Prevention of diabetes in the modern era of affluent society and economic constraints

KONSTANTINOS MAKRILAKIS, MD, MPH, PhD

ASSOCIATE PROFESSOR IN INTERNAL MEDICINE
NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS MEDICAL SCHOOL
IDF EUROPE BOARD MEMBER
Prevention of diabetes in the modern era of affluent society and economic constraints

KONSTANTINOS MAKRILAKIS, MD, MPH, PhD

ASSOCIATE PROFESSOR IN INTERNAL MEDICINE
NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS MEDICAL SCHOOL
**Primary:** folic acid administration for neural tube defects, immunizations, counseling for healthy lifestyle, chlorination-iodination of water, seat belts, helmets

**Secondary:** Pap smears, mammograms, fecal occult blood tests.

**Tertiary:** b-blockers after MI, diabetic general approach
DIABETES MELLITUS

• Various syndromes of abnormal metabolism of carbohydrates (sugars), lipids and proteins, characterized by hyperglycemia (high blood glucose)

• Relative or absolute disturbance in insulin secretion

• Varied peripheral resistance in the action of insulin
Blood vessel

Acinus

Islets of Langerhans containing Beta cells
**Anatomy of islet of Langerhans**  Schematic representation of the anatomic relationships in an islet of Langerhans. The insulin-producing β-cells (in blue) are in the center closest to the blood supply and are surrounded by the glucagon-producing alpha (A) cells (in orange). On the outside are the delta (D) cells (in yellow, which make somatostatin) and the PP cells (in green, which make pancreatic polypeptide).
CLASSIFICATION OF DM

• **Type 1** (Insulin-dependent, Juvenile) – 3-10%

• **Type 2** (Non-insulin dependent – at least initially, Adult onset) - 90%

• **Other specific types** (secondary DM)

• **Gestational DM**

American Diabetes Association 1997
CRITERIA FOR DIAGNOSING DM

1. Fasting plasma glucose $\geq 126$ mg/dl (7 mmol/L)
2. Plasma glucose 2 hrs after ingesting 75 g glucose (oGTT) $\geq 200$ mg/dl (11.1 mmol/L)
3. Random plasma glucose (independent of food intake) $\geq 200$ mg/dl (11.1 mmol/L), together with compatible symptoms of DM
4. $\text{HbA}_{1c} \geq 6.5\%$ (47.5 mmol/mol)
   (eAG: 140 mg/dl [7.8 mmol/L])

Confirmation with a 2\textsuperscript{nd} measurement
Pre-Diabetes

IFG
(Impaired Fasting Glucose)

IGT
(Impaired Glucose Tolerance)
Impaired glucose tolerance (IGT) – usual development

Initial diagnosis

Individuals with IGT

After 10 years follow-up

Normal

Diabetes

IGT
Suspicion for DM – Classical symptoms

- Polyuria, Nocturia
- Polydipsia
- Polyphagia
- Unexplained weight loss
- Genital organ infections (balanoposthitis, cystitis)
- Visual disturbances
- Neuropathic symptoms (pains, tingling of lower extremities)
TYPE 1 DM

- Destruction of pancreatic β-cells
- Two subtypes (depending on presence of pancreatic autoantibodies (ICA, anti-IA2, IAA, anti-GAD 65):
  - Autoimmune (90%)
  - Non-immune (10%)

- LADA (Latent Autoimmune Diabetes in Adults)
Natural History of Type 1 Diabetes

Genetic predisposition

Putative trigger

Cellular autoimmunity
Circulating autoantibodies (ICA, GAD65, ICA512A, IAA, ZnT8)

Time

β-Cell mass 100%

β-Cell injury

Loss of first-phase insulin response (IVGTT)

Abnormal glucose tolerance (OGTT)

β-Cell insufficiency

Clinical onset

Diabetes

Natural History of Type 2 DM Modification with Therapy

What should therapy do?

Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years)

North America and Caribbean
2015: 44.3 million
2040: 60.5 million

Europe
2015: 59.8 million
2040: 71.1 million

Middle East and North Africa
2015: 35.4 million
2040: 72.1 million

South and Central America
2015: 29.6 million
2040: 48.8 million

South East Asia
2015: 78.3 million
2040: 140.2 million

Western Pacific
2015: 153.2 million
2040: 214.8 million

World
2015: 415 million
2040: 642 million
Global Projections for the Diabetes Epidemic: 2003-2025 (millions)

World
2003 = 194 million
2025 = 333 million
Increase 62%

IDF Atlas 2003
Diabetes is a disease with serious complications

Microvascular complications
- Retinopathy
- Nephropathy
- Neuropathy

Macrovascular complications
- Strokes
- Coronary Heart Disease
- Peripheral Vascular Disease

World Health Organization, 2002; Fact Sheet N° 138
DIABETES MELLITUS

• Morbidity ↑
• Mortality ↑
• Tremendous financial burden

• Prevention of DM?
  – Prevention of its complications ?
The «Working Hypothesis»

Responsible genes + Environmental factors

Insulin Resistance

Normal Glucose Tolerance

IGT

↓ Secretion of insulin

Type 2 DM
Underlying causes of Type 2 Diabetes

- Obesity
- Insulin resistance
- Hyperinsulinaemia
- Impaired glucose tolerance
- β-cell defect
- Decreased insulin secretion
- Early diabetes
- Late diabetes
- β-cell failure


No Data  <10%  10%–14%  15%–19%  >20%

*BMI ≥30, or ~30 lb overweight for 5’4” person.
Obesity Trends

1990

Diabetes Trends

1990

2001

2001

BRFSS, 1990-2001
Obesity incidence in the next 25 years is going to double
Waist circumference is a surrogate marker of visceral fat

Lean et al, 1998

Women
>88 cm-increased risk

Men
>102 cm-increased risk
Vital Statistic – Waist Circumference
Obesity as CHD risk factor • The significance of visceral fat

Android
Obesity

Gynoid
Obesity

Sharma 2002
Obesity and Metabolic Risk
Abdominal vs. Peripheral Obesity

Large Insulin-Resistant Adipocytes

Small Insulin-Sensitive Adipocytes

Android Obesity

Gynoid Obesity

Sharma 2002
Obesity and Metabolic Risk
Abdominal vs. Peripheral Obesity

Adrenergic Receptors ↑

Android Obesity

Gynoid Obesity

Adrenergic Receptors ↓

Sharma 2002
Abdominal Obesity is associated with Increased Plasma Non-Esterified Fatty Acids

- Insulin-dependent Antilipolytic Action downarrow
- Catecholamine-dependent Lipolysis uparrow
- Plasma Free Fatty Acids uparrow

Sharma 2002
Obesity and Cardiovascular Risk

Dyslipidemia
- Total-C $\uparrow$
- LDL-C $\uparrow$
- Triglycerides $\uparrow$
- Apo-B $\uparrow$
- HDL-C $\downarrow$

Hypertension
- Left Ventricular Hypertrophy
- Congestive Heart Failure

Endothelial Dysfunction

Prothrombotic states
- Fibrinogen $\uparrow$
- PAI-1 $\uparrow$

Insulin Resistance
- Glucose Intolerance
- Hyperglycemia
- Type 2 Diabetes Mellitus

Renal Hyperfiltration
- Albuminuria

Inflammatory Reactions $\uparrow$
Economic crisis

• There is no doubt that being poor is not good for one’s health

• Being rich does not necessarily mean it is good for your health
Wealth-Associated Disparities in Death and Disability in the United States and England

Lena K. Makaroun, MD; Rebecca T. Brown, MD, MPH; L. Grisell Diaz-Ramirez, MS; Cyrus Ahalt, MPP; W. John Boscardin, PhD; Sean Lang-Brown, BS; Sei Lee, MD, MAS

**IMPORTANCE** Low income has been associated with poor health outcomes. Owing to retirement, wealth may be a better marker of financial resources among older adults.

