REVIEW

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Treating hyperglycemia in type 2 diabetes: New goals and strategies

ABSTRACT

To achieve glycemic goals in type 2 diabetes, one must usually use combinations of oral agents or oral agents plus insulin. This paper discusses the metabolic derangements of type 2 diabetes, the different classes of antihyperglycemic drugs, and strategies for using these drugs rationally.

KEY POINTS

The American Diabetes Association calls for a goal hemoglobin A_{1c} level of 7.0% in type 2 diabetes; other organizations set the goal at 6.5%. Plasma glucose levels that correspond to a hemoglobin A_{1c} level of 6.5% are a fasting level less than 110 mg/dL and a 2-hour postprandial level less than 140 mg/dL.

Both fasting and postprandial glucose levels need to be monitored and controlled, as do components of the metabolic syndrome such as insulin resistance, dyslipidemia, hypertension, and a procoagulant state.

Agents that decrease fasting plasma glucose levels selectively (eg, sulfonylureas and metformin) or in conjunction with lowering postprandial glucose excursions (eg, repaglinide, pioglitazone, and rosiglitazone) lower mean hemoglobin A_{1c} levels 1.5 to 2.0 percentage points.

Agents that primarily lower postprandial hyperglycemia are the alpha-glucosidase inhibitors and nateglinide. These decrease mean hemoglobin A_{1c} levels by 0.5 to 1.0 percentage points.

WE ARE TAKING type 2 diabetes mellitus a lot more seriously than in the past, and treating it more aggressively.

For starters, forget about the old term for the disease, "non–insulin-dependent diabetes." Many patients with type 2 or adult-onset diabetes *do* need insulin. In fact, some need basal insulin treatment with intermediate-acting or long-acting insulins, while a few may need pre-meal insulin treatment to control postprandial hyperglycemia in addition to basal treatment.

We now have a menu of oral antihyperglycemic drugs and new insulin preparations that, if used rationally, can greatly improve metabolic control and decrease complications in most patients.

This review provides a practical perspective on how to use the new drugs, discussing how they work, their effect on components of the metabolic syndrome, their adverse effects, and how they can be used in combination.

CONSEQUENCES OF TYPE 2 DIABETES

Type 2 diabetes is one of the major problems confronting the health care system. By 2010, its prevalence will have increased approximately 2.5-fold from 1990 figures.[1] It is the leading cause of new blindness[2] and end-stage renal disease,[3] it accounts for slightly more than one half of lower-extremity amputations,[4] and it is a major risk factor for cardiovascular disease.[5]

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TABLE 1

Antihyperglycemic drugs for type 2 diabetes

DRUG	DOSE	MECHANISM OF ACTION
Insulin secretogogues		
Sulfonylureas	(one or two divided doses)	Close K_{ATP} channel
Glipizide	2.5–25 mg/day*	and open Ca^{2+} channel of beta cells
Glipizide GITS	2.5–10 mg/day*	
Glyburide	1.25–15 mg/day*	
Micronized form	1–12 mg/day	
Glimepiride	1–8 mg/day	
Rapid-acting		Close K_{ATP} channel
Nateglinide	60–120 mg with each meal	and open Ca^{2+} channel of beta cells
Repaglinide	0.5–4.0 mg with each meal	
Basal insulins	Highly variable	Decrease hepatic glucose production
NPH		Increase glucose uptake
Lente		Decrease lipolysis
Ultralente		
Glargine		
Pre-meal insulins	Highly variable	Increase postprandial glucose uptake
Regular		
Lispro		
Aspart		
Insulin sensitizers		
Biguanide		Increases insulin action in liver
Metformin	500–1,000 mg twice daily	Decreases hepatic gluconeogenesis
Thiazolidinediones		Increase insulin-mediated glucose
Pioglitazone	15–45 mg/day	uptake in muscles and adipose tissue
Rosiglitazone	4–8 mg/day	Increase adipogenesis
Alpha-glucosidase inhibitors		Inhibit cleavage of oligosaccharides
Acarbose	25–100 mg with each meal	in intestine
Miglitol	50–100 mg with each meal	

*These are the dose ranges that have been shown to be effective in the clinic. The manufacturers recommend higher ranges: glipizide to 40 mg/day; glipizide GITS to 20 mg/day; glyburide to 20 mg/day.

