Understanding phenotypes of prediabetes: essential to influencing progression to type 2 diabetes
Acknowledgement

The content of this slide deck summarizes the key points presented during the 47th Claude Bernard lecture by Professor Hans-Ulrich Häring at the 51st Annual Meeting of the European Association for the Study of Diabetes, Sept 14–18 2015, Stockholm, Sweden
Introduction
Background and overview of The Tübingen Family Study (TÜF) and The Tübingen lifestyle intervention programme (TULIP)

Genetic mechanisms in the pathogenesis of diabetes
Summary of findings from Tübingen investigators on genes involved with regulating insulin secretion in the face of increased insulin resistance

Sub-phenotypes of obesity
What are the differences between metabolically healthy and metabolically unhealthy obese individuals?

Brain insulin resistance
Summary of early findings related to brain insulin resistance as a risk factor for diabetes

Conclusions
Introduction
The TÜF includes data from >3,000 individuals at risk of developing T2DM\(^1\)

![Diagram showing the relationship between insulin secretion and insulin sensitivity with quadrants labeled NGT, IGT, and T2DM]

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus, TÜF, Tübingen Family Study

The population shows a wide variety of phenotypes. Those with insulin resistance and low insulin secretion may develop IGT and then T2DM. Some individuals are able to counteract increasing insulin resistance by upregulating insulin secretion\(^1\)

1. Data presented by Häring HU at EASD 2015 (Claude Bernard Lecture; available at easdvirtualmeeting.org)
The TÜF is a clinical phenotyping programme identifying risk factors for diabetes\(^1\)

The data available from the TÜF are enabling investigation of the mechanisms occurring in key organs that lead to IGT and T2DM\(^1\)

1. Data presented by Häring HU at EASD 2015 (Claude Bernard Lecture; available at easdvirtualmeeting.org)
TULIP is investigating the impact of lifestyle interventions\textsuperscript{1,2}

\textbf{TULIP is an ongoing study of the effect of a 9-month individualized lifestyle intervention programme.}\textsuperscript{1,2}  
\textbf{Data were presented for an 8-year follow-up of 400 people who also participated in the TÜF\textsuperscript{3}}


- Increased physical activity
- Weight loss
- Healthier diet
TULIP: Lifestyle intervention was initially effective\(^1\)

In individuals with impaired glucose tolerance, moderate weight loss lead to significant reductions in total, visceral and ectopic fat, increased insulin sensitivity and improved glucose tolerance\(^1\)

Despite the initial effectiveness of lifestyle intervention, insulin resistance was increasing after eight years\(^1\)

Those with normal insulin sensitivity at baseline were able to counter increasing insulin resistance with compensatory hypersecretion of insulin; however, those who had insulin resistance at baseline could not compensate and went on to develop IGT or T2DM\(^1\)

1. Data presented by Häring HU at EASD 2015 (Claude Bernard Lecture; available at easdvirtualmeeting.org)
Key questions raised by the TÜbingen studies

What is pushing people towards insulin resistance over time?

What enables some people to counteract increased insulin resistance by upregulating insulin secretion:

• Genetic mechanisms?
• Sub-phenotypes of obesity?
• Brain insulin resistance?
Phenotypes observed in pre-diabetes
What is pushing people towards insulin resistance over time?

What enables some people to counteract increased insulin resistance by upregulating insulin secretion:

• Genetic mechanisms?
• Sub-phenotypes of obesity?
• Brain insulin resistance?
Many potential genes have been identified over recent years, but none have a high odds ratio for predicting type 2 diabetes.


TCF7L2 is a transcription factor influencing the transcription of several genes. Of the genes investigated, TCF7L2 had the highest odds ratio of 1.37 per effect allele for predicting type 2 diabetes. 

