

A Learning Manual for Physicians, Residents and Students

Recent Findings in the Diagnosis and Treatment of Type 2 Diabetes Mellitus

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TYPE II DIABETES MELLITUS

OBJECTIVES

1. The learner will be able to define the criteria for diagnosis of diabetes mellitus.
2. The learner will be able to define the complications of diabetes and the impact of treatment on the reduction of mortality and morbidity.
3. The learner will understand the usual management of diabetes, including education, self-monitoring, pharmacologic therapy and referral to specialists.

ABSTRACT

Type 2 diabetes mellitus affects almost 8% of the adult population. The criteria for diagnosis of diabetes are symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl or a fasting glucose of ≥ 126 mg/dl. Diabetes long term complications include retinopathy, nephropathy, neuropathy and cardiovascular disease. Studies have shown that intensive therapy reduces long term complications. The metabolic goal is a glycosolated hemoglobin value of $\leq 7\%$, plus a blood pressure $\leq 130/80$ and an LDL-C ≤ 100 . Diet and other lifestyle changes such as increased exercise and tobacco cessation, if indicated, are fundamental. There are five classes of oral hypoglycemic agents, with different mechanisms of action, each with advantages and disadvantages. Multiple options of oral combination therapy exist. Insulin therapy is usually not first line, but about 50% need it eventually, and it is very effective either as monotherapy or as part of combination therapy. Primary prevention of diabetes is currently being studied with promising results.

Monograph

Type II Diabetes Mellitus

BACKGROUND

Diabetes mellitus currently affects 17 million people in the United States, with the vast majority, 8% of the adult population, being Type 2 diabetes. It has become epidemic in the past several decades due to the advancing age of the population, increased prevalence of obesity and decreased physical activity. Diabetes causes considerable morbidity and mortality. The major complications are related to the micro- and macrovascular complication of the disease. The major macrovascular complication is atherosclerosis with an increased risk of a cerebrovascular accident and/or a myocardial infarction. The major microvascular complications are retinopathy, nephropathy, and neuropathy. Type 2 diabetes contributes to more cases of adult onset loss of vision, renal failure and amputation than any other disease. Patients with type 2 diabetes have two to four times the risk of cardiovascular disease and 70% die of cardiovascular disease.

DIAGNOSES

The criteria for the diagnosis of diabetes mellitus may be made when fasting plasma glucose is ≥ 126 mg/dl or when the patient has classical symptoms of diabetes and a casual plasma glucose of ≥ 200 mg/dl. Casual is defined as any time of day without regard to time since the last meal. Fasting is defined as no caloric intake for at least 8 hours. Classical symptoms of diabetes include polyuria, polydipsia and unexplained weight loss. The third criterion is a 2-hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test. These criteria should be confirmed by repeat testing on a different day. The fasting plasma glucose is greatly preferred because of ease of administering, convenience, acceptability to patients and lower cost. The oral glucose tolerance test is not recommended for routine clinical use.

The criteria for testing for diabetes in asymptomatic adult individuals vary by different guidelines from different organizations or task forces. The American Diabetes Association recommends that testing be considered in all individuals at 45 years and above and, if normal, it should be repeated at 3-year intervals. Testing should be considered at a younger age or be carried out more frequently in high risk individuals who:

- Are obese ($\geq 120\%$ desirable body weight or a BMI ≥ 27 kg/m²)
- Have a first degree relative with diabetes
- Have delivered a baby weighing > 9 lbs or have been diagnosed with gestational mellitus
- Are members of a high risk ethnic population
- Are hypertensive ($\geq 140/90$ mmHg)
- Have HDL cholesterol level < 35 mg/dl and/or a triglyceride level of ≥ 250 mg/dl
- On a previous testing, had impaired glucose tolerance or impaired fasting glucose
- Have other clinical conditions associated with insulin resistance (e.g., PCOS or acanthosis nigricans)

DIABETES CONTROL AND COMPLICATIONS

The importance of blood glucose control in preventing microvascular complications of diabetes mellitus, such as retinopathy and nephropathy, is now recognized. The Diabetes Control and Complication Trial (DCCT) proved that intensive treatment reduced the risks of retinopathy, nephropathy, and neuropathy by 35% to 90% compared with conventional treatment in type 1 diabetes. The reduction was proportional to the mean glycosylated hemoglobin (HbA_{1c}). The Kumamoto Study in Japan revealed that intensive glycemic control by multiple insulin injection therapy, when compared to conventional insulin treatment, can delay the onset and progression of the same complications in type 2 diabetes mellitus. The UK Prospective Type 2 Diabetes Study (UKPDS) reinforced the belief that improved control lowered microvascular morbidity 25%, but also any diabetes related death and total deaths related to diabetes. There was inconclusive evidence of a 16% risk reduction for myocardial infarction. Subsequent UKPDS studies have demonstrated that each 10mm Hg decrease in mean systolic blood pressure was associated with a 12% reduction in risk of any diabetic complication including, stroke and heart failure and an 11% reduction in myocardial infarction.