Insulin secretogogues work only if enough beta cells remain

WHAT GOES WRONG

Beta cell dysfunction

In type 2 diabetes, the normal physiologic relationship between plasma glucose levels and insulin secretion is impaired, due to disturbances in pancreatic beta cell function. These disturbances express themselves clinically in three major ways:

- The normal increase in insulin secretion that occurs after eating is delayed,[6] resulting in early, exaggerated postprandial hyperglycemia and, potentially, late postprandial hypoglycemia.[7]
- Not enough insulin is secreted to meet the needs of insulin-sensitive tissues.[8]
- The insulin-secreting function of beta cells progressively declines.[9]

Insofar as possible, treatment strategies need to address all of these issues.

Insulin resistance

Most patients who develop type 2 diabetes have insulin resistance, which precedes and probably promotes the progression from normal glucose tolerance to impaired glucose tolerance and then to type 2 diabetes.[10,11]

The pancreas tries to compensate for

Drug therapy for type 2 diabetes

Drug therapy for type 2 diabetes aims to control blood sugar levels both in the basal (fasting) state and postprandially; rational combinations of agents with different mechanisms of action can be used

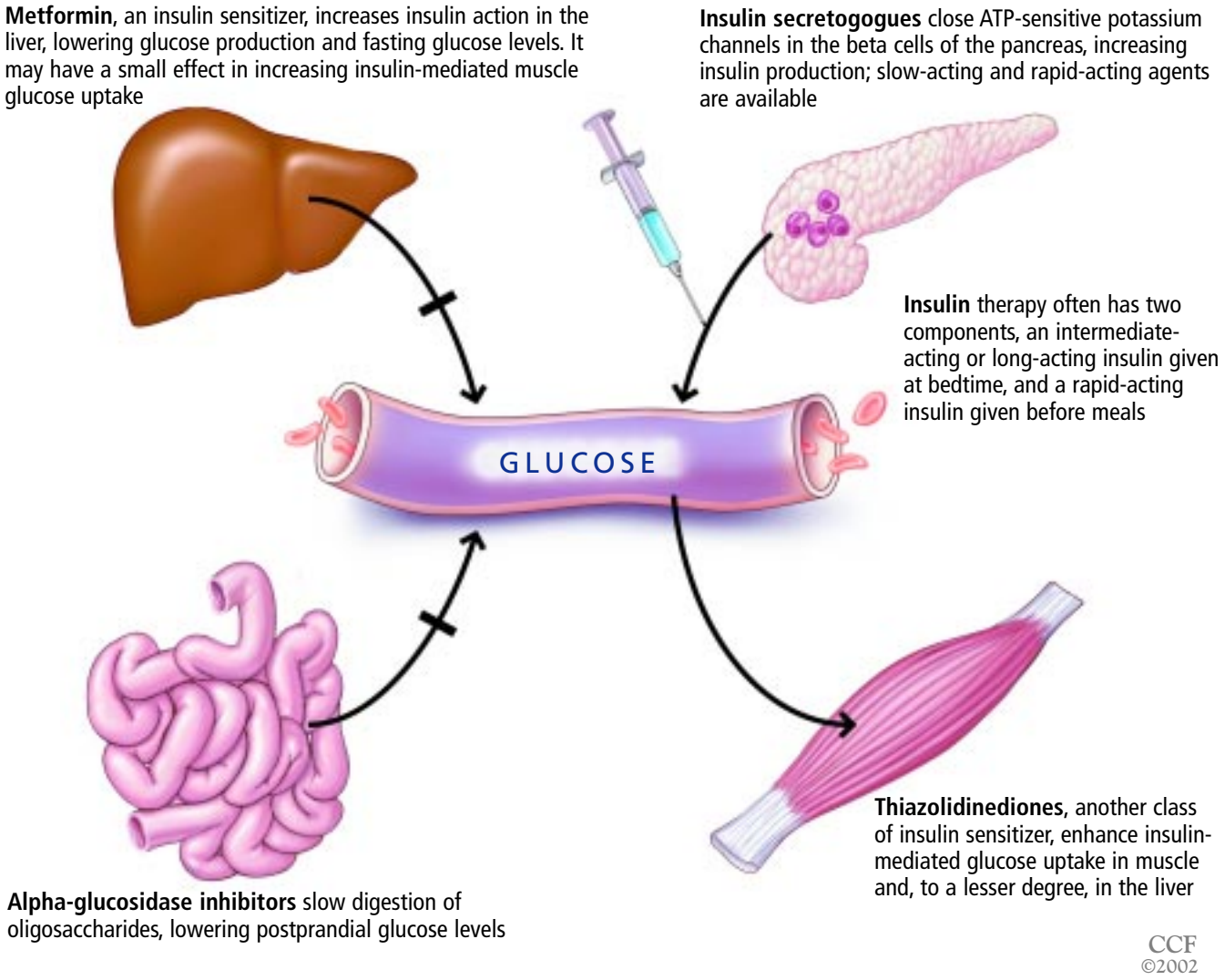

FIGURE 1

insulin resistance by secreting more insulin,[8] but patients with the genetic predisposition to develop type 2 diabetes cannot secrete enough.

