A promising future of preventive strategy for diabetes — Preemptive medicine
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July 28th, 2015 at Tokyo

Background of rapid increase of type 2 diabetes in Japan

Environmental factors
- Fat intake is 4 times in 50 years
- 4 times in 50 years
- 25 million people

Genetic factors
- Insufficient insulin action
- Insulin resistance
- Development of type 2 diabetes

Insulin secretion decrease
- Insulin secretion decrease
- Insulin resistant

Obesity, Visceral fat accumulation
- Lack of adiponectin
- Lack of exercise

Liver
- Skeletal muscle
- Pancreas
The energy surplus lifestyle and the super-aging makes to increase obesity, visceral fat accumulation and sarcopenia causes insulin resistance, type 2 diabetes, various complications, frail, and shortening of healthy life expectancy.

**Lifestyle (energy surplus)**
- High-fat meal, Lack of exercise
- Super-aging

**Obesity, Visceral fat accumulation**
- Sarcopenia

**Lack of adiponectin**
- Ectopic fat deposition
- Insulin resistance, Hyperinsulinemia

**Diabetic complications**
- Impaired glucose tolerance
- Type 2 diabetes
- Hypertension

**Microangiopathy**
- Cardiovascular and kidney diseases
  - Myocardial infarction, Stroke, CKD
  - NASH Cancer, Dementia, Osteoporosis and Frail

**Action Plan 2010 of the Japan Diabetes Society (DREAMS)**

- **Hope and Challenge**

  ① Diagnosis and Care
  ② Research to Cure
  ③ Evidence for Optimum Care
  ④ Alliance for Diabetes
  ⑤ Mentoring Program for Prevention
  ⑥ Stop the DM

**For you and your loved ones**

Keep your A1c below 7%
1. The primary prevention by promoting screening examination and post-guidance
   Improving diabetes management quality and promotion of clinical visits
   Promotion of medical collaboration

Mentoring Program for Prevention
Stop the DM
Diabetes Measures Promotion Conference

Chairman
Y. Yokokura
T. Kadowaki
M. Takagi
S. Imamura
Vice Chairman
Y. Seino

Ministry of Health, Labour and Welfare

Prefectural conference
Municipal conference

Public health center
Doctor
Nurse
Registered dietitian,
Others.

Ministry of Health, Labour and Welfare
National Health and Nutrition Examination Survey (2012)

Annual change in the number of 'Diabetic patients' and 'Pre-diabetic patients' (over 20 years old)

Percentage of dialysis initiation caused by diabetic nephropathy has become flat in these few years

Annual change in main causative diseases of dialysis

Diabetic nephropathy
Chronic glomerulonephritis
Renal sclerosis
Polycystic kidney disease
Chronic pyelonephritis
Rapidly progressive glomerulonephritis
SLE nephritis
Unclear
Necessity of establishment of the 3rd Strategic five-year Plan for Diabetes

- Increasing in number of the diabetic patients and the obesity (Dealing with, for the first time, the number of pre-diabetes decreased by National Health and Nutrition Examination Survey)

- Shortening of healthy life expectancy due to various complications
  - Diabetic nephropathy (dialysis initiation)
  - Eye sight disturbance by retinopathy
  - Myocardial infarction
  - Cerebral infarction
  - Dementia and bone fracture in elderly
  - Lower limb amputation
  - Periodontal disease

- Rising medical expenses
  - 15% of medical expense is paid for diabetes.
  - Diabetes is responsible for 30% of all death

Other:
- It is necessary to collect data about prevalence of diabetes and epidemiological data

An important point and a goal of the 3rd Strategic Five-year Plan for Diabetes

- Establishing of a base for super-aged society
- Establishing of a base for super-aged society
- Fruit of advanced researches of diabetes
- Evidence construction utilizing data from comprehensive database
- Nurturing medical personnel considering future countermeasures for diabetes
- Educating and informing the public
Preemptive Medical Care = What is personalized prevention and personalized medicine?

