Diabetes: Prevention and Treatment

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Outline

- Statistics
- Screening
- Diagnosis
- Review of major studies
- Management
- Medications
- Summary
Diabetes Types

- DM1-Autoimmune, Insulin dependent, honeymoon
- DM2-Insulin resistance, not autoimmune
- MODY-appears like DM1, DM2, strong family history
- Ketosis prone Type 2-usually older, African American, can be antibody positive
Diabetes Statistics

- There are 24 million Americans with diabetes.
- Every year 1.3 million new people are diagnosed with diabetes.
- There has been a rapid surge of new patients with DM2 between the ages of 30-39 and in teenagers and children.
- Worldwide rates of diabetes growing as well likely this is reflection of the obesity epidemic and increasing sedentary lifestyle.
Screening for Diabetes

- Age ≥45 years
- Overweight (body mass index ≥25 kg/m²)
- Family history diabetes mellitus in a first-degree relative
- Habitual physical inactivity
- Belonging to a high-risk ethnic or racial group (African-American, Hispanic, Native American, Asian-American, and Pacific Islanders)
- History of delivering a baby weighing >4.1 kg (9 lb) or of gestational diabetes mellitus
- Hypertension (blood pressure ≥140/90 mmHg)
- Dyslipidemia defined as a serum high-density lipoprotein cholesterol concentration ≤35 mg/dL (0.9 mmol/L) and/or a serum triglyceride concentration ≥250 mg/dL (2.8 mmol/L)
- Previously identified A1C ≥5.7 percent, impaired glucose tolerance or impaired fasting glucose
- Polycystic ovary syndrome
- History of vascular disease
Diagnosis of DM2

- HgA1c ≥ 6.5%

OR

- Fasting glucose ≥ 126 (Need 2 separate tests)

OR

- 2 hr glucose ≥ 200 during OGTT (75 gm glucose load)

OR

- Random glucose ≥ 200 with symptoms of increased urination, increased thirst and unexplained weight loss.
Pre-Diabetes

* Defined as impaired fasting glucose or impaired glucose tolerance.

Diagnostic Criteria:

* FPG 100-125

OR

* OGTT 140-199

* A1c data not as sensitive for this group as compared to fasting glucose value or results from glucose tolerance test.

Lorenzo, C et al.; Diabetes Care 2010
Pre-Diabetes

- Blood sugars are higher than normal but not at the level to diagnose diabetes.
- These patients have an increased risk of developing diabetes within 10 years. Also at risk for cardiovascular disease.

Diabetes Prevention Program:

- Improved weight management, diet and exercise can prevent or delay diabetes. (58% reduction from placebo)
- Metformin can reduce the risk of developing diabetes. (32% reduction from placebo)
Obesity Facts

* More than 1/3 U.S. adults (35.7%) are obese.

* Obesity-related conditions include heart disease, stroke, type 2 diabetes and certain types of cancer, some of the leading causes of preventable death.

* In 2008, medical costs = $147 billion

* Risk partially determined by ethnicity
  - Non-Hispanic blacks (49.5%)
  - Mexican Americans (40.4%),
  - All Hispanics (39.1%) and
  - Non-Hispanic whites (34.3%)*

* Men
  - Higher income = increased obesity (non-Hispanic black and Mexican-American)
  - Higher/lower education does not have a relationship with obesity

* Women
  - College degree = less obesity
  - Higher income = less obesity

* Obesity is increasing for everyone.

*JAMA. 2012;307(5):491-497
Diabetes Control and Complications Trial (DCCT)

- Landmark study for DM1 (Standard glucose control vs Intensive glucose control)
- 1440 volunteers randomly assigned
- Intensive group- (4 insulin shots, glucose checks) vs. routine care (less monitoring & less injections)
- Microvascular complications
  - Retinopathy 76%
  - Nephropathy 50%
  - Neuropathy 60%

Epidemiology of Diabetes Intervention and Complications Study (EDIC)

- Continuation of DCCT
- Mean follow up of 17 years after DCCT
- 90% of volunteers continued
- CV disease event was decreased by 42%
- Nonfatal MI, Stoke, Death from CV disease decreased by 57%
- Intensive therapy group (6.5 years) = sustained benefit

UKPDS (United Kingdom Prospective Diabetes Study)

- Investigated whether intensive glucose control would decrease complications in DM2 (20 year study)
- Mixture of therapies used: insulin vs. different oral meds
- 5100 patients with newly diagnosed DM2- 10 years. Goal fasting glucose was 108 mg/dL
- Results showed significant reduction in microvascular complications especially retinopathy (25%)
- MI reduction was not statistically significant.
- 10 year follow up: substantial reductions in CVD (metabolic memory or legacy effect like EDIC)

Action to Control CV Risk in DM (ACCORD)

- Evaluated the effect of intensive glucose control on CV events in patients with DM2 with established CV disease/risk factors. (very strict criteria)
- Study terminated after 3.5 years because of excessive deaths in the intensive treated group.
- Provided first evidence that intensive glucose control could be harmful.
- However, need to realize that the study included pts with higher baseline HgA1c levels, longer duration of DM (10 years), increased rates of hypoglycemia, and advanced CVD = increased risk of mortality.
Action in Diabetes and Vascular Disease (ADVANCE)

- Examined if intensive glucose control would provide any additional benefit compared with standard care.

