targets

- Clinical characteristics
  - Account for ~70% of variables
- Personal/psychosocial/economic factors
  - Account for ~30% of variables
- EDCS method offers a crude guide to individualizing care, is not meant to replace clinical judgement

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Table 1. Elements of Diabetes Care Scoring Scale

<table>
<thead>
<tr>
<th>Region</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy based on age (years)</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Microvascular</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes education</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure control</td>
<td>3</td>
</tr>
<tr>
<td>Glucose control</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes control</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. Suggested Glycemic Targets

<table>
<thead>
<tr>
<th>Target</th>
<th>5.0</th>
<th>6.4</th>
<th>7.8</th>
<th>&gt; 8.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Where Can We Go with Personalized Care?
Toward Precision Medicine: Predicting Response to Incretin-Based Agents (PRIBA) Study

- In 254 subjects with Type 2 diabetes, markers of increased insulin resistance were examined and correlated to responses to treatment with DPP-4 inhibitors and GLP-1 receptor agonists:
  - High fasting C-peptide levels
  - HOMA2 measure of insulin resistance
  - Triglycerides
  - Obesity
- All were associated with a decreased 6 month A1c responses to DPP-4 inhibitors but not to GLP-1 receptor agonists
- In a subset, obesity and elevated triglycerides were also associated with a less durable response

PRIBA Study

- There are important implications of these findings for clinical practice: BMIs and triglycerides are routinely available and add no cost to care
- This study represents a model of an approach which could be applied to other drug classes and thus have very broad application to diabetes treatment

Toward Precision Medicine: Lessons from Cancer Therapy

- Genetic testing:
  - Earlier diagnosis and targeted risk assessments
  - Intensified pre-disease screening
  - More effective treatments
  - Cascade testing of close relatives
- Personalized immunotherapeutic strategies can harness the power of the individual’s own immune system (particularly T cells) to target diseased tissues
  - Applicable targets for diabetes therapy could be β-cells or adipose tissue (others)
Toward Precision Medicine: Is it Time to Change the Classification Scheme for Diabetes?

Is it Time to Change the Classification Scheme for Diabetes?
Case in Point: The ANDIS Study

LADA
- Autoimmune diabetes defined by adult-onset (>age 30), presence of diabetes-associated autoantibodies, no insulin requirement for a period of time after diagnosis (typically months to <2 years)
- Phenotypically often misdiagnosed as T2D
- Shares genetic features with both T1D and T2D
- Patients often have worse A1c values than T2D at same disease duration
- Usually are lower age of onset, have lower BMI, & progress to the need for insulin more rapidly than most T2D's

Diabetic Medicine 2015:32;843–852
### LADA

- Many question that LADA is a distinct entity and propose instead that LADA and childhood-onset T1D are opposite ends of the same spectrum of autoimmune diabetes
- Others question whether it is a form of T2D with worsened \( \beta \)-cell function due to a low degree of \( \beta \)-cell autoimmunity
- Insulin resistance, not a significant factor in the development of most autoimmune diabetes, plays a unique pathogenic role in LADA, and may therefore represent an often overlooked therapeutic target
- Many questions remain surrounding the treatment of LADA: insulin is obviously required with severe \( \beta \)-cell deficiency, but would some patients benefit from other treatment: GLP-1 RA, metformin, TZDs

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### The ANDIS Study

- Data-driven cluster analysis was performed for 8,980 adults (n=5,344 men, 3,646 women) with newly diagnosed diabetes from the All New Diabetics in Scania (ANDIS) Study cohort in Sweden
- Clusters were based on 6 variables: the presence of glutamic acid decarboxylase antibodies (GADA), age at diagnosis, BMI, HbA1c, and HOMA2 estimates of \( \beta \)-cell function and insulin resistance
- Five distinct clusters (subgroups) were identified in both men and women (next slide), with distinctly identifiable characteristics
- Findings were later replicated in 3 other cohorts: the Scania Diabetes Registry (n=1,466), All New Diabetics in Upsala (n=844), and Diabetes Registry Vaasa (n=3,485)

