

Oral Hypoglycemics

AKA: Just a spoonful of sugar...

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Lynn Punnoose

Erika Wagner

Outline of presentation

- Sample case
- Pathogenesis of Diabetes Mellitus Type II
- Therapeutic approach using oral hypoglycemics
 - mechanisms and drug toxicities
 - structure of therapeutic regimen
- Role and timing of insulin therapy
- Overall strategy for the treatment of DM II

Case description

A 29 yr old male who works at your clinic believes he has diabetes mellitus. His father and paternal grandfather both developed this disease late in life. He has polyuria, polydipsia and polyphagia accompanied by weakness, weight loss and blurry vision. You test his urine and find 3+ glycosuria; blood glucose is 450 mg/dl. The patient does not want to take insulin and hopes that pills will be enough. On the other hand, he has heard that oral hypoglycemics can be bad for you.

Diabetes Mellitus

- Syndromes of abnormal carbohydrate metabolism characterized by hyperglycemia
- Diagnostic criteria include
 - thirst, polyuria, weight loss, visual blurring
 - fasting blood glucose >126 mg/dL on more than one occasion OR random value > 200 mg/dL
- Type I diabetes
 - absolute insulin deficiency: pancreatic β cell destruction by T cell lymphocytes
 - contribution of hereditary factors unclear
- Type II diabetes
 - insulin resistance and relative insulin deficiency
 - risk \uparrow between 20 and 40% if first degree relatives have Type II diabetes
 - linked to sedentary lifestyle and dietary habits

1. Other causes of beta cell destruction in type I: inflammatory cytokines, auto antibodies (ex, islet-cell antibodies (ICA), anti-GAD and anti-insulin)
2. general population risk for type II = 5-7%.
3. Strong link between type II and obesity: possibly due to (1) excess FFA deposition in liver and muscle, which inhibits insulin signaling or (2) adipokines such as leptin negatively influence insulin signalling.
4. With about 20% of the U.S. population characterized as obese (Mokdad et al. 2001), diabetes constitutes a serious medical concern.

NB:

1. To distinguish type I from type II:
 - (1) “marked unexplained weight loss (2) short history with severe symptoms (3) moderate to severe ketonuria”
2. 20 loci have been linked to Type I, and most important of these are the loci for MHC II. Possible mechanism unclear.
3. Some adults who appear to have type 2, actually have type 1: they have “circulating islet-cell antibodies (ICA), antibodies to glutamic acid dehydrogenase (GAD),” etc.

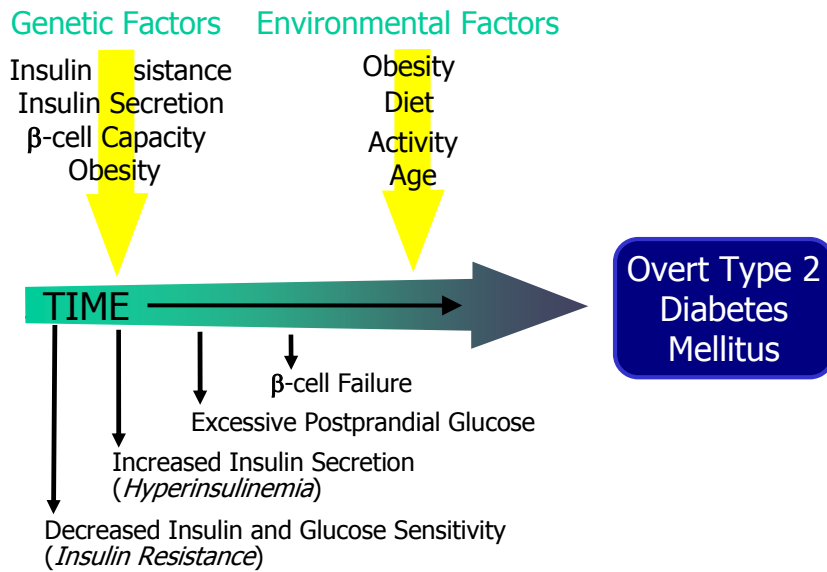
Insulin: role in normal physiology

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Downloaded from: Robbins & Cotran Pathologic Basis of Disease (on 7 March 2005 05:04 AM)
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Progression of Diabetes Mellitus Type II



Moses 2004

Relative insulin deficiency in type II caused by beta cell dysfunction:

- (1) Initially in type II, beta cells compensate for insulin resistance.
- (2) Subsequently, decompensate (mechanism unknown).