In addition, insulin resistance either causes or is associated with a cluster of metabolic abnormalities known as the *insulin resistance syndrome*, the *metabolic syndrome*, or the *dysmetabolic syndrome*.[10,12] The components of this syndrome—eg, glucose intolerance, dyslipidemia, hypertension, a procoagulant state, and a noninfective inflammatory state—are cardiovascular risk factors, and patients with the syndrome have a higher risk of cardiovascular diseases.[13,14]

The third Adult Treatment Panel (ATP III)[15] of the National Cholesterol Education Program has provided clinical criteria for diagnosing the metabolic syndrome. A patient can be considered to have the metabolic syndrome if he or she has any three of the following five criteria :

- Increased waist circumference (> 40 inches in men; > 35 inches in women)
- Plasma triglycerides ≥ 150 mg/dL
- Plasma high-density lipoprotein (HDL) cholesterol < 40 mg/dL (men) or < 50 mg/dL (women)
- Blood pressure ≥ 130/85 mm Hg
- Fasting plasma glucose ≥ 110 mg/dL.

TABLE 2

Sulfonylureas vs rapid-acting insulin secretogogues (nateglinide and repaglinide)

	SULFONYLUREAS	RAPID-ACTING SECRETOGOGUES
Early meal-mediated insulin secretion	No effect	Increase
Late meal-mediated insulin secretion	Marked increase	Increase
Early meal-mediated hyperglycemia	Slight effect	Decrease
Late meal-mediated hyperglycemia	Marked decrease	Decrease
Fasting hypoglycemia	Moderate occurrence	Small occurrence
Weight gain	Moderate	Small
Effect on K_{ATP} channels in myocardium and coronary arteries	Possible	None
Dosing	Once or twice daily	With each meal
Approximate cost	$7.50–$26.00/month	$75.00–$85.00/month

Treatment strategies for type 2 diabetes must target insulin resistance, as improvement in insulin action allows endogenous insulin to be more effective and reduces cardiovascular risk factors.

GLUCOSE METABOLISM: FASTING AND POSTPRANDIAL

Sulfonylureas decrease late but not early postprandial hyperglycemia

During fasting, glucose and insulin levels decline. The liver responds to low insulin levels by producing glucose in a process called *gluconeogenesis*, which plays the major role in controlling fasting plasma glucose levels.[16,17] In contrast, postprandial glucose levels are regulated largely by uptake by muscle cells.[16,17]

The insulin level necessary to turn off glucose production in the liver is significantly lower than the level necessary to drive glucose into muscle cells. Therefore, patients with type 2 diabetes have a dissociation between the regulation of fasting and postprandial hyperglycemia—specifically, they can have normal or even low fasting glucose levels but still have large excursions after meals. Continuous monitoring over 48 to 72 hours has confirmed that patients with type 2 diabetes cannot achieve target glycemic control unless both fasting and postprandial glucose levels are measured, and unless treatments are given to appropriately regulate each.

ANTIHYPERGLYCEMIC AGENTS

Diet and exercise are the first step of therapy for type 2 diabetes; if these do not keep blood sugar at goal levels, then antihyperglycemic agents are added.

Four major classes of antihyperglycemics can be used (TABLE 1, FIGURE 1), either as monotherapy or, more appropriately, in combination with one another:

- Insulin secretogogues
- Insulins
- Insulin sensitizers
- Alpha-glucosidase inhibitors.

INSULIN SECRETOGOGUES

Insulin secretogogues correct hyperglycemia by stimulating insulin secretion—but only if the patient still has enough functioning beta cells.

The mechanism uses the same final pathway as glucose itself.[7,18] When plasma glucose levels rise, potassium channels in the plasma membrane of beta cells normally close; these channels are sensitive to intracellular adenosine triphosphate levels and so are designated K_{ATP}. Closure of K_{ATP} channels causes adjacent calcium channels to open. The resultant increase in cytosolic calcium stimulates insulin granule secretion. In type 2 diabetes, the signal is deficient and delayed.

