Management of T1D (Type 1 Diabetes)

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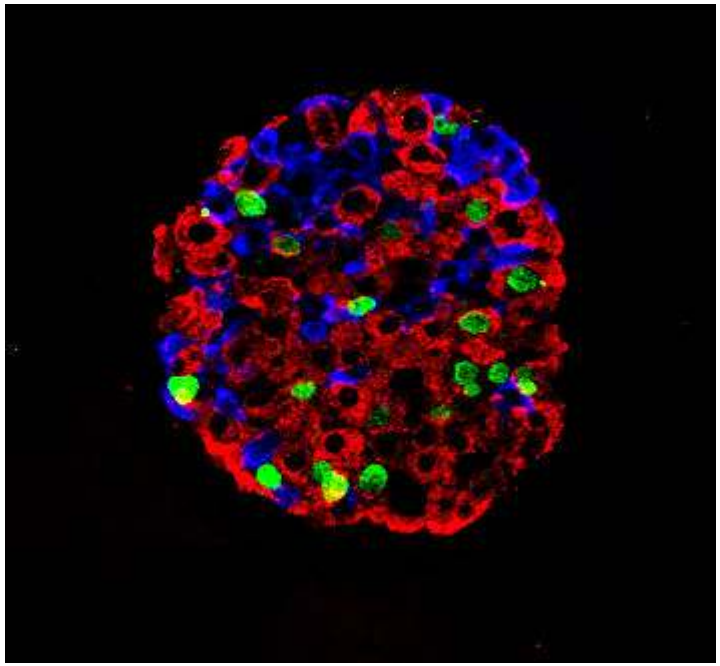
Disclosure


EASD
Islet
Study
Group
Joint Meeting of
The Islet Study Group &
Beta Cell Workshop
May 3-7, 2015
Menachem Begin Center
Jerusalem, Israel

Type 1 Diabetes (T1D)

β-cell (54%) : Insulin

α – cell (35%) : Glucagon



Alpha cells in type1 DM :

- anatomically intact, BUT
- secretion of glucagon is not normally regulated.

Mara Lorenzl, MD, Nancy Bohannon, MD, Eva Tsaliktan, MD, and john H, Karam, MD
Duration of Type I Diabetes Affects Glucagon and Glucose Responses to Insulin-Induced Hypoglycemia
(West J MED 1984 October, 141(4):467-471)

bihormonal closed loop approach

- Above 150 mg/dl, IV insulin pump on
- Below 50 mg/dl, glucagon or glucose pumps on
- Between 50-150 mg/dl, all pumps off

(Kadish AH, Am J Med Electron, 1964:82-86)

1963, Dr. Arnold Kadish
delivered both insulin and glucagon

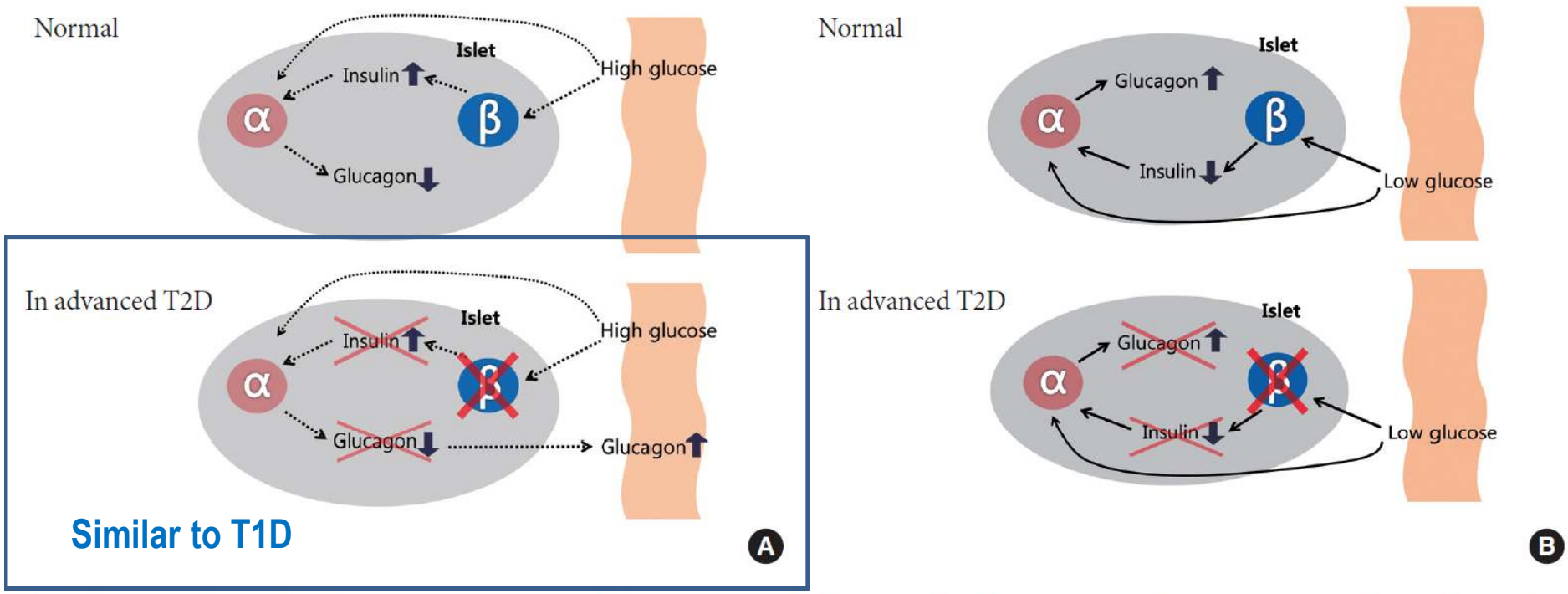
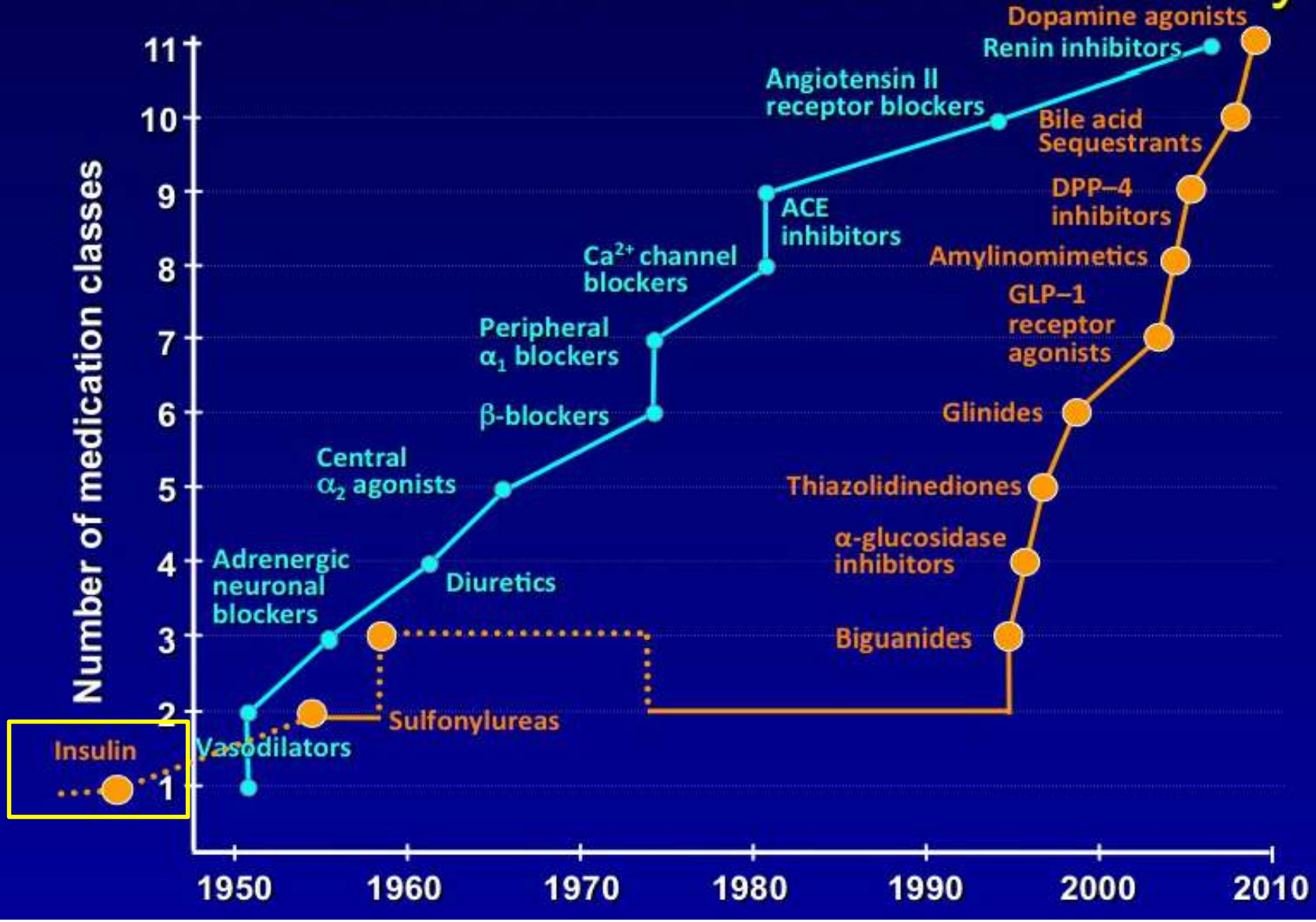


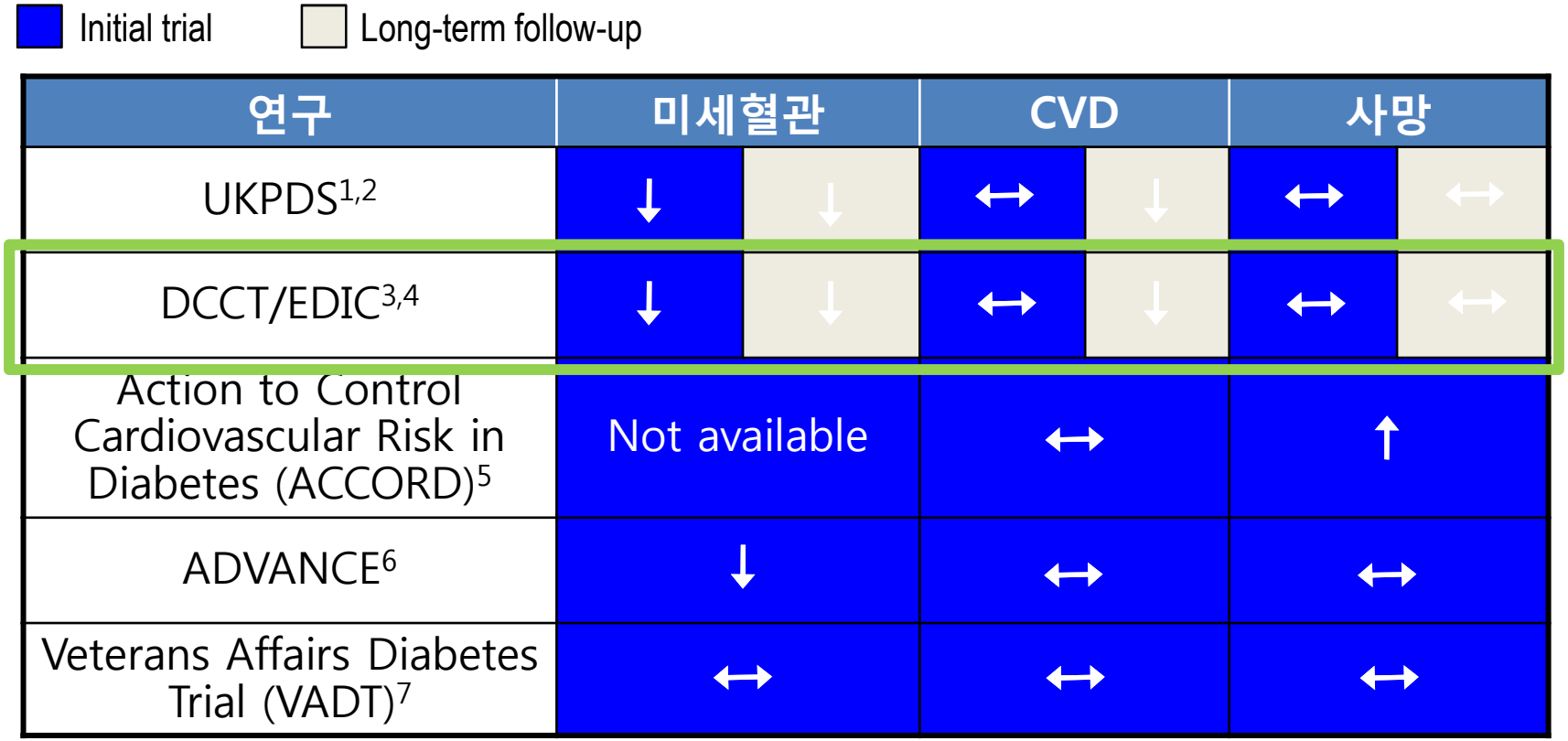
Fig. 1. Intra-islet insulin & glucagon secretion. Normal (in nondiabetes) and advanced type 2 diabetes (T2D) of the relationship between the inhibitory effects of pancreatic β-cell insulin secretion on pancreatic α-cell glucagon secretion. Normally, an increase in plasma glucose level causes an increase in β-cell insulin secretion that prevents an increase in α-cell glucagon secretion in response to meal. In advanced T2D, however, β-cell failure which is lack of intra-islet signaling result in not only fail to suppress but also an increase in pancreatic α-cell glucagon secretion (A). A decrease in plasma glucose level causes a decrease in β-cell insulin secretion that signals an increase in α-cell glucagon secretion during hypoglycemia. On the other hand, in the advanced T2D, a decrease in plasma glucose cannot cause a decrease in β-cell insulin secretion, and the absence of that signal results in no increase in pancreatic α-cell glucagon secretion during hypoglycemia (B).

(Moon JS & Won KC Diabetes Metab J 2015;39:1-9)

Hypertension & Diabetes: Drug Classes In the U.S. Over the Past Half-Century



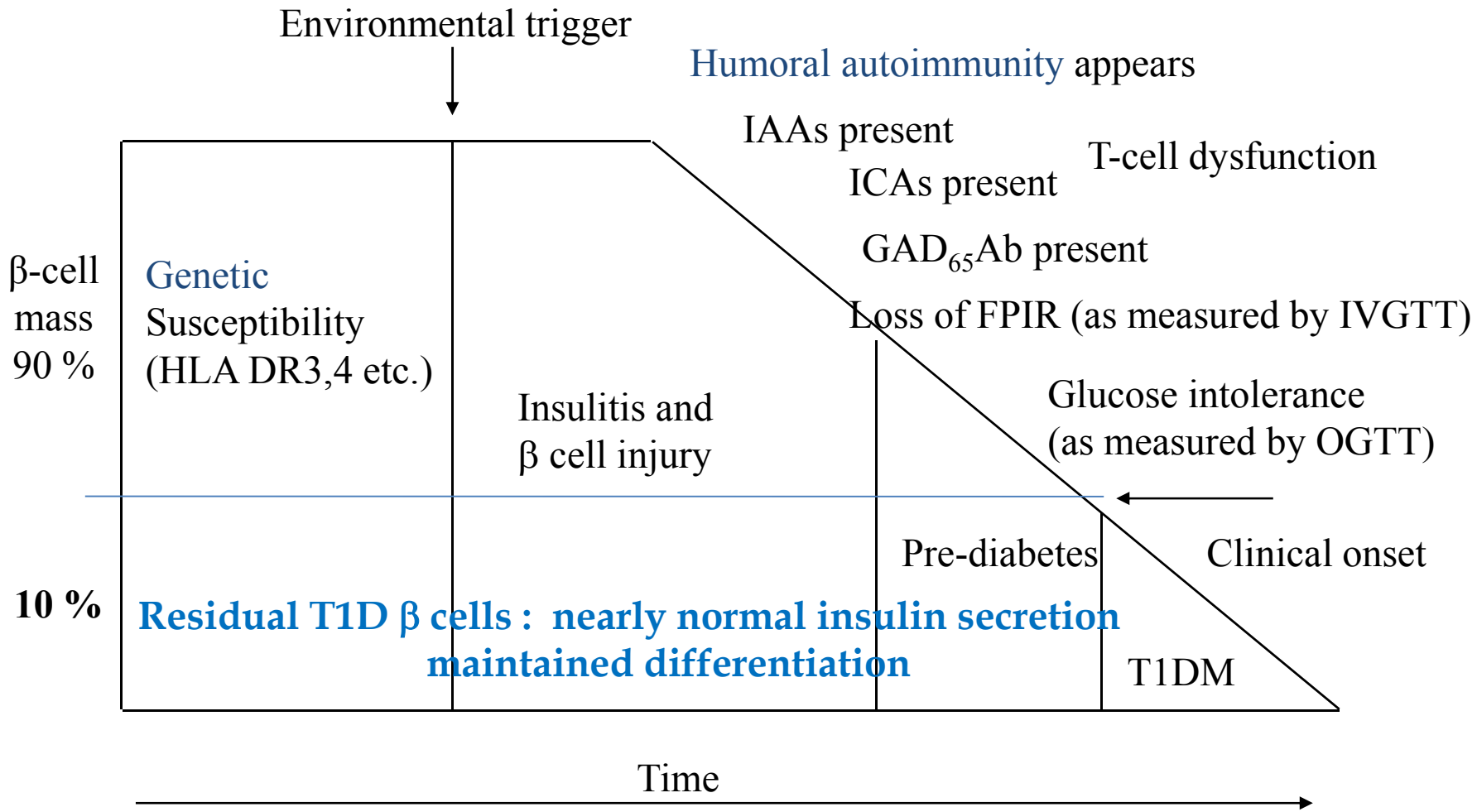
철저한 혈당 조절의 효과
주요한 임상시험 요약



[1] UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65.
[2] Holman RR, et al. *N Engl J Med* 2008;359:1577-89.
[3] The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329;977-86.
[4] Nathan DM, et al. *N Engl J Med* 2005;353:2643-53.
[5] Gerstein HC, et al. *N Engl J Med* 2008;358:2545-59.
[6] Patel A, et al. *N Engl J Med* 2008;358:2560-72.
[7] Duckworth W, et al. *N Engl J Med.* 2009;360:129-39.

