Maria F. Gomez
Lund University Diabetes Centre, Sweden
Reflections & learning lessons:

- The power of public private partnerships in diabetes research
- Precision Medicine
  “The right prevention and treatment, to the right patients at the right time”
- Preparedness to tackle health crises
SUrrogate markers for Micro- and Macro-vascular hard endpoints for Innovative diabetes Tools

- Genetic markers and soluble biomarkers
- Novel imaging techniques for monitoring progression in atherosclerosis and retinopathy
- Novel animal models for micro- and macrovascular complications to better replicate human disease
- Novel in silico methods for modelling and predicting diabetic complications
Pre-diabetes (N=2,291)

10 days ACC
Diet records
Frequently sampled OGTT
MRI

T2D (N=850)

Cohort data assimilation
Risk data scoring
Screening
MMTT
Fasting Blood; Anthropometry

“the citation impact of IMI papers is twice the world average and significantly higher than the EU average”
SUMMIT

RHAPSODY

BEAT DKD

IMIDIA

DIRECT

SOPHIA

2009

Accelerating research and development
Speeding up patient access to innovative treatments
Improving patient outcomes and safety of medicines

Maria F. Gomez
Lund University Diabetes Centre, Sweden
Biomarker Enterprise to Attack DKD

- Validation (ethnicities)
- Regulatory engagement (FDA & EMA)
- Dynamic biomarkers (treatment response)
Maximizing synergies between existing consortia, academia & industry for effective utilization of available resources – Data Federation for sensitive data
- ACE inhibitors (ACEi) in 1993
- Angiotensin-Receptor Blockers (ARBs) in 2001

= slow progression of renal disease in T2D patients by ~20% compared to the “standard” glucose lowering and blood pressure lowering therapies, but residual renal and cardiovascular risk remained extremely high

- endothelin receptor antagonist (ERa) atrasentan
- sodium glucose cotransporter 2 (SGLT2)
- aldosterone inhibitors (FINERENONE, EPLERENONE)
- statins

= not all patients benefit from the treatments – abandon the idea of “one size fits all”
SOPHIA Work Package (WP) overview

WP1: Management, dissemination and exploitation

WP2: Data federation and analysis

WP3: Risk and response in people with obesity

WP4: Obesity and type 1 diabetes

WP5: Obesity and type 2 diabetes

WP6: Biomarker validation and predictive algorithms

WP7: Fears and hopes of people with obesity

WP8: Shared value: definition to achievement
COVID Symptom Study

- ~4.6 million participants in 3 countries (UK, USA, Sweden)
- ~370 million data entries obtained through a mobile device app documenting symptoms, risk factors, use of PPE, behaviors, test results, vaccinations
- Weekly reports produced and sent to leaders of regional and national public health authorities
- A dashboard showing infection trends on a regional and national level is maintained (https://csss-resultat.shinyapps.io/csss_dashboard/)
- Webpage UK https://covid.joinzoe.com/
- Webpage Sweden https://www.covid19app.lu.se/
Clinical characteristics and genetics of novel subtypes of adult onset diabetes

Emma Ahlqvist, MSc, PhD
Associate Professor,
Lund University Diabetes Centre, Malmö, Sweden
Heterogeneity of diabetes

Diabetes is defined by high glucose but causes for hyperglycemia differ
Type 2 diabetes is a diagnosis of exclusion

Autoimmune:
Type 1 diabetes (T1D)
Latent Autoimmune Diabetes in Adults (LADA)

Genetic:
Maturity Onset Diabetes in Young (MODY)
Neonatal diabetes

Secondary diabetes

Type 2 diabetes (T2D)
Heterogeneity in T2D

• Individuals with T2D differ with respect to clinical characteristics, risk of complications and response to treatment

• Can we divide T2D patients into smaller more homogeneous groups that are clinically useful for predicting disease progression and selecting therapy?
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables


Summary
Background Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.
Cluster analysis

Cluster analysis is a method for data driven grouping of individuals by similarity.