Beta cell mass decreases

islets degenerate

amyloid is deposited in islets.

1. Effects of hyperinsulinemia
2. Effects of hyperglycemia

Targeted pathways for DM Type II

Diagram removed for copyright reasons.

(Inzucchi, JAMA, 2002)

Drug Groups

Increase Insulin Release

Sulfonylureas, Meglitinides

Improve Insulin Action

Metformin, TZDs

Reduce Dietary Intake

α -glucosidase inhibitors, Lipase inhibitors

SULFONYLUREAS (glipizide, glyburide)

Increase
Insulin
Release

- Binds SUR1 on the K⁺-ATP channel, closing channels -> alters the resting potential, leading to calcium influx and stimulation of insulin secretion
- Increase responsiveness of β -cells to secretagogues
- Also slight increase in peripheral insulin sensitivity
- 2nd-gen: more potent, longer effects (16-24+ hrs)
- Hepatic biotransformation key to clearance
- Key side effects
 - Hypoglycemia (rare, but \uparrow risk with longer-acting drugs)
 - CV mortality?
- Cheapest oral hypoglycemics on the market

2nd gen effects because of active metabolites

Most effective in patients whose weight is normal or slightly increased

Greater suppression of overnight hepatic glucose output lowers fasting blood glucose concentrations more. But increased risk of hypoglycemia.

Hypoglycemia (esp. w/ long-acting formulations)

Glyburide (19.9 episodes per 1000 patient-years)

Undernourished or alcoholic

Renal failure (\uparrow half-life of insulin)

With concurrent therapy with salicylates, sulfonamides, fibric acid derivatives (such as gemfibrozil), and warfarin

Nausea

Skin reactions (eg photosensitivity)

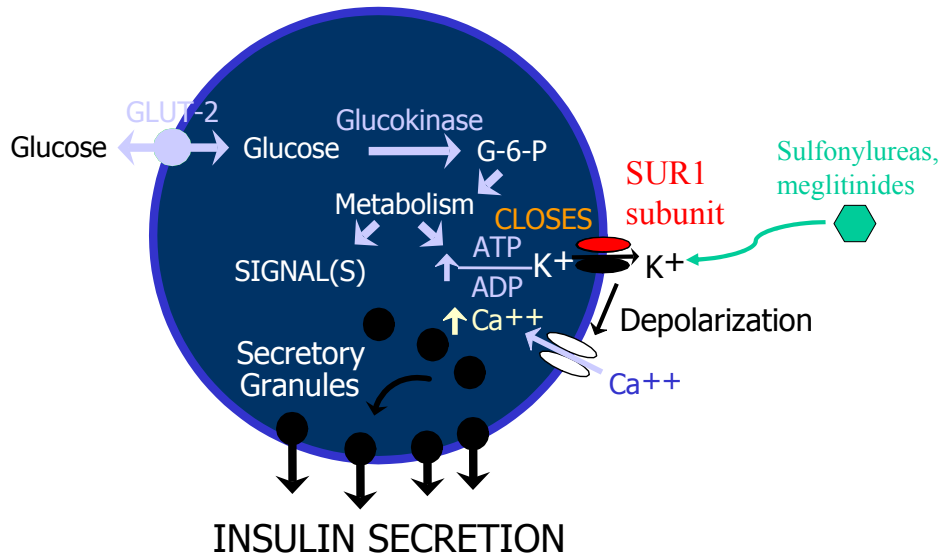
Abnormal liver function tests.

Chlorpropamide: SIADH and flushing reaction after alcohol ingestion

Poorer outcomes after MI?

β -cell Modulation

Increase
Insulin
Release



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Requires functioning β -cells!

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MEGLITINIDES (repaglinide and nateglinide)

Increase
Insulin
Release

- Same mechanism as sulfonylureas, different binding site
 - Meglitinides: manage mealtime glucose excursions
 - Sulfonylureas: manage fasting blood glucose concentrations
 - Overall, similar efficacy, but meglitinides more expensive
- Rapid onset, short duration (1-2 hrs)
- Good for irregular mealtimes
- As monotherapy, nateglinide is less effective than metformin, but combination therapy is more effective than either drug alone in reducing HbA1c values
- Less hypoglycemia due to more rapid kinetics
- Inhibitor of CYP2C9

Requires functioning β -cells!

nateglinide is predominantly metabolized by cytochrome P450 isoenzymes CYP2C9 (70%) and CYP3A4 (30%).