TABLE 3

Characteristics of insulin preparations and insulin analogues

PREPARATION	ONSET (HOURS)	PEAK (HOURS)	EFFECTIVE DURATION (HOURS)
Rapid-acting			
Lispro (analogue)	0.25	1	3
Aspart (analogue)	0.25*	1*	3–4*
Short-acting			
Regular (soluble)	0.5–1.0	2–3	3–6
Intermediate-acting			
NPH (isophane)	2–4	7–8	10–12
Lente (zinc suspension)	2–4	7–8	10–12
Long-acting			
Ultralente (zinc suspension)	4	Variable	18–20
Glargine (analogue)	1–2	Flat, predictable	24*

*Occasionally less

Insulin secretogogues close K_{ATP} channels by binding to specific receptors on these channels. Thus, they can supplement an insufficient response to glucose. On the other hand, they have no primary effect on the components of the metabolic syndrome.

The major side effects of insulin secretogogues (and insulin replacement) are hypoglycemia and weight gain.

Sulfonylureas

Sulfonylurea drugs—eg, glipizide (Glucotrol), glyburide (Diabeta, Micronase), glimepiride (Amaryl)—increase the quantity of insulin secreted in patients with type 2 diabetes, but do not correct the delay in meal-mediated insulin secretion because their binding to receptors on the K_{ATP} channel is slow and prolonged.[19–21] Thus, they decrease late but not early postprandial hyperglycemia.[19–21] In fact, in the early stages of type 2 diabetes, sulfonylurea therapy often leads to late postprandial *hypo*glycemia because of a marked increase in late meal-mediated insulin secretion.

Rapid-acting secretogogues

Two other available insulin secretogogues also work by binding to and closing K_{ATP} channels, but they bind and detach more rapidly than the sulfonylureas and have a shorter plasma half-life. Thus, they have a faster onset and shorter duration of action.[22–25]

Nateglinide (Starlix) binds to the same site as the sulfonylureas. Given either with or shortly before a meal, it rapidly increases meal-mediated insulin secretion, and this effect lasts 3 to 4 hours.[26] Its primary effect is to reduce postprandial hyperglycemia.[27]

Repaglinide (Prandin) binds to a different site on the K_{ATP} channel, and its binding is slightly slower and more prolonged than that of nateglinide.[28,29] It greatly reduces postprandial hyperglycemia, but because its effects are more prolonged, it also greatly reduces fasting hyperglycemia.[30]

Nateglinide and repaglinide will not work if a sulfonylurea did not

Relative advantages and disadvantages

The rapid-acting insulin secretogogues, given three times a day with meals, restore normal postprandial glucose metabolism more closely than do the sulfonylureas, which are given once or twice daily (**TABLE 2**). Moreover, unlike the sulfonylureas, they interact little or not at all with K_{ATP} channels in cardiovascular tissues. (There has been some concern, though still controversial, that causing closure of K_{ATP} channels in the myocardium and coronary arteries might interfere with some protection against acute ischemia.)

Both types of insulin secretogogues act by closing K_{ATP} channels; therefore, combining a sulfonylurea with a rapid-acting insulin secretogogue is likely to be of no benefit. Moreover, rapid-acting insulin secretogogues will not work in patients in whom sulfonylureas do not work.

INSULINS: BASAL AND BOLUS

As beta cell function deteriorates during the course of type 2 diabetes, insulin secretogogues eventually become ineffective.[4,31] At that stage, the patient needs insulin replacement (TABLE 3).

Basal insulin replacement

An early sign that the beta cells are becoming less responsive to insulin secretogogues is that fasting plasma glucose levels begin to rise. The reason: so much insulin is depleted during meals that little or none is left for secretion overnight to control hepatic glucose production.

This can be managed by giving neutral protamine Hagedorn (NPH) or Lente insulin at bedtime (10 to 11 PM).[32,33] Giving the dose at bedtime provides circulating insulin from 1 to 8 AM and can be used to regulate plasma glucose levels overnight.[34] The dose is adjusted every 3 or 4 days until the fasting plasma glucose level is 110 to 120 mg/dL.[33]

Adjust the bedtime insulin dose every 3 or 4 days until the fasting glucose is 110 – 120

The absorption and effects of NPH and Lente insulins vary substantially from day to day, however. A better option may be insulin glargine (Lantus), which has less variability in its action and a longer duration of action. It can be given at 6 PM or bedtime to achieve overnight glycemic control.[35]

At this stage, most patients should continue to take an oral agent in the daytime along with insulin at night.[33,35]

