Treating dual defects in diabetes: Insulin resistance and insulin secretion

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ABSTRACT: The therapeutic goals in patients with type 2 diabetes mellitus and the mechanisms of insulin resistance and secretion are discussed.

Sulfonylureas improve glycemic control, restore the acute insulin response, and help improve beta-cell function in the short term. Meglitinides and phenylalanine derivatives and a-glucosidase inhibitors may be useful for elderly patients and others with normal fasting blood glucose levels and postprandial hyperglycemia, but they are less effective in achieving goal HbA_{1c} levels in patients with marked fasting hyperglycemia. Metformin and thiazolidinediones act on hepatic, muscle, and adipose tissue through different mechanisms to improve glycemic control, beta-cell function, and the lipid profile. Thiazolidinediones have a greater impact on free fatty acids than metformin. They may have an additive effect with sulfonylureas, metformin, or insulin in improving glycemic control and the lipid profile. Many patients require combination therapy with one or more insulin sensitizers and an insulin secretagogue to achieve therapeutic goals. Insulin therapy should be initiated in patients in whom an HbA_{1c} level less than 7.0% cannot be maintained with other therapies. This is vital in preventing diabetes complications. Insulin sensitizers should be continued during insulin therapy to reduce insulin resistance and treat the insulin resistance syndrome.

Therapeutic goals for patients with type 2 diabetes mellitus include improvement in glycemic control and prevention of diabetes complications. Elevated levels of fasting blood glucose should be addressed before postprandial levels to reduce HbA_{1c} levels and glucotoxicity to the beta cell. Dyslipidemia, hypertension, and hypercoagulability should be treated to minimize the increased cardiovascular risk seen in people with diabetes, which is responsible for the majority of deaths.

INDEX TERMS: Antidiabetic agents; Diabetes mellitus; Enzyme inhibitors; Geriatrics; Insulin; Insulin resistance; Insulins; Meglitinides; Metformin; Phenylalanine derivatives; Sulfonylureas; Thiazolidinediones

Achieving glycemic control is a primary therapeutic goal for patients with type 2 diabetes mellitus. (1) Health care providers trying to achieve this goal should understand that pancreatic beta-cell sensitivity to blood glucose levels is often reduced in these patients, as Stolar described in this supplement. In healthy individuals, beta cells respond to small rises in blood glucose level by secreting insulin in the acute (first-phase) insulin response. The ambient blood glucose at which the acute insulin response is diminished because glucose toxicity is 115 mg/dL. (2) The higher the ambient blood glucose level, the less likely there will be an acute insulin response. Therefore, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommend a target preprandial blood glucose level below 110 mg/dL for every meal in patients with diabetes. (1,3) This approach restores the acute insulin response to the extent possible and optimizes nonpharmacologic secretion of endogenous insulin.

When fasting blood glucose levels are 140 mg/dL or higher, they contribute to a greater extent to glycosylated hemoglobin (HbA_{1c} levels, a measure of long-term (three-month) glycemic control, than do postprandial levels. (4) Therefore, correcting fasting blood glucose levels above that level has greater impact on HbA_{1c} than does simply reducing high postprandial levels in those patients. Reducing and controlling blood glucose, as reflected by HbA_{1c} levels, reduces the risk of microvascular complications of diabetes. (5) Once fasting blood glucose levels are adequately controlled, attention can be turned toward correcting postprandial values. When both premeal and postmeal blood glucose levels are controlled, HbA_{1c} values should be less than 7.0%.

By the time diabetes is diagnosed, patients' average beta-cell function is only half of that predicted in nondiabetics. In patients treated with only diet and exercise, further losses in beta -cell function occur at an average rate of 4% per year. (6) Therefore, preserving the remaining beta-cell function (to the extent possible) is another goal of pharmacologic therapy in diabetic patients.

Oral pharmacologic options

A variety of oral antidiabetic agents are available to treat type 2 diabetes mellitus (Table 1). Their mechanisms of action and pharmacokinetics vary and should be considered in planning pharmacologic therapy for an individual patient. Patient-specific considerations in selecting pharmacotherapy include age, comorbid conditions (e.g., dyslipidemia, hypertension), and specific individual needs for glycemic control (e.g., correction of postprandial hyperglycemia, avoidance of nocturnal hypoglycemia).

