The practical issues in Type 2 diabetes management - Pharmacogenomic considerations

Prof. Dr Sabina Semiz
Faculty of Pharmacy
University of Sarajevo

October 26, 2014.
Global Projections for the Diabetes Epidemic: 2010-2030 (millions)

1980-1990 by 18%.

World
2010 = 285 million
2030 = 438 million
Increase 54%

2011 - a staggering 366 million
2030 – 552 million

Dr Paul Zimmet, Baker IDI Heart and Diabetes Institute, Melbourne

Diabesity

- Obesity is driving the escalating diabesity epidemic: The biggest epidemic in human history.
- Continues to rise exponentially globally.
- Ageing, lifestyle change, and urbanisation have been targeted as the main drivers.
- By 2020, is set to bankrupt the economies of many nations unless action is taken.

Pharmacogenetics is the study of interindividual variations in DNA sequence related to drug response.

According to DUR/CRNP/307008-7; this is the paper on the anatomy of pharmacogenetics.
Pharmacogenetic Tests

- If genetic testing could be employed to predict treatment outcome, appropriate measures could be taken to treat T2D more efficiently and avoid extra costs for treating side-effects.
- Promote safe and cost-effective individualized diabetes treatment.
Pharmacogenomics in Diabetes

- T2D patients are often treated with more than one drug, including:
  - oral antidiabetic drugs (OAD), e.g., metformin and sulfonylureas (SU).
  - drugs used to treat diabetic complications, such as dyslipidemia and hypertension (e.g., statins).
### Oral Antidiabetic Drugs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Principal Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Decrease hepatic glucose production</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>Improve peripheral insulin sensitivity</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors</td>
<td>Acarbose, Miglitol</td>
<td>Delay carbohydrate absorption</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Glimepiride, Glipizide, Glyburide, Gliclazide</td>
<td>Stimulate insulin secretion from pancreatic beta cells</td>
</tr>
<tr>
<td>Short-acting insulinotropic agents</td>
<td>Repaglinide, Nateglinide</td>
<td>Stimulate insulin secretion from pancreatic beta cells</td>
</tr>
</tbody>
</table>
Sites of Action for Oral Therapies for Type 2 Diabetes

Pancreas
- Impaired insulin secretion

Gut
- \(\alpha\)-Glucosidase inhibitors
  - Acarbose (Precose)
  - Miglitol (Glyset)
  - Pramlintide
  - Exenatide

Liver
- ↑ Hepatic glucose output
- ↓ Biguanide
- ↓ TZDs

Adipose
- ↑ Biguanide
- ↑ TZDs

Muscle
- ↑ Glucose uptake
- ↑ Metformin (Glucophage)

↑ Sulfonylureas
- Glipizide (Glucotrol)
- Glyburide (DiaBeta, Micronase, Glynase)
- Glimepiride (Amaryl)

↑ Repaglinide (Prandin)

↑ Nateglinide (Starlix)
Pharmacogenomics in Diabetes

- Early stage of investigation.
- Although benefits from a personalized diabetes care are well established in patients with certain monogenic forms of diabetes, individualized treatment in more common polygenic forms of diabetes are also anticipated.
- GWA studies – identity of gene variants that impact on treatment response or side effects:
  - Severe hypoglycemia with sulfonylureas
  - Severe gastro-intestinal intolerance to metformin
  - Heart failure with thiazolidinediones
Pharmacogenomics in Diabetes

- The main objective is to improve drug therapy of diabetic patients.
- Analyze an association of genetic variations in:
  - drug-metabolizing enzymes (DME)
  - drug-transporters (DT)
  - specific drug targets with T2D treatment outcomes
Pharmacogenomics

DRUG TARGETS

DRUG TRANSPORTERS

DRUG METABOLIZING ENZYMES

PHARMACODYNAMICS

PHARMACOKINETICS

Variability in Efficacy/Toxicity

Johnson JA. Trends in Genetics 2003: 660-666
Pharmacogenetics in Diabetes

• Pharmacokinetic

• Pharmacodynamic
  – \textit{TCF1} (encoding HNF1\textsubscript{\alpha}) mutations - sulfonylureas as the first-line antidiabetic therapy for these patients.
  – \textit{PPAR}\textsubscript{\gamma} – variation associated marginally with changes in insulin sensitivity and response.
Summary of genetic variations involved in PGx of:

- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Biguanides
SULPHONYLUREAS

• KATP channel is essential for glucose - stimulated insulin secretion from pancreatic β-cells, modulates glucose uptake into skeletal muscle, glucose production and release from the liver.