Contents

- **Pathogenesis & Diagnosis of T1D**
- Prevention of T1D
- Emerging therapies in T1D

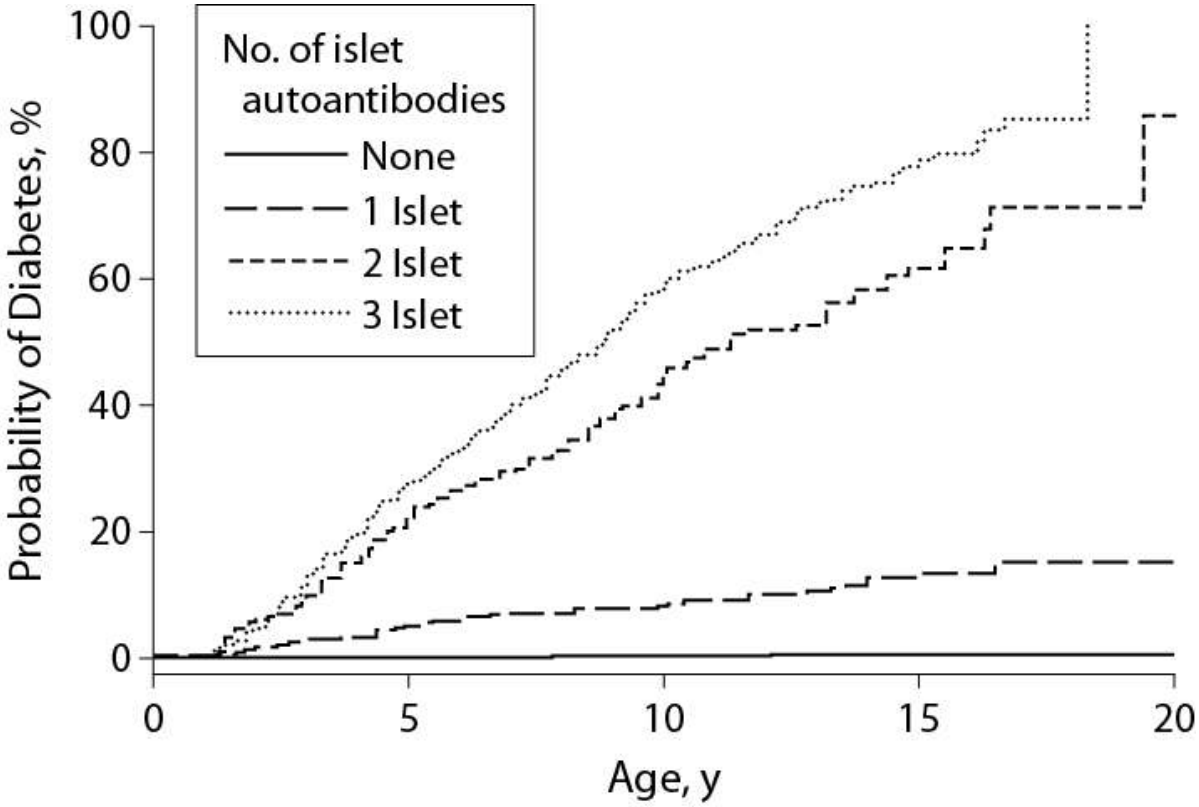


By Dr. Eisenbach and Powers

Sequence of events in the natural history of type 1 DM

Development of Diabetes in Children Stratified for Islet Autoantibody Outcome

(TEDDY)



No. at risk Islet autoantibodies, No.					
3 Islet	358	250	112	20	
2 Islet	227	168	82	19	1
1 Islet	474	430	272	118	9
None	12318	8875	5253	1161	44

JAMA. 2013 19;309(23):2473-9

Prediction of T1D

In a research setting, the following approach may be used:

- Test individuals at risk for type 1 diabetes progression for **GAD65 and IA-2 autoantibodies**

- If they are present and confirmed in a subsequent sample, tests for **insulin, zinc transporter (ZnT8), and islet cell antibodies** **the first phase insulin response to glucose (FPIR)** determined

Table 1. Clinical Characteristics in Study Group

	Type 1 DM			
	Child Onset	Adult Onset	Typical	Atypical
Number	32	40	39	33
Sex (M:F)	12:20	21:19	16:23	17:16
Age (yrs)	15±3	47±14*	23±13	45±18
Onset age (yrs)	11±2	39±12*	18±3	36±14
BMI (kg/m^2)	19.1±2.2	21.4±3.2	19±2.5	21±2
C-peptide (nmol/L)	0.18±0.19	0.23±0.19*	0.13±0.2	0.29±0.2*

* $p<0.05$

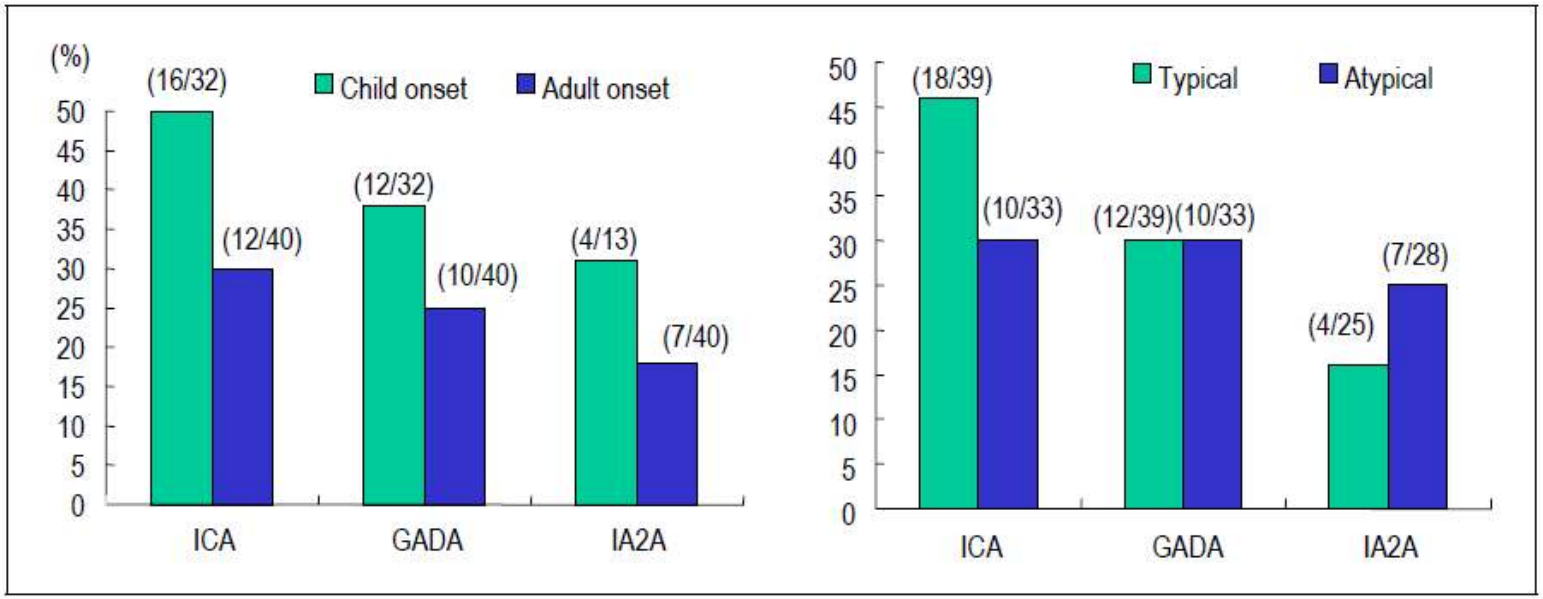


Fig. 1. Prevalence of GADA ,ICA and IA2A in study group

(Yoon HD et al. J Kor Diabetes Asso 444-456. 2000)

Contents

- Pathogenesis & Diagnosis of T1D
- **Prevention of T1D**
- Emerging therapies in T1D

Prevention of T1D

Immunomodulators
- Azathioprine
- Mycophenolate mofetil
- Cyclosporine
- Anti-CD3 antibodies
  - Teplizumab
  - Otelixizumab
- Rituximab
- Interleukin-1 inhibition
- Thymoglobulin
- Insulin
- Immunotherapy DAB486-IL-2
- GAD65 immunotherapy
- Costimulation modulation
- Bacillus Calmette-Guerin (BCG)
- DiaPep277
- Donor splenocytes

Antiinflammatory
- TNF-alpha inhibitors
- Interferon alpha

Supplements
- Nicotinamide
- Vitamin D supplements
- Omega-3 polyunsaturated fatty acids

Other
- Avoidance of cow's milk
- Hematopoietic stem cell transplant

SUMMARY AND RECOMMENDATIONS

the prevention of type 1 diabetes is **still at the stage of research** trials, the trials are often mentioned in the lay press.

Preliminary Communication

Effects of High-Dose Oral Insulin on Immune Responses in Children at High Risk for Type 1 Diabetes

The Pre-POINT Randomized Clinical Trial

Ezio Bonifacio, PhD; Anette-G. Ziegler, MD; Georgeanna Klingensmith, MD; Edith Schober, MD; Polly J. Bingley, MD; Marietta Rottenkolber, Dipl Stat; Anke Theil, PhD; Anne Eugster, PhD; Ramona Puff, PhD; Claudia Peplow, Dipl Eoc Troph; Florian Buettner, PhD; Karin Lange, PhD; Jörg Hasford, MD; Peter Achenbach, MD; for the Pre-POINT Study Group

IMPORTANCE Exposing the oral mucosa to antigen may stimulate immune tolerance. It is unknown whether treatment with oral insulin can induce a tolerogenic immune response in children genetically susceptible to type 1 diabetes.

OBJECTIVE To assess the immune responses and adverse events associated with orally administered insulin in autoantibody-negative, genetically at-risk children.

DESIGN, SETTING, AND PARTICIPANTS The Pre-POINT study, a double-blind, placebo-controlled, dose-escalation, phase 1/2 clinical pilot study performed between 2009 and 2013 in Germany, Austria, the United States, and the United Kingdom and enrolling 25 islet autoantibody–negative children aged 2 to 7 years with a family history of type 1 diabetes and susceptible human leukocyte antigen class II genotypes. Follow-up was completed in August 2013.

INTERVENTIONS Children were randomized to receive oral insulin (n = 15) or placebo (n = 10) once daily for 3 to 18 months. Nine children received insulin with dose escalations from 2.5 to 7.5 mg (n = 3), 2.5 to 22.5 mg (n = 3), or 7.5 to 67.5 mg (n = 3) after 6 months; 6 children only received doses of 22.5 mg (n = 3) or 67.5 mg (n = 3).

MAIN OUTCOMES AND MEASURES An immune response to insulin, measured as serum IgG and saliva IgA binding to insulin, and $CD4^+$ T-cell proliferative responses to insulin.

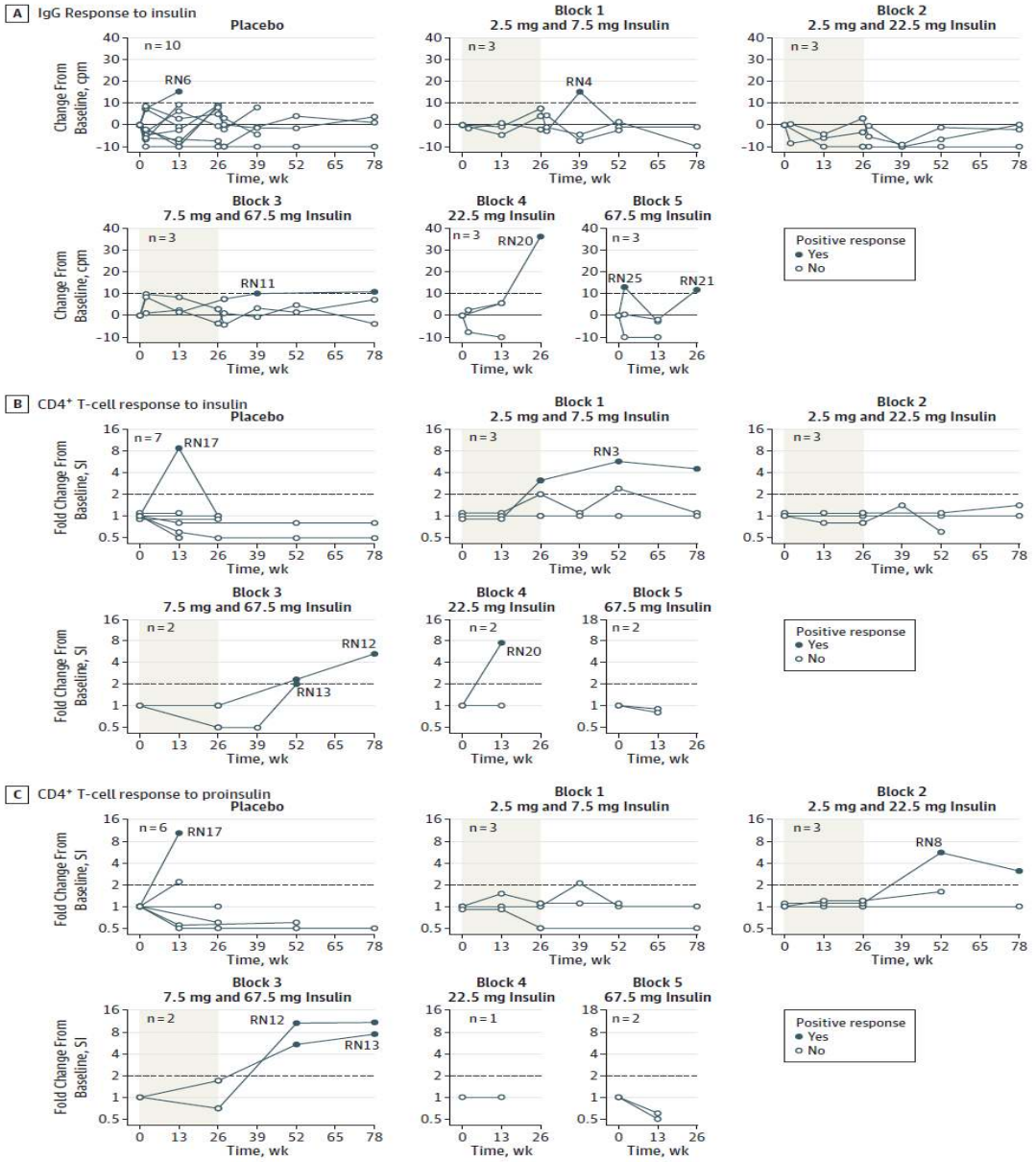
Editorial page 1520

Author Audio Interview at jama.com

Supplemental content at jama.com

(JAMA 313:1541-1549, 2015)

Figure 2. Serum IgG Binding to Insulin, CD4+ T-Cell Responses to Insulin, and CD4+T-Cell Responses to Proinsulin



Shading indicates period of treatment with the lower starting dose, before dose escalation; dashed lines indicate the threshold for a positive response in each assay. Samples with a positive response are indicated with solid symbols. One participant who received placebo and 1 child in block 1 had CD4+ T-cell responses that were 2-fold greater than baseline, but with stimulation index (SI) less than 3, and were therefore not defined as positive responses. The children with positive responses are indicated by their randomization number (RN; see eFigure 5 for randomization number sequence in trial). cpm indicates counts per minute.

