

Type 1 and Type 2 Diabetes

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Definition-Diabetes

- Group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.
- Deficient action of insulin on target tissues results in abnormalities in carbohydrate, fat and protein metabolism.

Classification of DM

- **TYPE 1**: immune mediated; autoimmune destruction of the insulin producing beta cells in the pancreatic islets 5-10% of DM, can occur at any age.
- **TYPE 2** : progressive insulin secretory defect on the background of insulin resistance. Typically obese or increased intra-abdominal fat. 90-95% of DM

Classification of DM

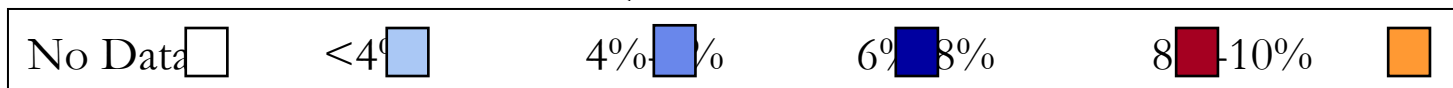
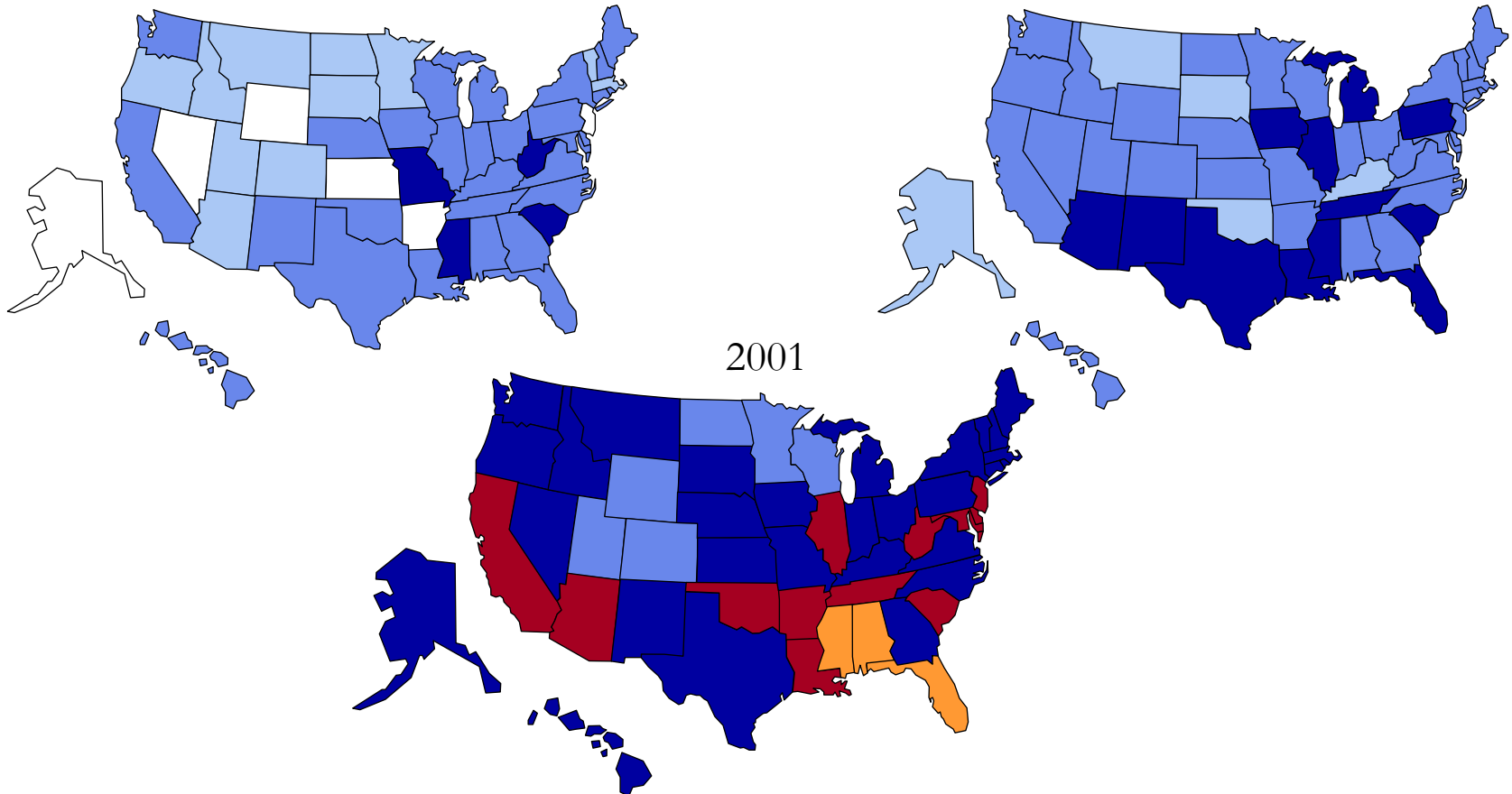
- Other specific forms of DM: genetic defects in B cell or insulin action, diseases of exocrine pancreas – cystic fibrosis, drug induced-AIDS, interferon, transplants
- **Gestational DM:** diabetes diagnosed during pregnancy