Repaglinide recipients

hypoglycemia (16%)(similar to sulfonylureas)

upper respiratory tract infection (10%)

rhinitis (7%)

bronchitis (6%)

headache (9%)

Mild weight gain (~6lbs)

Nateglinide

nausea, diarrhea, dizziness, and lightheadedness

Lower incidence of mild hypoglycemia, no reports of severe hypoglycemia due to more rapid kinetics

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α -glucosidase inhibitors, Lipase inhibitors

Biguanides (Metformin)

Improve
Insulin
Action

- Primary action at liver: suppresses hepatic glucose production
- Secondary action in periphery: increases glucose uptake
- Antilipolytic effect ↓ FFA and TGs leads to ↓ gluconeogenesis and LDL, ↑HDL
- Promotes modest weight loss: 1st line therapy for obese pts
- Metformin given in combination with a sulfonylurea lowers blood glucose concentrations more than either drug alone
- Risks
 - Renally cleared: risk of lactic acidosis in pts with renal failure
 - GI side effects: Nausea, cramping, and diarrhea

Effective only in the presence of insulin

Synthetic analog of guanidine (used since medieval times)

Increases intestinal glucose utilization via nonoxidative metabolism. Activation of the enzyme AMP-activated protein kinase may lower serum lipid and blood glucose concentrations

ve metabolism, (in exp animals), producing lactate -> substrate for gluconeogenesis....could protect against hypoglycemia.

Metformin Mechanism

Improve
Insulin
Action



THIAZOLIDINEDIONES (rosiglitazone and pioglitazone)

Improve
Insulin
Action

- Primary action in periphery: ↓ lipolysis, ↑ muscle uptake
- Secondary action at liver: ↓ hepatic glucose production
- Activates peroxisome proliferator-activated receptor-gamma (PPAR-gamma) predominantly in adipose tissue, a ligand-activated TF for insulin-responsive genes
- 4-12 week delay in onset of action
- Favorable lipid profile: ↓ triglycerides, ↑ LDL, HDL
- Most effective in combination drugs (Avandia w/ rosiglitazone, Glucotrol w/ glipizide)
- Risks:
 - Fluid retention: ↑ heart failure w/ rosiglitazone & insulin
 - Incidences of fatal hepatic failure

Also increase insulin secretion in response to glucose, at least in patients with impaired glucose tolerance
troglitazone may improve early β -cell dysfunction in patients with impaired glucose tolerance →
prevention of type 2 DM?

Decreased hematocrit and hemoglobin

Elevated (but reversible) alanine aminotransferase activity

Weight gain

PPAR- γ Pathway

Improve
Insulin
Action

Diagram removed for copyright reasons.

Source: <http://www.phoenixpeptide.com/Catalog%20Files/Adiponectin/adiponectin-receptor.htm>

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α -GLUCOSIDASE INHIBITORS (acarbose, miglitol)

Reduce
Dietary
Intake

- Modulate GI absorption of carbs
- Competitive inhibitor of brush border enzyme
 - reduces hyperinsulinism and hepatic TG synthesis
- Efficacy
 - decreases HbA_{1c} by 0.5-1.0%
 - most often used in combination with other drugs
 - most effective post-prandially
- Side effect/toxicity profile
 - may produce hypoglycemia in combination therapy:
treat with glucose!!
 - often causes bloating, flatulence, diarrhea and abdominal pain
 - unpredictable, but real, association with hepatic injury

Acarbose, miglitol, viglibose (not yet released in US)

Lactose absorption okay because beta-galactosidase present

A glucosidase present in “proximal part of SI”

polysaccharides not broken down to monosaccharides

GI side effects may decrease after 1-2 months; gradual increase in dose may minimize effects

Acarbose may cause hepatotoxicity

Not hypersensitivity

More details??

Limited absorption and therefore excreted in feces

LIPASE INHIBITORS (orlistat)

Reduce
Dietary
Intake

- Modulate GI absorption of fat
- Inhibits gastric and pancreatic lipases
 - induces weight loss since energy intake lowered
- Therapeutic role
 - not much effect in lowering HbA_{1c} (0.3%-0.9%)
 - may be used in obese patients with diabetes
 - used in combination with other oral hypoglycemics
- Side effect/toxicity profile
 - absorption of fat soluble vitamins may be reduced

Orlistat

Prevents fat hydrolysis into FFA and monoglycerides

Metabolized in intestinal wall and excreted

some gi problems:

In the first 3 months of treatment

Flatulence, discharge, oily spotting, fecal urgency, steatorrhea, increased frequency of defecation and fecal incontinence.