RESULTS Increases in IgG binding to insulin, saliva IgA binding to insulin, or $CD4^+$ T-cell proliferative responses to insulin were observed in 2 of 10 (20% [95% CI, 0.1%-45%]) placebo-treated children and in 1 of 6 (16.7% [95% CI, 0.1%-46%]) children treated with 2.5 mg of insulin, 1 of 6 (16.7%[95% CI, 0.1%-46%]) treated with 7.5 mg, 2 of 6 (33.3% [95% CI, 0.1%-71%]) treated with 22.5 mg, and 5 of 6 (83.3% [95% CI, 53%-99.9%]) treated with 67.5 mg (P = .02). Insulin-responsive T cells displayed regulatory T-cell features after oral insulin treatment. No hypoglycemia, IgE responses to insulin, autoantibodies to glutamic acid decarboxylase or insulinoma-associated antigen 2, or diabetes were observed. Adverse events were reported in 12 insulin-treated children (67 events) and 10 placebo-treated children (35 events).

CONCLUSIONS AND RELEVANCE In this pilot study of children at high risk for type 1 diabetes, daily oral administration of 67.5 mg of insulin, compared with placebo, resulted in an immune response without hypoglycemia. These findings support the need for a phase 3 trial to determine whether oral insulin can prevent islet autoimmunity and diabetes in such children.

TRIAL REGISTRATION isrctn.org Identifier: ISRCTN76104595

JAMA. 2015;313(15):1541-1549. doi:10.1001/jama.2015.2928

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the Pre-POINT study group are listed at the end of this article.

Corresponding Author: Ezio Bonifacio, PhD, DFG Center for Regenerative Therapies Dresden, Fetscherstrasse 105, 01307 Dresden, Germany (ezio.bonifacio @crt-dresden.de).

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  New insulin formula

  Insulin pump

  Artificial pancreas

  췌장 췌도 이식, 인슐린 분비 세포

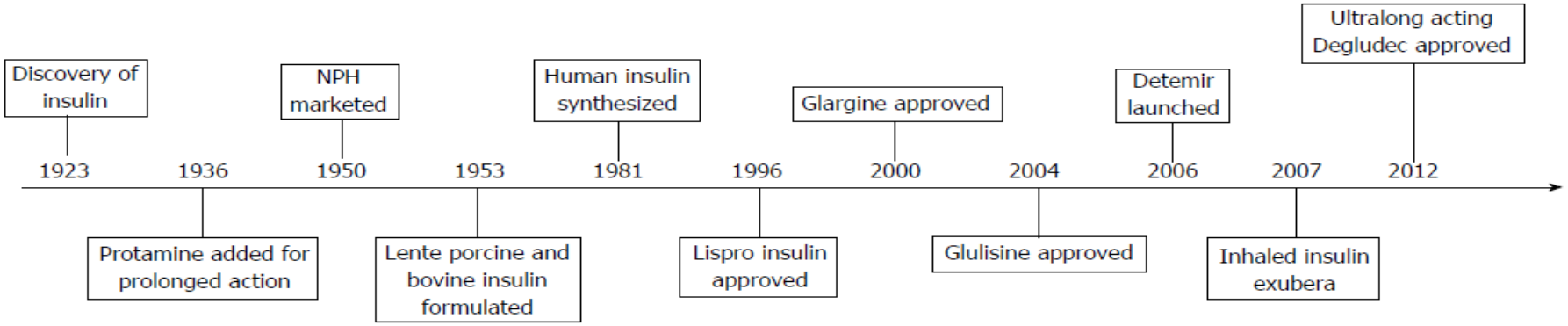
- (새로운) 혈당 강하제

1921

2015 ???

New Insulin formula

Time line of Insulin and its analogues



Getting over barriers of insulin therapy

- New insulin preparation
  - Insulin degludec (Approved in 2012)
  - PEGylated insulin lispro - specific activity on the liver (less weight gain)
  - Insulin degludec/insulin aspart (Ryzodeg, degludec plus)
  - FT-105 : insulin linked to the vitamin E via polyglutamic spacer
  - Long-acting oral basal insulin analogues : OI338GT, OI362GT, OI287GT

    : oral insulin capsule (ORMD-0801), oral insulin tablet (IN-105),
    : oral spray insulins (ORAL-LYN),
    : rectal insulin suppository (ORMD-0802)

- Combination with incretin-based therapy

Time-Action Profile of Inhaled Insulin in Comparison With Subcutaneously Injected Insulin Lispro and Regular Human Insulin

CONCLUSIONS — INH had a faster onset of action than RHI or ILP and a duration of action longer than ILP and comparable to RHI. These characteristics suggest that inhaled insulin is suitable for prandial insulin supplementation in patients with diabetes.

Diabetes Care 28:1077–1082, 2005

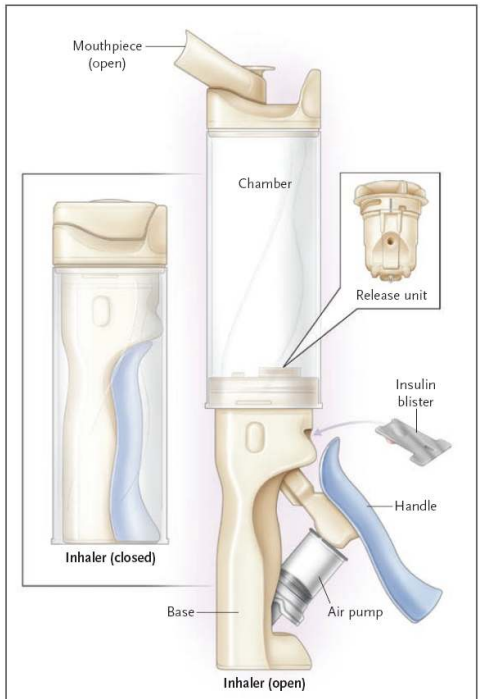


Figure 1. Inhaled Insulin Device.
The Exubera inhaled insulin device is closed for portability and opened before use. It is activated after insertion of an insulin blister. The release unit must be changed every 2 weeks.

AERx® iDMS: liquid

Exubera ® : powder

(N Engl J Med 356:497-502, 2007)

FDA News Release

FDA approves Afrezza to treat diabetes

For Immediate Release June 27, 2014

Release

This press release, issued June 27, 2014, was modified June 30, 2014 to correct language related to the administration of the drug. The correction was made to the first paragraph.

Español

The U.S. Food and Drug Administration today approved Afrezza (insulin human) Inhalation Powder, a rapid-acting inhaled insulin to improve glycemic control in adults with diabetes mellitus. Afrezza is a rapid-acting inhaled insulin that is administered at the beginning of each meal.

Inquiries

Media

Andrea Fischer
301-796-0393

Consumers

888-INFO-FDA

Journal of Diabetes Science and Technology
Volume 3, Issue 3, May 2009

REVIEW ARTICLE

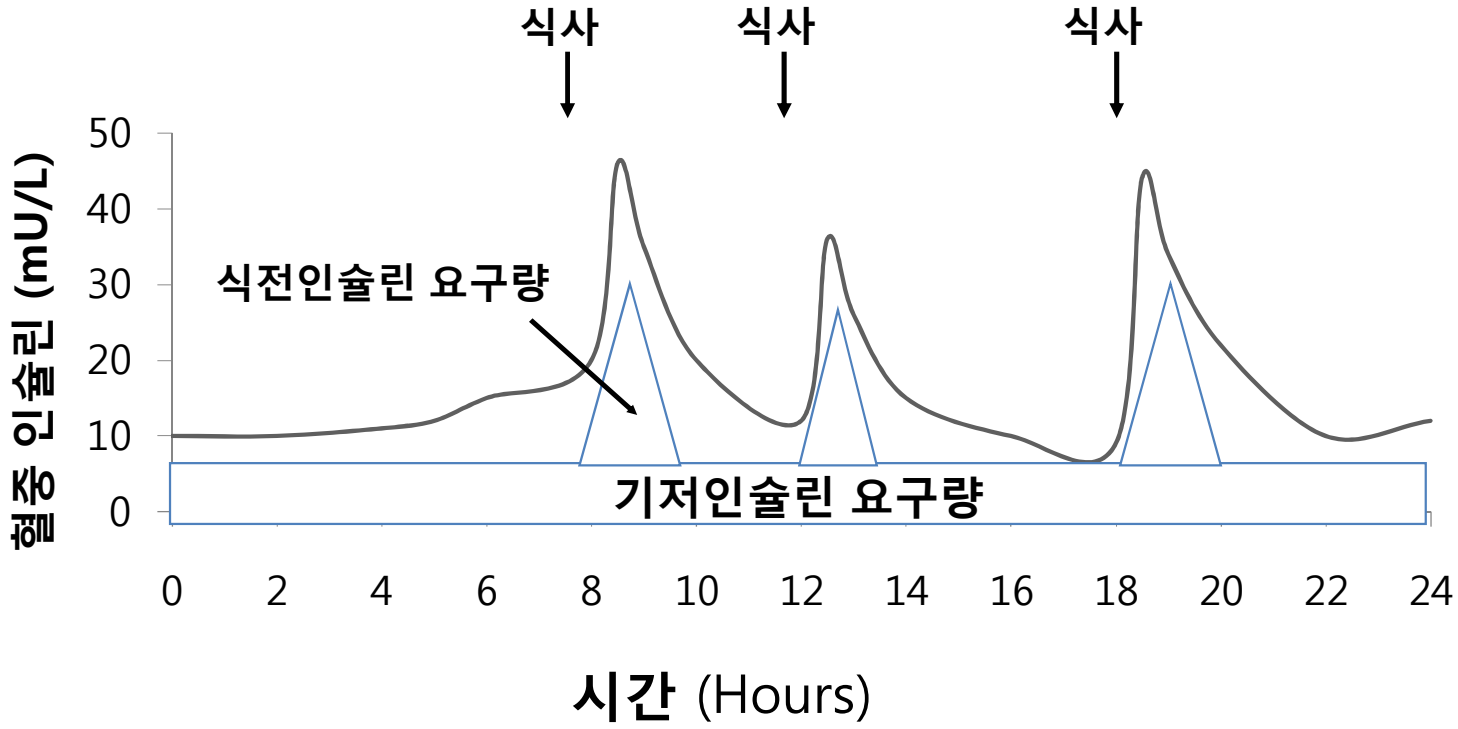
Oral Insulin and Buccal Insulin: A Critical Reappraisal

Lutz Heinemann, Ph.D.[1] and Yves Jacques, Ph.D.[2]

Abstract

Despite the availability of modern insulin injection devices with needles that are so sharp and thin that practically no injection pain takes place, it is still the dream of patients with diabetes to, for example, swallow a tablet with insulin. This is not associated with any pain and would allow more discretion. Therefore, availability of oral insulin would not only ease insulin therapy, it would certainly increase compliance. However, despite numerous attempts to develop such a "tablet" in the past 85 years, still no oral insulin is commercially available. Buccal insulin is currently in the last stages of clinical development by one company and might become available in the United States and Europe in the coming years (it is already on the market in some other countries). The aim of this review is to critically describe the different approaches that are currently under development. Optimal coverage of prandial insulin requirements is the aim with both routes of insulin administration (at least with most approaches). The speed of onset of metabolic effect seen with some oral insulin approaches is rapid, but absorption appears to be lower when the tablet is taken immediately prior to a meal. With all approaches, considerable amounts of insulin have to be applied in order to induce therapeutically relevant increases in the metabolic effect because of the low relative biopotency of buccal insulin. Unfortunately, the number of publications about clinical–experimental and clinical studies is surprisingly low. In addition, there is no study published in which the variability of the metabolic effect induced (with and without a meal) was studied adequately. In summary, after the failure of inhaled insulin, oral insulin and buccal insulin are hot candidates to come to the market as the next alternative routes of insulin administration.

J Diabetes Sci Technol 2009;3(3):568-584



정상인에서 식사에 따른 인슐린분비

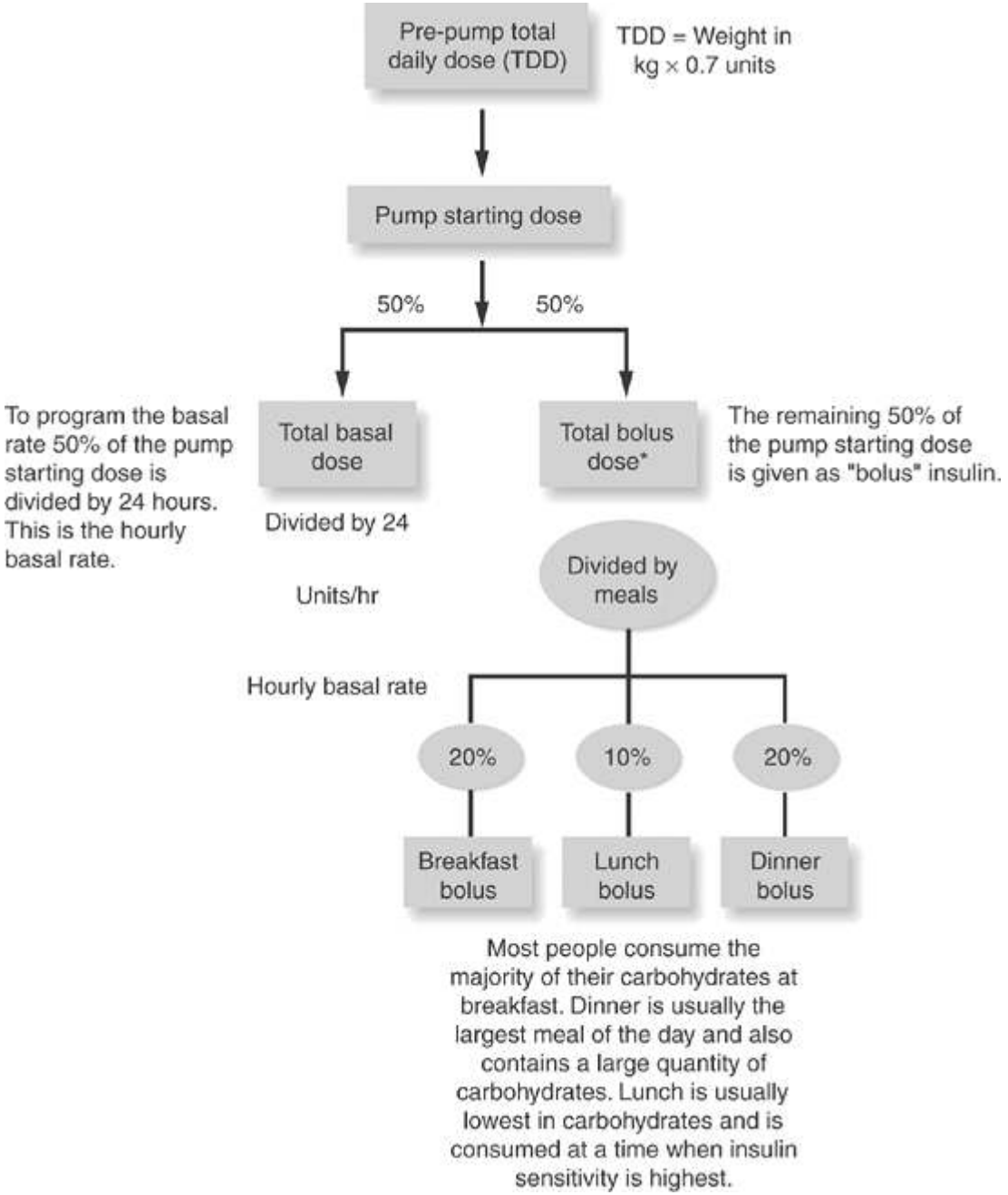
다회인슐린요법

다회인슐린요법에서는 하루 총 필요한 인슐린의 30~50%를 NPH, 울트라렌트, 또는 글라진(glargine), 디터머(determir)의 형태로 기저 인슐린으로 공급하고,
나머지 인슐린을 속효성이나 초속효성 인슐린의 형태로 식사의 양과 종류에 따라 각 식전에 1-3회 또는 식사를 가장 많이 하는 식전에 한번 공급하는 것이 일반적.

지속적 피하 인슐린 주입법 : 인슐린 펌프

인슐린펌프로 인슐린을 담는 용기와 이를 연결하는 카테터 그리고 바늘로 되어 있다. 이 바늘을 주로 복부의 피하 지방층에 고정하고 하루 종일 인슐린을 주입. 프로그램에 따라 기저 인슐린은 자동으로 주입.