The concept of diabetic measures

Countermeasures at each step in the whole process of diabetes development

Japan Diabetes Outcome Intervention Trial 3 (J-DOIT3) Overview

Subjects: Type 2 diabetes with high blood pressure or dyslipidemia (Age 45-69) 
Subjects: HbA1c > 6.2% 
Subjects: HbA1c > 6.9% 
Subjects: J-DOIT3 Overview 
NCT003000070
Evidence that was directed to the diabetic complications suppression in daily practice
(Target for blood sugar, pressure, & lipid
How to proceed lifestyle improvement and medication)

Before J-DOIT3

Healthy life expectancy
Medical care cost
QOL of patient

Vascular Complications in Diabetic Patients

After J-DOIT3

Healthy life expectancy
QOL of patient
Healthy life expectancy
QOL of patient
Medical care cost

Purpose and spillover effects of J-DOIT3

~ Construction of personalized countermeasures based on genetic information ~

The further promotion of diabetes research

History of identification of type 2 diabetes susceptibility genes
In this study, we will reveal the overall picture of the pathogenesis and severity for genetic basic factor about missing heritability.

Examples of disease prevention based on genetic information
Type 2 diabetes gene TCF7L2 and diabetes prevention (USA)
TCF7L2 SNP TT type has significantly higher diabetes risk compared to the CC type.
Those who have TCF7L2 SNP TT type were also suppressed like those in CC type by weight loss related to lifestyle change.
The influence of the gene can be minimized by improving lifestyle.

Future prospects:
The personalized prevention & medicine for the metabolic syndrome-related diseases
Preemptive medicine based on genome information and medical health checkups and health claim information (Personalized prevention & personalized medicine)

- Accurate diagnosis
- Accurate prediction
- Prevention for getting severe disease
- Prevention of relapsing disease
- Stop progression
- Recovery

Genome information + Medical checkup information + Personalized prevention

- Extend healthy life expectancy in the nation

Differential functions of small and large intestine in relation to microbial density

- pH
  - Duodenum: 4.4-5.4
  - Jejunum: 5.4-6.7
  - Ileum: 5.6-6.7
  - Colon: 6.6-7.7

- Density
  - 10^10-10^12 CFUs/g

GUT SEGMENT FUNCTION

- **Duodenum**
  - Proteins
  - Monosaccharides
  - SCFAs
  - Immunomodulation
- **Jejunum**
  - VFAs
  - SCFAs
  - Bacteroids
  - Butyrate
  - SCFAs
- **Ileum**
  - VFAs
  - SCFAs
  - Bacteroids
  - Butyrate
  - SCFAs
- **Colon**
  - Water
  - SCFAs
  - Lactobacillus
  - Bifidobacterium
  - Eubacterium
  - Ruminococcus

Differential functions of small and large intestine in relation to microbial density

- **Dietary Fibers**
  - Monosaccharides
  - SCFAs
  - Bacteroids
  - Butyrate
  - SCFAs
- **Bacterial Groups**
  - Lactobacillus
  - Streptococcus
  - Enterobacteriaceae
  - Bacteroids
  - Bifidobacterium
  - Clostridium
  - Eubacterium
  - Ruminococcus
Intestinal bacterial species associated with and/or predictive of insulin resistance/T2DM development as future potential clinical diagnostic markers of T2DM

<table>
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<th>Intestinal bacterial phyla</th>
<th>Increase in T2DM</th>
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<table>
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<td>E. coli</td>
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*Diabetes Care 38:159–165, 2015*

Gut microbiota–produced SCFAs in obese/T2DM

**The further promotion of diabetes research**

The elucidation of the physiological and pathophysiological action of the diet (nutrient) and exercise effecting on the homeostasis of the body

**The promotion of research which become the theoretical foundation of the diet and exercise therapy**
A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management

Xavier Pi-Sunyer, M.D., Anne Kritop, M.D., D.M.Sc., Ken Fujiioka, M.D., Frank Greenway, M.D., Alessio Hjalamar, M.D., Michel Emerero, M.D., Ph.D., David C.W. Lau, M.D., Ph.D., Carol W. Leop, F.R.C.P., Ph.D., Rafael Vitorino Ortiz, M.D., Christine Bjorn Jensen, M.D., Ph.D., and John P.W. Williams, D.M., for the SCALE Obesity and Prediabetes V48922-389 Study Group

Liraglutide and Body Weight

Shows the mean body weight for patients in the full-analysis set who completed each scheduled visit, according to presence or absence of prediabetes at screening.