• KATP channels are assembled from:
  – Kir6.2 potassium ion channel - encoded by *KCNJ11*
  – Sulphonylurea receptor 1 (SUR1) regulatory subunit - encoded by *ABCC8* gene
• SNPs of the genes encoding KATP channel are related to the efficacy of secretagogue drugs.

• A common Glu23Lys polymorphism (E23K) in \textit{KCNJ11} is associated with an increased risk of SU therapeutic failure.

• \textit{KCNJ11} variations have been associated with altered response to gliclazide and glibenclamide.

• Interestingly, the most promising gene variants affecting the SU response are those involved in drug pharmacodynamics, such as \textit{TCF7L2} that encodes a transcription factor Tcf-4, involved in the regulation of cellular proliferation and differentiation.
Common genetic variations associated with OAD therapy outcomes

- SU
- Meglitinides
- Metformin
- TZDs

Genes:
- KCNJ11
- TCF7L2
- KCNQ1
- ABCC8
- CYP2C9
Analysis of CYP2C9*2, CYP2C19*2, and CYP2D6*4 polymorphisms in patients with type 2 diabetes mellitus

Sabina Semiz¹, Tanja Dujic¹, Barbara Ostanek², Besim Prnjavorac¹³, Tamer Bego¹, Maja Malenica¹, Janja Marc² and Adlija Causevic¹

¹ Department for Biochemistry and Clinical Analysis, Faculty of Pharmacy, University of Sarajevo, Koševska 4 (Čekaluša 90), 71000 Sarajevo, Bosnia and Herzegovina. ² Department for Clinical Biochemistry, Faculty of Pharmacy, University of Ljubljana, Askerceva cesta 7, SI-1000 Ljubljana, Slovenia. ³ General Hospital Tesanj, Brace Pobrica 17, 74260 Tesanj, Bosnia and Herzegovina.
Analysis of \textit{CYP3A4*1B} and \textit{CYP3A5*3} polymorphisms in population of Bosnia and Herzegovina

Sabina Semiz\textsuperscript{1}, Tanja Dujić\textsuperscript{1}, Barbara Ostanek\textsuperscript{2}, Besim Prnjavorac\textsuperscript{1,3}, Tamer Bego\textsuperscript{1}, Maja Malenica\textsuperscript{1}, Barbara Mlinar\textsuperscript{2}, Janja Marc\textsuperscript{2}, Adlija Čaušević\textsuperscript{1}

\textsuperscript{1}Department for Biochemistry and Clinical Analysis, Faculty of Pharmacy, University of Sarajevo, Sarajevo, Bosnia and Herzegovina,
\textsuperscript{2}Department for Clinical Biochemistry, Faculty of Pharmacy, University of Ljubljana, Slovenia, \textsuperscript{3}General Hospital Tesanj, Tesanj, Bosnia and Herzegovina.
Meglitinides (glinides)

- A class of short-acting insulin secretagogues that act by binding to β-cells and closing KATP channel to stimulate insulin release.
- This is similar MOA of the sulfonylureas and both, meglitinides and SU, bind to the SUR1 subunit to inhibit channel activity.
- Due to their short action, repaglinide and nateglinide have a lower risk to induce hypoglycemia than SU.
- Furthermore, meglitinides offer an alternative OAD agent of similar potency to metformin, and may be indicated where side effects of metformin are intolerable or where metformin is contraindicated.
PG of Meglitinides

- **SLCO1B1** gene encodes the organic anion-transporting polypeptide 1B1 (OATP1B1) that transports repaglinide into hepatocytes.
  - Major factor that significantly affects the repaglinide pharmacokinetics, consistent with an enhanced hepatic uptake by OATP1B1.
Common genetic variations associated with OAD therapy outcomes

- Meglitinides
  - SLCO1B1
  - SLC30A8
  - MDR1
  - KCNQ1
  - KCNJ11
  - TCF7L2
  - CYP2C9