일반적으로 0.1 단위까지 미세하게 주입 가능.
주로 속효성이나 초속효성 인슐린을 사용하고 하루에 들어가는 인슐린 총량을 100으로 했을 때 식사전 총량 **(식사 인슐린)과 계속 주입되는 기초량(기저 인슐린)의 비를 50대50으로 하는 것이 기본**



Diabetes Management in the Primary Care Setting, 1st Edition,2007

Dose decision-Basal rate

- 공복에서 혈당을 일정하게 유지할 수 있는 인슐린 양
- 총 하루 인슐린 양 (total daily insulin dose; TDD) 의 40-60 %
- 주입량 (rate) 결정
  - 총 기저 인슐린 ÷ 24 (시간)
  - 총 하루 인슐린 양 (TDD)의 40-50 % ÷ 24 (시간)
- 1형당뇨병환자는 하루에도 다른 basal rate 가 필요
  - Dawn phenomenon : 새벽에 높은 basal rate 투여 요함
  - Exercise : 심한 운동뒤에는 낮은 basal rate 투여
  - 저혈당 불감증 : 밤에 낮은 rate 투여를 통한 야간 저혈당 방지

Dose decision – Bolus dose (1)

- Correction bolus : 혈당치가 높은 상황에서 필요한 투여량
- Food bolus : 탄수화물 섭취에 대한 투여량

1. Correction bolus :
   - Insulin sensitivity factor (ISF) : 1 단위 인슐린 투여 시 강하되는 혈당치(㎎/㎗)
     - **"1800 Rule" : 1800/TDD = ISF**

     ex) ISF 1:40 → 1단위 인슐린 투여시 40 mg/dl 감소

   - Correction dose (units) = (현재 혈당 – 목표혈당)/ISF

※ 예) 현재 혈당 220 mg/dl , 목표 혈당 100 mg/dl, 총 하루 인슐린 45 u 투여 할 교정 bolus 양은?

(1) ISF = 1800/45 = 40

(2) Correction dose : (220-100) ÷ 40 = 3 units

Dose decision – Bolus dose (2)

2. Food bolus
   - Insulin-carbohydrate ratio (ICR):
     - ICR = grams of carbohydrate for each unit of insulin
     - **"450 Rule" : 450 / TDD = ICR**
   - Timing of boluses important factor
     - 식전 > 식후
     - 특히 고혈당일 때는 식사 중 투여가 더 낫다

※ 예) 총 하루 인슐린 45 u, 100 g (밥 ½ 공기) 탄수화물 섭취 시 투여 할 food bolus 양은?

ICR = 450/45 = 10

즉, 1단위에 탄수화물 10g을 cover할 수 있으므로 10 단위 추가필요

Advance Insulin Pump

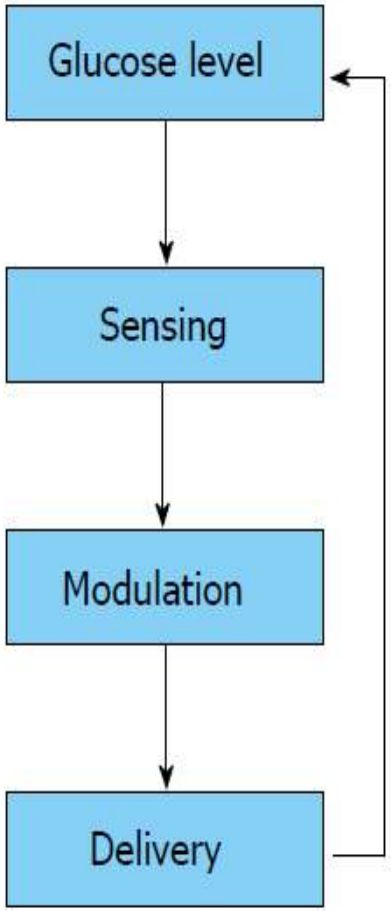
Advantages of Insulin Pump Therapy

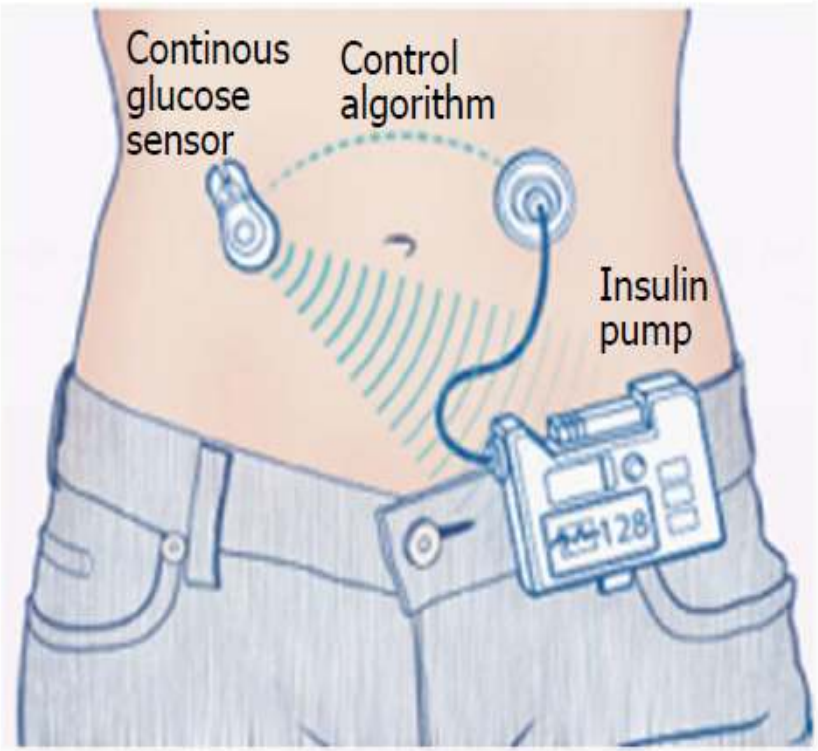
- Reduce the with-in and between-day glycemic variability
  - Less absorption variability
  - Reduction in glycemic fluctuations
- Less hypoglycemia
- Flexible, preprogram basal insulin
  - Temporary basal, suspend basal
- Better meal treatment
  - Bolus calculator, extended-wave insulin(dual and square)
- Data can be downloaded and analyzed
- Flexibility, no injections, improved feeling of well being more compliance with therapy
  - Advantage in infants and toddlers

N Engl J Med 2012; 366:1616-1624

Artificial (bionic) pancreas - Closed loop systems

priciples of closed loop system





World J Diabetes 2014;5:689-696


http://www.artificialpancreasproject.com/milestones/default.html
JDRF Artificial Pancreas Pr...
ARTIFICIAL PANCREAS PROJECT
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A A
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IMPROVING LIVES. CURING TYPE 1 DIABETES.
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JANUARY - "JDRFs CGM Trial" Named Top 10 Breakthrough
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JANUARY - CGM As Standard of Care
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APRIL - Health Plans Expand CGM Coverage Due to JDRF
2009
MAY - JDRF Study Further Shows CGM Benefits
2009
JUNE - Two JDRF Studies Show CGMs Benefits
2009
SEPTEMBER - JDRF Artificial Pancreas Roadmap Published
2009
JANUARY - JDRF Historic Partnership
2010
You Make A Difference
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1920s-1950s
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Medical News & Perspectives

Fully Automated Artificial Pancreas Finally Within Reach

Tracy Hampton, PhD

JAMA June 11, 2014 Volume 311, Number 22

Howard Zisser, MD, and Frank Doyle, PhD, of the department of chemical engineering at the University of California, Santa Barbara, monitor the performance of an artificial pancreas system during a clinical trial.

"Artificial pancreas systems will be the most revolutionary advance in diabetes care since the discovery of insulin," said Aaron Kowalski, PhD, a vice president at JDRF.

"a true automated device is maybe 3 to 5 years in the future," said Frank Doyle, PhD, chair of the chemical engineering department at the University of California.

A first-generation model of an artificial pancreas system is now available in many countries.

Outpatient Glycemic Control with a Bionic Pancreas in Type 1 Diabetes

Steven J. Russell, M.D., Ph.D., Firas H. El-Khatib, Ph.D., Manasi Sinha, M.D., M.P.H., Kendra L. Magyar, M.S.N., N.P., Katherine McKeon, M.Eng., Laura G. Goergen, B.S.N., R.N., Courtney Balliro, B.S.N, R.N., Mallory A. Hillard, B.S., David M. Nathan, M.D., and Edward R. Damiano, Ph.D.

ABSTRACT

CONCLUSIONS

As compared with an insulin pump, a wearable, automated, bihormonal, bionic pancreas improved mean glycemic levels, with less frequent hypoglycemic episodes, among both adults and adolescents with type 1 diabetes mellitus. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; ClinicalTrials.gov numbers, NCT01762059 and NCT01833988.)

for 5 days in 20 adults and 32 adolescents with type 1 diabetes mellitus. The automatically adaptive algorithm of the bionic pancreas received data from a continuous glucose monitor to control subcutaneous delivery of insulin and glucagon.

RESULTS

Among the adults, the mean plasma glucose level over the 5-day bionic-pancreas period was 138 mg per deciliter (7.7 mmol per liter), and the mean percentage of time with a low glucose level (<70 mg per deciliter [3.9 mmol per liter]) was 4.8%. After 1 day of automatic adaptation by the bionic pancreas, the mean (±SD) glucose level on continuous monitoring was lower than the mean level during the control

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Drs. Russell and El-Khatib contributed equally to this article.

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DOI: 10.1056/NEJMoa1314474

Bionic-Pancreas Glycemic-Control system

- **Insulin and glucagon were administered by a fully automated, bihormonal, bionic pancreas with the use of control algorithms**
- The device consisted of an **iPhone 4S** , which ran the control **algorithm, and a G4 Platinum continuous glucose monitor (DexCom)** connected by a custom hardware interface.
- The user interface displayed the continuous-glucose-monitor tracing and insulin and glucagon doses, and allowed announcement of meal size as "typical," "more than usual,""less than typical," or "a small bite" and the meal type as "breakfast," "lunch," or "dinner."
- This triggered a partial meal-priming bolus, which automatically adapted insulin dosing to meet 75% of the 4-hour postprandial insulin need for that meal size and type. The first meal-priming bolus of each type was based on the patient's weight (0.05 U per kilogram). Insulin and glucagon were administered subcutaneously by t:slim **infusion pumps (Tandem Diabetes Care),** which were controlled wirelessly by the iPhone. The control algorithm received continuous glucose monitoring data and commanded dosing every 5 minutes.

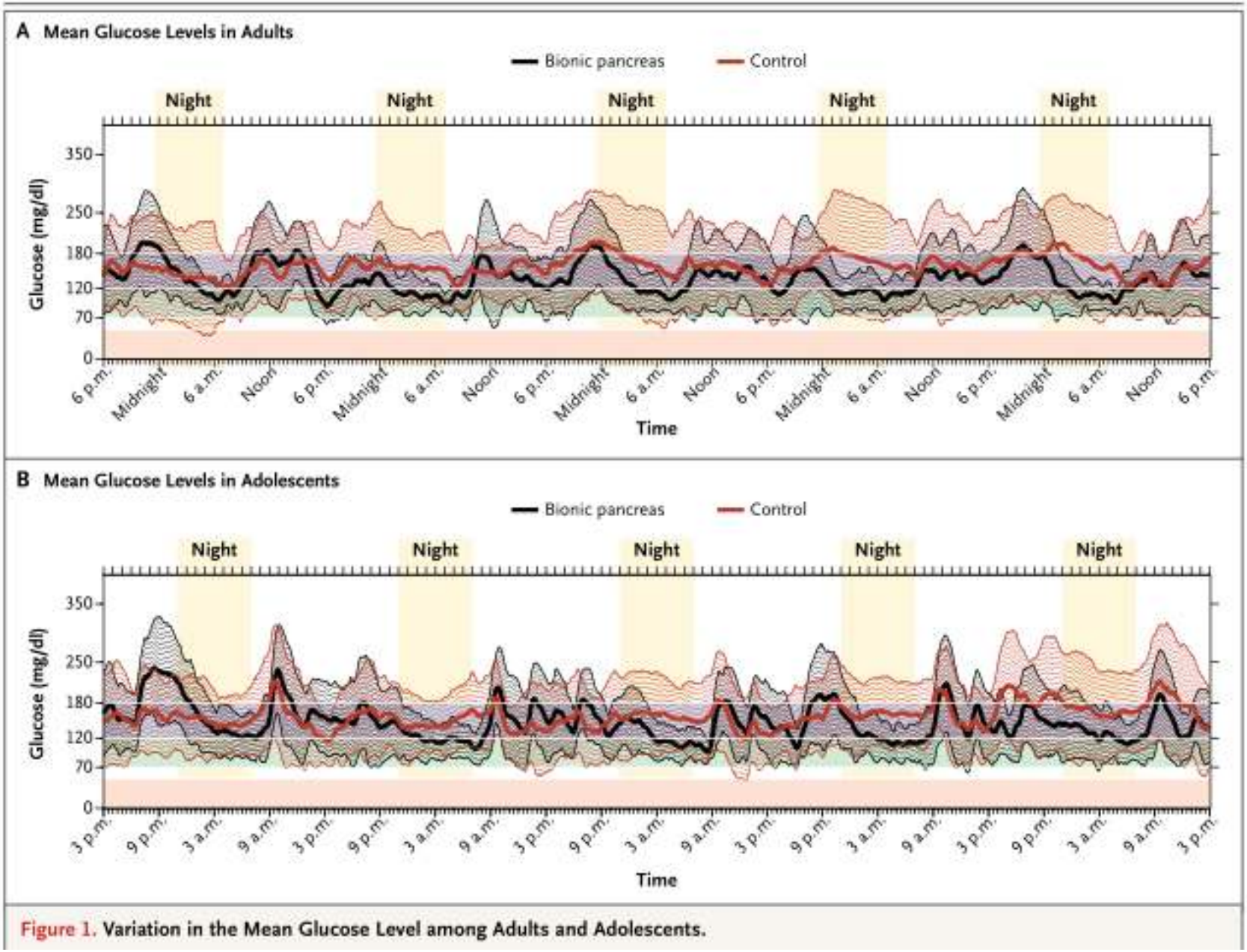


Figure 1. Variation in the Mean Glucose Level among Adults and Adolescents.

(N Engl J Med 2014;371:313-25)


CLOSED LOOP
163 mg/dl
Next meal: --
Last bolus: 0.36 U at 07:24 PM
Stop
Hyper
Hypo
10:09 AM

Artificial Pancreas Studies

Day and Night

Steil GM et al Diabetes 55:3344-50, 2006	10 Adults	30 hrs CL Vs. CSII
Atlas E et al Diabetes Care 33:1072-6, 2010	7 Adults	24 hrs CL
Steil GM et al JCEM 96 : 1402-8, 2011	8 Adults	30 hrs CL
Weinzimer SA et al Diabetes Care 31:934-9, 2008	17 Adolescents	34 hrs full/hybrid CL Vs. CSII
Elleri D et al Diabetes Care 36:838-44, 2013	12 Adolescents	36 hrs CL Vs. CSII
Murphy HR et al Diabetes Care 34:406-11, 2011	10 Pregnant Women	24 hrs CL Vs. CSII
Breton et al Diabetes 61:2230-7, 2012	11 Adolescents/27 Adults	22 hrs CL

Dual Hormone (Insulin and Glucagon)

El-Khafib FH et al Sci Transl Med 14;27ra27, 2010	11 Adults	27 hrs CL
Russell S et al Diabetes Care 35:2148-55, 2012	6 Adults	51 hrs CL
Haidar A et al CMAJ 5;185:297-305, 2013	15 Adults	15 hrs CL Vs. CSII

Artificial Pancreas Studies

Overnight		
Hovorka R et al Lancet 27; 375:743-51, 2010	17 Children & Adolescents	3 Studies: 12 hrs CL Vs. CSII
Clarke WL et al J Diabetes Sci 1;3:1031-8 , 2009	8 Adults	12 hrs CL Vs. CSII
Nimri R et al Diabetes Tec Ther; 14:728-35, 2012	7 Adolescents & young Adults	12 hrs CL
Elleri D et al Diabetes Tec Ther; 1;3:419-24, 2011	8 Children	
Nimri R et al Pediatr Diabetes 14:159-67, 2013	12 Adolescents & young Adults	12 hrs CL Vs. CSII
Dauber A et al Diabetes Care 36:222-7, 2013	10 Children	2 Consecutive nights Vs. CSII
O`Grady MJ et al Diabetes Care 35:2182-7, 2012	8 Adolescents & young Adults	2 Consecutive nights Vs. CSII