Sulfonylureas. Sulfonylureas improve insulin secretion by beta cells by improving the acute response to increases in blood glucose levels. They improve fasting blood glucose levels. Results of the United Kingdom Prospective Diabetes Study revealed that sulfonylurea therapy results in a 25-30% increase in beta-cell function during the first year of therapy, after which function declines and reaches baseline levels after about six years of therapy. (6)

Meglitinides and phenylalanines. The meglitinide derivative repaglinide and the phenylalanine nateglinide stimulate beta-cell insulin secretion through a mechanism similar to sulfonylureas (i.e., binding to the sulfonylurea receptor on the beta cell and leading to increased acute insulin secretion); however, the response to these types of drugs is largely pharmacologic, even though the relative insulin-stimulating effect is greater at higher blood glucose levels. The drugs have a short duration of action and are taken shortly before meals. They are primarily used for controlling postprandial blood glucose elevations and are appropriate for patients with normal fasting and premeal blood glucose levels but high postprandial levels, which are more common in the very early stages of type 2 diabetes and in the elderly. However, meglitinides and phenylalanines less effectively reduce HbA_{1c} levels in patients with fasting hyperglycemia.

α-Glucosidase inhibitors. The α-glucosidase inhibitors acarbose and miglitol delay gastrointestinal absorption of glucose by inhibiting enzymes that break down ingested carbohydrates, which leads to a slower and lesser postprandial rise in blood glucose levels and results in improved HbA_{1c} levels. As with meglitinides, α-glucosidase inhibitors are useful for patients with postprandial hyperglycemia if premeal blood glucose levels are normal. In contrast with meglitinides and sulfonylureas, there is no risk of hypoglycemia with α-glucosidase inhibitor monotherapy. However, troublesome intestinal gas often develops as a result of carbohydrate fermentation in the intestines, especially if the dosage is adjusted too rapidly; this can negatively affect patient adherence to therapy. Ideally, the dosage should be adjusted slowly over four to six months; titrating to full therapeutic effect.

Metformin. Metformin improves peripheral insulin sensitivity, decreases hepatic glucose output and increases glucose uptake in the liver and skeletal muscle. It also inhibits lipolysis in adipose tissue, resulting in reduced free-fatty acid release. Elevated free-fatty acids cause insulin resistance in the liver and are preferentially absorbed and oxidized by muscle tissues, resulting in decreased glucose utilization. Metformin provides an initial improvement in beta-cell function during the first year of therapy, followed by a decrease of about 4% per year, with a return to baseline levels after about four years of therapy. (6) It also reduces total and low-density-lipoprotein (LDL) cholesterol and triglyceride levels. (7)

Thiazolidinediones. Thiazolidinediones act on adipose, muscle, and hepatic tissue as does metformin. They decrease lipolysis in adipose tissues, thereby decreasing free-fatty-acid output and reducing insulin resistance in the liver and muscle tissue. (8) Hepatic glucose output decreases, glucose uptake by the liver and muscle cells increase, and insulin processing within the beta cell improves, as is reflected by an improved proinsulin to insulin ratio. Thiazolidinediones exert their effects in muscle tissue by upregulating mRNA for the GLUT-4 transporter protein. In adipose tissue, these agents act on peroxisome proliferator-

activated receptor-γ to increase the differentiation of precursor cells to form new adipocytes (immature fat cells), which use and store free fatty acids and triglycerides, thereby clearing these lipids from the bloodstream. The decrease in circulating free fatty acids increases insulin sensitivity. These effects may explain the weight gain and reduction in triglyceride concentrations associated with thiazolidinedione therapy. The newly formed fat tissue tends to be peripheral in nature, and there is a shift of fat storage from visceral fat to the less metabolically active subcutaneous depots, resulting in improved insulin sensitivity despite an increase in total body fat. It takes approximately three months for the thiazolidinediones to achieve maximum effect, yet effects may be seen within two to four weeks.