Diabetes Trends* Among Adults in the U.S., (Includes Gestational Diabetes)

BRFSS, 1990, 1995 and 2001

1990

1995



>10%

Source: Mokdad et al., *Diabetes Care* 2000;23:1278-83; *J Am Med Assoc* 2001;286:10.

Criteria for the Diagnosis of Diabetes

1. Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl
2. **Fasting plasma glucose ≥ 126 mg/dl (7mmol/l)**
3. 2-hr plasma glucose ≥ 200 mg/dl during OGTT. (75 gm glucose)

In absence of unequivocal hyperglycemia, confirm on a separate day

Report of the Expert committee on the Diagnosis and Classification of Diabetes Mellitus, Diabetes Care 1997

Diagnosis of DM

- Incidence of retinopathy increases above FBG 126.
- **FPG preferred test** in children and non pregnant adults
- OGTT discouraged due to inconvenience, cost , less reproducible
- A1c for diagnosis not recommended at this time

HbA1c

- Substrate dependent non-enzymatic reaction, glucose irreversibly binds to Hb
- A1c : glucose binds amino terminus of valine on beta chain
- Non Glycemic Factors:
hemoglobinopathies anemia,
pregnancy

International A1c-Derived Average Glucose Study

- 507 patients , 268 T1DM, 159 T2DM, 80 nondiabetic
- AG calculated from combining 2 days continuous sensing X4, 7 point daily SMBG 3 days per week, 2700 glucose values
- Compared to A1c monthly over 3 months