"Pump-Centric" Diabetes Treamtment

Sensor Augmented pump

Low Threshold Suspend

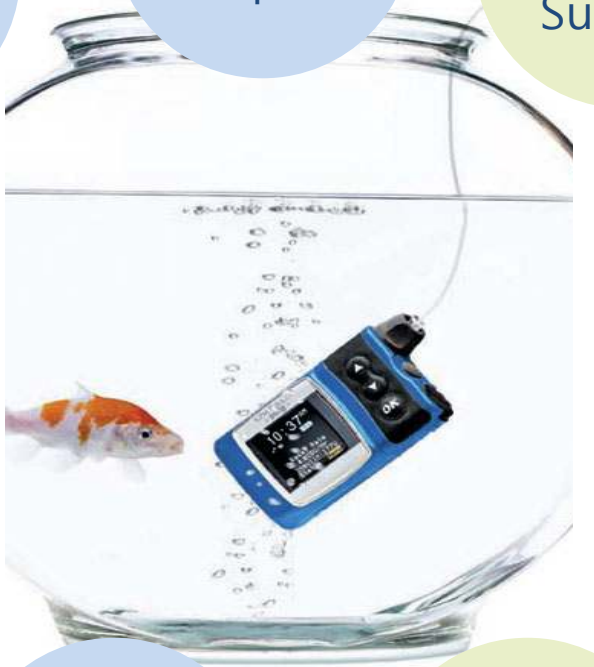
Predicted Threshold Suspend

Data Sharing And Cloud Storage

Remote monitoring

Automated Carbohydrates Counting

Bolus Calculator



Automated Patients Settings Adjustment

Flexible Basal

Download And View Data

Closed Loop Augmented Pump

Adopted by slide of Stuart Weinzimer, MD, Yale university School of Medicine

Cell Therapy for Diabetes Mellitus

Transplantation therapy – cell therapy for diabetes

① **Whole pancreas transplant**

② **Islet cell transplant**

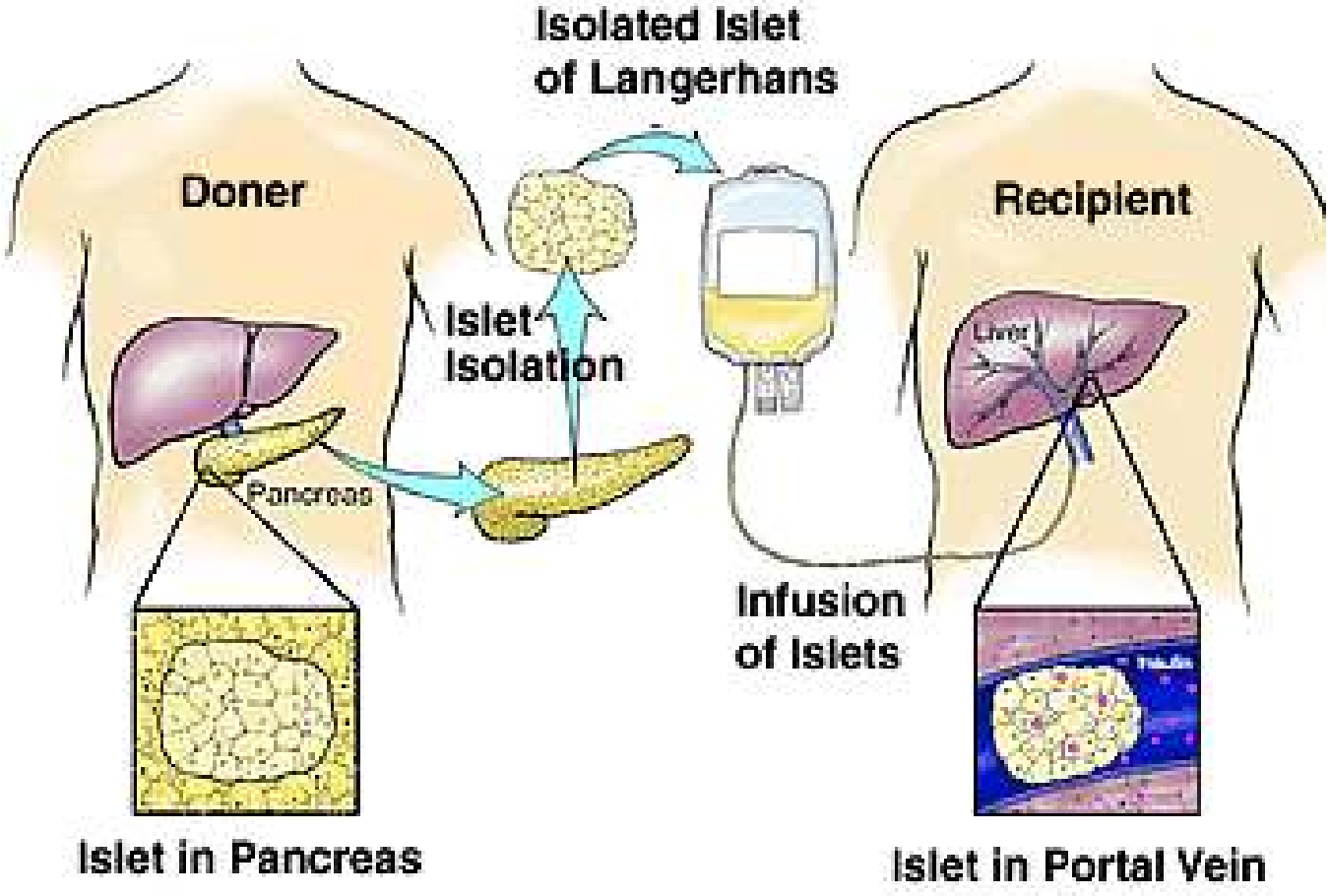
③ **Stem cell therapy**

Limitation

- **Insufficient donors** for the current demand
- **Difficulty of differenciation**

  - Beta Cells are unique cells organized in a **complex microorgan called the pancreatic islet**

Islet transplantation



(By Dr. Ricordi)

Islet transplantation

- Clinical islet transplantation : similar to whole pancreas transplantation
- Edmonton protocol series (NEJM 2000)
  high rates of 1 year insulin dependence,
  but most returned to insulin at low dose by 3 to 5 years
- The islet transplant group in Edmonton
  has now carried out almost 500 intraportal islet infusions
- 6 international centers report
  insulin independence rates of over 50% at 5 years
  with T-depletional induction with anti-inflammatory agents
- A large Phase 3 trial in North America, conducted under FDA
  jurisdiction, will likely lead to Biological Licensure
  for islet transplantation in the US within the next 2 years

- Decreased human organ donor supply

(By Dr. Shapiro)

- Embryonic & adult inducible pluripotential **stem cell** therapies

- **β-cell**

Protection, Regeneration

Differentiation, Proliferation, Replication

Kinds of stem cells from animals and humans

- **embryonic stem cells (ESC)**

  :Stem cells are derived from embryos that develop from eggs that have been fertilized *in vitro*

- **"somatic" or "adult" stem cells (ASC)**

  :Undifferentiated cell, found among differentiated cells in a tissue or organ that can renew itself and can differentiate to yield some or all of the major specialized cell types of the tissue or organ.

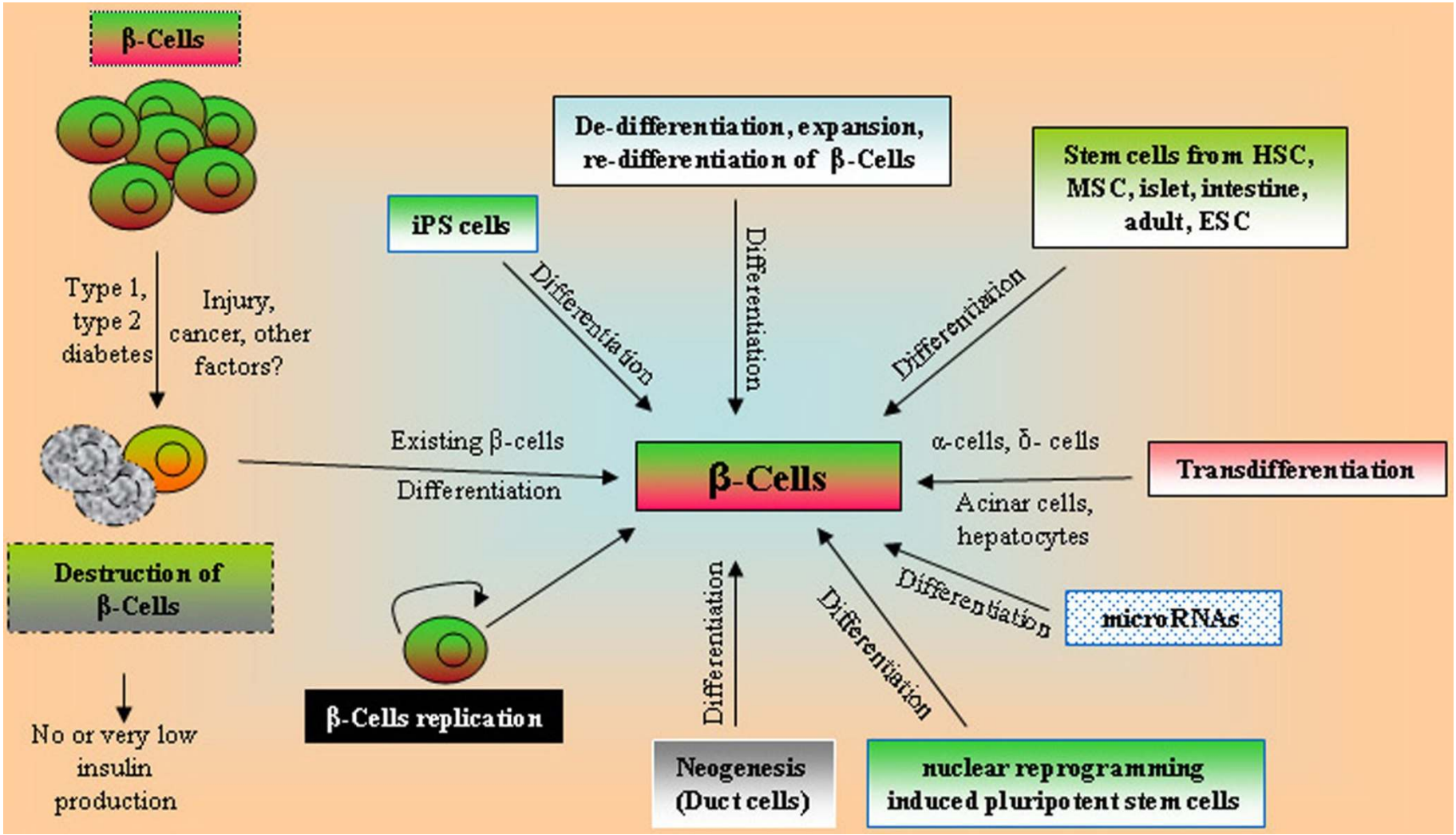
Induced pluripotent stem cells (iPSCs)

: Adult cells that have been genetically reprogrammed to an embryonic stem cell–like state by being forced to express genes and factors important for maintaining the defining properties of embryonic stem cells.

Sources of stem cells to obtain insulin producing cells

	Number of manuscripts
From ESC	*38*
Mouse ESC	29
Human ESC	9
From adult stem cells and progenitors	*54*
(i) Intrapancreatic progenitors	19
(1) Exocrine tissue	
(2) Duct cells	
(3) Intraislet progenitors	
(ii) From endodermal-derived extra-pancreatic tissues	
(1) Liver	11
(2) Gut	3
(iii) From mesodermal-derived tissues	
(1) Bone marrow	10
(2) Umbilical cord	3
(3) Peripheral blood	1
(4) Mesenchymal stem cells	5
(iv) From ectodermal-derived tissues	2

Possible sources of β-cells for cell replacement therapy



Infusion of Mesenchymal Stem Cells Ameliorates Hyperglycemia in Type 2 Diabetic Rats

Identification of a Novel Role in Improving Insulin Sensitivity

Yiling Si,[1] Yali Zhao,[1] Haojie Hao,[1] Jiejie Liu,[1] Yelei Guo,[1] Yiming Mu,[2] Jing Shen,[2] Yu Cheng,[2] Xiaobing Fu,[1] and Weidong Han[1]

We hypothesized that infused MSCs might also contribute to amelioration of the insulin resistance of peripheral insulin target tissues. To test the hypothesis, we induced a diabetic rat model by highfat diet/streptozotocin (STZ) administration, performed MSC infusion during the early phase (7 days) or late phase (21 days) after STZ injection, and then evaluated the therapeutic effects of MSC infusion and explored the possible mechanisms involved. MSC infusion ameliorated hyperglycemia in rats with type 2 diabetes (T2D). Infusion of MSCs during the early phase not only promoted β-cell function but also ameliorated insulin resistance, whereas infusion in the late phase merely ameliorated insulin resistance. Infusion of MSCs resulted in an increase of GLUT4 expression and an elevation of phosphorylated insulin receptor substrate 1 (IRS-1) and Akt (protein kinase B) in insulin target tissues. This is the first report of MSC treatment improving insulin sensitivity in T2D. These data indicate that multiple roles and mechanisms are involved in the efficacy of MSCs in ameliorating hyperglycemia in T2D.
(Diabetes 61:1616–1625, 2012)

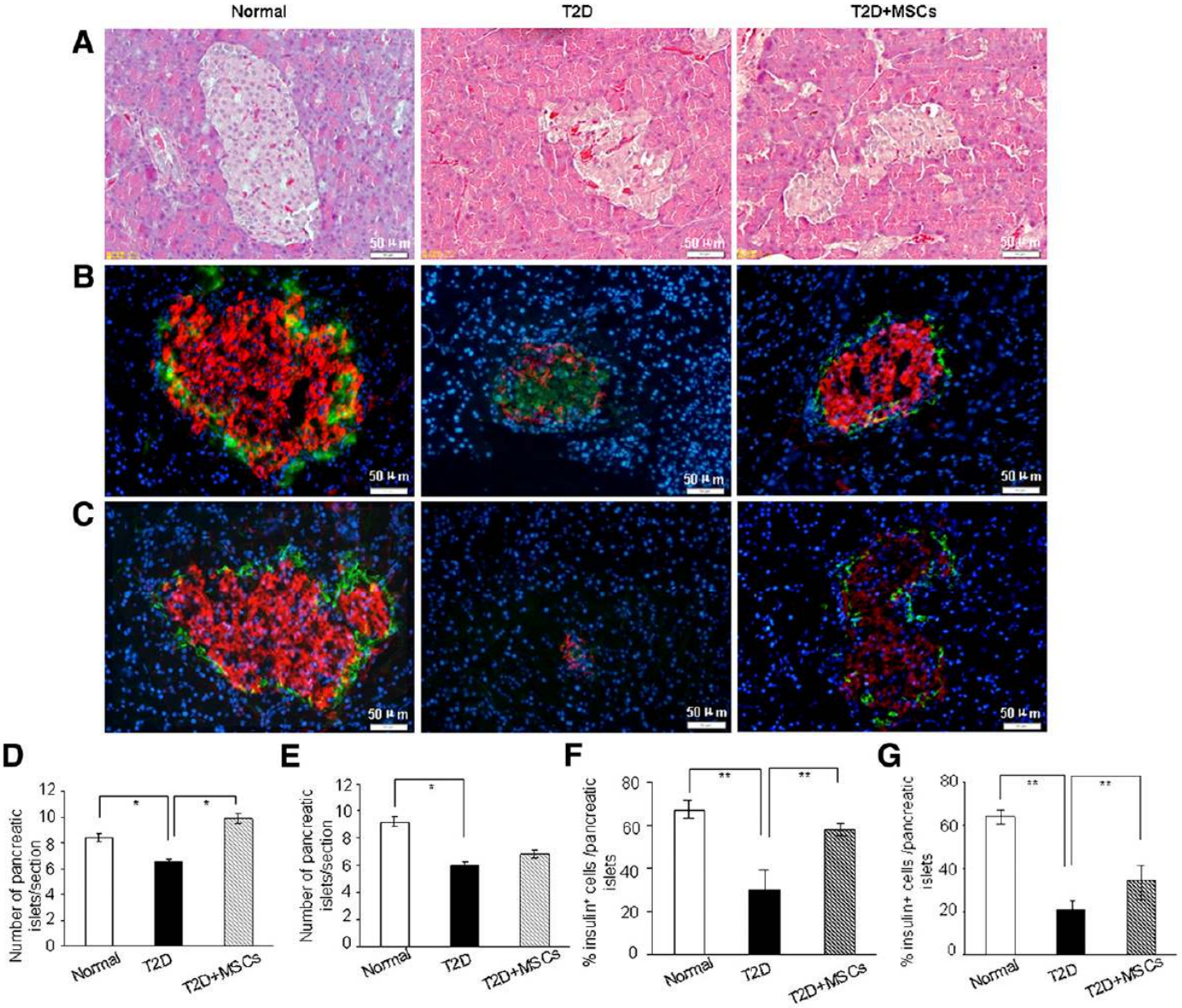


FIG. 3. Infusion of MSCs promotes restoration of pancreatic islet function in T2D rats. *A*: Pancreas histology was studied in hematoxylin/eosin-stained sections, observed under light microscopy and focusing on islet structures indicated by arrows. Pancreatic islets were characterized by immunofluorescence according to the presence and distribution of insulin- (red) and glucagon-producing (green) cells in the T2D rats that received MSC infusion at 7 (*B*) or 21 days (*C*) after STZ injection. Pancreatic islets observed in hematoxylin/eosin-stained sections were quantified in the T2D rats that received MSC infusion at 7 (*D*) or 21 days (*E*) after STZ injection. β-Cells in pancreatic islets were quantified in the T2D and MSC-treated T2D rats that received MSC infusion at 7 (*F*) or 21 days (*G*) after STZ injection. Images were composite overlay of the individually stained nuclei, insulin and glucagon from the continuous pancreatic cryosections. Scale bar, 50 μm (*A–C*). Values of *D–G* are means ± SE. $n = 5$ sections per group. *$P < 0.05$ and **$P < 0.01$. (A high-quality digital representation of this figure is available in the online issue.)