Patients should take multivitamin supplement at least 2 hours before/after drug administration

CV Risk with Oral Hypoglycemics

- **Biguanides:** GI disturbances reduce intestinal absorption of B vitamins (esp. folate) -> increased plasma homocysteine levels -> adverse effects on platelets, clotting factors, and endothelium
- **Sulfonylureas & Meglitinides** may prevent opening of cardiac K-ATP channels during an MI, impeding cardioprotective hyperpolarization. Reduce ischemic preconditioning.
- **TZDs:** Fluid retention and risk of worsening heart failure
- University Group Diabetes Program (UGDP) found increased risk of cardiac events for tolbutamide (SU), UKPDS re-examined intensive treatment and found no adverse CV effects

(Fisman et al., 2004; Chandler & Helfand, 2004)

In "Exposure to Glitazone Antidiabetics and Risk of Heart Failure Among Persons With Type 2 Diabetes: A Retrospective Population-Based Cohort Analysis," Delea used information from health insurance claims to compare risk of heart failure in 8288 patients with diabetes taking a glitazone antidiabetic drug with 41 440 patients who received other oral antidiabetic medications. Patients were included in the study if they had one or more diagnoses of diabetes and one or more claims for an oral antidiabetic drug between September 1995 and October 2001. Those with a prior diagnosis of heart failure were excluded.

Delea estimated that, after 36 months of follow-up (mean, 9 months), patients receiving glitazones had a 12.4% risk of heart failure compared with 8.4% in the control group. These percentages reflect adjustment for confounders such as age, a history of complications from diabetes, risk of heart failure, use of medications for diabetes and heart disease, and pretreatment medical care costs.

Delea noted that the study was observational and hypothesis-generating only, and did not prove causality between use of glitazones and increased risk of heart failure. (Mitka, JAMA, 2002)

The relation of sulfonylurea use to cardiovascular events, particularly postinfarction mortality, has been debated for over 30 years.⁸ The reassuring findings of the UKPDS study

(discussed below) greatly reduced but did not eliminate these concerns. For example, in a retrospective analysis of diabetic patients undergoing angioplasty at the Mayo Clinic from 1985

to 1994, diabetics who took sulfonylureas were almost three times as likely to die after PTCA

following myocardial infarction than diabetics who did not take sulfonylureas.⁹ This study had

serious flaws, but it revived interest in ischemic preconditioning as a possible mechanism for the

increased risk of postinfarction and post-intervention complications among diabetics.

Experts disagree about the clinical significance of these findings. One editorial, for example, has recommended that use of glyburide be "retired," especially for hospital use.

¹⁰ On the other hand, one review of 21 studies concluded:

"in experimental studies the cardiac effects of sulfonylureas differ: both deleterious and protective for glyburide, nil for glimepiride and gliclazide on ischemic preconditioning.

In all

cases the clinical consequences seem to be nil." A third concluded, "...studies [have] failed to

establish a definite link between sulfonylurea treatment before acute myocardial infarction and

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in-hospital mortality. However, when the myocardium becomes exposed to repeated or prolonged periods of ischaemia, ischaemic preconditioning may become clinically important.

Myocardial ischaemia can also develop during emergency or elective angioplasty and during

coronary bypass surgery. Therefore discontinuation of sulfonylurea treatment should be considered in these circumstances." (Chandler & Helfand, 2004)

Therapeutic strategies for Diabetes Mellitus type II (I)

Diagram removed for copyright reasons.

Nathan DM. (2002). [NEJM](#) 347: 1342-1349

Despite “successful initial response to oral regimen, patients fail at the rate of 5-10% per year”

Options for modifying regimen include: adding a second oral hypoglycemic that relies on a separate mechanism; adding insulin to the regimen; stopping oral hypoglycemics altogether and switching to insulin. There is “no consensus” on which approach is better.

Initial strategies:

Diet changes to reduce obesity, hypertension and to increase insulin release and sensitivity. A “low calorie” diet has been shown to decrease “fasting blood glucose and increase insulin sensitivity in 5 days.” this effect is heightened in individuals with higher initial blood glucose values.

Exercise, on the other hand, increases “insulin sensitivity” and “delays the progression of impaired glucose tolerance to overt diabetes.”

