A novel cholesterol-lowering PCSK9 variant is associated with low blood glucose level and lower cardiovascular risk in type 2 diabetes

Edgard S.R. Tchéoubi,1,2 Casimir D. Akpovi,2 Frédérique Coppée3, Anne-Emilie Declèves,3 Gaétan J. Sègbo,2,4 Clément Agbangla4, Sophie Laurent1 and Carmen Burtea1

1Laboratory of NMR and Molecular Imaging, General, Organic and Biomedical Chemistry Unit, University of Mons, Belgium
2Non-Communicable Diseases and Cancer Research Unit, Laboratory of Applied Biology Research, University of Abomey-Calavi, Benin
3Laboratory of Metabolic and Molecular Biochemistry, University of Mons, Belgium
4Laboratory of Molecular Genetics and Genome Analyzes, Faculty of Sciences and Technics, University of Abomey-Calavi, Benin
Introduction

- Diabetes mellitus is a major problem of public health (WHO, 2016)

- Type 2 Diabetes mellitus (T2DM): >50% of dyslipidemia; atherosclerotic cardiovascular diseases (ACVD)

- Use of cholesterol lowering drug

**Statins**
- Resistance
- New onset T2DM

**Proprotein convertase subtilisin-kexin type 9 inhibitors (PSK9i)**

mAb authorized by FDA and EMA since 2015
Introduction

PCSK9i
- Decrease LDLc level by 50-60%
- Important reduction of ACVD
- New onset T2DM?

PCSKi mAb binds to secreted PCSK9 and prevents its association with cell surface LDLR and subsequent lysosomal destruction
Objective

To assess the association of a PCSK9 variant to T2DM, precisely through
- lipid profile and
- glucose homeostasis parameters.
## Results and Discussion

Socio-demographic and anthropometric characteristics of the study subjects (n=171)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>T2DM (n=132)</th>
<th>Control (n=39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (ans)</td>
<td>57±11</td>
<td>46±12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female sex</td>
<td>61%</td>
<td>69%</td>
<td>0.823</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>95.00 (88.25-103.00)</td>
<td>94.00 (83.00-107.00)</td>
<td>0.587</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>27.13 (23.18-30.09)</td>
<td>29.03 (22.68-35.57)</td>
<td>0.215</td>
</tr>
<tr>
<td>Physical activity</td>
<td>57.58%</td>
<td>89.74%</td>
<td>0.281</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10.77%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Tobacco</td>
<td>6.87%</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>130 (120-150)</td>
<td>130 (120-140)</td>
<td>0.137</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>80 (70-90)</td>
<td>80 (70-90)</td>
<td>0.725</td>
</tr>
<tr>
<td>HTA</td>
<td>58.01%</td>
<td>51.28%</td>
<td>0.643</td>
</tr>
</tbody>
</table>

- 132 T2DM and 39 Ctrl (F>60%)

- 97.73% on metformin+Glibenclamide (22.73%)

- No significant difference between T2DM patients and controls according to gender, anthropometric and clinical characteristics.
Results and Discussion

Genetic analysis

The variant was detected in 2.34% (2.27% of T2DM patients and 2.56% of control subjects respectively).

There was no statistical association of the variant with T2DM (p=0.621).

**Figure**: Distribution of the variant according to T2DM status
Presence of the variant associated with
- HDL-c ↑ in non diabetic Control (p=0.006)
- LDL-c ↓ in non diabetic Control (p=0.0264) and T2DM patients (0.069) (Cohen and al., 2005)
- TG ↓ in non diabetic Control (p<0.001)
Results and Discussion

Glucose homeostasis parameters

Presence of the variant associated with

- Trend to low Glucose level in T2DM patients (p=0.06) (Chikowore et al., 2018 vs Schmidt et al., 2017)
- High insulin level and HOMA2 β% in T2DM (p=0.028), not HOMA2-IR (Da Dalt et al, 2019)
- Better response to glibenclamide (Reviewed in Aquilante, 2010)
Results and Discussion

Cardiovascular complications

Presence of the variant associated with

- Low %HTA: control (Carriers:0%; non carriers:52.63% ); DT2M (carriers 33.33%; non carriers:58.59% )
- Low DBP in nondiabetic Control (p<0.001)
- SBP: No significant difference
Conclusion and Perspectives

- We identified a PCSK9 variant associated with:
  - low LDL-cholesterol level
  - a better glucose homeostasis in T2DM patients on insulin secretagogue therapy and
  - a lower cardiovascular risk.

- Next step:
  - assess if the variant has a functional impact (mRNA and protein) and
  - describe its mechanism of action
Aknowledgement
THANK YOU FOR YOUR ATTENTION