Diabetic Ketoacidosis at Diagnosis Influences Complete Remission After Treatment With Hematopoietic Stem Cell Transplantation in Adolescents With Type 1 Diabetes

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Lirong Li, MD[3]
Wei Tang, MD[2]
Shouyue Sun, MD[1]
Weijuan Cui, MD[3]
Lei Ye, MD, PHD[1]
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Jie Hong, MD, PHD[1]
Dalong Zhu, MD[3]
Guang Ning, MD, PHD[1,4]

OBJECTIVE—To determine if autologous nonmyeloablative hematopoietic stem cell transplantation (AHSCT) was beneficial for type 1 diabetic adolescents with diabetic ketoacidosis (DKA) at diagnosis.

RESEARCH DESIGN AND METHODS—We enrolled 28 patients with type 1 diabetes, aged 14–30 years, in a prospective AHSCT phase II clinical trial. HSCs were harvested from the peripheral blood after pretreatment consisting of a combination of cyclophosphamide and antithymocyte globulin. Changes in the exogenous insulin requirement were observed and serum levels of HbA_{1c}, C-peptide, and anti-glutamic acid decarboxylase antibody were measured before and after the AHSCT.

RESULTS—After transplantation, complete remission (CR), defined as insulin independence, was observed in 15 of 28 patients (53.6%) over a mean period of 19.3 months during a follow-up ranging from 4 to 42 months. The non-DKA patients achieved a greater CR rate than the DKA patients (70.6% in non-DKA vs. 27.3% in DKA, $P = 0.051$). In the non-DKA group, the levels of fasting C-peptide, peak value during oral glucose tolerance test (C_{max}), and area under C-peptide release curve during oral glucose tolerance test were enhanced significantly 1 month after transplantation and remained high during the 24-month follow-up (all $P < 0.05$). In the DKA group, significant elevation of fasting C-peptide levels and C_{max} levels was observed only at 18 and 6 months, respectively. There was no mortality.

CONCLUSIONS—We have performed AHSCT in 28 patients with type 1 diabetes. The data show AHSCT to be an effective long-term treatment for insulin dependence that achieved a greater efficacy in patients without DKA at diagnosis.

Diabetes Care 35:1413–1419, 2012

Cell

Resource

Generation of Functional Human Pancreatic β Cells In Vitro

Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]

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http://dx.doi.org/10.1016/j.cell.2014.09.040

Insulin-producing cells previously generated from **human pluripotent stem cells (hPSC)** lack many functional characteristics of bona fide β cells. Here, we report a scalable differentiation protocol that can generate hundreds of millions of glucose-responsive β cells from hPSC in vitro. These stem-cell-derived β cells (SC- β) express markers found in mature β cells, flux Ca2+ in response to glucose, package insulin into secretory granules, and secrete quantities of insulin comparable to adult β cells in response to multiple sequential glucose challenges in vitro. Furthermore, these cells secrete human insulin into the serum of mice shortly after transplantation in a glucose-regulated manner, and transplantation of these cells ameliorates hyperglycemia in diabetic mice.

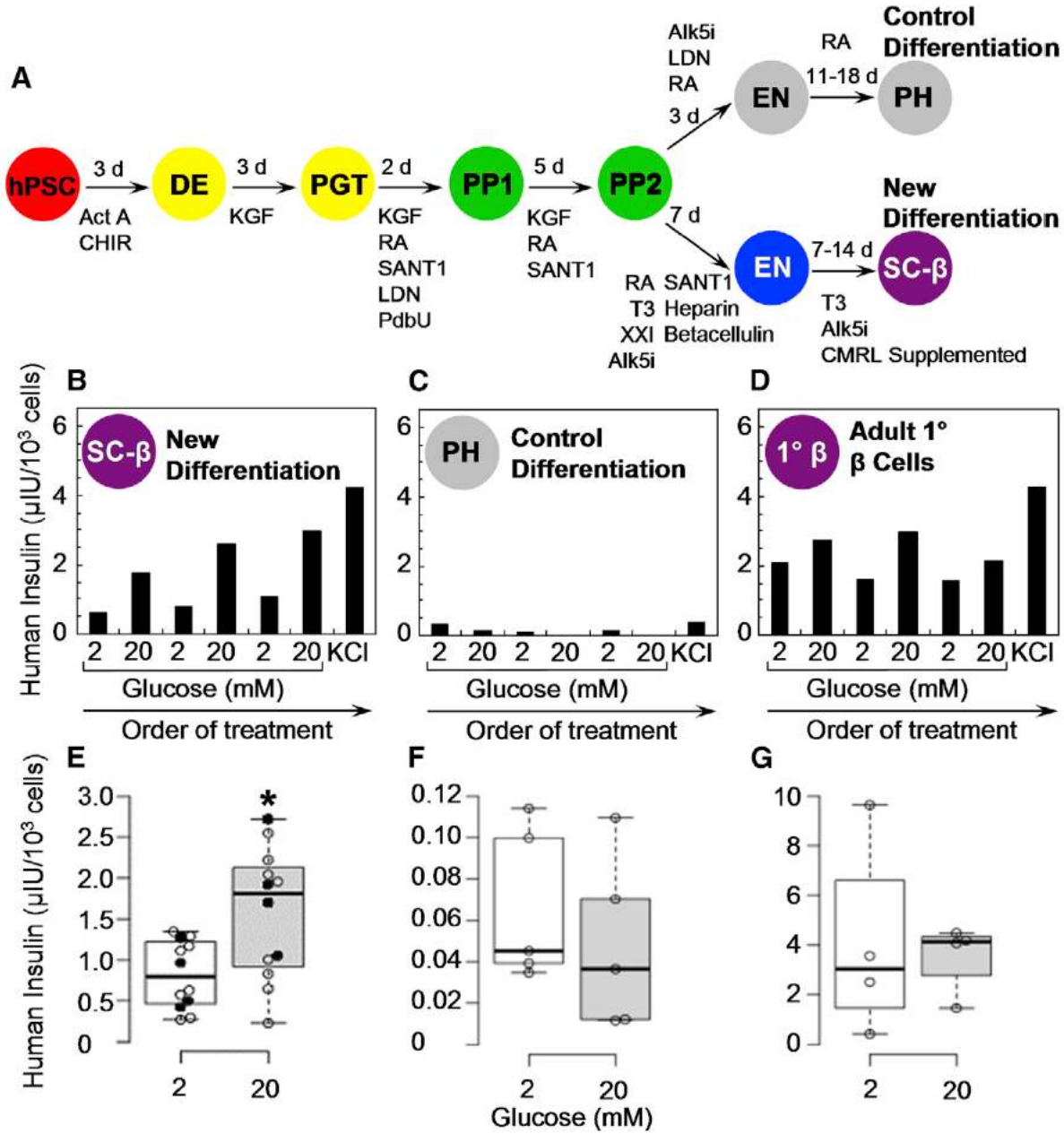


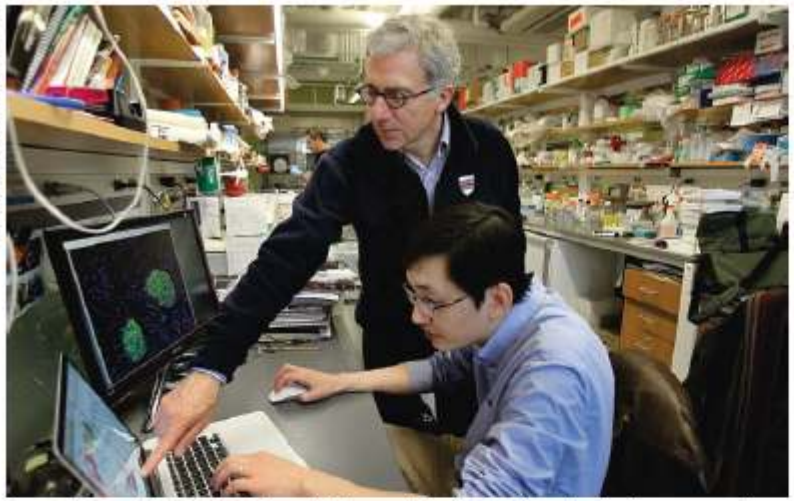
Figure 1. SC-β Cells Generated In Vitro Secrete Insulin in Response to Multiple Sequential High-Glucose Challenges like Primary Human β Cells

(A) Schematic of directed differentiation from hPSC into INS+ cells via new or previously published control differentiations.

(B–D) Representative ELISA measurements of secreted human insulin from HUES8 SC-β cells (B), PH cells (C), and primary β (1°β) cells (D) challenged sequentially with 2, 20, 2, 20, 2, and 20 mM glucose, with a 30 min incubation for each concentration (see Experimental Procedures). After sequential low/high-glucose challenges, cells were depolarized with 30 mM KCl.

(E–G) Box and whisker plots of secreted human insulin from different biological batches of HUES8 (open circles) and hiPSC SC-β (black circles) cells (E; n = 12), biological batches of PH cells (F; n = 5), and primary β cells (G; n = 4). Each circle is the average value for all sequential challenges with 2 mM or 20 mM glucose in a batch. Insulin secretion at 20 mM ranged 0.23–2.7 $\mu IU/10^3$ cells for SC-β cells and 1.5–4.5 $\mu IU/10^3$ cells for human islets, and the stimulation index ranged 0.4–4.1 for SC-β cells and 0.6–4.8 for primary adult. The thick horizontal line indicates the median.

See also Figures S1 and S2A and Table S1. *$p < 0.05$ when comparing insulin secretion at 20 mM versus 2 mM with paired t test. Act A, activin A; CHIR, CHIR99021, a GSK3α/β inhibitor; KGF, keratinocyte growth factor or FGF family member 7; RA, retinoic acid; SANT1, sonic hedgehog pathway antagonist; LDN, LDN193189, a BMP type 1 receptor inhibitor; PdbU, Phorbol 12,13-dibutyrate, a protein kinase C activator; Alk5i, Alk5 receptor inhibitor II; T3, triiodothyronine, a thyroid hormone; XXI, γ-secretase inhibitor; Betacellulin, EGF family member.



SUZANNE KREITER/BOSTON GLOBE/GETTY

A research team led by Douglas Melton (left) has made insulin-secreting cells using human stem cells.

REGENERATIVE MEDICINE

Stem-cell success aids diabetes fight

Now the challenge is to protect cell transplants from the immune systems of people with type 1 diabetes.

BY HEIDI LEDFORD

Each year, surgeon Jose Oberholzer frees a few people with type 1 diabetes from daily insulin injections by giving them a transplant of the insulin-secreting β-cells that the disease attacks. But it is a frustrating process. Harvested from a cadaver's pancreas, the β-cells are in short supply and vary in quality. And the patients must take drugs to suppress their immune response to the foreign cells, which can in turn cause kidney failure.

On 9 October, stem-cell researcher Douglas Melton of Harvard University in Cambridge, Massachusetts, and his colleagues reported an advance that has the potential to overcome Oberholzer's frustrations and allow many more people with type 1 diabetes to receive transplants. Melton and his team have achieved a long-term goal of stem-cell science: they have created mature β-cells using human stem cells that can be grown from a potentially unlimited supply, and that behave like the real thing (F. W. Pagliuca *et al. Cell* 159, 428–439; 2014). The next challenge is to work out how to shield these β-cells from the body's immune response.

Researchers had previously created immature β-cells from stem cells and transplanted them into diabetic mice. But they take months to mature into insulin-secreting cells, and it is unclear whether they would do so in humans.

The β-cells reported by Melton's team were grown from adult cells that had been reprogrammed to resemble stem cells. In response to glucose, the β-cells quickly secreted insulin, which the body uses to regulate blood sugar. When implanted in diabetic mice, the cells relieved symptoms within two weeks. The β-cells even formed clusters that are similar to those found in a pancreatic structure called the islet of Langerhans. "If you took these cells and showed them to somebody without telling them what they are, I guarantee you an expert would say that is a perfect human islet cell," says Oberholzer, who is working with Melton's team to test the cells in non-human primates.

A remaining hurdle is shielding the cells from immune attack. This is necessary if the treatment is to become more widely available, because immunosuppressant drugs can be justified only in the most severe cases of diabetes. And although mature β-cells could be derived from a patient's own skin cells, type 1 diabetes is an autoimmune disease, so transplanted cells would still be vulnerable to attack.

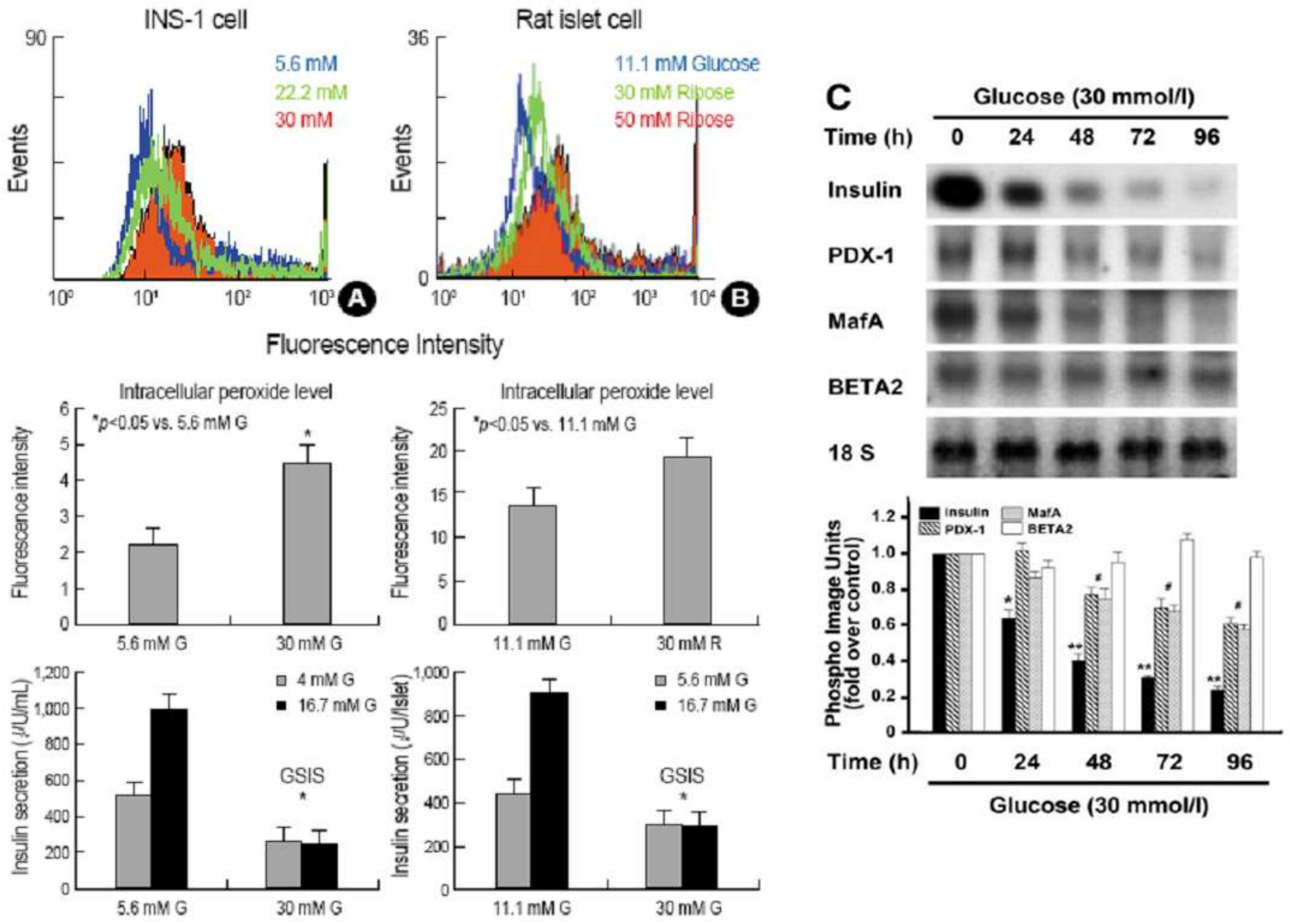
One solution might be to encapsulate the cells in a credit-card-sized, biocompatible sheath made by ViaCyte of San Diego, California. The company will implant its first device — loaded with immature β-cells — in a patient on 21 October. Studies in animals have been promising, but some researchers worry that the cells inside the device are packed too densely and might become starved of oxygen and nutrients.

Another option is to coat cells in a protective hydrogel, which results in thousands of separate balls of cells. But a potential drawback is that it would be much harder to remove such cells if there was a safety concern, says Albert Hwa, director of discovery science at JDRF, a diabetes-research foundation in New York.

Neither technique avoids the body's tendency to enclose foreign bodies inside scar tissue, which could cut the transplanted cells off from nutrients. Bioengineer Daniel Anderson of the Massachusetts Institute of Technology in Cambridge and his team are screening chemical compounds for a hydrogel that does not trigger this. Some, used with Melton's cells, have shown promise in unpublished studies of diabetic primates, he says.