Efficacy of Monotherapies in Diabetes Mellitus Type II

Agent Class	↓ Fasting Plasma Glucose		↓ HbA _{1c} (%)	Insulin	Lipids	Body Weight	Major Side Effects
	(mg/dl)	(mmol/l)					
Sulfonylureas	60-70	3.3-3.9	0.8-2.0	Increase	No effect	Increase	Hypoglycemia
Meglitinides	65-75	3.6-4.2	0.5-2.0	Increase	No effect	Increase	Hypoglycemia
Biguanide (Metformin)	50-70	2.8-3.9	1.5-2.0	Decrease	↓ TG ↓ LDL ↑ HDL	Decrease	GI events, Lactic acidosis
TZD's Pioglitazone Rosiglitazone	60-80	3.3-4.3	1.4 -2.6	Decrease	↓ TG ↑ HDL ↑ LDL, HDL	Increase	Fluid retention; decreased Hb
α-glucosidase inhibitors	25-30	1.9-2.2	0.7-1.0	No effect	No effect	No effect	GI disturbances

<http://www.endotext.org/diabetes/diabetes16/diabetes16.htm>

SEE ALSO:

<http://www.cdup.org/pdf/files/diabetes%20fall%20winter%202002%202003.pdf>

1. Except for the AGIs and nateglinide, which are generally less effective, all of these drugs lead to a similar reductions in HbA_{1c}.
2. sulfonylureas and metformin are first line agents. Metformin is most popular because of associated weight loss/ neutrality, low risk of hypoglycemia, and favorable effects on lipid profile
3. insulin recommended for underweight or ketotic patients

Adding a second line hypoglycemic

- After 3 years, only 50% of patients adequately controlled with monotherapy; 25% after 9 years.
- Hyperglycemia may persist because of:
 - poor compliance
 - concurrent medications or illness that increases insulin resistance
 - progressive worsening of dz or development of DM type 1
- Most combinations effective by attacking different pathways
 - metformin/sulfonylurea slightly more effective than metformin/thiazolidinediones (TZD)
 - TZD plus sulfonylurea or meglitinide may be useful for patients in whom metformin is contra-indicated

NB:

1. Metformin + SU: average glucose drops from 240 to 140 mg/dL
additive effect reduces HbA1c by 2.2%
2. metformin and thiazolidinediones (TZ): increase insulin sensitivity through different mechanisms, reducing HbA1c by 1.0%
3. TZ plus SU/met: not as desirable because of expense and probability of weight gain. reduce HbA1c by 0.9%
4. α -glucosidase inhibitors combined with any other oral medication, additional decrease in HbA1c by 0.5-1.0 %

Incorporating insulin into regimen

- Insulin plus oral medications
 - insulin with one oral drug more effective than a regimen of three oral hypoglycemics
- Insulin monotherapy
 - side effects include weight increase and more episodes of hypoglycemia
- Brief intensive insulin monotherapy
 - used to induce normal glucose levels after (a) onset of disease or (b) poor glycaemic control with oral hypoglycemics
 - shown to improve insulin release and sensitivity
 - glycaemic control subsequently maintained with oral hypoglycemics, diet and exercise

1. Insulin acts to inhibit hepatic glucose production
2. Patients taking three oral medications displayed poorer glycaemic control, increased side effects and increased atherogenic profile.
3. When oral hypoglycemic agents can keep the blood sugar levels down during most of the day, but are unable control fasting values. Take pills during the day and intermediate acting insulin at bedtime.
4. different insulin formulations available; often in combo therapy, insulin administered at bedtime.

NB

1. insulin monotherapy required higher dose of insulin, and there was no improvement in “glycaemic control” over time. Combo therapy showed decrease in glucose levels, using lower level of insulin. Small benefit compared to insulin monotherapy
2. Few severe hypoglycemic episodes with insulin monotherapy.
3. When insulin requirements are exceptionally high due to resistance (e.g., >100 units/day)
 - Metformin or TZD's can help to reduce this insulin resistance and allow the insulin to work better.
 - Note, however, risk of heart failure!
4. a) monotherapy with NPH/lente/glargine
b) combined: NPH at bedtime/ glargine at bedtime or morning

Summary

- Poorly controlled diabetes causes wide-ranging damage to normal physiology
- Oral hypoglycemics are effective early in the course of treatment
 - Can be used as monotherapy or in combination with each other
 - Drug choices and therapeutic regimen structure are often determined by side effect profiles
- Insulin may be brought in to replace or complement this regimen if glycemic control fails