REAL PEOPLE

Percentages and predictions can mask the enormity of the diabetes problem. Large numbers of people with diabetes are unaware they have the disease because they have not been diagnosed (shown as the shaded ridge in the country bubbles). The imperative for public-health professional is to diagnose and treat people as soon as possible.

CHINA

90M

Underestimated until only recently, the Chinese diabetes epidemic is the largest in the world.

INDIA

61.3M

MIDDLE EAST

Rapid economic development has led to soaring rates of diabetes, from around 6% in 1990 to over 20% in parts today.

INDIA

Nationwide prevalence now tops 9%, and is as high as 20% in the relatively prosperous southern cities. The resulting healthcare costs and depletion of productivity threaten to undo recent economic development.

AFRICA

Diabetes is relatively rare in sub-Saharan Africa, affecting only 4.5% of adults. But prevalence is predicted to double over the next 20 years—the fastest rise of any region in the world.
Subphenotypes in prediabetes: Role of fatty liver and brain insulin resistance

H.U. Häring

Berlin 2014
Dualities of interest

- Hans Häring has received honoraria for speaking, research support or advising from Sanofi, Novo Nordisk, Boehringer Ingelheim and Daiichi Sankyo
Pathogenesis of prediabetes and type 2 diabetes – dysbalance of insulin sensitivity and secretion

TÜbingen Family study (TÜF) N>3300

Insulin secretion vs. Insulin sensitivity

NGT (1905)
IFG/IGT (839)
T2D (178)
Major diabetes risk gene TCF7L2

Incretin resistance TCF7L2 (homozygous 12%, heterozygous 40%)

Schäfer et al. Diabetologia 2007
Haupt et al. Diabetes 2010
Heni et al. Diabetes 2010
Heni et al. Diabetes Care 2012
Müssig K, Staiger H, Machicao F, Häring HU, Fritsche A, Diabetologia 2010 (review)
Wagner et al. Molecular Metabolism 2014 (review)
Glycemia determines the effect of type 2 diabetes risk genes on insulin secretion

Current glycemia (30 min glucose level during OGTT) determines the effect of type 2 diabetes risk genes *TCF7L2* and *WFS1* on 30 min C-peptide level during OGTT

Heni et al, Diabetes 2010
Nor-1, a novel incretin-responsive regulator of insulin genes and insulin secretion

**ABSTRACT**

B-cell failure at the onset of type 2 diabetes is caused by a decline in β-cell function in the postprandial state and loss of pancreatic β-cell mass. Recently, we observed an association between increased insulin secretion and a single nucleotide polymorphism (SNP, SNP rs12686676, in the NR4A3 gene locus) encoding the nuclear receptor Nor-1. Nor-1 is expressed in β-cells, however, not much is known about its function with regard to insulin gene expression and insulin secretion. Nor-1 is induced in a glucose-incretin-dependent manner via the PKA pathway and directly induces insulin gene expression. Additionally, it stimulates insulin secretion possibly via regulation of potentially important genes in insulin secretion.

Moreover, we show that the minor allele of NR4A3 SNP rs12686676 fully rescues insulin resistance provided by a well-described polymorphism in TCF7L2. Thus, Nor-1 represents a promising new target for pharmacological intervention to fight diabetes.

**Keywords** Nor-1; Insulin gene expression; Insulin secretion; Incretin resistance; TCF7L2.

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**Figure Description**

- **TCF7L2 wildtype (N=728)** and **TCF7L2 risk allele carriers (=728)**
  - Adjusted insulogenic index
  - p-values: p=0.4 and p=0.0084
  - SNP rs7903146
  - SNP rs12686676

**Diagram**

- Incretin receptors
- cAMP
- PKA
- CREB
- NR4A3
- TCF7L2
- NR4A3
- Insulin
- secretion genes
Fatty acids stimulate insulin secretion through a G protein coupled receptor, the free fatty acid receptor 1 (FFA1/GPR40)
FFA1/GPR40 agonists augment glucose-induced insulin secretion of human islets

Reevaluation of Fatty acid receptor 1 (FFAR1/GPR40) as drug target for the stimulation of insulin secretion in humans

Robert Wagner, Gabriele Kaiser, Felicia Gerst, Elisabeth Christiansen, Maria Elisabeth Due-Hansen, Manuel Grundmann, Fausto Machicao, Andreas Peter, Evi Kostenis, Trond Ulven, Andreas Fritsche, Hans-Ulrich Häring and Susanne Ullrich
The minor allele of Ffar1 correlates with reduced insulin secretion at high fasting non-esterified fatty acids (NEFA)

rs1573611
major allele
minor allele

Wagner R, Kaiser G,...Ullrich S; Diabetes, 2013
Signalling pathways activated by fatty acids