Still, for those people with diabetes who face life-threatening changes in blood-sugar level each day, mature β-cells could offer a big improvement without such devices, says Oberholzer. Many of his patients are relieved to be free of insulin injections: "They would much rather take immunosuppression," he says. ■

β cell protection



The effects of high glucose on the intracellular peroxide level, transcription factors and GSIS in the INS-1 cells and rat islets.

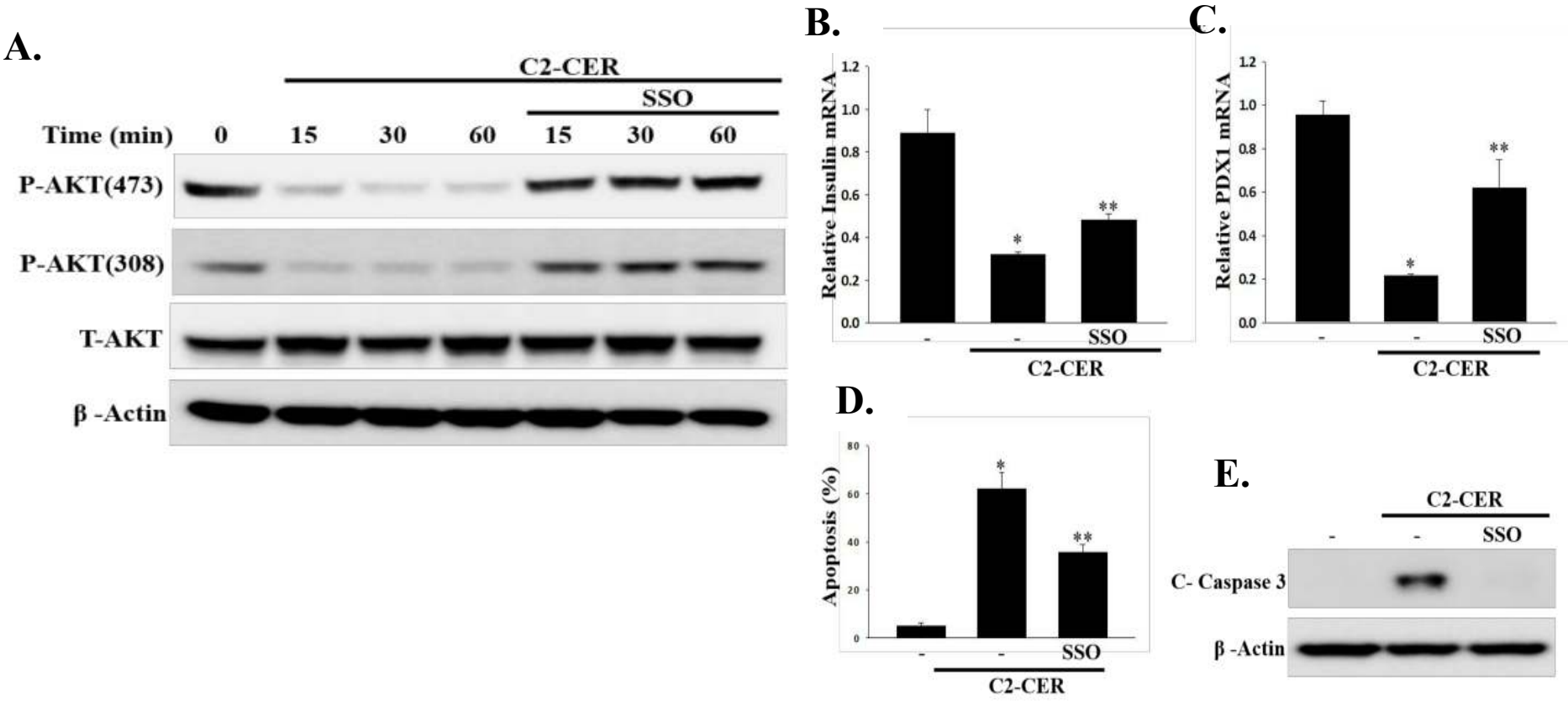
(Won KC et al. J Korean Med Sci 21:418-24, 2006)

(Park KG et al. Diabetes 56:431-37, 2007)

(By Dr. Robertson)

(Kim YW , Moon JS et al. Biochem Biophys Res Commun ,420:462-466, 2012)

Inhibition of CD36 recovered ceramide reduced Insulin, PDX1 mRNA and apoptosis



(Unpublished data)

β-cell proliferation

- Insulin/ IGF-1 signals
- GLP-1
- Leptin, Resistin from WAT
- Prolactin
- Osteocalcin, Osteoprotegeron from bone
- Neural signals
- HGF, IGF-1 from liver
- IL 6

(By Dr. Kulkarni)

β-cell regeneration

In vivo reprogramming of adult pancreatic exocrine cells to β-cells

Qiao Zhou[1], Juliana Brown[2], Andrew Kanarek[1], Jayaraj Rajagopal[1] & Douglas A. Melton[1]

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2. Department of Pathology, Children's Hospital, Boston, Harvard Medical School, Harvard Stem Cell Institute, 300 Longwood Avenue, Boston, Massachusetts 02115-5724, USA

Correspondence to: Douglas A. Melton[1] Correspondence and requests for materials should be addressed to D.A.M. (Email: dmelton@harvard.edu).

One goal of regenerative medicine is to instructively convert adult cells into other cell types for tissue repair and regeneration. Although isolated examples of adult cell reprogramming are known, there is no general understanding of how to turn one cell type into another in a controlled manner. Here, using a strategy of re-expressing key developmental regulators *in vivo*, we identify a specific combination of three transcription factors (*Ngn3* (also known as *Neurog3*) *Pdx1* and *Mafa*) that reprograms differentiated pancreatic exocrine cells in adult mice into cells that closely resemble β-cells. The induced β-cells are indistinguishable from endogenous islet β-cells in size, shape and ultrastructure. They express genes essential for β-cell function and can ameliorate hyperglycaemia by remodelling local vasculature and secreting insulin. This study provides an example of cellular reprogramming using defined factors in an adult organ and suggests a general paradigm for directing cell reprogramming without reversion to a pluripotent stem cell state.

▲ Top

Nature **455**, 627-632 (2 October 2008)

- 인슐린 투입방법

  New insulin formula

  Insulin pump

  Artificial pancreas

  췌장 췌도 이식, 인슐린 분비 세포

- (새로운) 혈당 강하제

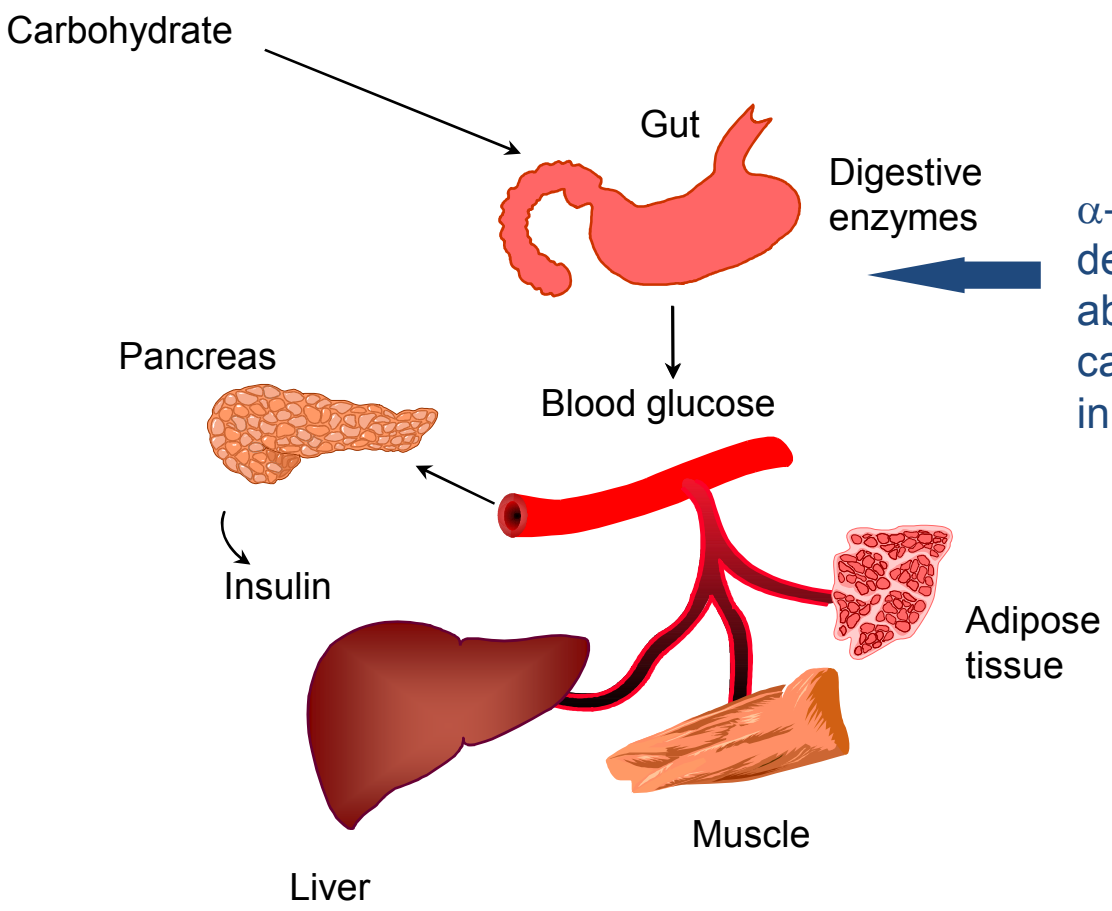
Nat Rev Endocrinol. 2010 Jun;6(6):326-34. doi: 10.1038/nrendo.2010.49. Epub 2010 Apr 20.

Adjunct therapy for type 1 diabetes mellitus.

Lebovitz HE[1].

Agents that decrease intestinal carbohydrate digestion (alpha-glucosidase inhibitors) or decrease insulin resistance (metformin) might be alternative adjunctive therapies in T1DM, though its benefits are marginally suppo-rted by clinical data.

α-Glucosidase inhibitors



α-Glucosidase inhibitors delay digestion and absorption of carbohydrates in GI tract

LETTER

doi:10.1038/nature11808

Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP

Russell A. Miller[1], Qingwei Chu[1], Jianxin Xie[2], Marc Foretz[3,4,5], Benoit Viollet[3,4,5] & Morris J. Birnbaum[1]

Glucose production by the liver is essential for providing a substrate for the brain during fasting. The inability of insulin to suppress hepatic glucose output is a major aetiological factor in the hyperglycaemia of type-2 diabetes mellitus and other diseases of insulin resistance[1,2]. For fifty years, one of the few classes of therapeutics effective in reducing glucose production has been the biguanides, which include phenformin and metformin, the latter the most frequently prescribed drug for type-2 diabetes[3]. Nonetheless, the mechanism of action of biguanides remains imperfectly understood. The suggestion a decade ago that metformin reduces glucose synthesis through activation of the enzyme AMP-activated protein kinase (AMPK) has recently been challenged by genetic loss-of-function experiments[4]. Here we provide a novel mechanism by which metformin antagonizes the action of glucagon, thus reducing fasting glucose levels. In mouse hepatocytes, metformin leads to the accumulation of AMP and related nucleotides, which inhibit adenylate cyclase, reduce levels of cyclic AMP and protein kinase A (PKA) activity, abrogate phosphorylation of critical protein targets of PKA, and block glucagon-dependent glucose output from hepatocytes. These data support a mechanism of action for metformin involving antagonism of glucagon, and suggest an approach for the development of antidiabetic drugs.

we tested 24-h exposure of hepatocytes to phenformin or metformin for a reduction in glucagon-increased cAMP levels. After long-term treatment, phenformin was effective at considerably lower concentrations, with concentrations of 10 μM or greater causing significant reductions in glucagon-stimulated increases in cAMP levels (Fig. 1c). Metformin also inhibited cAMP accumulation at concentrations of 125 μM or greater, levels slightly higher than in the serum of diabetic patients after taking a 1 mg dose of metformin but probably similar to those accumulated in splanchnic tissues[14,15] (Fig. 1d). In rats, administration of a therapeutic dose of 50 mg kg^{-1} leads to levels greater than 250 μM in the liver [14,15]. Like phenformin, therapeutic concentrations of metformin elicited significant increases in AMP levels in primary hepatocytes (Supplementary Fig. 2a–c). Glucagon did not alter adenine nucleotide levels or activate AMPK in primary hepatocytes and did not affect the changes produced by metformin (Supplementary Fig. 2a–d).

To determine the effects of phenformin on the kinetics of activation of PKA, we used the AKAR3 fluorescence resonance energy transfer (FRET) reporter[16]. Primary hepatocytes were infected with adenovirus encoding AKAR3 and 18 h later confocal images were acquired over time (Supplementary Fig. 3a). Glucagon increased the FRET ratio (FRET/cyan fluorescent protein (CFP)) of AKAR3 in the cytoplasm of hepatocytes within 1 min and reached a maximum at 2 min, there-

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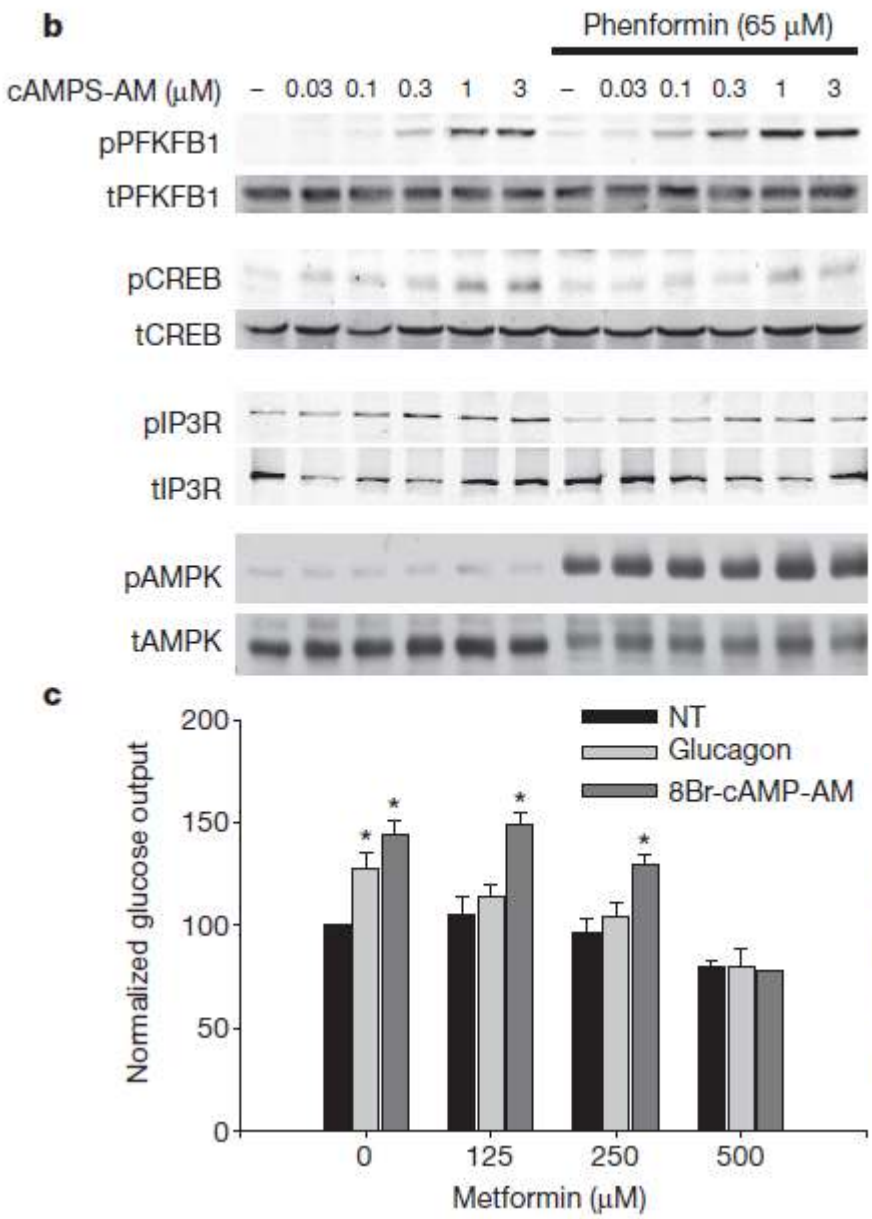


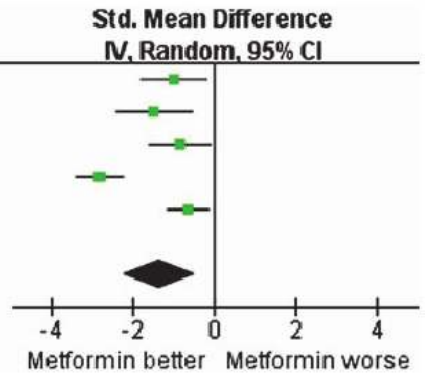
Figure 2 | Biguanides inhibit glucagon signalling. a, b, Primary hepatocytes were cultured for 18 h in the presence or absence of 65 μM phenformin and for 15 min with the indicated concentrations of glucagon (a) or the cell-permeable PKA agonist SP-8Br-cAMPS-AM (b). Western blot analysis of total (t) and phosphorylated (p) PFKFB1, CREB, IP3R and AMPK. c, Cells were treated with the indicated concentration of metformin and either 1 nM glucagon or 3 μM SP-8Br-cAMPS-AM, or were left untreated (NT), for 14 h and then glucose output measured for 5 h. Data represent the means of three experiments, $N = 6$ for each experiment. Error bars represent s.e.m.