TCF7L2, transcription factor 7-like 2 (T-cell specific, high mobility group box)
Genetic effects do not fully explain regulation of insulin secretion¹

The combined effect of all of the genes investigated by the Tübingen investigators was significant, but the effect size only accounted for ~10–15% of the observed differences in insulin secretion between those with NGT and those with IGT¹

The TCF7L2 gene has the strongest association with type 2 diabetes\(^1\) and is related to incretin resistance\(^2\)

Hyperglycemic clamp studies show that wild-type individuals have 2-fold higher insulin secretion in response to GLP-1 infusion than those with the TCF7L2 gene\(^2\)

The TCF7L2 gene is also associated with compensatory hypersecretion\(^1\)

In individuals who were homozygous for the TCF7L2 gene (TT), compensatory hypersecretion of insulin does not occur; however, it does in those who of heterozygous (CT) or do not have the gene (TT)\(^1\)

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Key questions raised by the TÜbingen studies

What is pushing people towards insulin resistance over time?

What enables some people to counteract increased insulin resistance by upregulating insulin secretion:

- Genetic mechanisms?
- Sub-phenotypes of obesity?
  - Metabolically healthy versus metabolically unhealthy
  - Presence of pancreatic fat
  - Exercise responders versus non-responders
  - Brain insulin resistance?
Metabolically healthy and metabolically unhealthy phenotypes of obesity have been identified\textsuperscript{1,2}

Metabolically healthy obese people tend to have high levels of subcutaneous fat and little visceral fat and are able to maintain insulin sensitivity; the opposite is true in metabolically unhealthy obese individuals\textsuperscript{1,2}

Liver fat also affects metabolic health in obesity

Some obese individuals have a metabolically healthy ‘benign fatty liver’ with limited lipotoxicity. In this scenario, PNPLA3 is still secreted from the liver and TLR4 is not affected.

PNPLA3, patatin-like phospholipase domain-containing protein 3; TLR4, toll-like receptor 4

Liver fat also affects metabolic health in obesity. Those with a metabolically unhealthy ‘malign fatty liver’ have ectopic fat storage in the liver, which is associated with micro-inflammation and increased insulin resistance, and thought to be related to secretion of fetuin-A.  

Cross-talk between Fetuin-A, free-fatty acids, hepatocytes and immune cells in the liver may decrease the effect of TLR4\(^{1,2}\)

Based on mouse studies\(^1\), the Tübingen investigators think that this may be leading to increased insulin resistance in the liver\(^2\). This theory is unproven but there is some evidence to suggest that it is a valid theory.

Key questions raised by the Tübingen studies

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Pancreatic fat is thought to be similar to perivascular fat\(^1,2\)

Perivascular fat cells secrete high levels of interleukin (IL)-6, IL-8 and MCP-1 in the presence of Fetuin-A and palmitate\(^1\). These characteristics are also present in pancreatic fat cells\(^2\).

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1. Image adapted from Siegel-Axel DI et al. Diabetologia 2014;57:1057–66; 2. Data presented by Häring HU at EASD 2015 (Claude Bernard Lecture; available at easdvirtualmeeting.org)
Pancreatic fat was unexpectedly observed in the TÜF and it correlated with insulin secretion in people with IGT\(^1\)

- This unexpected finding has been observed in ~250 people participating in the TÜF\(^2\)
- Pancreatic fat content was significantly and negatively associated with insulin secretion (C-peptide-based index: \(p=0.0002; \ r=-0.70\)) in people with impaired glucose tolerance but not in people with normal glucose tolerance (C-peptide-based index: \(p=1.0; \ r=0.00\))\(^1\)
- The fat substrate is unknown

The clusters of fat cells in the pancreas lie close to or in contact with the islets, and are associated with increased macrophage infiltration.\(^3\) People with a fatty pancreas also have a fatty liver\(^2\), and there is evidence that fetuin-A may be mediating cross-talk between the fatty liver and pancreatic fat cells\(^4\)–\(^8\)
Fetuin-A levels correlate with insulin secretion in this population

This also supports the validity of the hypothesis of Fetuin-A mediated cross-talk between the fatty pancreas and fatty liver

1. Image adapted from Stefan et al. PloS One 2014;9:e92238
Key questions raised by the Tübingen studies

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**TULIP: Presence of liver fat is one of the strongest indicators of people that will not respond to lifestyle intervention**

1. Stefan N et al. Diabetologia 2015; ePub ahead of print;

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Exercise is one of the most successful methods for reducing liver fat, and reductions of ~30–40% can be attained in exercise responders.\(^2,3\)

Reducing liver fat is more difficult in exercise non-responders (~25% of the TULIP population)\(^1\)

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*Lifestyle intervention included modifications to dietary intake and composition, as well as three or more hours of moderate exercise per week*
Exercise non-responders have different mitochondrial activity compared with responders\textsuperscript{1,2}

The TÜbingen investigators have not identified any exercise-response plasma biomarkers, but have observed different levels of TGF-beta regulation. TGF-beta seems to interact with PGC-1 alpha expression and links exercise response to differences in mitochondrial activities.