Rapid-acting insulins

As beta cell function deteriorates further, the patient may need both a basal insulin to control fasting blood sugar levels and boluses of a rapid-acting insulin to cover postprandial levels.[36] This goal can be best achieved by giving a long-acting insulin such as insulin glargine in the evening and a rapid-acting insulin such as insulin lispro (Humalog) or insulin aspart (NovoLog) before each meal (TABLE 3).[37]

If a patient needs a less-intensive regimen, for whatever reason, the regimen most often used is a mixture of a short-acting and an intermediate-acting insulin, given twice a day, ie, before breakfast and before the evening meal.[38] Several premixed formulations are available.

INSULIN SENSITIZERS

Two classes of insulin sensitizers are currently available. They increase insulin sensitivity by different mechanisms and have their primary effects in different tissues.

Metformin, a biguanide

Metformin (Glucophage), a biguanide, has been used to treat type 2 diabetes for more than 40 years.

Metformin's mechanism of action is still unknown, despite extensive studies. Its primary effect on glucose metabolism is to decrease the exaggerated hepatic glucose production that causes fasting hyperglycemia.[39] It does so by increasing insulin action in the liver, thereby reducing hepatic gluconeogenesis.[40]

Whether metformin affects glucose uptake in the muscles and other peripheral tissues is controversial. Earlier studies[41,42] showed modest increases in whole-body insulin-mediated glucose uptake, but they did not control for weight loss and improvement in glycemia. Later studies that controlled for these confounding factors showed little or no effect.[43,44]

Clinically, metformin decreases plasma insulin levels, causes a small amount of weight loss, and improves some of the components of the insulin resistance syndrome (TABLE 4).[45,46] It lowers fasting hyperglycemia but has little or no effect on postprandial hyperglycemia.[45]

Metformin may even reduce the incidence of coronary artery disease. Overweight patients with type 2 diabetes who received metformin in the United Kingdom Prospective Diabetes Study (UKPDS)[47] had a 39% lower incidence of myocardial infarction and a 42% lower incidence of diabetes-related deaths compared with patients undergoing conventional treatment (ie, lifestyle modifica-

TABLE 4

Effects of insulin sensitizers

EFFECT	METFORMIN	THIAZOLIDINEDIONES
Insulin sensitivity—liver	Significant increase	Small increase
Insulin sensitivity—muscle	Controversial	25% to 40% increase
Hyperinsulinemia	Small decrease	Decrease
Plasma free fatty acids	Small decrease	25% reduction
Dyslipidemia*	Minimal effect	Significant improvement
Procoagulant state	Decreased PAI-1†	Decreased PAI-1
Hypertension	No effect	2–4 mm Hg reduction in diastolic blood pressure
Visceral adiposity	Some decrease	No effect
Body weight	Decrease or no change	Weight gain of 2–3 kg
Endothelial dysfunction	Improved	Improved
Edema	None	4% to 5% incidence
Urinary albumin excretion	No primary effect	Glycemia-independent reduction

*Dyslipidemia consists of increased plasma triglycerides, decreased plasma high-density lipoprotein cholesterol, and a shift in low-density lipoprotein cholesterol particle size from large and buoyant to small and atherogenic. Thiazolidinediones reverse these abnormalities.
†Plasminogen activator inhibitor-1

tion). These differences were highly statistically significant and did not occur in overweight patients treated with insulin or sulfonylureas, although the improvement in glycemic control was similar.

Metformin contraindications. Metformin is contraindicated in patients with impaired renal function (serum creatinine ≥ 1.5 mg/dL in men, ≥ 1.4 in women; or creatinine clearance < 60 mL/minute), symptomatic congestive heart failure being treated by drugs, or confirmed acidosis. These all predispose to metformin-induced lactic acidosis, which, however, is rare in the absence of these factors.[46,48]

Since radiographic contrast material can occasionally cause impaired renal function, metformin should be stopped at the time of such studies and restarted when it is clear that renal function has not been compromised.

Metformin side effects. The major problems with metformin treatment are abdominal discomfort and diarrhea. These are dose-related and preclude full dosing in 10% to 20% of patients. Giving metformin with meals and titrating the dose from 0.5 g/day up to 2.0 g/day over a week or so decreases the severity of gastrointestinal side effects. The slow-release form of metformin seems to cause fewer gastrointestinal side effects.

