IGRH model: a mechanistic model integrating the relationship between average glucose levels (Cg,avg), RBCs & HbA1c in a mixed population of healthy volunteers and diabetic subjects

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Background

HbA1c?

- Chronic glycemia biomarker (2-3 months)

Standard biomarker for:
- Diagnosis (ADA 2010)
- Adequacy of glycemic management
Background

FPG – HbA1c Model
Hamrén et al. 2008

• Mechanistic PKPD model:
RBC ageing and glycosilation to HbA1c

• Gaps:
  FPG X chronic glycemia → to relate to HbA1c
  HbA1c depends on RBC LS → the LS model from a small group of Tesaglitazar therapy

Rationale - Why?

- We wanted to explore more and fill up these gaps!
- To use average glucose concentration (Cg,avg) better descriptor of chronic glycemia
- Better RBC LS description
- Empirical models exist that relate:

\[ C_{g,\text{avg}} \sim HbA1c \]

Lacking mechanism-based model
To derive a dynamic mechanism-based model for describing the underlying relationship between $C_g, \text{avg}$- $HbA1c$ using information from literature. Including sources of variability (i.e: IIV RBC life-span,...)
How to build the model when you have different sources of data?

Integrating the data
formal analysis Nonmem
Overview – Integrating different sources

Digitized data Nathan et al. 2008: $C_{g,avg} \sim HbA1c$ at steady state

Mechanistic re-inforcement by literature priors in structural & variability components (i.e. LS, IIV-LS, KG,...)

Digitized data & clinical data as external validation: hypothesis testing of specific mechanisms with high impact

Mechanistic model in NONMEM: IGRH model
Main analysis: ADAG study - Nathan et al. 2008

Cg,avg ~ HbA1c relationship

(N=507 ; Diabetic & Non-diab.)

HbA1c formation:
i) RBC life-span and life-span distribution
ii) Synthesis rate of HbA1c: $f(C_g, \text{avg})$
iii) HbA1c contribution in RBC precursors
iv) Impact of HbA1c and $C_g, \text{avg}$ measurement imprecision
v) The fractional nature of HbA1c
Methods: Structural model

i) RBC life-span and life-span distribution

Prior: Kalicki et al. (PAGE meeting 2009)
Methods: Structural model

i) RBC life-span and life-span distribution

Influence of Cg,avg on RBC life-span

\[ LS = TVLS \cdot \left( \frac{149}{Cg, avg} \right)^{\delta} \cdot \exp^{\eta} \]
ii) Synthesis rate of HbA1c

Linear

\[ \text{Glycosilation rate} = KG \cdot C_{g, \text{avg}} \cdot Hb \]

Non-Linear

\[ \text{Glycosilation rate} = KG \cdot \left( \frac{149}{C_{g, \text{avg}}} \right)^{\delta} \cdot Hb \]

Non-Linear due to Glut1 saturation

\[ \text{Glycosilation rate} = KG \cdot \left( \frac{C_{g, \text{avg}} \cdot Km}{C_{g, \text{avg}} + Km} \right) \cdot Hb \]

PRIORS from literature:

- Beach et al. 1979
- Higgins et al. 1981
- Mortensen-Volund et al. 1984
- Ladyzynski et al. 2008
Methods: Structural model

iii) HbA1c contribution in RBC precursors

PRIORS from literature

Digitized literature data:

• Virtue et al. 2004 data (LS vs GHb – T2D N=23)

Clinical data (shared by the authors)

• Nuttall et al. 2004 data (LS & GHb vs FPG - Non-diab. N=37)

• Ribbing et al. 2010 data (HbA1c vs FPG – T2D N=1460)
The integration of the data allowed to derived the Integrated Glucose RBC HbA1c model.
**Results – Final Integrated Glucose RBC HbA1c model**

![Diagram of RBC life span and kinetics]

- **Prec** = \( \exp(-KGP \cdot C_{g, avg} \cdot LSP) \)

- **Power**
  
  \[ LS = TVLS \cdot \left( \frac{149}{C_{g, avg}} \right)^{\delta} \cdot \exp^{\eta} \]

- **Linear**
  
  \( \text{Glycosilationrate} = KG \cdot C_{g, avg} \cdot Hb \)
OFV = -4499.935

OFV = -4888.172

Without mechanism of LS = f(Cg, avg)

Dots: Observations
Red lines: 5th, 50th & 95th percentiles of the observations
Black lines: 5th, 50th & 95th percentiles of the predictions (1000 simulations)
Blue area: 90% CI of prediction intervals
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimated value</th>
<th>RSE%</th>
<th>Prior</th>
<th>RSE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>KG (dL/mg/day)</td>
<td>8.37x10^-6</td>
<td>3.4%</td>
<td>8.23x10^-6</td>
<td>27%</td>
</tr>
<tr>
<td>LS RBC (days)</td>
<td>91.7</td>
<td>3.6%</td>
<td>91.8</td>
<td>3.6%</td>
</tr>
<tr>
<td>IIV LS RBC (CV%)</td>
<td>8.22 %</td>
<td>5.5%</td>
<td>12.4%</td>
<td>19%</td>
</tr>
<tr>
<td>LS Prec. (days)</td>
<td>8.20</td>
<td>9.8%</td>
<td>8.11</td>
<td>10%</td>
</tr>
<tr>
<td>IIV LS Prec. (CV%)</td>
<td>11.5%</td>
<td>20%</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Prop. RE</td>
<td>2.27 %</td>
<td>35%</td>
<td>2.5%</td>
<td>40%</td>
</tr>
<tr>
<td>δ (LS - Cg,avg)</td>
<td>0.381</td>
<td>4.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OFV</td>
<td>-4888.172</td>
<td></td>
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</tr>
</tbody>
</table>

Results – Final Integrated Glucose RBC HbA1c model
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Data supporting this relationship between LS- Cg,avg:

Ribbing et al. (HbA1c vs FPG) $\delta=0.48$ vs $\delta$ IGRH model=0.38
Nuttall et al. (LS vs FPG) $\delta=0.49$ vs $\delta$ IGRH model=0.38
Virtue et al. (GHB vs LS)
Results – Final Integrated Glucose RBC HbA1c model
Conclusions - Integrated Glucose RBC HbA1c model

- 1st quantitative description of the Cg,avg-HbA1c relationship on mechanistic basis.

- The model describes well the relationship in both diabetic and non-diabetic patients.
Conclusions - Integrated Glucose RBC HbA1c model

- To predict the impact of changes in Cg,avg (due to diet or therapeutic interventions) on the time-course of HbA1c levels.
Conclusions - Integrated Glucose RBC HbA1c model

- If any of the processes involved are subjected to change in an individual patient, the expected temporal and steady state change of HbA1c can also be predicted

(e.g. uremic patients (LS decreased))
Conclusions - Integrated Glucose RBC HbA1c model

- Literature data can be used not only to support parameter estimates, but combined from different sources to test hypothesis and build structurally novel models!
Acknowledgements

- Prof. Frank Nuttall for sharing data

- F. Hoffmann-La Roche for financial support