HbA1c and AVG new standardization

AVG mg/dl = 28.7 HbA1c - 46.7

HbA1c	AVG mg/dl
5%	97
6%	126
7%	154
8%	183
9%	212

Diabetes Care June 2008,
Nathan et al

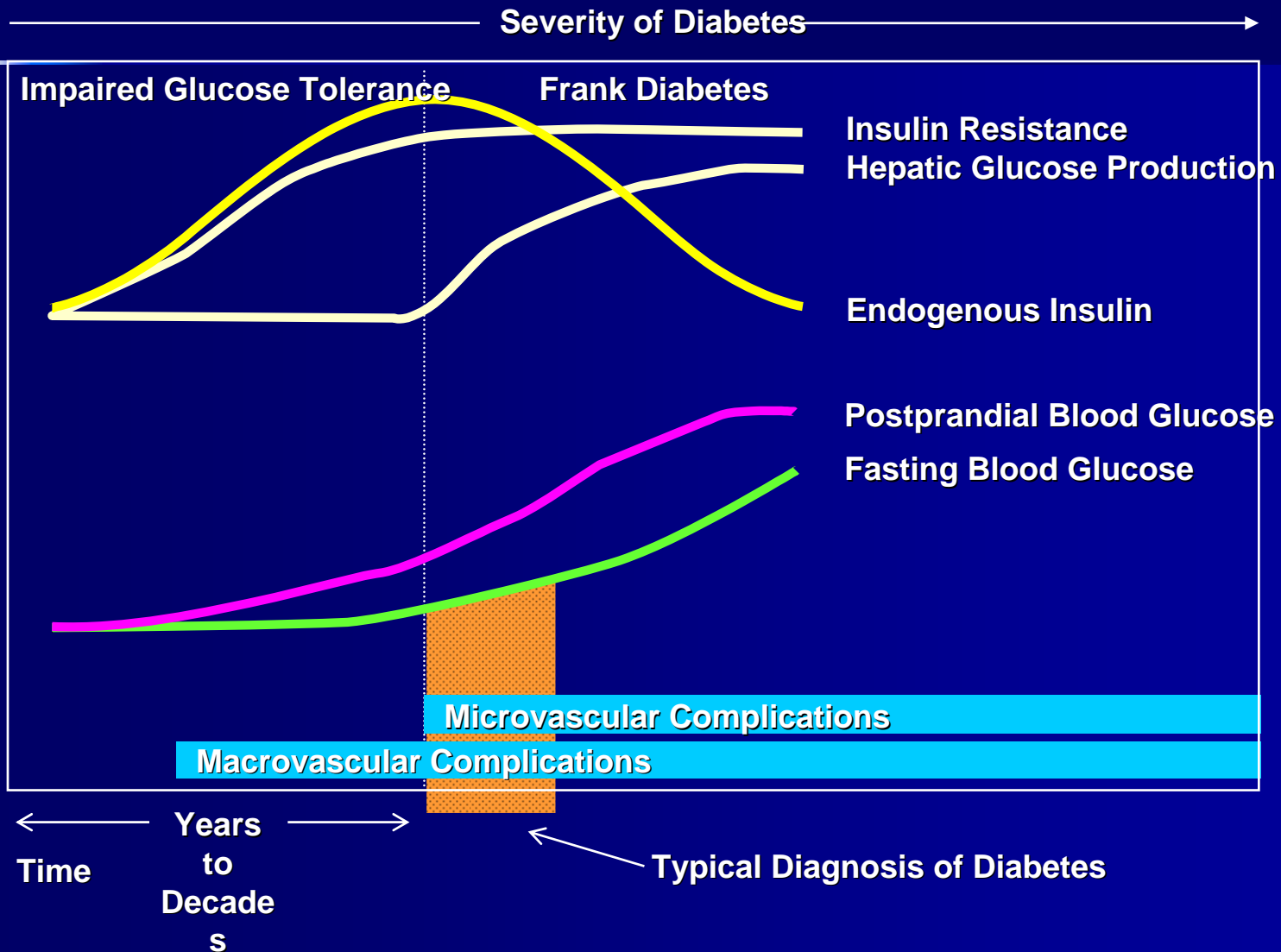
Prediabetes

- IFG- impaired fasting glucose:
100-125 mg/dl
- IGT- impaired glucose tolerance:
2 hr PG 140-199 mg/dl
- DPP 80% with IGT also had IFG
- IGT associated with CV disease risk factors and events
- 25.9% >age 20, 57 million

Insulin Resistance Syndrome

- metabolic syndrome: any 3 of the following:
- abdominal obesity, Waist circ. >40 in. male, >36 in. female
- HTN,
- Low HDL, elevated triglyceride
- abnormal glucose tolerance

Natural History of Type 2



Type 2 Diabetes

- Superimposition of insulin resistance on beta cell that cannot compensate leads to deterioration in glucose tolerance
- More than 80% are obese, obesity causes insulin resistance
- Increased incidence in African American, Hispanic, Native American, Asian American

Insulin Resistance

- **Muscle:** reduced glucose uptake
- **Liver:** reduced glucose storage, lack of suppression of glucose formation
- **Adipose tissue:** reduced inhibition of lipolysis

Acanthosis nigricans



Impaired Insulin Secretion

- T2DM can occur in lean individuals with no insulin resistance
- Most obese individuals with insulin resistance do not develop DM, rather increase insulin secretion
- **B-cell dysfunction**, like insulin resistance, occurs in genetically predisposed individuals with normal glucose tolerance

Matching Hyperglycemia to Pathophysiology



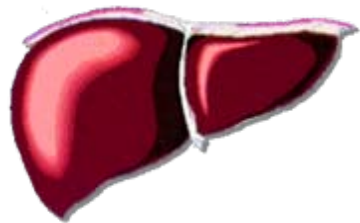
Glucose Influx



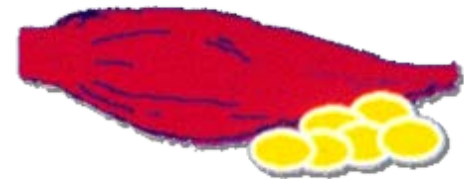
↓ Insulin Secretion

↑ Hepatic Glucose Output

Hyperglycemia



↓ Peripheral Glucose Uptake



T2DM

- Frequently undiagnosed for years
- Hyperglycemia develops gradually
- Insulin levels, C peptide normal or high
- Strong genetic pre-disposition