**OBJECTIVE** To determine the association of wealth with mortality and disability among older adults in the United States and England.

**DESIGN, SETTING, AND PARTICIPANTS** The US Health and Retirement Study (HRS) and English Longitudinal Study of Aging (ELSA) are nationally representative cohorts of community-dwelling older adults. We examined 12,173 participants enrolled in HRS and 7,599 enrolled in ELSA in 2002. Analyses were stratified by age (54-64 years vs 66-76 years) because many safety-net programs commence around age 65 years. Participants were followed until 2012 for mortality and disability.
Figure 1. Cumulative Incidence of Death by Wealth Quintile
Figure 2. Cumulative Incidence of First ADL Difficulty by Wealth Quintile

ADL indicates activity of daily living; ELSA, the English Longitudinal Study of Aging.
Figure 1. Prevalence of obesity among adults aged 20 years and over, by poverty income ratio, sex, and race and ethnicity: United States 2005–2008

Significant trend.

NOTES: PIR is poverty income ratio. Persons of other race and ethnicity included in total.

Levine J.A. Poverty and Obesity in the U.S. Diabetes 2011;60:2667-8
Hamburgerology
Where the sacred ground is. BY JANE AND MICHAEL STERN

BEST BURGERS
Clockwise from above: eyeing a fully dressed SoCal patty from The Cottage, stopping for a Bobcat Bite in New Mexico, going for a triple at South Dakota's Hamburger Inn and dropping by for one with fried onions at the White Hut in Massachusetts.
Fat World
We’re Eating More Junk And Getting Less Exercise.
Obesity Is The Globe’s Newest Epidemic.
THE EVOLUTION OF MAN
Genes and environment in the development of obesity, type 2 DM and atherosclerosis

20,000 B.C.

- Palaeolithic sup. age
- Neolithic age
- 19th century
- 21st century

Homo sapiens sapiens Cro-Magnon

- Hunting-gathering subsistence
- High level of physical activity

- Processed foods
  - ↑ Animal fats and glucides
  - ↓ Dietary fibres

- Sedentary life

Thrifty genotype

Susceptibility genotype
Eat to Live!

Live to Eat!
High-Tech increases Body Weight

Cellular phones and remote controls deprive us from walking!

20 times daily x 20 m = 400 m

Walking distance lost/year
400x365 = 146,000 m

146 km = 25 h of walking

1 h of walking = 113-226 kcal

Energy saved = 2800-6000 kcal

⇒ 0.4-0.8 kg adipose tissue

Rössner, 2002
Markers of Inactivity related to Obesity Incidence

% of Mean of All Time Points

% Obese | Cars/household | TV viewing (hours/week)

Prentice AM, BMJ 1995;311:437-9
**RISK FACTORS FOR T2DM DEVELOPMENT**

- Family history of T2DM
- **Obesity** – Central fat distribution
- Low birth weight
- Dietary habits (diet high in saturated fat)
- History of Gestational DM
- Smoking
- **Pre-Diabetes** (IGT – IFG)
“The Working Hypothesis”

Genes + Environmental factors

Insulin Resistance → Normal Glucose Tolerance

Insulin Secretion

IGT → Type 2 DM
Possible ways of Preventing T2DM

- NGT
  - Insulin Resistance
    - Nutrition
    - Physical activity
    - Metformin
    - Glitazones
  - IGT
    - Acarbose
    - GLP-1
    - Amylin
    - Insulin
    - Sulphonylureas
    - Meglitinides

- Impaired Insulin secretion

Type 2 Diabetes Mellitus
Feasibility of Preventing Type 2 Diabetes

- A long period of glucose intolerance precedes the development of diabetes
- Screening tests can identify persons at high risk
- There are safe, potentially effective interventions that can address modifiable risk factors
# Prevention of Type 2 Diabetes: Completed Trials in Impaired Glucose Tolerance