Metformin lowers fasting hyperglycemia, but not postprandial

Thiazolidinediones

The thiazolidinediones pioglitazone (Actos) and rosiglitazone (Avandia) decrease peripheral insulin resistance by enhancing insulin-mediated glucose uptake by muscle.[12,49–51] They have a lesser effect on insulin action in the liver.

Thiazolidinediones act by binding to and activating a specific transcription factor in the nucleus of the cell.[50,51] When activated, this factor binds to specific genes and either stimulates or inhibits their transcription. Some of these genes regulate proteins involved in adipose tissue differentiation, lipid metabolism, and the intracellular insulin action cascade.

Thiazolidinediones improve insulin action in patients with type 2 diabetes by approximately 25% to 40%, depending on the population studied.[52,53] They also decrease

circulating free fatty acid levels approximately 25%,[52] and this is one of the mechanisms thought responsible for the decrease in insulin resistance.

A major effect of thiazolidinediones is the differentiation of stem cells into adipocytes. This occurs in subcutaneous adipose tissue, but not in visceral adipose tissue,[54] and accounts for some of the weight gain associated with thiazolidinedione therapy.

The mean decrease in hemoglobin A_{1c} with thiazolidinedione therapy is 1.5 percentage points. These drugs also mitigate many of the features of the metabolic (insulin resistance) syndrome (**TABLE 4**),[12,49] such as diabetic dyslipidemia and the procoagulant state. Therefore, it is reasonable to speculate that these drugs will reduce the incidence of cardiovascular diseases. A number of in vitro and small in vivo animal and human studies support such a conclusion. Several large clinical outcome studies are under way to test this hypothesis definitively.

Moreover, thiazolidinediones might preserve beta cell function. The UKPDS[9] demonstrated that neither sulfonylureas, metformin, nor dietary treatments had any effect on the progressive deterioration of pancreatic beta cell function. Studies in animal models of insulin-resistant diabetes[55] and preliminary studies in humans raise the possibility that long-term treatment with thiazolidinediones may slow such deterioration. Several long-term clinical trials are under way to examine this.

UKPDS: Fewer MIs, deaths with metformin vs lifestyle modification

Adverse effects of thiazolidinediones. The major adverse effects of the thiazolidinediones are fluid retention and weight gain.[48,49]

As monotherapy, both rosiglitazone and pioglitazone cause a modest increase in plasma volume and are reported to cause mild to moderate edema in 4% to 5% of patients. When a thiazolidinedione is taken with a sulfonylurea, 6% to 7% of patients develop edema; when it is taken with insulin, approximately 15% of patients develop edema.

Occasionally, congestive heart failure develops during thiazolidinedione treatment, but there are no published data to define either the prevalence or the relationship of this to drug therapy. It is not unreasonable to suspect that an increase in plasma volume might precipitate clinical congestive heart failure in patients who have cardiovascular disease and are in borderline compensation. Thiazolidinediones are not recommended in patients with New York Heart Association functional class III or IV heart failure.

Weight gain is due to an increase in subcutaneous adipose tissue and in fluid retention. Monotherapy is associated with a weight gain of 1.6 to 3.5 kg in the first year. A slightly greater weight gain occurs when a thiazolidinedione is combined with a sulfonylurea or insulin. Rarely and for unknown reasons, some patients develop severe edema, gain 10 to 20 kg, or both.

Hepatotoxicity was seen with troglitazone, an earlier thiazolidinedione, and was responsible for its removal from the market, but it does not appear to occur with rosiglitazone or pioglitazone.[56] However, as a precaution, patients receiving thiazolidinediones should undergo baseline and periodic monitoring of liver enzymes. These drugs should not be given to patients with baseline alanine aminotransferase (ALT) levels 2.5 or more times the upper limit of the normal range. Persistence of ALT levels more than three times the upper limit of the normal range during therapy is an indication to stop the drug.

Role of insulin sensitizers in type 2 diabetes

Insulin sensitizers improve hyperglycemia by decreasing insulin resistance. Their unique contribution to the management of type 2 diabetic patients is that they treat many of the components of the metabolic syndrome (dyslipidemia, procoagulant state, endothelial dysfunction, inflammatory responses) and reduce the risk for cardiovascular complications. For metformin, this has been shown to result in fewer clinical cardiovascular events.