Cohorts

- ANDIS (All New Diabetics in Scania) (N=8980)
  - New onset diabetes of all types
  - Children and monogenic/secondary diabetes were excluded

Cluster variables

- Presence of GAD65 antibodies
- HbA1c at diagnosis
- BMI
- Age at diagnosis
- C-peptide based HOMA2-B (insulin secretion)
- C-peptide based HOMA2-IR (insulin resistance)

Ahlqvist et al, Lancet Diabetes and Endocrinology, 2018
Clustering results in ANDIS

**Men n=5.334**

- HBA1C
- BMI
- AGE
- HOMA2-B
- HOMA2-IR

**Women n=3.646**

- HBA1C
- BMI
- AGE
- HOMA2-B
- HOMA2-IR

Ahlqvist et al, Lancet Diabetes and Endocrinology, 2018
Summary clusters

We can reproducibly divide patients into five subgroups with different characteristics and progression.

- **Type 1 diabetes / LADA**
  - **SAID = Severe Autoimmune Diabetes**
    - GAD antibodies, low insulin secretion, poor metabolic control
  - **SIDD = Severe Insulin Deficient Diabetes**
    - Low insulin secretion, poor metabolic control

- **Type 2 diabetes**
  - **SIRD = Severe Insulin Resistant Diabetes**
    - Insulin resistance, obesity, late onset
  - **MOD = Moderate Obesity-Related Diabetes**
    - Obesity, early onset
  - **MARD = Moderate Age-Related Diabetes**
    - Late onset, good metabolic control

This clustering approach has been replicated in numerous cohorts.
MARD - Moderate age-related diabetes

- 39% of patients
- Relatively old at diagnosis (mean age 67 years)
- Moderately over weight (mean BMI = 28)
- Relatively low blood glucose
- Relatively low risk of complications

MOD – Moderate Obesity-related Diabetes

- 22% of patients
- Obese (mean BMI = 36)
- Early onset (mean age at diagnosis = 49 years)
- Relatively low blood glucose levels
- Relatively low risk of complications
- BUT early onset means a long time for complications to develop
SAID - Severe autoimmune diabetes

- 6% of patients (>18 years old)
- Autoantibody positive (GADA) = includes T1D and LADA
- Poor insulin secretion
- Relatively early onset of diabetes (mean ~50 years)
- High glucose levels (HbA1c) = poor metabolic control

SIDD - Severe insulin-deficient diabetes

- 18% of patients
- Poor insulin secretion
- Poor metabolic control
- Overweight (mean BMI = 29)
- Relatively early onset (mean age at diagnosis = 57 years)
- More difficult to treat
Diabetic complications

Retinopathy

Neuropathy
SIRD - Severe insulin-resistant diabetes

- 15% of patients
- Severe insulin resistance and obesity (mean BMI = 34)
- Late onset (mean age at diagnosis = 65 years)
- Approximately the same glucose levels as mild diabetes forms, MARD and MOD
- Approximately the same treatment
- Much higher risk of kidney complications and fatty liver disease

**ANDIS**

\[ \text{eGFR}<45 \text{ mL/min/1.73m}^2 \]

**SDR**

\[ \text{eGFR}<15 \text{ mL/min/1.73m}^2 \]

**German Diabetes Study**

Hepatocellular lipid content

Adapted from Zaharia et al, Lancet Diabetes and Endocrinology, 2019
Genome-Wide Association Study (GWAS)
Compared with diabetes free individuals N=2744

Risk variants are differentially associated with subtypes

<table>
<thead>
<tr>
<th>Risk score</th>
<th>SAID</th>
<th>SIDD</th>
<th>SIRD</th>
<th>MOD</th>
<th>MARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>17%</td>
<td>12%</td>
<td>22%</td>
<td>29%</td>
<td>4%</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>1%</td>
<td>33%</td>
<td>5%</td>
<td>29%</td>
<td>31%</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>8%</td>
<td>17%</td>
<td>16%</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Mansour Aly et al, MedRxiv, 2020
Summary

- Three severe forms of diabetes
  - Autoimmune (SAID)
  - Insulin deficient (SIDD)
  - Insulin resistant (SIRD)
- Two moderate forms of diabetes
  - Obesity-related (MOD)
  - Age-related (MARD)
- SIDD has the highest risk of diabetic retinopathy and neuropathy
- SIRD has the highest risk of diabetic kidney disease and NAFLD
- Important not to focus only on HbA1c to evaluate disease progression and response to therapy
- SIDD and SIRD patients develop complications very early and would benefit from early identification and treatment
- Genetics suggest differences in pathogenesis
Extra slides
Targeting Vascular Stress in CKD: Endothelin Signaling Pathway