- TZD
  - NAMPT
  - CYP2C9
Thiazolidinediones (TZDs)

- Activate their molecular target PPARs (peroxisome proliferator - activated receptors).
- Bind with greatest specificity for PPARγ to promote adipogenesis and fatty acid uptake.
- By reducing circulating fatty acid levels and lipid availability in liver and muscle, these drugs improve the patients’ sensitivity to insulin and reduce hyperglycemia.
PG of TZDs

- Variation in $\text{PPAR}_\gamma$ would likely affect response to TZD and this was suggested in a recent study that analyzed pioglitazone response.
- Recently, several additional gene variants have been also associated with the TZD therapy outcomes, including adiponectin, leptin, resistin, and TNF-$\alpha$ that are of a particular interest due to their important role in insulin resistance.
Common genetic variations associated with OAD therapy outcomes

- **SU**
  - KCNJ11
  - ABCC8
  - KCNQ1
  - TCF7L2
  - CYP2C9

- **Meglitinides**
  - SLCO1B1
  - SLC30A8
  - MDR1
  - KCNQ1
  - KCNJ11
  - TCF7L2
  - NAMPT
  - CYP2C9

- **Metformin**
  - PPARG
  - PGC1α
  - Adiponectin
  - Leptin
  - PTPRD
  - TNFα
  - CYP2C8

- **TZDs**
First-line drug used to treat newly diagnosed T2D

- Antiglycemic efficacy
- Prevention
- Treatment
- Insulin sensitizing
- Anti-inflammatory
- Attenuation of metabolic syndrome
- Modifies endothelial dysfunction
- Modifies non-alcoholic fatty liver disease
- Lipid-lowering benefits
- Cost effective
- Weight neutral or reduction
- Anti-neoplastic potential
- Cardiovascular protection
Pharmacogenomics of Metformin

- The glycemic response to metformin is highly variable.
- About 35-40% of patients receiving the drug do not achieve acceptable control of glucose levels.
- Associations with glucose-lowering effect of metformin in the at-risk population were found in:
  - Drug target gene - *STK11*
Common genetic variations associated with OAD therapy outcomes

<table>
<thead>
<tr>
<th>SU</th>
<th>Meglitinides</th>
<th>TZDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>KCNJ11</td>
<td>SLC10A8</td>
<td>SLC22A1</td>
</tr>
<tr>
<td>ABCC8</td>
<td>MDR1</td>
<td>SLC22A2</td>
</tr>
<tr>
<td>KCNQ1</td>
<td>KCNJ11</td>
<td>SLC47A1</td>
</tr>
<tr>
<td>TCF7L2</td>
<td>TCF7L2</td>
<td>SLC47A2</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>NAMPT</td>
<td>ATM</td>
</tr>
</tbody>
</table>

- SLC22A1
- SLC22A2
- SLC47A1
- SLC47A2
- ATM

- Resistin
- Adiponectin
- Leptin
- TNFα
- CYP2C8
Metformin Pharmacokinetic Pharmacogenomics

Metformin in the Gut Lumen
- SLC29A4
- SLC22A3

Enterocyte
- SLC22A1

Bloodstream
- Metformin
- SLC29A4
- SLC22A3

Hepatocyte
- SLC22A3
- SLC22A1

Bile Duct
- SLC47A1

Renal Tubular Lumen
- SLC47A2
- SLC47A1
- SLC22A2

Diabetes Volume 63, August 2014
Pharmacodynamic effects of metformin
# Pharmacogenomics of Metformin