ALPHA-GLUCOSIDASE INHIBITORS

The alpha-glucosidase inhibitors acarbose (Precose) and miglitol (Glyset) competitively inhibit digestion of oligosaccharides to monosaccharides, so that glucose is slowly absorbed throughout the length of the small intestine, rather than rapidly in the proximal jejunum.[57,58] Advantages:

- They specifically lower postprandial plas-

ma glucose levels
- Their action is independent of and additive to all other forms of pharmacologic therapy
- They do not cause weight loss or gain
- They are relatively nontoxic.[57,58]

When given to patients already taking insulin, sulfonylureas, or metformin, the alpha-glucosidase inhibitors decrease maximal postprandial plasma glucose levels by approximately 50 mg/dL and hemoglobin A_{1c} by approximately 0.5 percentage points.[59,60]

Alpha-glucosidase inhibitors must be given with the start of each meal. They are effective only if more than 40% of the calories in the diet come from complex carbohydrates—a high content.[57]

If hypoglycemia occurs when an alpha-glucosidase inhibitor is used in combination with insulin or a sulfonylurea, glucose—not disaccharides—must be given because of the delayed digestion of complex carbohydrates.

Side effects. The major disadvantage of alpha-glucosidase inhibitors is their gastrointestinal side effects, which include abdominal discomfort, flatulence, and, occasionally, diarrhea.[59,60] These effects are due to carbohydrate spilling into the colon, where it is fermented by bacteria. These side effects can be minimized by starting with very small doses with the evening meal and titrating upward very slowly. This allows the distal jejunum and ileum time to increase their normally low concentrations of alpha-glucosidase enzymes, so that the oligosaccharides that reach those segments can be digested.

CHANGING GOALS OF THERAPY

The goals of therapy for patients with type 2 diabetes have changed in the last several years.

Trials show that chronic vascular complications increase in prevalence and severity with the duration of type 1 and type 2 diabetes and with the magnitude of hyperglycemia, beginning at hemoglobin A_{1c} levels above the mean normal value (ie, > 5.2%).[61,62] This means that the ideal goal for glycemic control should be a hemoglobin A_{1c} level as close to 6.0% as possible without causing serious side effects. The American Diabetes Association sets the goal as less than 7.0%; the European Diabetes Association and the American Association of Clinical Endocrinologists set the goal at 6.5% or lower.

Plasma glucose levels that correspond to a hemoglobin A_{1c} level of 6.5% are a fasting level less than 110 mg/dL and a 2-hour postprandial level less than 140 mg/dL.

The exact goal should be tailored to the individual patient, based on his or her clinical characteristics.

Blood pressure and lipid control

The goal for blood pressure control in diabetic patients is 130/80 mm Hg or lower.[63]

The goals for the management of dyslipidemia as defined by the ATP III of the National Cholesterol Education Program[15] are a low-density lipoprotein cholesterol level lower than 100 mg/dL, with no specific goals for plasma triglycerides or high-density lipoprotein cholesterol. However, studies suggest that a target plasma triglyceride level of 150 mg/dL or lower and a plasma high-density lipoprotein cholesterol level of 40 mg/dL or higher are desirable.

EFFECTS ON GLYCEMIC CONTROL

Diabetes goals:
- **$A_{1c} \leq 6.5$ or 7**
- **BP ≤ 130/80**
- **LDL < 100**

The effect of all antihyperglycemic agents on overall glycemic control as measured by reduction in hemoglobin A_{1c} depends on the baseline hemoglobin A_{1c} level.[49] Interventional studies with rosiglitazone, metformin, and insulin secretogogues have shown that they decrease mean hemoglobin A_{1c} by 1.5 to 2.0 percentage points vs placebo when the baseline hemoglobin A_{1c} is between 8.5% and 9.5%, but only about 1 percentage point when the baseline is between 6.5% and 7.5%.[48]

Chronic plasma glucose levels over 300 mg/dL have direct inhibitory effects on insulin secretion and cause some impairment of insulin action.[64] Any treatment of hyperglycemia decreases glucose toxicity as it lowers hyperglycemia.

Agents that have major effects in decreasing fasting plasma glucose levels (sulfonylureas, repaglinide, metformin, pioglitazone, rosiglitazone) lowered mean hemoglobin A_{1c} levels 1.5 to 2.0 percentage points vs placebo in the registration studies submitted

to the US Food and Drug Administration (FDA).[48]

In the few comparative studies available (metformin vs glyburide, repaglinide vs glyburide, rosiglitazone vs glyburide), these agents appeared to be equally effective in decreasing hemoglobin A_{1c}, though they have different mechanisms.[45,65] There are no direct comparative studies demonstrating the superiority of any single agent in decreasing hemoglobin A_{1c}.