Prevalence of T2DM

- Prevalence in 2007: 9.2% non Hispanic white, 14.7% non Hispanic Black, 35% certain Native Americans
- Age >20 10.7% or 23.5 million
- US lifetime risk if born 2000: 33% for males, 39% for females

Screening for T2DM Adults

- Overweight: BMI >25, additional risk factors:
- Inactive, relative DM, ethnic, hx GDM, HTN, HDL <35 or trig >250, PCOS, Prediabetes, vascular disease
- Age > 45
- Screen FBG at 3 year intervals

Prevention of T2DM

- With IGT , IFG counseling on weight loss, increasing physical activity
- Intensive lifestyle modification 58% reduction after 3 years
- Insufficient evidence for drug therapy, studies with metformin, acarbose, orlistat, rosiglitazone

Testing for T2DM in children

- Test FBG, if weight $>120\%$ of ideal for height or BMI $>85^{\text{th}}$ percentile plus any 2 :
- FH T2DM, race/ethnicity, signs of insulin resistance, maternal Hx GDM
- Begin at age 10 or at onset of puberty, repeat at 2 year intervals

Case 1

- 38 YO female G3P3, Gestational diabetes with 2nd and 3rd pregnancies- 1 hr value 253 at 11 weeks, treated with insulin
- 6 mo post partum- FBG 150, placed on metformin, FBG:100-132, PC: 95-225
- PMH: HTN 4 years
- FH: no DM

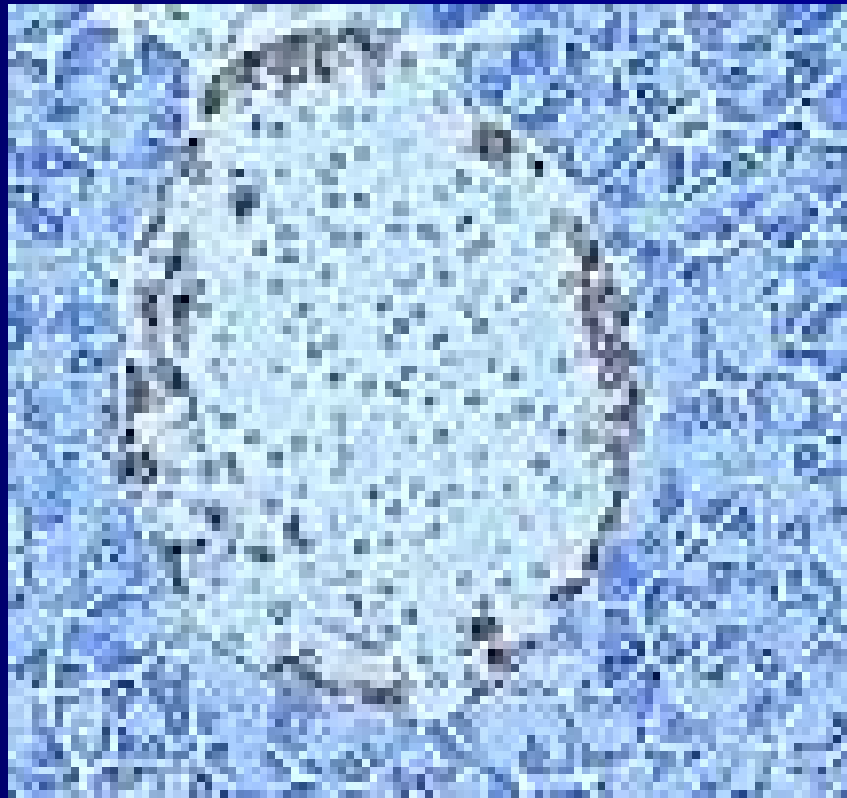
Case 1 cont.