<table>
<thead>
<tr>
<th>Gene</th>
<th>Note</th>
<th>Summary of effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC22A1</td>
<td>OCT1</td>
<td>Decreased function alleles linked to reduction in metformin effect on initial A1C and lipid responses; incidence of diabetes</td>
<td>18, 40, 41, 52–56</td>
</tr>
<tr>
<td>SLC22A2</td>
<td>OCT2</td>
<td>No associations with clinical outcomes, only changes in metformin PK reported</td>
<td></td>
</tr>
<tr>
<td>SLC22A3</td>
<td>OCT3</td>
<td>No associations with clinical outcomes, only changes in metformin PK reported</td>
<td></td>
</tr>
<tr>
<td>SLC47A1</td>
<td>MATE1</td>
<td>Increased metformin response to A1C; incidence of diabetes</td>
<td>18, 42, 52</td>
</tr>
<tr>
<td>SLC47A2</td>
<td>MATE2</td>
<td>Poorer response to metformin; changes in A1C</td>
<td>42, 43</td>
</tr>
<tr>
<td>SRR</td>
<td>Serine racemase</td>
<td>Associated with changes in FPG, PPG, and CHO</td>
<td>57</td>
</tr>
<tr>
<td>ATM</td>
<td>Serine/threonine kinase; SNP in large LD block with 6 other genes</td>
<td>Metformin treatment success by A1C</td>
<td>29–31</td>
</tr>
<tr>
<td>LKB/STK11</td>
<td>AMPK upstream kinase</td>
<td>Decrease in ovulation in women with polycystic ovarian syndrome on metformin; incidence of diabetes</td>
<td>18, 58</td>
</tr>
<tr>
<td>PRKAA1, PRKAA2, PRKAB2</td>
<td>AMPK subunits</td>
<td>Incidence of diabetes</td>
<td>18</td>
</tr>
<tr>
<td>ABCC8-KCNJ11</td>
<td>Subunit of β-cell potassium channel</td>
<td>Incidence of diabetes</td>
<td>18</td>
</tr>
</tbody>
</table>

CHO, cholesterol; FPG, fasting plasma glucose; LD, linkage disequilibrium; PK, pharmacokinetics; PPG, postprandial plasma glucose.
Study: Pharmacogenomics of Metformin Treatment

- Patients are recruited prior to development of an overt diabetes (prediabetes) and prior to treatment.
- Thus, newly diagnosed diabetic patients are closely monitored for the drug effectiveness and development of adverse outcomes.
Research projects:

Pharmacogenetic factors associated with optimal therapy of Type 2 Diabetes.


Personalized Therapy of Type 2 Diabetes Through European Research Network

Semiz, S. Grant for EU-FP7 project preparation by the Council of Ministers BH, 2013-2014.
Study: Pharmacogenomics of Metformin Treatment

- Characterize genetic variations of:
  - DT (e.g., OCT, MATEs)
  - drug targets (e.g., AMPK, ATM)
- associated with T2D treatment outcomes:
  - HbA1c
  - FPG levels
  - Side-effects (GI)
- Explore genotype-phenotype associations.
Current Study Status

• Recruited about **100 T2D patients on metformin treatment** and collected blood samples.
• Large-scale phenotype are being collected, such as:
  – Hb1Ac, FPG, insulin, BP, total and HDL cholest.
  – anthropomorphomic measures - BMI, waist circum.
• in following time intervals:
  – prior to therapy with metformin
  – 3, 6 months
  – 12 months
• Explore genotype-phenotype associations
• Compliance with therapy,...
• Expect to finalize preliminary study by the end of 2014.
CONCLUSIONS

- PGx has the potential to promote safe and cost-effective individualized diabetes treatment.
- PGx studies on diabetes treatment performed to date are small and inadequately replicated, and must be further tested in adequately designed and rigorously conducted clinical trials.
- With recent scientific and technological advances, PGx has a great potential to yield therapeutic advances leading the way towards personalized diabetes care.
Targeted prescription of medicine: applied pharmacogenomics

Today

empirical prescription

“One drug fit all”

Drug A

Drug B

Drug C

Drug D

Individual physician experience
Cost: time, money & well-being

Future

Rational prescription

“individualized”

Patient genetic’s profiles

Drug A

Drug B

Drug C

Drug D

Informed physician diagnosis
Saving: time, money & patient’s life
"Here's my sequence..."
Acknowledgements

University of Sarajevo
Faculty of Pharmacy
• Adlija Čaušević
• Tanja Dujić
• Tamer Bego
• Maja Malenica
• Zelija Velija-Ašimi

CCUS

Leif Groop
LUDC, Malmo, Sweden
• B. Prnjavorac
General Hospital Tešanj

• National grant from the Federal Ministry for Education & Science BH, 2012-2013.
• Grant for EU-FP7 project preparation from the Council of Ministers BH (MCA), 2009; 2010, 2014.
A CENTURY OF PEACE after THE CENTURY OF WARS