Agents that primarily lower postprandial hyperglycemia (alpha-glucosidase inhibitors, nateglinide) decreased mean hemoglobin A_{1c} 0.5 to 1.0 percentage points compared with placebo in registration studies presented to the FDA.[48]

Insulin supplementation can lower hemoglobin A_{1c} to any desired level, but its use is limited by unacceptable rates of severe hypoglycemia.

Monotherapy or combination therapy?

The degree to which a single drug can achieve glycemic control is limited by its intrinsic antihyperglycemic activity, by the patient's residual beta cell function, and by its side effects. Consequently, monotherapy achieves target glycemic control in type 2 diabetic patients with only mild elevations of hemoglobin A_{1c} (probably no higher than 7.0%).

Combination regimens lower A_{1c} levels to 7.0% or less in 30%–50% of patients

The agent of choice for these patients should be one that does not cause hypoglycemia, ie, metformin, a thiazolidinedione, or an alpha-glucosidase inhibitor. The concomitant presence of the metabolic syndrome would dictate the use of an insulin sensitizer. If an insulin secretogogue were to be used, a rapid, short-acting one would be preferable to minimize late hypoglycemia. Recent studies[66] found that monotherapy with metformin decreased the rate of progression from impaired glucose tolerance to type 2 diabetes over 3 years by 31%, and acarbose decreased it by 25%.

More severe elevations of hemoglobin A_{1c} are best treated with combinations of submaximal doses of two or more agents, each of which corrects hyperglycemia by a different mechanism. Type 2 diabetic patients with severe insulin deficiency require either bedtime insulin as a component of their treatment or intensive insulin replacement therapy.

COMBINATION THERAPY OF TYPE 2 DIABETES

The most effective treatment of moderate hyperglycemia (hemoglobin A_{1c} 7% to 8%) or severe hyperglycemia (hemoglobin A_{1c} > 8%) is a combination either of oral agents that have different modes of action or of oral agents with insulin replacement.[48]

Combinations of oral agents

Combination oral therapy usually involves an insulin sensitizer and an insulin secretogogue. The addition of the second agent usually lowers the mean hemoglobin A_{1c} level 1.0 to 1.4 percentage points more than monotherapy when the baseline value is between 8.5% and 9.5%.[48] Data are available on glyburide-metformin, repaglinide-metformin, nateglinide-metformin, sulfonylurea-pioglitazone, sulfonylurea-rosiglitazone, repaglinide-pioglitazone, and repaglinide-rosiglitazone.[48,67–70] From 30% to 50% of patients taking these regimens lower their hemoglobin A_{1c} levels to 7.0% or less.

Some combinations can be given in a single pill: eg, glyburide and metformin (Glucovance). The advantage of a single pill is lower cost, a single copayment for the patient, and better compliance. The disadvantage is the fixed ratio of the drugs, which rules out dosage adjustment of an individual agent.

Combination therapy can start with submaximal doses of each agent, or after the dose of the first agent has been maximized. Few data are available to prove which approach is better, but starting with a combination has the potential advantages of more expeditious control of glycemia and fewer side effects.

Metformin plus a thiazolidinedione has been shown to improve glycemic control, lowering hemoglobin A_{1c} by 1.0 to 1.2 percentage points compared with maximum doses of either drug alone, when the mean baseline hemoglobin A_{1c} level was between 8.5% and 9.5%.[67,70] This additive benefit in glycemic control occurs because these agents improve insulin resistance by different mechanisms and in different tissues.

Adding a third or fourth oral agent

One can consider adding a third or fourth oral drug with yet another mechanism of action if the hemoglobin A_{1c} level achieved with two agents is 8.0% or less, since one may anticipate a potential decrease of approximately 0.5 to 1.3 percentage points, which could bring the value to below 7.0%.

However, if the hemoglobin A_{1c} on two agents is above 8.0%, the likelihood that adding a third oral agent will bring it to the target range is small, and adding bedtime insulin replacement is more likely to result in target glycemic control.

The third agent could be an alpha-glucosidase inhibitor; if the patient has been taking an insulin secretogogue and an insulin sensitizer, the third agent could be another insulin sensitizer.

Combining oral therapy with insulin replacement

The addition of an insulin sensitizer to full insulin replacement therapy lowers the hemoglobin A_{1c} level by approximately 1.3 percentage points while reducing the required insulin dose by 20% to 25%.

The cost of combination therapy must be considered in addition to the potential benefits. The combination of three oral antihyperglycemic agents is likely to cost more than bedtime insulin replacement and a daytime insulin sensitizer.

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