- **PE:** 67", 138 lbs, BP 148/96 BG 117
- **LAB:** A1c 7.2%, Chol 173, Trig 159, HDL 36, LDL 105; C-peptide 2.4, GAD 65 <1.0
- **CLINICAL COURSE:** responded to oral agents, A1c 6.6-7.2%, after 4-5 years basal insulin added

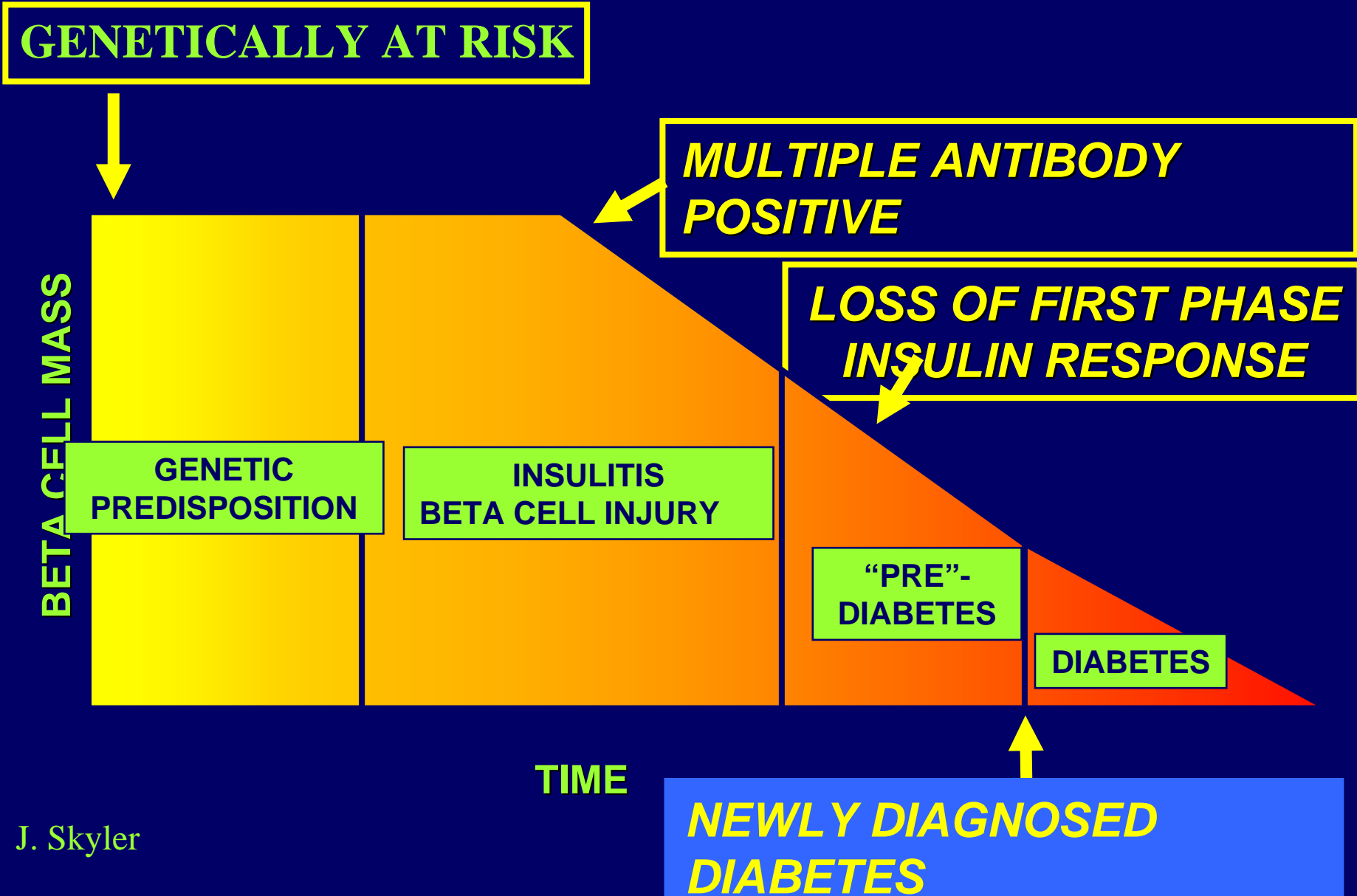
Summary

- Previous gestational DM
- Gradual onset of hyperglycemia
- Did not have central obesity, or FH
- Did have HTN, Low HDL, elevated Trig
- C-peptide elevated, GAD neg
- Consistent with T2DM

