The regenerative therapy of type 1 diabetes mellitus

21 April 2017
Girne, Northern Cyprus
53rd Turkish National Diabetes Congress

Thomas Linn
Clinical Research Unit
Centre of Internal Medicine
Justus Liebig University
Giessen, Germany
Natural history of type 1 diabetes

Diagnosis of type 1 diabetes

- Beta cell auto-antibodies GAD, insulin, IA2, Zinc transporter
- Loss of FPIR (prediabetes)
- C-peptide basal or stimulated after diabetes diagnosis
- Initial insulin treatment
Evidence for Pancreatic regeneration in T1DM

- Persistent fasting C-peptide > 0.03 nmol/l in 67.4% of type 1 diabetic (T1DM) patients
- >0.2 nmol/l fasting C-peptide responsive to mixed meal tolerance test (MMTT)
- Insulin positive cells in exocrine and ductular pancreas in T1DM brain-dead donors
- 40% of normal $[^{11}\text{C} ]$ 5-hydroxytryptophan retention in position emission tomography

Meier, J.J., Diabetologia 48: 2221, 2010


Medalist Study

Eriksson O et al. Diabetes, 63:3428, 2014
Evaluation of beta cell reserve

- **Applied Research** - Positron emission tomography – hydroxytryptophan, vesicular monoamine transporter type 2
- **Basic Research** - Immunohistochemistry of pancreas, morphometry
- **Clinical** – C-peptide level (nmol/l), insulin daily dose, risk assessment for loss of beta cell reserve

**Inclusion criteria** for current intervention trials
- C-peptide > 0.2 nmol/l
- 1 autoantibody in significant titre
- Intensive insulin therapy (not conventional, not insulin pump) with self measurement of blood glucose, initial insulin therapy (no temporary administration of OAD)
Endogeneous Insulin Reserve by Stimulation Tests

C-peptide Stimulation Tests
- Mixed meal tolerance test (MMTT) 6 kcal/kg
- Glucagon stimulation test (GST) Glucagon 1 mg i.v.

Type 1 diabetes family risk screening
- Intravenous glucose tolerance test 5g/kg (maximum 35 g) First phase insulin release (FPIR) 1+3 min
- Oral glucose tolerance test OGTT) 75 g

C-peptide
Basal 0.17 nmol/l
Peak Stimulated with MMTT 0.40 nmol/l
Peak Stimulated with Glucagon 0.30 nmol/l
90 min MMTT 0.36 nmol/l, all (mean nmol/l) 0.31
6 min GST 0.27 nmol/l
Present cutoff’s for inclusion criteria of intervention studies
Stimulated > 0.2 nmol/l

Cutoff for > 45% 5 y risk of type 1 diabetes
FPIR 1+3 min > 60 µU/ml insulin older than 8 yrs of age
OGTT > 114 mg/dl 2 h 75 g (IGT > 140 mg/dl !!)

Diabetes Prevention Trial Study Group-1, NEJM 346:1685, 2002
Technological approaches to regeneration or replacement

• **Therapy aiming at Replacement of beta cells**
  - Pancreas and islet transplantation
  - Stem cell based approaches
    - **Direct reprogramming** Mesenchymal stem cells (MSC) in clinical trials
    - Generation of beta-cell like cells from iPS cells generated from somatic cells – **indirect reprogramming**

• **Therapy aiming at Regeneration of beta cells**
  - Intensive insulin therapy to foster honeymoon period (functional regeneration)
  - Immunintervention as a means to support pancreatic islet regeneration
  - Transdifferentiation from non-stem cells
Pancreas and islet transplantation

**Pancreas**
In Germany 100-120 per year, 250 patients on waiting list,
Eurotransplant region 192 patients transplanted (2015), but 961 brain-dead organ donors

www.eurotransplant.org

Simultaneous Pancreas-Kidney transplantation beneficial in patients with kidney failure, but not pancreas transplantation alone

**Pancreatic Islet**

**Pro**
90% of subjects permanently without severe hypoglycemia
70% of subjects 2 years of improved glycemia
40% achieve 2 years of insulin independence

**Contra**
Only 50% of donor pancreases allocated, the rest with insufficient quality for islet isolation
2 or more donors required, many islets die shortly after Tx
Islet allograft supply limits applicability to 1000 patients/year in Eurotransplant region
Allograft function decreases with time

Immunosuppression-related complications: decline of renal function
Infections, malignancy risk
No clear survival benefit

Alternative medical treatments rapidly improving (insulin pump, hybrid closed loop system, CGM)

Pancreatic islet isolation –

- In vitro expansion of human pancreatic beta cells leads to dedifferentiation of beta-cells
Stem cell based Approaches

- Mesenchymal stem cells (MSC) – 5 clinical trials
- 3# favour regeneration without initial culture to induce/support insulin secretion
- 2## favour reprogramming/replacement as they claim to have attained insulin secreting cells prior to implantation
- Embryonic stem cells (ESC) and Induced pluripotent stem cells (iPS) – human beta-cell like cells, but no clinical trial available to this end

Generating beta cells from stem cells

Rekittke NE et al. Stem Cells Int. 2016:3764681
Intensive insulin therapy – near normal glucose control

- Intensive insulin therapy slows down stimulated C-Peptide decrease
- 30% higher C-Peptide compared to conventional insulin therapy
- Glp-1 agonist exenatide reported to protect transplanted beta cell mass in 50% of studies

Linn T et al. BMC Endocr Disord 3:5, 2003
Immunintervention

Ongoing trials in Adult newly diagnosed patients

- IL-8 antagonist ladarixin (small molecule), Dompe, Italy. NCT02814838
- Vaccination with proinsulin-related peptide with CSSC redox motif (Imcyse; Belgium)

Hagopian W et al. Diabetes 2013;62:3901-3908
Screening in human pancreatic beta cells

Benthuysen JR et al
J Clin Invest
126:3651-3660, 2016
Adult pancreatic alpha cells into beta cells

Thanks for your attention

Giessen, Justus Liebig University, Experimental Diabetes and Islet transplantation

Deepa Kandula, Nadine Rekittke, Birte Hussmann

Istanbul University, Institute for Experimental Medical Research

M Temel Yilmaz

Mehves Poda

Feyza Tuncer

Ali Osman Gürol