Initiation and Adjustment of Therapy in Type 2 Diabetes

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This article is a synopsis of a consensus statement published in 2006 by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). The original article, 'Management of Hyperglycemia in Type 2 Diabetes: a Consensus Algorithm for the Initiation and Adjustment of Therapy,' can be accessed in its entirety at www.diabetes.org or www.easd.org. The consensus statement was authored on behalf of the ADA and the EASD by David M Nathan, MD, John B Buse, MD, PhD, Mayer B Davidson, MD, Robert J Heine, MD, Rury R Holman, FRCP, Robert Sherwin, MD, and Bernard Zinman, MD.

The epidemic of type 2 diabetes in the late 20th/early 21st centuries, and the recognition that achieving specific glycemic goals can substantially reduce morbidity, have made the effective treatment of hyperglycemia a top priority.[1–3] Maintaining glycemic levels as close to the non-diabetic range as possible has been demonstrated to have a powerful beneficial impact on diabetes-specific complications in the setting of type 1 diabetes[4,5] and type 2 diabetes.[6–8] Intensive glycemic management resulting in lower hemoglobin (A_{1c}) levels has also been shown to have a beneficial effect on cardiovascular disease (CVD) in type 1 diabetes;[9,10] however, the role of intensive diabetes therapy on CVD in type 2 diabetes remains under active investigation.[11,12]

The development of new classes of blood glucose-lowering medications to supplement older therapies has provided an increased number of choices for practitioners and patients, but perhaps heightened uncertainty regarding the most appropriate means of treating this widespread disease. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) developed a consensus approach to the management of hyperglycemia in non-pregnant adults to help guide healthcare providers caring for patients with type 2 diabetes.[13]

Glycemic Goals of Therapy

Controlled clinical trials, such as the Diabetes Control and Complications Trial (DCCT)[4] in type 1 diabetes and the UK Prospective Diabetes Study (UKPDS)[6,7] in type 2 diabetes, have helped to establish the glycemic goals of therapy that result in improved long-term outcomes. Both the DCCT and the UKPDS had as their goals the achievement of glycemic levels in the non-diabetic range. Neither study was able to sustain A_{1c} levels in the non-diabetic range in their intensive-treatment groups, achieving mean levels over time of 7%.

Although the ADA and the EASD advocate slightly different goals for A_{1c}, the consensus was that an A_{1c} of ≥7% should serve as a call to action to initiate or change therapy, with the goal of achieving an A_{1c} level as close to the non-diabetic range as possible or, at a minimum, decreasing the A_{1c} to <7%. This goal is not appropriate or practical for some patients, and clinical judgment, based on factors such as life expectancy and risk for hypoglycemia, needs to be applied for every patient.

Choosing Specific Diabetes Interventions and Their Roles in Treating Type 2 Diabetes

The choice of interventions is predicated on their effectiveness in lowering glucose, extra-glycemic effects that may reduce long-term complications, safety profiles, tolerability, and expense. There are insufficient data at this time to support a recommendation of one class, or one combination, of glucose-lowering medications over others with regard to effects on complications. The UKPDS compared three classes of glucose-lowering medications (sulfonylurea, metformin, insulin) but was unable to demonstrate clear superiority of any one drug over the others with regard to complications.[6,7] However, the different classes do have variable effectiveness in decreasing glycemic levels (see *Table 1*), and the over-arching principle in selecting a particular intervention is its ability to achieve and maintain glycemic goals. In addition, specific effects of individual therapies on CVD risk factors such as body weight or dyslipidemia were considered important.

Lifestyle Interventions

The major environmental factors that increase the risk of type 2 diabetes are overeating and a sedentary lifestyle, with consequent overweight and obesity.[14] Not surprisingly, interventions that reverse or improve these factors have a beneficial effect on control of glycemia in established type 2 diabetes.[15] While there is still active debate regarding the most beneficial types of diet and exercise, weight loss almost always improves glycemic levels. In addition, weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity.[16–19]

Given these beneficial effects, a lifestyle intervention program to promote weight loss and increase activity levels should, with rare exceptions, be included as part of diabetes management. The benefits of lifestyle change are usually seen rapidly, within weeks to months, often before there has been substantial weight loss.[20] Weight loss of as little as 4kg will often ameliorate hyperglycemia. However, the limited long-term success of lifestyle programs to maintain glycemic goals in patients with type 2 diabetes suggests that a large majority of patients will require the addition of medications over the course of their diabetes.