- International study, recruited over 11k high risk pts with T2DM (HgA1c 7.2%). Follow up was over a 5 yr period.

- Results showed significant reduction in microvascular events mostly nephropathy and microalbuminuria.

- No significant reduction in macrovascular events.

- No increased risk of mortality as compared to ACCORD.

Management of DM2

* Lifestyle modifications (diet and exercise) are essential for all patients with diabetes.
  * Losing weight can have major beneficial effects (
  * Expected to reduce HgA1c with monotherapy 1-2%

* Diabetes education is also essential.

* Achieving HgA1c of ≤ 7% (ADA) or ≤ 6.5% (AACE).

* Using complimentary medications to improve glycemic control.

* Minimize hypoglycemia and weight gain.
Monitoring

- Glucose monitoring:
  - HgA1c
    - If meeting treatment goals (every 6 months)
    - If not meeting goals or change in meds (every 3 months)
- Yearly eye exams
- Foot exam annually
- Fasting lipid panel yearly
- Microalbumin assessment yearly
- BP goal ≤ 140/80 (recently changed)
- LDL <100; HDL >50; TG <150
- ASA in men >50 yo, women >60 yo
- CAD screening, assess risks and stratify
The revised recommendations include raising the treatment goal for high blood pressure from < 130 mm Hg to < 140 mm Hg, based on several new meta-analyses showing there is little additional benefit to achieving the lower targets. Clinical trials have demonstrated health benefits to achieving a goal of <140 mm Hg, such as reducing cardiovascular events, stroke or nephropathy (kidney disease), but limited benefit to more intensive blood pressure treatment, with no significant reduction in mortality or non-fatal heart attacks. There is a small but statistically significant benefit in terms of reducing risk of stroke, but at the expense of a need for more medications and higher rates of side effects.
Metformin

- Biguanide that improves the effectiveness of insulin by suppressing excess hepatic glucose production in both the fasting and postprandial states.
- Expected to decrease HgA1c 1-2% as monotherapy
- Side effects: GI upset (nausea, diarrhea), lactic acidosis (rare).
- Max dose is 2500 mg but no drug effect seen over 2000 mg/day.
- Contraindicated:
  - Impaired renal function: Creatinine in Men ≥ 1.5 mg/dL, Women ≥ 1.4 mg/dL or creatinine clearance <60 mL/min.
  - Those at increased risk of lactic acidosis: CHF, elderly with decreased Creatinine clearance, active liver disease, chronic alcohol use, sepsis
  - IV contrast
Secretagogues: Sulfonylureas & Meglitinides

- **Sulfonylureas** (Glipizide, Glyburide)
  - Stimulate the delayed, second phase of insulin secretion after meal ingestion
  - Side effects: Hypoglycemia, weight gain
  - Expected reduction in HgA1c 1-2%
  - Renal impairment decreases drug clearance leading to increased side effects. Contraindicated in ESRD.

- (Repaglinide [Prandin], Nateglinide [Starlix])
  - Increase earlier insulin secretion and decrease risk of late postprandial hypoglycemia.
  - Must administer before each meal.
  - Expected reduction in HgA1c 0.5-1.5%
  - Side effects: Hypoglycemia, weight gain
  - Use cautiously in patients with hepatic impairment.
Thiazolidinediones (TZD)

- Pioglitazone (Actos); Rosiglitazone (Avandia)

- Insulin sensitizing agent which increases the insulin sensitivity of skeletal muscle, adipose tissue, and to a lesser extent liver resulting in increased stimulated glucose uptake and metabolism. It is also effective at suppressing hepatic glucose production.

- Expected HgA1c reduction 0.5-1.4%

- Side effects: Water retention

- Contraindications: CHF, liver disease

- Black box warning for Avandia—increase risk of CV event
“Recently, French and then German regulators have withdrawn approval for Actos therapy in type 2 diabetes owing to a small but significantly increased risk of urinary bladder cancer noted in 1 study in patients taking the drug for longer than 5 years. Japanese regulators plan no action against Actos at present. Suggestions of such a link to bladder cancer have appeared in various data sets elsewhere, including the United States. These findings have shown small and not significant increases and so the matter has been under study by the US FDA, which has been aware of the issue since last summer. AACE supports the present investigation of the data by the US FDA and awaits their conclusions and recommendations. Until that time, we recommend that no change in diabetic medications be undertaken at present without a thorough understanding of the risks and benefits of any change in light of the individual clinical situation at hand. Discussions between physicians and patients should be the basis for any and all therapeutic decisions, including those surrounding the continued use of Actos.”
**Alpha Glucosidase Inhibitors**

- Acarbose & Miglitol

- Inhibit the conversion of oligosaccharides into monosaccharides at the intestinal brush border which decreases the rise in plasma glucose after eating.