The American Diabetes Association's recommended targets for glycemic control include a preprandial blood glucose level of 80 mg/dl to 120 mg/dl, a bedtime blood glucose level of 100 mg/dl to 140 mg/dl and an HbA_{1c} level of less than 7%. The HbA_{1c} is the best determinant of glycemic exposure and the mean is a quality indicator.

Aggressive treatment of hypertension, initially with an ACE inhibitor or ARB, and hyperlipidemia can decrease the risk of cardiovascular disease as diabetes mellitus is a risk factor equivalent to having coronary artery disease. ACEIs or ARBs can also slow the progression of renal disease, so it is important to screen annually for microalbuminuria, unless a patient already has known proteinuria.

GOALS	
Blood Pressure (mm/Hg)	Lipids
Systolic < 130	LDL-C \leq 100mg/dl
Diastolic < 80	HDL-C \geq 45 mg/dl ♂ \geq 55 mg/dl ♀
	Triglycerides \leq 150 mg/dl
	Non HDL-C < 130 mg/dl

NON-PHARMACOLOGIC THERAPY

Life style changes include diet, exercise, and weight loss. Hypocaloric diets will cause plasma glucose levels to fall, in some cases to a normal level. A high intake of dietary fiber reduces hyperglycemia and hyperinsulinism. Unfortunately, most dietary interventions are short lived, but remain important for those who sustain it. Other components of care include aspirin use, foot care exams, tobacco cessation, pneumococcal and influenza vaccinations and an annual dilated retinal exam.

PHARMACOLOGIC THERAPY

The coexisting defects in type 2 diabetes mellitus are: resistance to insulin action in muscle, defective pancreatic insulin secretion and unrestrained hepatic glucose production, aggravated by increased lipolysis in adipose tissue. Drug therapy is targeted to each of these defects, in addition to that of reducing carbohydrate absorption in the small intestine.

Sulfonylureas (SUs) and nonsulfonylurea secretagogues (non SUs) increase insulin secretion by allowing for insulin release at lower glucose thresholds than normal. They are both effective with a relatively recent diagnosis of type 2 diabetes mellitus. SUs lead to an HbA_{1c} decrease of 1% to

2%, but the glucose lowering effect plateaus after half the maximal recommended dose is reached. SU advantages include rapid glucose reduction, low cost and convenient daily dosing; disadvantages include weight gain and an increased risk of hypoglycemia. Non-SU disadvantages are high costs and more complex dosing schedules.

Biguanides have been available internationally for decades, but metformin was not released in the U.S. until 1995. Its predominant effect is to reduce hepatic glucose production in the presence of insulin. It reduces HbA_{1c} 1-2%. Predominant advantages are no weight gain and less hypoglycemia. Disadvantages include GI side effects, high cost, and rare lactic acidosis, approximately 1 in every 30,000 patients. Contraindications include renal impairment, with a serum creatinine (≥ 1.5 mg/dl for men) and (≥ 1.4 for women). In overweight patients, metformin is considered the first line agent at this time.

Thiazolidinediones (TZDs) exert their effect by increasing the insulin stimulated glucose uptake by skeletal muscles cells. TZDs enhance the responsiveness and efficiency of beta cells and also at higher doses reduce hepatic glucose production. Advantages include: decreased need for insulin, less hypoglycemia rates, and lowered blood pressure and lipid levels, plus convenient dosing. Disadvantages include high cost, weight gain, slow onset of action, edema, and the possibility of liver toxicity, necessitating hepatic function monitoring. They are contraindicated in NYHA Class 3 and 4 CHF patients and should be used with caution in patients with other cardiovascular disease. They reduce HbA_{1c} about 1.5%.

Alpha-Glucosidase Inhibitors (AGIs) delay intestinal carbohydrate absorption and mitigate postprandial glucose excursion. Efficacy is less, with HbA_{1c} reductions of .5-1%. Advantages include no hypoglycemia or weight gain and they are non systemic in action. Disadvantages are high cost, GI side effects, and no long-term data.