Beta Cells in the Islet



Stages in Development of Type 1 Diabetes



T1DM Susceptibility Gene

- IDDM 1
- HLA region on 6P
- MHC class 2 molecules expressed on cell surface of antigen presenting cells
- >90% HLA DR3-DQ2, DR4-DQ8
- 5% with this genotype develop T1DM

Autoantibodies in T1DM

- Sequenced **autoantigens** with recombinant autoantibody assays
- Antibodies themselves do not cause the Beta cell destruction
- **IAA**- insulin autoantibodies, often 1st to appear, high in children before age 5, usually negative in diabetes after age 12

Autoantibodies

- **GAD 65**- glutamic acid decarboxylase- present in islets, CNS, testes. Antibodies found in 70% of patients with T1DM at time of diagnosis. Most common in adults with onset of T1 DM
- **IA-2**- insulinoma assoc. protein; tyrosine phosphatases, last to appear, most disease specific

T1DM

- Rate of **B cell destruction variable**
- Rapid- mainly infants and children
- Slow- mainly adults
- In later stage **low or undetectable C-peptide**: connecting peptide of the pro-insulin molecule

T1DM association

- Graves Hyperthyroidism,
- Hashimotos Hypothyroidism : screen antibodies at Dx, TSH q 1-2 years
- Celiac Disease
- Addisons Disease,
- Vitiligo,
- Pernicious anemia

Risk of Type 1 DM

- 6% in offspring
- 5% in siblings
- 50% in identical twins
- 0.4% if no family history

Prevention of T1DM

- Sufficient data exist to warrant intervention studies for prevention T1DM
- Only in context of defined clinical studies , IRB oversight
- Screening of high risk if can be referred to center participating in studies

Diabetic Ketoacidosis

- Mostly in T1DM but can occur in T2DM
- **Cause:** reduction in effective action of insulin coupled with elevation of counter- regulatory hormones- glucagon, catecholamines, cortisol
- **Resultant:** increased glucose production, decreased utilization, release of free fatty acids- oxidation to ketone bodies

DKA

- **Precipitating factors:** infection, MI, stroke, new onset T1DM, discontinuation of insulin
- **Presentation:** polyuria, polydipsia, nausea, vomiting, dehydration, abdominal pain, impaired mental status
- **Laboratory:** glucose > 250, metabolic acidosis, serum and urine ketones elevated

Case 2

- 35 YO Caucasian male- 74", 199 lbs
- DM onset 2002, GAD 6.3 (<1.5)
- Treatment: initially glimepiride, insulin in 2004, glargine, prandial insulin
Currently insulin pump therapy .
Exercise-cycling
- BG averages on meter download: 111-133, A1c 6.6%

Summary

- Normal BMI
- Positive antibodies
- Gradual progression to insulin
- No insulin resistance
- Adult onset T1DM

Gestational DM

- 7% of pregnancies in US
- High risk: test as soon as possible
- Average risk: test 24-28 weeks
- Screening glucose 1hr after 50-g oral glucose: \geq 140 identifies 80%
- **100-g OGTT: 2 or more values above**
- \geq 95 mg/dl fasting
- \geq 180 mg/dl at 1 hr
- \geq 155 mg/dl at 2 hr
- \geq 140 mg/dl at 3 hr

Gestational Diabetes

- 6 -12 weeks post partum screen for DM
- 5 year incidence for T2DM, 4.7-50%
- 12% in those with normal pp OGTT vs 84% with IGT

Genetic Defects of Beta Cell- MODY

- Autosomal Dominant monogenic defects in beta cell function
- Impaired insulin secretion, minimal or no defect in insulin action
- Onset age < 25
- Most common HNF-1 chromosome 12
- Glucokinase gene chromosome 7, glucose to glucose 6 PO4 – insulin secretion

Conclusions

- Reviewed epidemiology and criteria for Dx Pre-diabetes, Diabetes, Gest DM
- Classification: discussed clinical and laboratory features that suggest T1DM and T2DM. Yet: age, body weight, clinical presentation not necessarily helpful