DIABETES MELLITUS:
WHAT IT IS AND WHAT CAN BE DONE ABOUT IT

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DIABETES MELLITUS:

WHAT IT IS

(CLINICALLY)
DEFINITION

Diabetes mellitus is a disease that is defined by increased blood glucose levels and associated with:

a) small blood vessel complications involving the eyes, kidneys and nerves;

b) large blood vessel complications involving the heart, brain and legs.
Possible Complications of Diabetes

Eyes
Vision problems

Heart
Atherosclerosis - plaque build-up in blood vessels can cause heart disease, peripheral vascular disease and reduced cardiac output

Gastrointestinal System
Digestive disorders

Kidney
Renal failure, Hypertension

Circulatory System
Circulation in lower limbs can be affected

Muscular System
Abnormal energy metabolism

Skin
Pruritus (itching)

Nervous System
Neuropathy (nerve damage)
DIABETIC EYE DISEASE

Leading cause of blindness in this country in people between the ages of 20 and 74 years
Normal Retina
Hemorrhage
Macular Edema
Hemorrhage & Macular Edema
Although only approximately 7%-8% of our population is known to have diabetes mellitus, almost half of the patients going onto dialysis have kidney failure secondary to diabetes.
The peritoneal cavity is filled with dialysate, using gravity.

At the end of the exchange, the dialysate is drained into the bag, again using gravity.
Figure 1. Survival estimates are plotted by renal diagnoses. PK = polycystic kidney disease; CGN = chronic glomerulonephritis; DM = diabetes mellitus; RVD = renal vascular disease; other = all other diagnoses.
Fig. 1. The prevalence of peripheral neuropathy in Type 1 (□) and Type 2 (○) diabetic patients by duration of diabetes.

Diabetologia 36:150-154, 1993
For millions with diabetes, this feeling is all too real.
Fig. 1. Relationship of impotence to age in diabetic and normal male subjects. The normal male data are derived from Kinsey et al. [13].

- Normal
- Diabetics
LARGE BLOOD VESSEL COMPLICATIONS

**Heart attacks** – twice as common in men and four times more common in women with diabetes; 75% of people with type 2 diabetes will die from a heart attack.

**Strokes** – twice as common in people with diabetes.

**Leg arteries** – 2½ times as common in people with diabetes, especially smokers (can lead to gangrene).
CLASSIFICATION OF DIABETES MELLITUS

Type 1 – 5% (Autoimmune)

Type 2 – 90% (Insulin resistance and decreased insulin secretion)

Other Types – 5%
  Specific genetic lesions
  Certain drugs (e.g., steroids)
  Diseases of the pancreas
  Certain endocrine diseases
INHERITANCE OF DIABETES

**Identical twins**
- Type 1 diabetes - \(~35\%\) concordance
- Type 2 diabetes - \(~95\%\) concordance

**First degree relatives (siblings, parents)**
- Type 1 diabetes - \(~10\%\)
- Type 2 Diabetes - \(~40\%\) (more if both parents have diabetes)
Prevalence of Diagnosed Diabetes by Race

- All Races: 6.5%
- Non-Hispanic Whites: 5.2%
- Non-Hispanic Blacks: 11.0%
- Mexican Americans: 10.4%

Prevalence of Diabetes at Age 45 to 74 Years

DIABETES MELLITUS:

WHAT IT IS
(METABOLICALLY)
DIETARY CONSTITUENTS


Fats (Triglycerides): C - FA
  |   C - FA
  |   C - FA

AA = amino acids; G = glucose; C = carbon; FA = fatty acids
### β- and α-Cells in the Pancreas of Normal Individuals

<table>
<thead>
<tr>
<th>β-Cells</th>
<th>α-Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Comprise about 70%–80% of the endocrine mass of the pancreas&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>- Comprise about 15% of the endocrine mass of the pancreas&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Located in the central portion of the islet&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>- Located in the periphery of the islet&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Produce insulin and amylin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>- Produce glucagon&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>- Insulin released in response to elevated blood glucose levels&lt;sup&gt;1&lt;/sup&gt;</td>
<td>- Glucagon released in response to low blood glucose levels&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Insulin Increases and Glucagon Falls in Response to Meals in Normal Subjects

N=11.
Adapted with permission from Woerle HJ et al. Am J Physiol Endocrinol Metab. 2003;284:E716–E725.
Deficient Insulin: Hypersecreted Glucagon

TYPE 2 DIABETES

- Defects in diabetes:
  - Deficient insulin release
  - Glucagon not suppressed (postprandially)
  - Hyperglycemia

Insulin Resistance and Insulin Secretion in Healthy Subjects

Hollenbeck and Reaven. J Clin Endocrinol Metab. 1987;64:1169-1173.
Insulin Resistance
With Normal $\beta$ Cells

‘Climbing the Curve’

Insulin level

Resistant

Insulin sensitivity

Sensitive

Normal curve
Pathogenesis of Type 2 Diabetes

‘Falling off the Curve’

- Resistant
- Insulin sensitivity
- Sensitive

Type 2 diabetes

Normal curve

The Relationship Between Insulin Secretion and Insulin Action During the Development of Type 2 Diabetes

N=277 Pima Indians; NGT=normal glucose tolerance; IGT=impaired glucose tolerance; T2DM=type 2 diabetes; EMBS=estimated metabolic body size.