Insulin is the oldest available therapy and has no upper dose limit. It works by increasing insulin levels and can reduce HbA_{1c} 1.5-2.5%. Insulin is usually not introduced early in type 2 diabetes mellitus, but it can be very effective. Fifty percent need it eventually. It decreases gluconeogenesis and increases glucose uptake. Disadvantages are weight gain, hypoglycemia and patient reluctance to give injections. Various insulin regimens are available including very

rapid acting (lispro and aspartine), rapid acting (regular), intermediate acting (NPH and lente) and very long acting (ultralente and glargline). Glargline insulin (Lantus) has more predictable absorption than NPH, lente, and ultralente. The use of Lantus compared with NPH has been shown to be associated with less nocturnal and postprandial hypoglycemia. This is consistent with the peakless and longer duration of Lantud compared with NPH. Humalog and Novolog have a more rapid peak and fall than does regular insulin.

Combination insulin options available are 70 NPH/30 regular, 50 NPH/50 regular and 75 lispro protamine/ 25 lispro. Various combination of insulin regimens have been used successfully. The typical range of insulin needed for monotherapy is .4-1 U/kg body weight/day. Once daily injection of intermediate acting or long acting insulins at bedtime or before breakfast, daily, or twice-daily combinations of intermediate and rapid acting insulins, and more complex regimens have been used to good effect. With multiple dose insulin intensive therapy, a basal dose suppresses hepatic glucose output and the bolus doses enhance postprandial glucose uptake. This intensive insulin treatment reduces mortality in patients critically ill in the surgical intensive care unit and in those with acute myocardial infarction.

COMBINATION THERAPY AND CONSULTATION

Multiple options are available when monotherapy fails, often seen within five years. The principal is to combine drugs with different mechanisms of action. Options include SUs or non-SUs with metformin, TZDs, or AGIs; metformin with TZDs or AGIs; SUs with metformin and TZDs; SUs with metformin and AGIs. There should be no hesitation to use insulin with any of the oral agents although caution is needed with TZD use for patients with cardiovascular disease. When introducing insulin, a nighttime regimen of NPH or Lantus, 10 U at bedtime would be an appropriate dose. Most patients will require combination therapy as their disease progresses.

Consultation with an endocrinologist may be essential in some complicated patients dependent on the primary providers' level of knowledge and experience.

QUALITY IMPROVEMENT MEASURES

Multiple methods have been shown to cause clinical improvements in diabetes mellitus outcomes within practices and organization. They include education interventions with physicians,

outcomes reporting, audit or computer enhanced monitoring, continuity of care, patient education, on self-management and diabetes education centers. Cumulative survey data reveals a wide gap between guidelines and care.

CONCLUSIONS

Type 2 diabetes mellitus is a very common chronic disease with significant health and economic burdens, which requires a multifaceted management approach. This includes lifestyle interventions and pharmacotherapy to address hyperglycemia, hypertension and hyperlipidemia. Primary prevention can be accomplished through lifestyle changes in the obese and sedentary. Intensive therapy has been shown to reduce both microvascular and macrovascular complication. The goal should be to have the HbA_{1c} at $\leq 7\%$, with testing at least two times a year in patients meeting treatment goals and quarterly in patients whose therapy has changed or who are not meeting treatment goals.

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Therapy Options Tables

Options For Monotherapy					
	Sulfonylureas	Meglitinides	Biguanides	TZDs	AGIs
Target Population	- Recent Type 2 DM diagnosis - Type 2 DM < 5 years duration	- Recent Type 2 DM diagnosis - Elevated PPG	- Overweight / obese - Insulin resistant	- Insulin resistant - Overweight / obese	- Elevated PPG - Contraindications to other agents
Advantages	- Rapid FPG reduction - Low cost	- Reduced risk of hypoglycemia - Short-acting - Meal-adjusted dosing	- No weight gain - Reduced risk of hypoglycemia	- Reduced amount of insulin - Reduced risk hypoglycemia	- Reduced risk of hypoglycemia - Non-risk systemic action
Disadvantages	- Weight gain - Increase risk of hypoglycemia	- Higher costs - Frequent dosing	- GI side effects - High costs - Rare lactic acidosis	- High cost - Weight gain - Slow onset of action - Issue of liver toxicity	- High cost - GI side effects
Total Daily Dose & Dosing Interval	<u>Glyburide</u> 1.25 – 20 QD or BID Micronized 0.75 – 12 QD or BID <u>Glipzide</u> 2.5 – 40 QD or BID Extended-release 2.5 – 20 QD <u>Glimepiride</u> 1-8 QD	<u>Nateglinide</u> 180 – 360 TID <u>Repaglinide</u> 1.5 – 16 TID or QID	<u>Metformin HCl</u> 1000 – 2500 BID or TID Extended-release 1000 – 2000 QD or BID	<u>Rosiglitazone Maleate</u> 4 – 8 QD or BID <u>Pioglitazone HCl</u> 15 – 45 QD	<u>Acarbose</u> 150 – 300 TID <u>Miglitol</u> 150 – 300 TID

