Biomarkers: what can be learned from type 2 diabetes?

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GLUCOSE

Diagnose

Treatment decisions

Discovery and registration of new drugs

HbA1C
The bar is higher now...

EMPA-REG: Death from CV causes

Primary endpoint = composite outcome of CV death, nonfatal MI, nonfatal stroke.

TOPLINE results = Superior reduction of MACE derived from all three components... with established CVD/multiple CV RFs.
Evolving beyond glucose...

Intense biomarker activity focusing on faster and better prediction of disease:

- Progression
- Outcomes

Disease Modification

- E.g. Remission of diabetes

Glucose

End organ damage
Insulin Resistance – Hall mark of Type 2 Diabetes

- Pathways in NAFLD likely to overlap with T2D - common soil of IR
- NASH more frequently seen in diabetic pts vs. non-diabetic pts
- NAFLD-NASH can be both a cause and a consequence of diabetes

BMx Needs in Type 2 Diabetes (and NASH):
1. Disease staging
2. Mark disease progression and disease modification
3. Identify surrogate markers of clinical outcomes
I. Identifying prediabetes and progression to overt T2D

II. Progression of disease – treatment progression and progression to end-organ damage

III. Disease modification – remission of T2D
I.

**Ins Resistance Pre-diabetes**

**Obesity**

**Insulin Resistance**

**β-cell compensation**

**β-cell dysfunction**

**Hyperinsulinemia**

**Impaired insulin secretion**

**Hyperglycemia**

**Normoglycemia**

**Pre-diabetes**

**Overt T2D**

1. Clinical parameters
2. Dynamic assessments
3. Multi-hormonal
4. "Omics"

Modified from van Greevenbroek et al, 2013
Metabolic syndrome criteria can predict incident type 2 diabetes

Most commonly used criteria is NCEP-ATPIII:
1. FPG >100 mg/dl
2. WC >102 cm in men and >88 cm in women
3. BP ≥130/85
4. TG ≥150 mg/dL
5. HDL-C <40 mg/dL in men or HDL-C <50 mg/dL in

Jeong-Ah Shin et al. (J Diabetes Invest, doi: 10.1111/jdi.12075, 2013)
Dynamic assessments predicting incident T2D

Glucose Tolerance Testing for Disposition Index

Relationship between Insulin Sensitivity and Response = The Disposition Index

T2DM incidence with Pioglitazone/PBO in ActNOW
(Combined Pioglitazone and Placebo groups)

T2DM incidence (%/year)

$\Delta I_{0-120}/\Delta G_{0-120} \times$ Matsuda Index based on oGTT at baseline and study end (mean 2.4 years)

$r = 0.99$

$P < 0.0001$
Combining markers to increase T2D risk prediction: Inter99 Cohort

- A longitudinal population-based study of 6,600 Danes
- Primary outcome = 5-year conversion to type 2 diabetes
- A “Diabetes Risk Score (DRS)” was derived from a model that included 64 candidate biomarkers
- 6 biomarkers emerged from the model:
  - ADIPOQ, CRP, FTH1, glucose, IL-2RA, and insulin
- DRS performs better than single risk indicators; better stratification than fasting plasma glucose alone

*Kolberg et al. Diabetes Care 32:1207–1212, 2009*
“Omics” based approaches spanning the spectrum to characterize diabetes risk

Could also be used for:
• Monitoring at-risk pt groups
• Assessing effects of intervention

Plasma amino acids – positive and negative association with T2D

<table>
<thead>
<tr>
<th>Metabolic pathways</th>
<th>Disease</th>
<th>Association</th>
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<tbody>
<tr>
<td><strong>Aromatic amino acids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>Phenylalanine, tyrosine, and tryptophan</td>
<td>Diabetes$^{33,34,40}$, Insulin resistance$^{31}$, Obesity$^{37}$</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>Glycine, arginine, and tryptophan</td>
<td>Diabetes$^{34}$</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>Phenylalanine, tyrosine, and tryptophan</td>
<td>Diabetes$^{6}$, Insulin resistance$^{36,36}$, Obesity$^{37}$</td>
</tr>
<tr>
<td><strong>Aliphatic amino acids and BCAAs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>Alanine, Glutathione, Glycine and serine, Bile-acid biosynthesis, Methionine</td>
<td>Insulin resistance$^{47}$, Obesity$^{37}$, Diabetes$^{34,47}$</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>BCAA catabolism</td>
<td>Diabetes$^{46,49}$, Insulin resistance$^{30,34,40}$, Obesity$^{37}$</td>
</tr>
<tr>
<td>Leucine</td>
<td>BCAA catabolism</td>
<td>Diabetes$^{14,36}$, Insulin resistance$^{30,33,34,36}$, Obesity$^{37}$</td>
</tr>
<tr>
<td>Valine</td>
<td>BCAA catabolism</td>
<td>Diabetes$^{34,41}$, Insulin resistance$^{34}$, Obesity$^{37}$</td>
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</table>

Top quartile of the combined (Phe+Tyr+Ile) score had an odd ratio of 5.99 after adjustment for estab’d risk factors (age, sex, BMI, etc) providing predictive value in addition to std clinical measures.

Validated in the Malmo Diet and Cancer study.

Predicts onset of CVD, and onset of new DM during 5 yr f/u in ~9300 Finnish men.