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1 (n=577)</td>
<td>early onset disease, low BMI, poor metabolic control, insulin deficiency, and ( \text{+GADA} )</td>
</tr>
<tr>
<td>2 (n=1,575)</td>
<td>similar to cluster 1 but ( \text{–GADA} )</td>
</tr>
<tr>
<td>3 (n=1,373)</td>
<td>severe insulin resistance and high BMI</td>
</tr>
<tr>
<td>4 (n=1,942)</td>
<td>obese but not insulin resistant</td>
</tr>
<tr>
<td>5 (n=3,513)</td>
<td>modest metabolic derangements, older patients</td>
</tr>
<tr>
<td>6</td>
<td>clusters 1 &amp; 2; higher A1c at diagnosis, with persistent poor control, more prone to DKA</td>
</tr>
<tr>
<td>7</td>
<td>more likely to develop retinopathy</td>
</tr>
<tr>
<td>8</td>
<td>high prevalence of NA fatty liver disease, more likely to develop CKD</td>
</tr>
</tbody>
</table>
The ANDIS Study

• "...this new clustering of patients with adult-onset diabetes is superior to the classic...classification because it identifies patients at high risk for diabetes complications at diagnosis and provides information about underlying disease mechanisms, thereby guiding choice of therapy"
• "This...might eventually help to tailor and target early treatment to patients who would benefit most, thereby representing a first step towards precision medicine in diabetes"
• "...we used variables reflective of diabetes that are monitored in patients. Thus, this clustering can be applied to both existing diabetes cohorts (eg, from drug trials) and patients in diabetes clinics"

Is it Time to Change the Classification Scheme for Diabetes?

• We see obese type 1's, thin type 2's, late-onset autoimmune diabetes, and monogenic defects masking as type 2...and there's likely more heterogeneity out there!
• The current classification scheme presents challenges to diagnosis and treatment of patients, in part due to conflicting and confounding definitions of T1D, T2D, and LADA
• Discovery of the role that autoimmunity plays in the pathogenesis of T1D created the assumption that T1D and T2D have unique etiologies, disease courses, and treatment approaches; however, overlap exists in even the most “typical” patients

Is it Time to Change the Classification Scheme for Diabetes?

• The classification of DM should evolve as we learn more about the pathogenesis and unique features of individuals
• It should allow for overlap in clinical features that should drive different treatment strategies – eg, targeting obesity and/or insulin resistance, and β-cell deficiency, present to varying degrees in T2D
• Disease identification impacts disease management – the potential exists to provide a more personalized approach to treatment based on underlying pathogenesis, and even on anticipated risk of complications
• We should consider classifying diabetes by factors including: β-cell functionality, presence/absence of autoimmunity, insulin resistance, genetic defects, other factors (eg, risk for complications), which should drive treatment choices
• An entirely new nomenclature may be best fit to bring classification in line with known and evolving understanding of DM etiology and disease course
Personalized Medicine: Filling the Research Gaps

- Define causative factors associated with the known correlations among different demographic subgroups and the corresponding risks for T2D (race, ethnicity, SES)
- Develop better understanding of genetic risk and inheritance profiles, through GWAS, and molecular genetic tools for next-generation sequencing to differentiate likely subclasses of diabetes, to learn how genetic variations affect the rate of progression of diabetes and its complications, and to predict response to – and side effects of - therapeutic approaches

*Diabetes. 2018;41:705-712*

Personalized Medicine: Filling the Research Gaps

- Define causal relationships between specific environmental factors and mechanisms leading to diabetes (obesity, inactivity, nutritional factors)
- Develop biomarkers and imaging tools for measuring β-cell mass and function at diagnosis, and to monitor progression and response to therapeutic interventions
- Identify and exploit mechanisms by which β-cells can overcome an insulin resistant environment
- Better delineate mechanisms underlying the development of complications

*Diabetes. 2018;41:705-712*
Beyond Patient-Centered to Personalized Diabetes Care: Conclusions

• Increasing evidence suggests that subtypes of disease with distinct etiologies exist within the broad categorization of type 2 (and, type 1) diabetes, that have distinct etiologies that may be clinically characterized
• With more focused research we can approach a point where categorizing diabetes in a more precise manner will then better inform individual treatment decisions
• Understanding the pathways to loss of β-cell mass and function is critical to addressing all forms of diabetes and avoiding complications
• Studies such as the ANDIS Study represent a model of an approach that, with additional refinement, could lead to the development of meaningful classifications based on demographics and laboratory and clinical characteristics, and to new biomarkers for disease risk, progression, and complications in distinct subpopulations

Beyond Patient-Centered to Personalized Diabetes Care: What Will We Tell Our Future Patients?

Simple...

got diabetes?
YOU'RE MY TYPE!

unite • support • learn
thrive • help • encourage
promote • celebrate • change
enlighten • applaud • share
know • empower • advocate

blame the disease; love the people.

Thank you!