Fatty acids

β-oxidation

GPR40

PLC

IP₃

DAG

Ca²⁺

ATP

DAG

Ceramide

ROS

Fatty acyl-CoA

SCD1

TG

FA Transporter

Insulin secretion

APOPTOSIS

CYTOKINES
Pathogenesis of prediabetes and type 2 diabetes – dysbalance of insulin sensitivity and secretion

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NGT (1905)
IFG/IGT (839)
T2D (178)
Magnetic Resonance Imaging and Spectroscopy

Subphenotypes of Obesity

Stefan et al., Arch Intern Med. (2008), Lancet D&E 2013

Benign Obesity

Malign Obesity

N >800
The Metabolically Benign and Malignant Fatty Liver

Norbert Stefan and Hans-Ulrich Häring

Glucose production
Insulin resistance
Dyslipidemia

Stefan, Kantartzis, Häring, Endocrine Reviews 2008
Dissociation of fatty liver and insulin sensitivity

SNP rs738409 C>G in PNPLA3 – Relationships with Liver Fat and Insulin Sensitivity

Insulin sensitivity

OGTT

(arb. u.; adjusted for age, sex, TAT, VAT, arb. u.)
P=0.99

Liver fat
(%; adjusted for age, sex, TAT, VAT)
P<0.0001

P<0.0001

P=0.005

Kantartzis et al, Diabetes 2009
The role of hepatokines in metabolism

Norbert Stefan and Hans-Ulrich Häring

Metabolic Diseases
Atherosclerosis
Hyperglycemia
Dyslipidemia
Insulin resistance

Positive Energy Balance

Genetic predisposition

Metabolically Malign Fatty Liver

Lipotoxicity
Hyperglycemia
Dyslipidemia
Fetuin-A

Metabolically Benign Fatty Liver

Beta-cell dysfunction and apoptosis
Atherosclerosis
Insulin resistance

Dysregulated Hepatokines

2013

Fetuin

Metabolic Diseases
Fetuin-A interacts with free fatty acids in insulin resistant humans

Circulating fetuin-A and free fatty acids interact to predict insulin resistance in humans

Stefan N, Häring HU. Nat Med. 2013
Fetuin predicts CVD (Circulation 2008)

Role of PVAT (perivascular adipose tissue)

Perivascular fatty tissue at the brachial artery is linked to insulin resistance but not to local endothelial dysfunction

The secretion pattern of perivascular fat cells is different from that of subcutaneous and visceral fat cells.

Exercise-induced albuminuria is associated with perivascular renal sinus fat in individuals at increased risk of type 2 diabetes.

Fetuin-A influences vascular cell growth and production of proinflammatory And angiogenic proteins by human perivascular fat cells
Fetuin-A downregulates HGF mRNA expression and protein secretion and upregulates other angiogenic and inflammatory factors in perivascular cells.
The role of hepatokines in metabolism

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TÜbingen Family study (TÜF) N>3300

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IFG/IGT (839)
T2D (178)
Insulin sensitive brain areas in humans

Heni et al., Hum Brain Mapp. 2013
Kullmann et al., Neuroendocrinology. 2012
Kullmann et al., Cereb Cortex. 2012
Sartorius et al., Diabetes. 2012
Heni et al., Diabetologia. 2012
Stingl et al., Neuroimage. 2012
Tschritter et al., Diabetologia. 2012
Heni et al., PLoS One. 2011
Guthoff et al., PLoS One. 2011
Kullmann et al., Hum Brain Mapp. 2012
Grichisch et al., Hum Brain Mapp. 2012

Guthoff et al., J Clin Endocrinol Metab. 2010
Tschritter et al., J Clin Endocrinol Metab. 2009
Tschritter et al., Diabetologia. 2009
Tschritter et al., PLoS One. 2007
Tschritter et al., Diabetologia. 2007
Tschritter et al., Proc Natl Acad Sci U S A. 2006
Impaired insulin action in the human brain

BMI↑, VAT, age↑, SFA↑

Genes: IRS-1, FTO, MC4R, Canabinoid R2

Insulin

Brain insulin resistance

Tschritter et al., PNAS 2006
Tschritter et al. Diabetologia 2007
Tschritter et al., Diabetologia 2009

Tschritter et al. JCEM 2009
Satorius et al. Diabetes 2012
Frank et al. AJCN 2012
Sartorius et al. FASEB 2012

Tschritter et al. PNAS 2006
Diabetologia 2009
J. Obes 2011
Ketterer et al. Obesity 2013
Concept of the pathogenesis of type 2 diabetes mellitus

Brain insulin resistance

Benign obesity

Malign obesity
Insulin resistance
Hepatokines
Fatty acids

hypersecretion

β-cell dysfunction

genetics/epigenetics
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