- Endothelin 1 (ET1, EDN1) is increased by range of factors present in proteinuric glomerular diseases
- EDN1 is mainly produced by endothelial cells
- Targets vascular smooth muscle, mesangial, inflammatory and epithelial cells
- Endothelin Receptor blockade successfully developed for DKD and glomerular diseases
Identification of molecular pathways & biomarkers associated with response to atrasentan

Atrasentan

Mesangial cells

BTBR Ob/Ob mouse

Urine

Serum

Plasma

Agilent Arrays
34183 features

RNA sequencing
17338 features

Metabolomics
189 features

Metabolomics
215 features

miRNA
641 features

OLink assays
254 features

OLink assays
368 features

SOMAscan panels
1317 features

W. Ju, P. Perco, V. Nair, S. Belur, F. Burdet, A. Thorenz, A. Kannt, M. Gomez, C Alpers, M. Kretzler, H L Heerspink on behalf of the BEAt-DKD consortium.
GENERAL APPROACH FOR BM DISCOVERY IN BEAt-DKD

1: Literature search to assess effects of drug of interest on molecular markers

2: Transcriptomic profiling of a drug’s molecular effect in cells, tissues and human blood/urine samples

3: Bioinformatics to retrieve a drug effect signature

4: Mapping drug (SOC) MoA model with established diabetic nephropathy model

5: Creating a short-list of biomarkers involved in DN and targeted by the drug of interest

Table 2. Clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Drug class</th>
<th>N patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEPHRON-D</td>
<td>Lisinopril / Losartan</td>
<td>ACEi/ARB</td>
<td>1448</td>
</tr>
<tr>
<td>ONTARGET²</td>
<td>Ramipril / Telmisartan</td>
<td>ACEi/ARB</td>
<td>6972</td>
</tr>
<tr>
<td>VARIETY⁴</td>
<td>Benazepril / Valsvartan</td>
<td>ACEi/ARB</td>
<td>613</td>
</tr>
<tr>
<td>VALID³</td>
<td>Benazepril / Valsvartan</td>
<td>ACEi/ARB</td>
<td>103</td>
</tr>
<tr>
<td>RIMA/2</td>
<td>Irbesartan</td>
<td>ARB</td>
<td>165</td>
</tr>
<tr>
<td>SPRI²</td>
<td>Spironolactone</td>
<td>MRA</td>
<td>116</td>
</tr>
<tr>
<td>PRIORITY⁵</td>
<td>Spironolactone</td>
<td>MRA</td>
<td>670</td>
</tr>
<tr>
<td>PLANET I</td>
<td>Atorvastatin / Rosuvastatin</td>
<td>Statin</td>
<td>325</td>
</tr>
<tr>
<td>SUN/maestro</td>
<td>Sulfonamide / Glycosaminoglycan</td>
<td>1167</td>
<td></td>
</tr>
<tr>
<td>RADAR</td>
<td>Atorvastatin</td>
<td>ESA</td>
<td>211</td>
</tr>
<tr>
<td>SONAR⁶</td>
<td>Atrasentan</td>
<td>ESA</td>
<td>4000</td>
</tr>
<tr>
<td>ACCORD-BP</td>
<td>Intensive BP, HbA1c lowering</td>
<td>BP targets, HbA1c</td>
<td>10251</td>
</tr>
<tr>
<td>IMPROVE</td>
<td>Diapagliurin / SGLT2</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Lilly GFRE²</td>
<td>TGβ1 monoclonal Ab</td>
<td>Novel target</td>
<td>315</td>
</tr>
<tr>
<td>DIABASS³</td>
<td>Acetyl-L-carnitine</td>
<td>Antioxidant</td>
<td>229</td>
</tr>
<tr>
<td>CRESO⁴</td>
<td>Diet</td>
<td></td>
<td>74</td>
</tr>
<tr>
<td>CRESO 2⁵</td>
<td>Diet</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>PROCEED⁶</td>
<td>Pumice toluene</td>
<td>VDR agonist</td>
<td>115</td>
</tr>
<tr>
<td>Iron-deficient patients</td>
<td>Iron isomaloside</td>
<td>Iron isomaloside</td>
<td>351</td>
</tr>
</tbody>
</table>

- ACEi / ARB combinations (VALID / NEPHRON-D / ONTARGET)

- Statins (PLANET 1 and PLANET 2)

- Endothelin Receptor Antagonists (RADAR / SONAR)

- Sodium Glucose Co-transport inhibitors (IMPROVE – DAPKID / RED-D)