TGF, transforming growth factor; PGC-1, peroxisome proliferator-activated receptor gamma co-activator 1

- Improvements in anaerobic threshold
- Muscle growth
- Changes in adiposity
- Reductions in liver fat storage
- Improvements in insulin sensitivity

Genetic variants of PPARD and PPARGC1A are associated with response to exercise and mitochondrial function.
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Insulin receptors in the brain control energy homeostasis and food intake/reward mechanisms

It is thought that brain insulin resistance leads to problems with eating control because the desire to continue eating after food ingestion is not down-regulated

1. Image adapted from Heni M et al. Nat Rev Endocrinol 2015; ePub ahead of print
Brain insulin signalling is also thought to play a role in fuel distribution through the tissues in the body.

Research in mice suggests that the brain determines glucose uptake in the periphery. This suggests that in people with brain insulin resistance, glucose deposition in visceral adipose tissue may be favoured over subcutaneous deposition.

Foetal imaging is allowing investigation of brain insulin sensitivity in-utero\(^1\)

The foetus can hear and react to tones applied to the stomach of the mother, and the velocity of brain reactions to the tone can be measured. Latencies in response to glucose intake provide insights into the brain-insulin sensitivity of the foetus\(^1\)

1. Linder K et al. Diabetologia 2014;57:1192–8
Insulin sensitivity has been observed in-utero, challenging the assumption that brain insulin sensitivity occurs as a response to obesity\(^1,2\)

Effect of OGTT in insulin sensitive or insulin resistant mothers

<table>
<thead>
<tr>
<th>Time after OGTT</th>
<th>Insulin (pmol/l)</th>
<th>Latency (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
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<tr>
<td>0'</td>
<td>100</td>
<td>350</td>
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OGTT, oral glucose tolerance test

In insulin sensitive mothers, latency in the fetal brain response decreases when glucose levels are at their highest (~60 mins after an OGTT), but this response does not occur in the fetus’ of insulin resistant mothers\(^1\). The effect is even more pronounced in mothers with gestational diabetes\(^2\)

1. Images adapted from Linder K et al. Diabetologia 2014;57:1192–8;
2. Linder K et al. JCEM 2015; ePub ahead of print
Conclusions
Consequences for prevention of type 2 diabetes

Sub-phenotypes determine the success of prevention methods, such as lifestyle intervention.

Lifestyle non-responders should be treated according to their phenotype and may need therapeutic intervention.

Type 2 diabetes prevention needs to start early in life, with a focus on the gestational period.

Studies are required to investigate and develop pharmacological interventions to treat fatty liver, fatty pancreas, exercise non-response and brain insulin resistance.
Future studies

The Tübingen investigators are interested in future studies focusing on:

The fatty liver and the fatty pancreas
- How do they affect compensatory hypersecretion?
- How do they affect beta-cell dysfunction?
- Can beta-cell dysfunction be reversed by treating the fatty liver and/or fatty pancreas?

Brain insulin resistance
- How early in life does it start?
- Is it a consequence of obesity?
- Does it lead to obesity?
- Can we establish new preventative measures for type 2 diabetes?
Further information

To view the webcast of Professor Hans-Ulrich Häring’s Claude Bernard lecture, copy the following link into your browser:


Notable related presentations at EASD 2015 were:

The hepatokine fetuin-A has TLR4 dependent and independent effects in islets (F. Gerst)

Webcast available at: http://www.easdvirtualmeeting.org/resources/the-hepatokine-fetuin-a-has-tlr4-dependent-and-independent-effects-in-islets

Rising Star Symposium presentation: Insulin and the human brain (M. Heni)


All links last accessed November 10th 2015