Substantial decreases in HbA_{1c}, fasting blood glucose (FBG), and serum triglyceride levels, along with increases in high-density-lipoprotein (HDL) cholesterol levels are seen with thiazolidinediones. Slight increases in LDL cholesterol levels have been reported with both pioglitazone and rosiglitazone, but more substantial rises are associated with rosiglitazone. (9) Increases in total, LDL, and HDL cholesterol levels without changing the total cholesterol-HDL cholesterol ratio or serum triglyceride levels were observed in patients receiving rosiglitazone. (10)

For patients with inadequate glycemic control using a sulfonylurea, metformin, or insulin alone, the addition of pioglitazone resulted in improved HbA_{1c}, decreased serum triglyceride, and increased HDL cholesterol levels. (11-13) In patients with inadequate glycemic control with insulin monotherapy, the addition of a glitazone may improve glycemic control. (14-15) However, rosiglitazone does not have FDA-approved labeling for use in conjunction with insulin, whereas pioglitazone does. Pioglitazone is always administered once daily. Rosiglitazone is usually administered once daily, but a 4-mg dose twice daily is given to achieve maximum efficacy in many patients.

Treatment paradigm

Figure 1 depicts the current approach to treating type 2 diabetes mellitus. By the time of diagnosis, most patients with diabetes require a combination of an insulin sensitizer (e.g., metformin or a thiazolidinedione) to reduce insulin resistance and an insulin secretagogue (e.g., a sulfonylurea or a meglitinide or phenylalanine derivative) to restore acute insulin response and control postprandial blood glucose levels. The transition from oral drug therapy to insulin therapy often occurs later than it should to prevent complications from diabetes. The AACE recommends intensifying therapy in patients with HbA_{1c} levels above 6.5%. The goal HbA_{1c} concentration, based on ADA recommendations, is less than 7.0%. This implies that, if the HbA_{1c} concentration cannot be maintained at less than 6.5% (or at 7.0%) with lifestyle modifications and combinations of oral agents, then insulin therapy should be initiated.

Most patients with type 2 diabetes need treatment with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers to treat hypertension or prevent kidney damage. Statins are also frequently recommended to normalize blood lipids. Aspirin therapy is recommended for diabetes patients to reduce platelet adhesiveness.

Insulins

Bedtime basal insulin is often the first insulin used in patients with poor glycemic control, especially those with fasting hyperglycemia. This is intended to "fix the fasting first." When an insulin that peaks (such as NPH, Lente, or Ultralente) (Table 2) is used, nocturnal hypoglycemia frequently results. Since these insulins do not have a 24-hour duration of action, there may be inadequate background insulin to last throughout the day. Insulin glargine is now being promoted as a basal insulin. This long-acting insulin is administered subcutaneously once daily, usually at bedtime (although morning doses are sometimes more effective in type 2 diabetes mellitus). Insulin glargine precipitates at the injection site and is slowly released, providing relatively constant plasma levels over a 24-hour period that mimic normal background fasting endogenous-insulin release. There is no pronounced peak plasma concentration, so the hypoglycemia associated with other insulins is less likely. (19)

Controlling fasting blood sugar levels reduces glucose toxicity and improves beta-cell function. Continuation of therapy with insulin sensitizers and secretagogues is recommended when insulin is initiated, until the fasting blood glucose levels have

been reduced and normalized for a period of time. Continuation of insulin sensitizers is particularly important because they address the problems of metabolic insulin resistance and reduce insulin requirements. If postprandial blood glucose levels are not adequately controlled with a basal insulin plus a secretague, the rapid-acting insulin asp art or lispro may be added before meals, at which time the insulin secretagogues would be discontinued. The risk of hypoglycemia is lower if the use of rapid-acting insulins is not necessary, but that risk is lower with rapid-acting insulin than it is with regular insulin. (20) In most cases, it is possible to control blood glucose levels with oral agents plus a basal insulin injection for quite a while if the basal insulin is started as soon as HbA_{1c} exceeds 7.0%.

The risk of hypoglycemia may be lower with insulin glargine than with other longor intermediate-acting insulins. In studies of patients with poor glycemic control taking oral antidiabetic agents, the addition of once-daily bedtime doses of insulin glargine or NPH insulin provided comparable improvements in glycemic control (HbA_{1c} levels) (21-23); however, insulin glargine caused significantly less nocturnal hypoglycemia.

