Interdisciplinary Research to Understand the Interplay of Diabetes, Cerebrovascular disease and Alzheimer’s Disease (DiCAD; RF1AG051556)

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Overarching hypothesis and approach

• HYPOTHESIS:
Hyperglycemia causes both CVD and AD which interact and mediate the association with cognitive impairment

• APPROACH:
To conduct complementary human and mice studies to understand mechanisms
Primary aim. To examine the association of diabetes with the interplay of AD and CVD in humans and mice.

- **Humans**
  - Cohort study of 200 late middle aged adults
  - Metabolic profile: OGTT, HbA1c, insulin, extended panel
  - Cognition: with NS battery
  - AD pathology: Amyloid and Tau PET
  - Cerebrovascular disease: MRI
  - Physiology: brain DMN on MRI
  - Discovery: Metabolomics, proteomics, genomics

- **Mice**
  - Experiments in young and old mice (db/db, db/+, APP/PS1, C57, mixed)
  - Metabolic profile: HbA1c, glucose, insulin, extended panel
  - Cognition/behavior: PPA, APA,NOR
  - AD pathology: IHC/histology
  - Cerebrovascular disease: tMCAo
  - Physiology: EP profile EC-HC
  - Metabolomics, proteomics
## Human sample characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>139</td>
</tr>
<tr>
<td>Age in years</td>
<td>63.3 ± 4.3</td>
</tr>
<tr>
<td>Women</td>
<td>74.8%</td>
</tr>
<tr>
<td>Education in years</td>
<td>10.0 ± 3.8</td>
</tr>
<tr>
<td>APOE-ε4 %</td>
<td>27.4%</td>
</tr>
<tr>
<td>HbA1c in %</td>
<td>6.1 ± 1.4</td>
</tr>
<tr>
<td>Normal glucose tolerance %</td>
<td>44.6%</td>
</tr>
<tr>
<td>Pre-diabetes %</td>
<td>30.9%</td>
</tr>
<tr>
<td>Undiagnosed diabetes</td>
<td>4.3%</td>
</tr>
<tr>
<td>Known diabetes %</td>
<td>22.3%</td>
</tr>
</tbody>
</table>
Figure 12. Example of regional WMH quantification for one subject in WHICAP study. Upper left: raw FLAIR image. Upper right and lower two: WMH labeled with “hottest” colors indicating most intense voxels. Colors correspond to cerebral lobes (green: frontal, brown: parietal, dark green: temporal, blue: occipital, mauve: cerebellum.)
Mouse models

- Db/Db mice, Db/WT
- J20, APP/PS1, C57
- Mixed Db APP/PS1
- Young and old
- With and without stroke
Future directions

- Conduct metabolomics, lipidomics in human sera and in mouse sera, brain, liver, gut in coordination with the AD metabolomics consortium
- Conduct proteomics and genomics in collaboration with M²OVE-AD AND AMP-AD partners
- Examining insulin resistance and adipokines
Data sharing

• All data uploaded in Synapse
• Biospecimen repository
Conclusions

• Hyperglycemia seems to increase vascular disease and neurodegeneration but its relation with amyloid burden needs further exploration
  • Examination of tau pending
• Sex is an important modifier that needs to be examined
• AD and neurodegeneration have important metabolic signatures that require further study
Acknowledgements

• Duke University
  • Rima Kaddurah-Daouk

• Rush University
  • Chris Gaiteri

• Columbia University
  • William Kreisl
  • Qulamreza Razlighi
  • Phil DeJager

• Hebrew Home at Riverdale
  • Jeanne Teresi

• SUNY Downstate
  • Frank Barone

• NIH
  • Suzana Petanceska

• SAGE
  • Lara Mangravite
  • Mette Peters