Table 1: Summary of Antidiabetic Interventions as Monotherapy

Interventions	Expected Decrease in A_{1c} (%)	Advantages	Disadvantages
Step 1: Initial			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in first year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: Additional therapy			
Insulin	1.5–2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycemia, weight gain
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycemia*
TZDs	0.5–1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Other Drugs			
α-glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5	Short duration	Three times/day dosing, expensive
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience

** Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents—e.g. chlorpropamide, glyburide (glibenclamide), and sustained-release glipizide—are more likely to cause hypoglycemia than glipizide, glimepiride, and gliclazide. Repaglinide is more effective at lowering A_{1c} than nateglinide. GI = gastrointestinal.*

Medications

The characteristics of currently available antidiabetic interventions when used as monotherapy are summarized in *Table 1*. A major factor in selecting a class of drugs to initiate therapy or when changing therapy is the ambient level of glycemic control. When levels of glycemia are high (e.g. A_{1c} >8.5%), classes with greater and more rapid glucose-lowering effectiveness or potentially earlier initiation of combination therapy are recommended; conversely, when glycemic levels are closer to the target levels (e.g. A_{1c} <7.5%), medications with lesser potential to lower glycemia and/or a slower onset of action may be considered. The choice of glycemic goals and the medications used to achieve them must be individualized for each patient, balancing the potential for lowering A_{1c} and anticipated long-term benefit with other characteristics of regimens, including side effects, tolerability, patient burden, long-term adherence, expense, and the non-glycemic effects of the medications. Finally, type 2 diabetes is a progressive disease with worsening glycemia over time. Therefore, addition of medications is the rule, not the exception, if treatment goals are to be sustained over time.

Metformin

Metformin's major effect is to decrease hepatic glucose output and lower fasting glycemia. Typically, metformin monotherapy will lower A_{1c} by 1.5%.[21,22] It is generally well tolerated, with the most common adverse effects being gastrointestinal. Although a matter of concern because of its potentially fatal outcome, lactic acidosis is quite rare (less than one case per 100,000 treated patients).[23] Metformin monotherapy is usually not accompanied by hypoglycemia. The major non-glycemic effect of metformin is either weight stability or modest weight loss, in contrast to many of the other blood glucose-lowering medications. The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes that needs to be confirmed.[7]

Sulfonylureas

Sulfonylureas lower glycemia by enhancing insulin secretion. Like metformin, they lower A_{1c} by 1.5%.[24] The major adverse side effect is hypoglycemia, but severe episodes, characterized by need for assistance, coma, or seizure, are infrequent. Such episodes are more frequent in the elderly and can be prolonged and life threatening. Weight gain of 2kg is common with the initiation of sulfonylurea therapy. This may have an adverse impact on CVD risk, although this has not been established. Concerns raised by the University Group Diabetes Program study that sulfonylurea therapy may increase CVD mortality in type 2 diabetes[25] were not substantiated by the UKPDS.[6]