Conclusion

Pharmacologic therapeutic goals in patients with type 2 diabetes mellitus include improvement in glycemic control, restoration of the acute insulin response, and preservation of beta-cell function. Elevated fasting blood glucose should be addressed before postprandial levels. If postprandial blood glucose control is not adequate, then that should be addressed therapeutically in order to also reduce HbA_{1c} levels and the risk of diabetes complications.

TABLES, FIGURES, & REFERENCES on FOLLOWING PAGES

Table 1
Currently Available Oral Therapeutic Options for Type 2 Diabetes Mellitus[a]

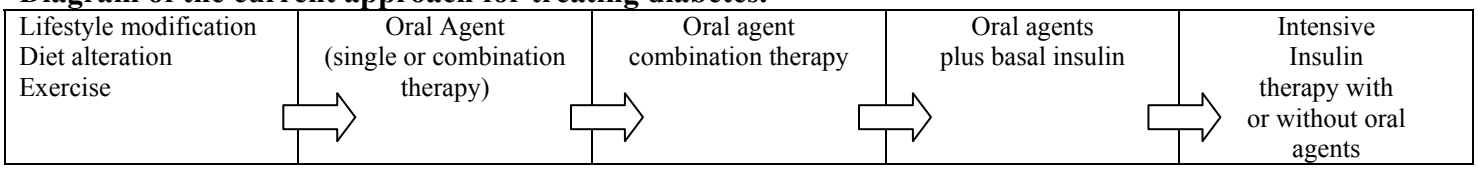
Sulfonylureas (SUs)	Non-SU Secretagogues	Biguanides	α-Glucosidase Inhibitors	Thiazolidinediones
Mechanism of action				
Increased pancreatic insulin secretion	Increased pancreatic insulin secretion	Decreased hepatic glucose production	Decreased rate of Carbohydrate absorption	Increased peripheral glucose disposal
Advantages				
Well established Improves fasting and postprandial glucose Decreases microvascular risk Convenient once-daily dosing	Targets postprandial glycemia Possibly less hypoglycemia and weight gain than with some SUs	Well established Weight loss No hypoglycemia Decreases microvascular risk Decreases macrovascular risk Nonglycemic benefits (decreased lipid levels, increased fibrinolysis, decreased hyperinsulinemia) Convenient once-daily dosage form available or twice-daily dosing	Targets postprandial glycemia No hypoglycemia Nonsystemic	Decreased hepatic glucose output No hypoglycemia Improves insulin Resistance Nonglycemic benefits (decreased triglyceride levels, increased fibrinolysis, decreased hyperinsulinemia, improved endothelial function) Possible beta-cell preservation Convenient once- or twice-daily dosing
Disadvantages				
Hypoglycemia Weight gain Hyperinsulinemia (role uncertain)	More complex (3 times daily) dosing schedule Hypoglycemia Weight gain No long-term data Hyperinsulinemia (role uncertain)	Adverse gastrointestinal effects Several contraindications Lactic acidosis (rare)	More complex (3 times daily) dosing schedule Adverse gastrointestinal effects No long-term data	Liver function test monitoring Weight gain Edema Slow onset of action No long-term data Not recommended in liver disease and stage III-IV congestive heart failure
Food and Drug Administration approval status				
Monotherapy Combination with insulin, metformin, thiazolidinedione, (X-glucosidase inhibitors	Monotherapy Combination with metformin	Monotherapy Combination with insulin, SU, non-SU secretagogue, thiazolidinedione	Monotherapy Combination with SU	Monotherapy Combination with insulin (pioglitazone only), SU, metformin

[a]Adapted from Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes. JAMA. 2002; 287:367

Table 2
Pharmacodynamics of Insulins (16-18)

Type of Insulin	Hours		
	Time to Onset of Action	**Time to Peak Action**	**Effective Duration of Action**
Rapid Acting			
Insulin aspart	0.17-0.33	1-3	3-5
Insulin lispro	0.25-0.5	0.5-2.5	3-6.5
Short Acting			
Regular Insulin	0.5-1	2-3	4-8
Intermediate Acting			
NPH/Lente insulin	2-4	6-14	10-18
Long Acting			
Ultralente insulin	4-6	8-16	18-20
Insulin glargine	1-2	No peak	24

Figure 1
Diagram of the current approach for treating diabetes.



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