Roberts et al. Lancet Diabetes Endocrinol 2014; 2: 65–75
Plasma Bile Acids

Haeusler...Accili. Diabetes 62:4184–4191, 2013:
- 200 non-diabetic subjects [part of the Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) study] by quartiles of insulin sensitivity
- 35 patients with T2D
- Measured plasma BAs

Summary of Part I

- Plethora of biomarkers to identify prediabetes and for predicting progression to overt T2D
  - But their overall clinical utility still remains to be proven
- Relatively simple clinical /laboratory measures (such as metS criteria) and dynamic assessments (e.g. GTT) appear to provide sufficient resolution to satisfy the above needs
“The real challenge is not the need for new ways to identify pre-diabetes. The challenge is to find better approaches to help at-risk patients to change their lifestyle and lose weight because we know for certain that these changes are powerful means to prevent the development of type 2 diabetes…”

JAMES B. MEIGS, MD, MPH
(Edited; DIABETES CARE, 2009)

...AND, finding markers that identify disease progression and remission.
I. Identifying prediabetes and progression to overt T2D

II. Markers of progression within overt T2D (esp. treatment progression)

III. Disease modification – remission of T2D
The natural history of T2D manifests clinically as:
1) development of overt hyperglycemia,
2) progressive loss of response to NON-insulin therapies, and
3) development of diabetes complications (end-organ damage)

Role of chronic inflammation?
Exploring the role of low grade inflammation

- **NHANES (1999-2010):**
  - T2DM and controls – weighted to have equivalent age, gender, and ethnicity distribution
  - Standard biochemical markers

- **Time in various treatment groups were evaluated**
  > specifically, the relative holding time within each treatment to maintain euglycemia

Thanawala, Krishnan, ...Lilly

Liver continues to provide a signal of disease progression within T2D
Patients with high ALT are significantly likely to progress through the disease continuum from healthy to diabetic and onto 1st oral.

These patients are also likely to progress rapidly from 2nd oral to 3rd oral.

It will take 0.5 yr for someone with a high ALT to progress from 2nd oral to 3rd oral vs. 3 yrs for normal.

Thanawala, Krishnan, ...Lilly
I. Identifying prediabetes and progression to overt T2D

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III. Disease modification – remission of T2D
III. Possible disease modification strategies in T2D:

- Delay or prevent onset of disease
- Delay or prevent disease progression (reduce/eliminate glucose-lowering Tx)
- Disease remission
- Delay or prevent disease complications
Bariatric surgery can induce T2D remission within days.

Bariatric surgery can induce T2D remission

Over years....

T2D remission in bariatric surgery pts >> matched non-bariatric surgery pts with T2D

Yska et al. JAMA Surg. 2015;150(12):1126-1133
Using the DiaRem score to predict the probability of T2D remission after bariatric surgery

<table>
<thead>
<tr>
<th>4 Components of DiaRem</th>
<th>Score</th>
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<tbody>
<tr>
<td><strong>1</strong> Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>1</td>
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<tr>
<td>50-59</td>
<td>2</td>
</tr>
<tr>
<td>≥60</td>
<td>3</td>
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<tr>
<td><strong>2</strong> HbA1c (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;6.5%</td>
<td>0</td>
</tr>
<tr>
<td>6.5-6.9%</td>
<td>2</td>
</tr>
<tr>
<td>7.0-8.9%</td>
<td>4</td>
</tr>
<tr>
<td>≥9.0%</td>
<td>6</td>
</tr>
<tr>
<td><strong>3</strong> Other diabetes drugs</td>
<td></td>
</tr>
<tr>
<td>No sulfonylureas or insulin-sensitising agent other than metformin</td>
<td>0</td>
</tr>
<tr>
<td>Sulfonylureas and insulin-sensitising agent other than metformin</td>
<td>3</td>
</tr>
<tr>
<td><strong>4</strong> Treatment with insulin</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
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</tbody>
</table>

Robustness of this tool was **validated in 3 additional, independent cohorts**: Scottsdale, Danville, and Cleveland Clinic -- these cohorts were different from that used for the development of the DiaRem score .... *(lessons for NASH BMx validation?)*

Other biomarker efforts in *Disease Modification* for diabetes...

- Biomarkers for glycemic deterioration and successful diabetes remission
- Genetic and genomic analyses supporting biomarker identification and characterization
- Validation of biomarkers for drug response in clinical trials
Summary (1)

• Diabetes/obesity as common soil for NASH development
  • Learning from BMx research in T2D can be applied to BMx needs for NASH

• Identifying prediabetes and markers of progression to overt T2D are robust, even with relatively straightforward clinical/laboratory and dynamic assessments

• Inflammation markers (e.g. ALT, AST) appear to track with treatment regimen progression indicative of worsening glycemic control
  • Underscores hepatic inflammation as a common pathophysiological basis for T2D and NASH

• Diabetes remission is possible -- phenotypic and clinical markers can predict remission
  • Inflammatory pathways in adipose tissues most significantly affected following bariatric surgery
Summary (2)

- Diabetes remission *per se* may not be the most important outcome.
  - **Impacting hard endpoints**—e.g., *CV risk, end-organ damage, mortality*—is the way

➤ Need a continuous, quantitative, and validated biomarker that predicts risk across the spectrum of disease vs. those that merely provide a snap-shot

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**Continuum of CV risk with increasing LDL**

- Low risk
- Medium risk
- High risk

**Continuum of T2D risk with increasing DRS**

- LOW
- MEDIUM
- HIGH
BMx continuum for NASH - is it possible?


↓ DNL
• ↓ LOX activity
• ↑ peroxisomal fxn
⇒ ↑ oxd. of eicosanoid products

Can such a continuum also be extended to mark the progression of **HEPATIC FIBROSIS** and/or other **LIVER-RELATED OUTCOMES**?
Acknowledgements

Lilly Research Laboratories
• Tao Wei
• Venkatesh Krishnan

Cornell University
• Ninad Thanawala

THANK YOU
FOR YOUR ATTENTION!