Liraglutide group was associated with a lower incidence of developing type 2 diabetes

Cumulative No. of Patients Receiving a Diagnosis of Diabetes over 56 Weeks (No. at Risk)

Liraglutide: 1(2219) 2(2210) 3(2137) 4(2130)
Placebo: 1(1225) 2(1210) 3(1204) 4(1096) 5(1035) 8(984) 9(911) 10(908) 11(818) 12(817) 13(816) 14(813)

P<0.001

Effects of adiponectin is decreased by decreased expression of AdipoR1

Hypoadiponectinemia

- Decreased Adiponectin secretion
- Decreased Adiponectin receptor expression

Hypothesis

- Cancer cell
- Nerve cell
- Liver cell
- Skeletal muscle cell
- Type 2 diabetes
- Atherosclerosis
- Fatty liver
- Endothelial dysfunction
- Alzheimer disease
- Decreased Adiponectin effect

Development of orally-administrable type 2 diabetes medicine, calorie restriction/exercise mimic drugs, or life extension drug targeting AdipoR

- Calorie restriction
- Exercise

Adiponectin/AdipoR

SIRT1

AMPK

PPAR

Extension of life expectancy
Inhibition of Diabetes, Cardiovascular diseases, NASH, and Cancer

AdipoRon binds to AdipoR1-R2 and improves insulin resistance, glucose metabolism and muscle endurance via AdipoR1-R2.

AdipoRon:

- Increase the amount of mitochondria
- Improve mitochondrial glucose metabolism
- Improve mitochondrial muscle endurance

AdipoRon (p.o.):

- Improve muscle endurance
- Improve mitochondrial DNA
- Improve mitochondrial protein

AdipoRon agonist:

Sirtuin agonist

PPAR agonist

First in Class

⇒ Adiponectin Receptor Agonist: AdipoRon
Oral administration of AdipoRon improved lifespan shortened by high-calorie, high-fat diet

Kaplan–Meier survival curves

Improvement of insulin resistance, glucose and lipid metabolism
Improvement of inflammation and vascular endothelium function

Extension of life expectancy

Clarified a tertiary structure of AdipoR

AdipoR2-Fv complex

C-terminal extracellular domain

Fv domain of the antibody for AdipoR2

N-terminal intracellular domain

8 April 2015 Nature electric edition

Optimization of the compound based on tertiary structure analysis of Adiponectin receptor activation small molecule compound (AdipoRon) and AdipoR—Aiming to development of molecule target medicine for type 2 diabetes, lifestyle diseases and for healthy longevity medicine—

The further promotion of diabetes research

Semin cell research such as IPS cell

Regeneration or reconstruction of organ function lost by diabetes

Gene therapy

Promotion of translational researches from fundamental research as a frontier medical science to the clinical field
Aiming the definitive treatment of diabetes and its complications

Regenerative medicine using iPS cell (induced pluripotent stem cell)

2013.2.1
New roadmap for iPS cell research
Start Clinical study in retina, 2015
Preclinical study; 2015-2016
Pancreatic β cell; 2016-2017

2014.3.12
The first clinical application using iPS cell
Retina an ARMD
Dr. Masayo Takahashi, PhD, Riken

Promotion of the international cooperation
aiming at diabetes conquest

DEVELOPMENT AND PROVISION OF MEDICAL SERVICES AND INFRASTRUCTURE IMPROVEMENT FOR DIABETES WITH ENJOYABLE LIFE

Living with Diabetes 糖尿病と共に生きる
The Japan Diabetes Society’s action plan (DREAMS) makes a dream “advance from Control-Care to prevention & radical Cure of diabetes” come true.