- Mainly used to treat postprandial hyperglycemia.

- Expected HgA1c reduction is 0.5-0.8%

- Side effects: Abdominal discomfort, Flatulence, diarrhea
Incretins:
Dipeptidyl-Peptidase-4 (DPP-4) Inhibitors

- Sitagliptin (Januvia), Saxagliptin (Onglyza)
- Decreases the metabolism of incretin hormones (GLP-1 and GIP) by inhibiting DDP-4 enzyme.
- Increased levels of GLP-1, GIP inhibits glucagon release, increases insulin secretion and delays gastric emptying all which lead to overall decrease in blood glucose levels.
- Expected HgA1c reduction is 0.5-0.8%
- Side effects: Nausea, diarrhea, pancreatitis, cancer risk
- Dosing adjustment for renal impairment based on creatinine clearance
Incretins: GLP-1 Analogues

- Exenatide (Byetta) or Liraglutide (Victoza)
- Similar action to DPP-4 Inhibitors, in that they increase GLP-1 levels which increases insulin secretion and decreases glucagon release.
- Expected HgA1c reduction 0.5-1%
- Side effects: Nausea, pancreatitis
Pramlintide

- Synthetic analogue of amylin
- Decreases glucagon release, delays gastric emptying, and promotes satiety.
- Major effects are to decrease postprandial hyperglycemia and promote weight loss.
- Given subQ with each meal in patients taking pre-meal insulin.
- Expected HgA1c reduction 0.5-1%
- Side effects: Nausea, hypoglycemia
**Insulin Types**

- **Rapid-acting insulin**, such as insulin lispro (Eli Lilly), insulin aspart (Novo Nordisk), or insulin glulisine (sanofi-aventis), begins to work about 5 minutes after injection, peaks in about 1 hour, and continues to work for 2 to 4 hours.

- **Regular or Short-acting insulin** (human) usually reaches the bloodstream within 30 minutes after injection, peaks anywhere from 2 to 3 hours after injection, and is effective for approximately 3 to 6 hours.

- **Intermediate-acting insulin** (human) generally reaches the bloodstream about 2 to 4 hours after injection, peaks 4 to 12 hours later, and is effective for about 12 to 18 hours.

- **Long-acting insulin** (ultralente) reaches the bloodstream 6 to 10 hours after injection and is usually effective for 20 to 24 hours. There are also two long-acting insulin analogues: glargine and detemir. They both tend to lower glucose levels fairly evenly over a 24-hour period with less of a peak of action than ultralente.

Insulin

- 3 pillars: Basal, Bolus, Correction
- Best to have a 50:50 basal: bolus split
- Basal: Fasting blood glucose
- Bolus: Pre-prandial blood glucose
- Correction dose: Correct while fasting
Insulin Dependent Possibilities

- U500 insulin
- Insulin pumps
- Subcutaneous insulin delivery systems (VGO)
Healthy eating, weight control, increased physical activity

Metformin
- high
- low risk
- neutral/loss
- GI/lactic acidosis
- low

If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonlurea
  - high
  - moderate risk
  - gain
  - hypoglycemia
  - low

- Metformin + Thiazolidinedione
  - high
  - low risk
  - gain
  - edema, HF, Fx’s
  - high

- Metformin + DPP-4 Inhibitor
  - intermediate
  - low risk
  - neutral
  - rare
  - high

- Metformin + GLP-1 receptor agonist
  - high
  - low risk
  - GI
  - hypoglycemia
  - variable

If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonlurea + TZD
- Metformin + Thiazolidinedione + DPP-4-i
- Metformin + DPP-4 Inhibitor + GLP-1-RA
- Metformin + GLP-1 receptor agonist + Insulin
- Metformin + Insulin (usually basal) + DPP-4-i

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:

- Insulin (multiple daily doses)
Summary

- Obesity is everyone’s problem
- Diabetes can be prevented
- Early, effective treatment of diabetes is key to reduction of CVD (legacy effect, metabolic memory)
- Effective treatment = decreased microvascular complications
- Treatment is individualized but options exist
References


* AACE Consensus statement 2009, [www.aace.org](http://www.aace.org)

* ADA. Executive Summary: Standards of Medical Care in Diabetes— 2010. *Diabetes Care* 2010; 33: S4-S10.

* JAMA. 2012;307(5):491-497

* [www.diabetes.org](http://www.diabetes.org) ---ADA website

* [http://www.cdc.gov/obesity/data/adult.html](http://www.cdc.gov/obesity/data/adult.html)

* Lorenzo, C et al.; Diabetes Care 2010


References