Options For Combination Therapy					
	Sulfonylureas	Meglitinides	Biguanides	TZDs	AGIs
Double Combination Therapy Option	√		√		
Double Combination Therapy Option	√			√	
Double Combination Therapy Option	√				√
Double Combination Therapy Option		√	√		
Double Combination Therapy Option			√	√	
Double Combination Therapy Option			√		√
Triple Combination Therapy Option	√		√	√	
Triple Combination Therapy Option	√		√		√

If therapeutic goals are not met using the above combinations; switch to insulin +/- oral agent.

CASE STUDY QUESTIONS WITH APPROPRIATE ANSWERS

Case #1:

J.S. is a 47-year-old male with fatigue, weight loss, and nocturia. His FBS was 133 and 3 days later when repeated was 137. His urinalysis was negative. Does he have diabetes mellitus, and if so, what type?

Yes, he does, with two measurement of FBS > 125. The type is Type 2 diabetes mellitus, because of insidious onset, age at onset, and absence of ketosis.

Case #2:

C.S. is a known Type 2 diabetic who is an obese, 55 year old female with a BMI of 34 who hasn't responded adequately to diet only over a 3-month period. Her HbA_{1c} is 8.9% and her creatinine is 1.1. Which is the most appropriate oral hypoglycemic agent to start her on?

Metformin would be the best choice in a patient with normal renal function and obesity, because of the likelihood of no weight gain on that medication. The other oral agents would be appropriate to use, but with some limitations. The sulfonylureas (SUs) and thiazolidinediones (TZDs) can cause weight gain. The meglitinides (non SUs) require frequent dosing. The alpha-glucosidase inhibitors (AGIs) have less impact on the HbA_{1c} and have frequent GI side effects.

Case #3

M.H. is a 57-year-old female diabetic who has just developed a change of blood pressure reading in the past 6 months, with repetitive readings of about 145/90. Should she be treated and for what?

The first choice for treatment is an ace inhibitor or an angiotension reuptake blocker because of renal protection. If necessary the usual next agent to add would be a thiazide diuretic. A third agent is often necessary and options include a low dose beta-blocker, alpha/beta blocker, or calcium channel blocker.

Case #4

G.B. is a 70 year old male diabetic who has been fairly well controlled with metformin monotherapy at 2 grams daily for the past five years. However, his HbA_{1c} has slowly tended upward, reaching a level of 8.5% recently. What needs to be done?

Combination therapy would be appropriate with a goal to bring the HbA_{1c} down to \leq 7.0%. Acceptable options would be the SUs, Non SUs, TZDs, AGIs, or insulin. The most frequently used would be an SU, to stimulate additional insulin, or a TZD to enhance the effect of his natural insulin. Where insulin is chosen, a nighttime regimen of NPH or Lantus (gargline) at a modest dose of 10u at bedtime would be appropriate.

FAMILY AND GENERAL INTERNAL MEDICINE

REVIEW QUESTIONS

(Correct answers in bold)

1. The criteria for diagnoses of diabetes mellitus includes:
 - a) Fasting blood glucose ≥ 126 mg/dl
 - b) Casual plasma glucose ≥ 200 mg/dl and diabetes symptoms
 - c) 2 hr plasma glucose ≥ 200 mg/dl during OGTT
 - d) **All of the above**

2. Prevention of microvascular complications in Type 2 DM with oral pharmacologic agents has been shown as:
 - a) DCCT (The Diabetes Control & Complication Trial)
 - b) Kumamoto Study in Japanese patients
 - c) **UKPDS (UK Prospective Diabetes Study)**
 - d) All of the above

3. The following American Diabetes Association (ADA) targets have been established for glycemia control:
 - a) **HbA_{1c} of $\leq 7\%$**
 - b) Preprandial plasma glucose value of 80-120
 - c) Bedtime plasma glucose value of 100-140
 - d) All of the above

4. The following goals for blood pressure and lipids have been established by ADA:
 - a) Blood pressure SBP < 130 mm/Hg, DBP < 80 mm/Hg
 - b) LDL ≤ 100 mg/dl
 - c) HDL ≥ 45 mg/dl males, ≥ 55 mg/dl females
 - d) **All of the above**

5. The preferred pharmacologic agent for oral monotherapy of Type 2 DM patient with obesity and normal renal function would be:
 - a) Sulfonylurea
 - b) Thiazolidinedione
 - c) **Biguanide**
 - d) 2-Glucosidase Inhibitor