Metformin for Patients with Type 1 Diabetes: A Meta-Analysis

Insulin dose

Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Hamilton J. 2003	-0.14	0.1	14	0.02	0.2	13	19.4%	-0.99 [-1.80, -0.19]
Jacobsen IB. 2009	-5.9	2.2	12	-2.9	1.7	12	18.5%	-1.47 [-2.39, -0.55]
Khan ASA 2006	-10	9.67	15	-2	8.95	15	19.8%	-0.84 [-1.59, -0.08]
Lund SS. 2008	-3.2	2	48	2.5	2	50	21.0%	-2.83 [-3.39, -2.26]
Meyer L. 2002	-4.3	9.9	31	1.7	8.3	31	21.3%	-0.65 [-1.16, -0.14]
Total (95% CI)			**120**			**121**	**100.0%**	**-1.36 [-2.28, -0.45]**

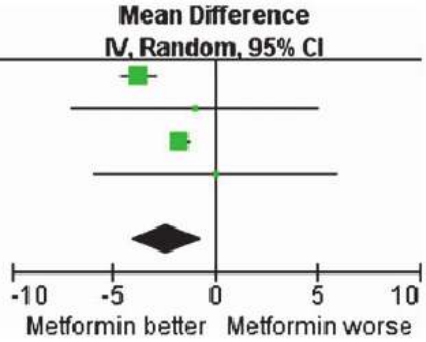
Heterogeneity: Tau² = 0.96; Chi² = 35.92, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.92 (P = 0.004)



Weight change

Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Jacobsen IB. 2009	-3	1	12	0.8	1.1	12	41.2%	-3.80 [-4.64, -2.96]
Khan ASA 2006	-2	8.24	15	-1	8.59	15	7.2%	-1.00 [-7.02, 5.02]
Lund SS. 2008	-1.21	1.1	48	0.53	1.13	50	44.2%	-1.74 [-2.18, -1.30]
Särnblad S. 2003	1	7.04	13	1	8.37	13	7.4%	0.00 [-5.95, 5.95]
Total (95% CI)			**88**			**90**	**100.0%**	**-2.41 [-4.17, -0.65]**

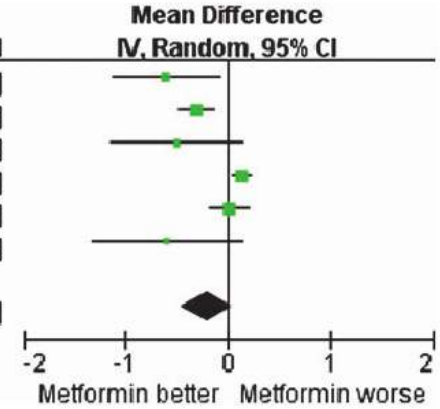
Heterogeneity: Tau² = 1.77; Chi² = 18.73, df = 3 (P = 0.0003); I² = 84%
Test for overall effect: Z = 2.68 (P = 0.007)



HbA1c

Study or Subgroup	Metformin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Hamilton J. 2003	-0.3	0.7	14	0.3	0.7	13	12.0%	-0.60 [-1.13, -0.07]
Jacobsen IB. 2009	-0.48	0.26	12	-0.17	0.17	12	22.9%	-0.31 [-0.49, -0.13]
Khan ASA 2006	-0.7	0.9	15	-0.2	0.9	15	9.5%	-0.50 [-1.14, 0.14]
Lund SS. 2008	-0.1	0.22	48	-0.23	0.22	50	25.0%	0.13 [0.04, 0.22]
Meyer L. 2002	0.19	0.38	31	0.18	0.38	31	22.5%	0.01 [-0.18, 0.20]
Särnblad S. 2003	-0.9	0.98	13	-0.3	0.93	13	8.0%	-0.60 [-1.33, 0.13]
Total (95% CI)			**133**			**134**	**100.0%**	**-0.20 [-0.45, 0.05]**

Heterogeneity: Tau² = 0.06; Chi² = 30.18, df = 5 (P < 0.0001); I² = 83%
Test for overall effect: Z = 1.60 (P = 0.11)



Diabetes Technol Ther. 2015 Feb;17(2):142-8

- **SGLT-2 inhibitor**
- Dual PPAR agonist
- G protein coupled receptors
- Glucokinase activator
- Orally active GLP-1 receptor agonist
- GIP/GLP-1 co-agonist
- Dopamin D2 receptor

Summary of SGLT 2 inhibitor

- **SGLT 2 inhibitors ….**

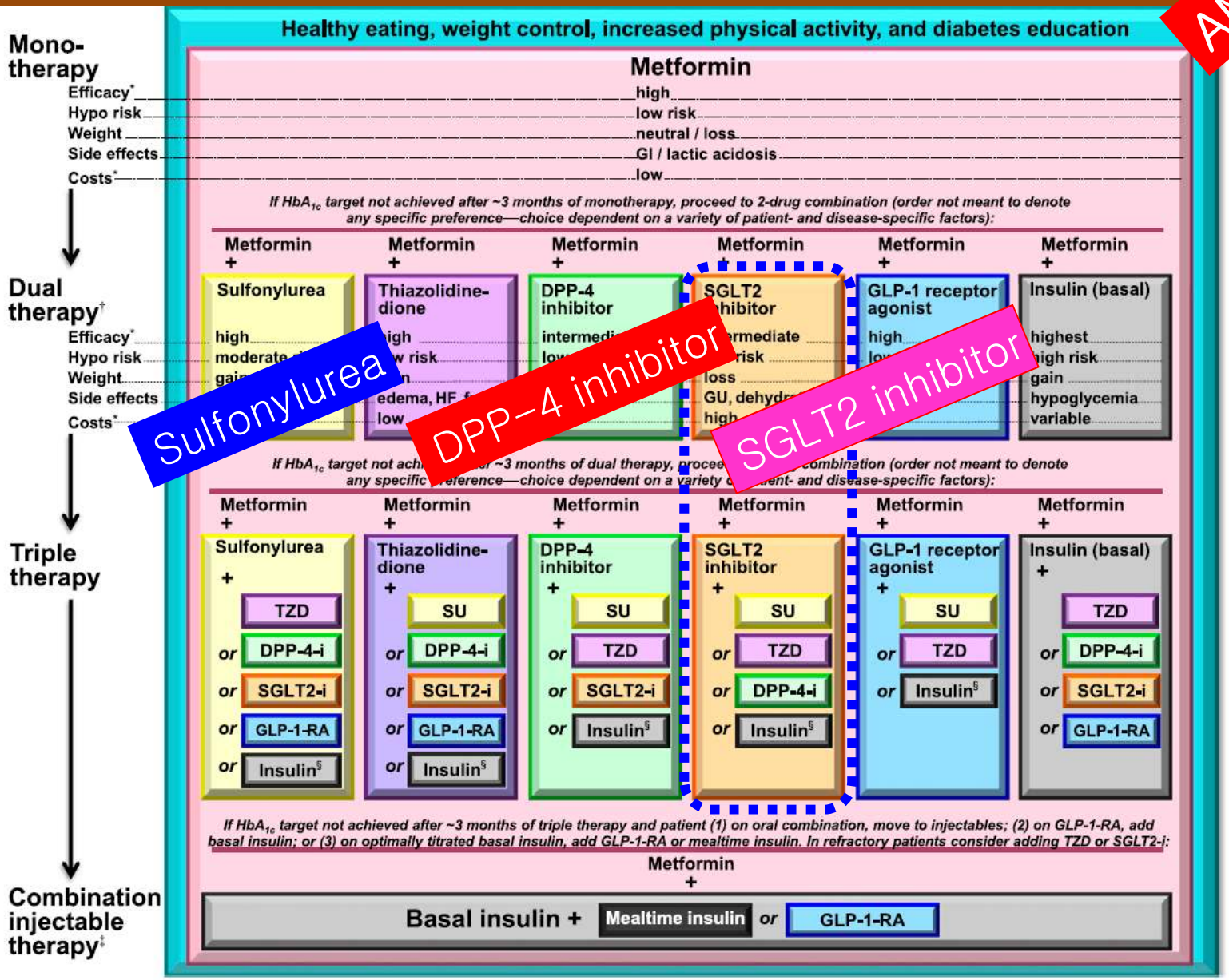
- Insulin independent mechanism

- Reduction of Hb A1c (0.5-1%)
- Reduction of blood pressure
- Reduction of weight (2-3 kg)

- Rare hypoglycemia
- Increased risk of mycogenital infection and UTI but manageable

Section 7: Approach to Glycemic Treatment

AMENDED



SGLT-2 Inhibitor has a Durable Effect on the Restoration of Glucose Homeostasis by Preserving Beta-Cell Mass

Figure 1: *Analysis of a) weekly fed blood glucose levels and b) insulin levels*

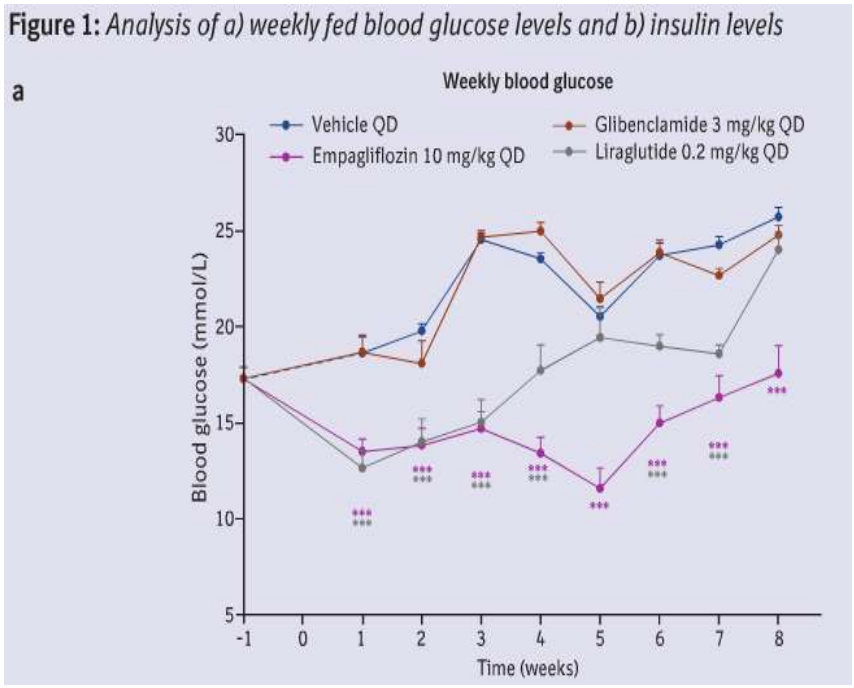
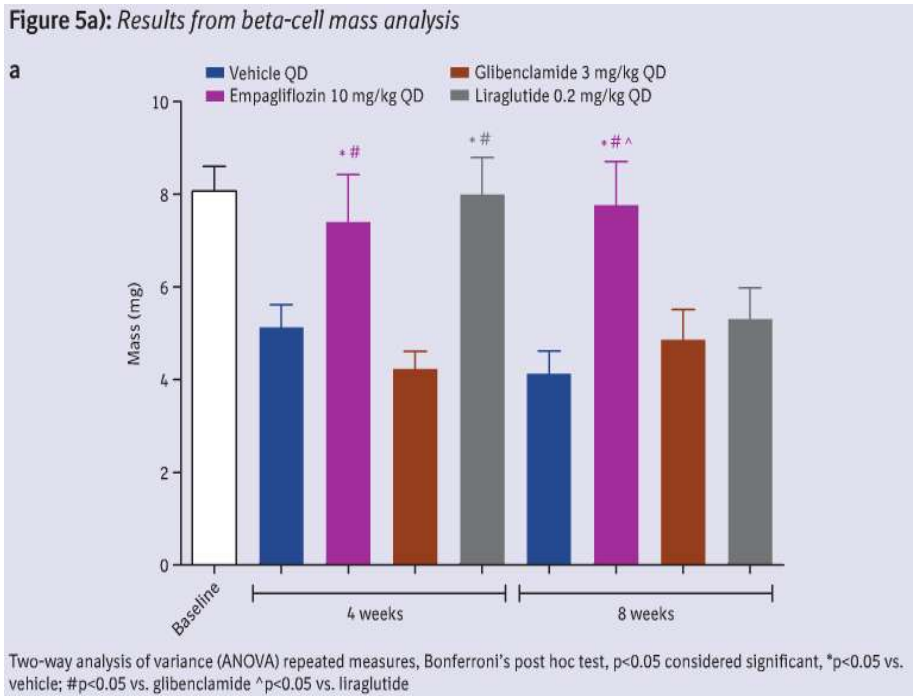


Figure 5a): *Results from beta-cell mass analysis*



Two-way analysis of variance (ANOVA) repeated measures, Bonferroni's post hoc test, $p<0.05$ considered significant, *$p<0.05$ vs. vehicle; #$p<0.05$ vs. glibenclamide ^$p<0.05$ vs. liraglutide

2012 ADA 1018-P Title: The Sodium Glucose Cotransporter-2 (SGLT-2) Inhibitor Empagliflozin has a Durable Effect on the Restoration of Glucose Homeostasis by Preserving Beta-Cell Mass in Zucker Diabetic Fatty Rats

Exploring the Potential of the SGLT2 Inhibitor Dapagliflozin in Type 1 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

Robert R. Henry,[1,2] Julio Rosenstock,[3] Steven Edelman,[1,2] Sunder Mudaliar,[1,2] Alexandros-Georgios Chalamandaris,[4] Sreeneeranj Kasichayanula,[5] Allyson Bogle,[5] Nayyar Iqbal,[5] James List,[5] and Steven C. Griffen[5]

Diabetes Care 2015;38:412–419 | DOI: 10.2337/dc13-2955

A 2-week,dose-ranging, randomized, double-blind, placebo-controlled proof-of-concept study randomly assigned 70 adults with type 1 diabetes (HbA1c7–10%),who were receiving treatment with stable doses of insulin, to one of four dapagliflozin doses (1,2.5,5,or10mg) or placebo.

…This exploratory study of dapagliflozin in adults with type 1 diabetes demonstrated acceptable short term tolerability and expected pharmacokinetic profiles and increases in urinary glucose excretion.

2015년 5월… 진료실

Diabetes Care Volume 38, Supplement 1, January 2015

Standards of Medical Care in Diabetes—2015: Summary of Revisions

Diabetes Care 2015;38(Suppl. 1):S4 | DOI: 10.2337/dc15-S003

요 약
(SMBG and CGM for T1D, 2015 ADA)

- When prescribed as part of a broader educational context, **SMBG** results may help guide treatment decisions and/or self-management for patients using less frequent insulin injections (B) or noninsulin therapies (E).
- Patients on multiple-dose insulin or insulin pump therapy should perform **SMBG** prior to meals and snacks, occasionally postprandially, at bedtime, prior to exercise, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and prior to critical tasks such as driving (B).
- When used properly, **CGM** in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥ 25 years) with type 1 diabetes (A).

- **미래**

  새로운 CGM, pump, algorithm, Smartphone….

  e.g. Flash glucose monitoring system : T1D-ongoing trial, 유럽, non-invasive

요 약

(Insulin therapy for type 1 diabetes Recommendations, 2015 ADA)

- **Most people with type 1 diabetes should be treated with MDI injections (three to four injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion (CSII). (A)**
- **Most people with type 1 diabetes should use insulin analogs to reduce hypoglycemia risk. (A)**
- **Insulin-treated patients with hypoglycemia unawareness or an episode of severe hypoglycemia should be advised** to raise their glycemic targets to strictly avoid further hypoglycemia for at least several weeks in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. (A)
- Most people with type 1 diabetes should be educated in how to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity. (E)
- Consider screening those with type 1 diabetes for autoimmune diseases (e.g., thyroid dysfunction, celiac disease) as appropriate. (E)

미래 치료 방법 ??

- **Prevention**

Autoimmunity

- **β-cell**

Protection, Regeneration

Differentiation, Proliferation, Replication

Transplantation

- **Insulin & Glucagon**

Artificial pancreas

Recent-onset T1D

- Inhibiting autoimmunity
- Enhancing β-cell survival
- Replenishing the β-cell mass

Cure for Diabetes !!!

감사합니다.