Changes in β-cell function, measured as acute insulin response to glucose (AIR glucose) relative to changes in insulin sensitivity, measured by clamp technique at a low insulin concentration (M-low). Adapated with permission from Weyer C et al. J Clin Invest. 1999;104;787–794.
Insulin Resistance: Inherited and Acquired Influences

Inherited
- Rare Mutations
  - Insulin receptor
  - Glucose transporter
  - Signaling proteins
- Common Forms
  - Largely unidentified

Acquired
- Inactivity
- Overeating
- Aging
- Medications
- Hyperglycemia
- Elevated FFAs

INSULIN RESISTANCE
Development and Progression of Type 2 Diabetes*

NGT → Insulin → IGT/IFG → Type 2 Diabetes

Glucose

Postprandial glucose
Fasting glucose

Relative Activity

Insulin level
Beta-cell function

Insulin resistance — hepatic and peripheral

Years from Diabetes Diagnosis

*Conceptual representation.

NGT=normal glucose tolerance; IGT=impaired glucose tolerance; IFG=impaired fasting glucose.
DIABETES MELLITUS:

WHAT CAN BE DONE ABOUT IT
PREVENT THE DISEASE
Prevalence of Obesity in the United States

1991

2000

- No Data
- <10%
- 10%-14%
- 15%-19%
- ≥20%

Prevalence of Overweight* Among US Children and Adolescents

*≥95% of BMI for age.

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Prevalence of Overweight* Among US Children and Adolescents

*BMI for age ≥95th percentile.

Data from Ogden CL et al. JAMA. 2006;295:1549-1555.
Prevalence of Overweight and Obesity Among US Adults by Sex and Ethnicity

Men ≥20 years of age

Women ≥20 years of age

- Overweight (BMI ≥25-29 kg/m²)
- Obese (BMI ≥30 kg/m²)

Prevalence of Diagnosed and Undiagnosed Diabetes and IFG in US Population ≥20 Years by Sex and Racial/Ethnic Group

DPP: Diabetes Prevention Program

Incidence of Diabetes

Overall risk reduction:
58% Lifestyle
31% Metformin

*P<0.001 vs placebo

Years from randomization
Cumulative incidence (%)

Placebo
Metformin
Lifestyle

11%/yr
7.8%/yr
4.8%/yr

PREVENT THE COMPLICATIONS
DCCT
Relative risk of progression of diabetic complications by mean HbA$_{1c}$

*Based on DCCT data

FIGURE 1. Body weights and fasting glucose concentrations of the 12 patients who completed the weight loss program, before (B) and after (A) the weight loss period. The data for each patient (means ± SEM) are connected by lines, and the heights of the bars represent the means of the groups.

J Am Geriatr Soc 33:95, 1985
β-Cell Function Declines After Diagnosis, Whereas Insulin Sensitivity Remains Relatively Stable

HOMA=Homeostasis Model Assessment; HOMA % B=β-cell function; HOMA % S=Insulin sensitivity.

N=432. 10-year follow-up of the Belfast Diet Study. Data from Group 2 shown: newly diagnosed T2DM subjects who required additional treatment (due to secondary failure to diet therapy) at 5–7 years.

TREATMENTS

Diet (weight loss)
Exercise
Oral drugs
  sulfonylureas  thiazolidinediones
  glinides  alpha-glucosidase inhibitors
  biguanides  DPP-IV inhibitors
Injectables
  insulin (also inhaled)
  GLP-1 analogues
IT IS ESTIMATED THAT ONE IN THREE CHILDREN BORN IN THE UNITED STATES TODAY WILL DEVELOP DIABETES IN THEIR LIFETIME !!!
African-Americans – 1 in 2

Latinos - ???? (probably similar)
FINAL MESSAGE

SO – GOOD LUCK IN DOING WHAT YOU NOW KNOW WHAT YOU HAVE TO DO TO PREVENT YOURSELF FROM GETTING DIABETES!

SPREAD THE WORD!
THANK YOU