<table>
<thead>
<tr>
<th>Trial</th>
<th>Journal/Year</th>
<th>Treatment</th>
<th>Results (risk reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Qing IGT and Diabetes Study(^1)</td>
<td><em>Diabetes Care</em> 1997</td>
<td>Diet +/- or exercise</td>
<td>31%-46%</td>
</tr>
<tr>
<td>Finnish Prevention Study (FPS)(^2)</td>
<td><em>N Engl J Med</em> 2001</td>
<td>Intensive lifestyle</td>
<td>58%</td>
</tr>
<tr>
<td>Diabetes Prevention Program (DPP)(^3)</td>
<td><em>N Engl J Med</em> 2002</td>
<td>Metformin</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lifestyle changes</td>
<td>58%</td>
</tr>
<tr>
<td>STOP-NIDDM(^4)</td>
<td><em>Lancet</em> 2002</td>
<td>Acarbose</td>
<td>25%</td>
</tr>
</tbody>
</table>

Finnish Diabetes Prevention Study

Cumulative Probability of Remaining Free of Diabetes

Study Year

Subjects at Risk
Total no. | 507 | 471 | 374 | 167 | 53 | 27
Cumulative no. with diabetes:
Intervention group | 5 | 15 | 22 | 24 | 27 | 27
Control group | 16 | 37 | 51 | 53 | 57 | 59

58%
Finnish Diabetes Prevention Study Follow-up

Figure 2: Diabetes by treatment group
Follow-up time is truncated at 8 years, since number of participants at risk beyond this point was low, but they are included in the calculation of hazard ratios.

Lindstrom J, et al. The Lancet 2006 (Nov 11); 368: 1673-79
Mean Weight Change

![Graph showing Mean Weight Change over Years from Randomization. The graph compares three conditions: Placebo, Metformin, and Intensive Lifestyle. The y-axis represents Weight Change (kg), ranging from -8 to 0. The x-axis represents Years from Randomization, ranging from 0 to 4. The Placebo condition shows a steady weight decrease, the Metformin condition shows a gradual weight decrease, and the Intensive Lifestyle condition shows a gradual weight increase.](image-url)
Incidence of Diabetes

- Placebo (n=1082)
- Metformin (n=1073, p<0.001 vs. Placebo)
- Lifestyle (n=1079, p<0.001 vs. Metformin, p<0.001 vs. Placebo)

Risk reduction:
- 31% by metformin
- 58% by lifestyle

Cumulative incidence (%) vs. Years from randomization.
MEDITERRANEAN DIET

MONTHLY
- Red meat
  4 servings

WEEKLY
- Sweets, 3 servings
- Eggs, 3 servings
- Potatoes, 3 servings
- Olives, pulses, nuts
  3 - 4 servings
- Poultry
  4 servings
- Fish
  5 - 6 servings

DAILY
- Dairy products
  2 servings
- Olive oil
  as the main added lipid
- Fruit
  3 servings
- Vegetables
  (including wild greens)
  6 servings
- Non-refined cereals and products
  (whole grain bread, whole grain pasta, brown rice, etc)
  8 servings

One serving equals approximately half of the portions as defined in the Greek market regulations (portions served in restaurants)

Also remember to:
- drink plenty of water
- avoid salt and replace it by herbs (e.g. oregano, basil, thyme, etc)

Source: Supreme Scientific Health Council, Hellenic Ministry of Health
General Guidelines for Physical Activity

• Physical activity does not necessarily mean “gym”
• Incorporation in daily life of simple routines is many times enough:
  – Using the stairs instead of the lift
  – Using public transportation means instead of own car
  – Getting off the bus 1 stop before destination
  – Do not use the car for short distances up to 1-2 kms
  – Park a few blocks away from home or work in order to walk
Walking the dog is a good exercise
Gym at work
Conclusions

• DM incidence is rising in our society in epidemic proportions
• Obesity is also rising, driving the epidemic
• Mixed effects of affluent society and poverty on obesity trends – DM trends
• Decrease of DM incidence should deal with both of these opposing issues
  – Self-restraint and moderation in eating patterns
  – Decrease of poverty in our society
• Education and Self management
THANK YOU