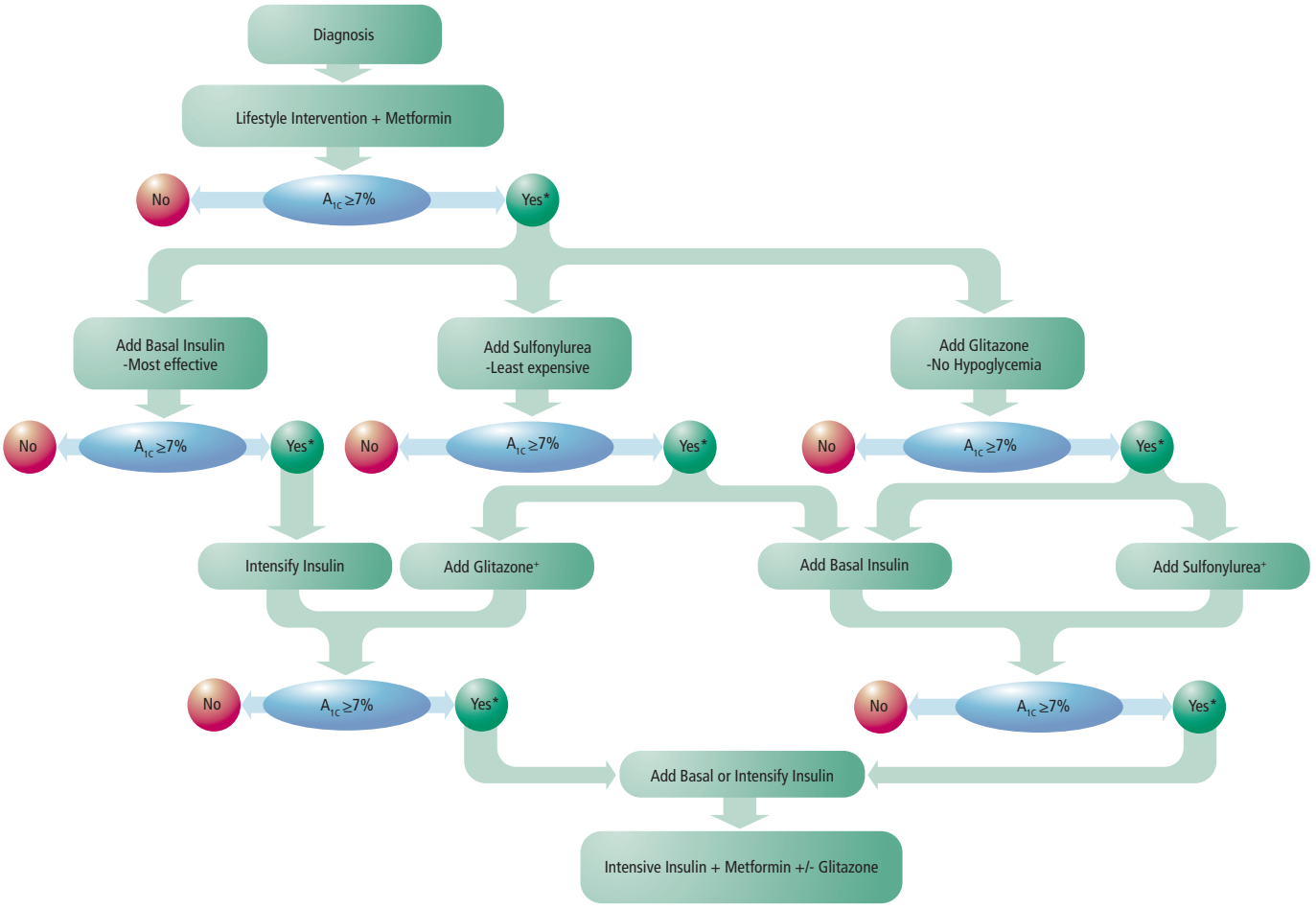
Thiazolidinediones

Thiazolidinediones (TZDs or glitazones) increase the sensitivity of muscle, fat, and liver to insulin.[26] When used as monotherapy, TZDs have demonstrated a 0.5–1.4% decrease in A_{1c}. The most common adverse effects are weight gain and fluid retention. There is an increase in adiposity, largely subcutaneous, with redistribution of fat from visceral deposits shown in some studies. The fluid retention usually manifests as peripheral edema, though new or worsened heart failure can occur. The TZDs have either a beneficial or neutral effect on atherogenic lipid profiles, with pioglitazone having a more beneficial effect than rosiglitazone.[27,28] The PROspective PioglitAzone Clinical Trial In MacroVascular Events Study (PROactive) demonstrated no significant effects of pioglitazone compared with placebo on primary CVD outcome after three years of follow-up, but a 16% reduction in a subset of CVD outcomes—a secondary end-point—with marginal statistical significance.[29] (The ADA/EASD Consensus Statement was developed prior to the recent reports of a possible risk of myocardial infarction with rosiglitazone.)

Insulin

Insulin is the oldest of the currently available medications, has the most clinical experience, and is the most effective medication in lowering glycemia. Insulin therapy has beneficial effects on triglyceride and high-density lipoprotein cholesterol (HDL-C) levels,[30] but is associated with weight gain of 2–4kg. As with sulfonylurea therapy, the weight gain may have an adverse effect on cardiovascular risk. Insulin therapy is also associated with hypoglycemia, albeit much less frequently than in type 1 diabetes. In clinical trials aimed at normoglycemia and achieving a mean A_{1c} of 7%, severe hypoglycemia (defined as requiring help from another person to treat) occurred at a rate of between one and three per 100 patient-years[8,30–33] in the type 2 population compared with 61 per 100 patient-years in the type 1 population.[4]

Figure 1: Algorithm for the Metabolic Management of Type 2 Diabetes



*Reinforce lifestyle intervention at every visit. *Check A_{1c} every three months until <7% and then at least every six months. +Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense.*

How to Initiate Diabetes Therapy and Advance Interventions

The patient is the key player in the diabetes care team and should be trained and empowered to prevent and treat hypoglycemia, and to adjust medications with the guidance of healthcare providers to achieve glycemic goals. The measures of glycemia that are initially targeted are the fasting and pre-prandial glucose levels. Self-monitoring of blood glucose (SMBG) is an important element in adjusting or adding new interventions and, in particular, in titrating insulin doses.

The levels of plasma glucose (most meters that measure capillary samples provide plasma-equivalent values) that should result in A_{1c} in the target range are fasting and pre-prandial levels between 70 and 130mg/dl. If these levels are achieved but A_{1c} remains above the desired target, levels measured 90–120 minutes after a meal may be checked. They should be lower than 180mg/dl to achieve A_{1c} levels in the target range.

Algorithm

The algorithm (see *Figure 1*) takes into account the characteristics of the individual interventions, their synergies, and expense. The goal is to achieve and maintain glycemic levels as close to the non-diabetic range as possible and to advance interventions at as rapid a pace as necessary. Pramlintide, exenatide, α-glucosidase inhibitors, the glinides, and inhaled insulin were not included in the algorithm owing to their generally lower overall glucose-lowering effectiveness, limited clinical data, and/or relative expense (see *Table 1*). However, they may be appropriate choices in selected patients. More information about these drugs may be found in the consensus statement.[13]

Step 1—Lifestyle Intervention and Metformin

Based on the numerous demonstrated short- and long-term benefits from weight loss and increased physical activity, the consensus was that lifestyle interventions should be initiated as the first step in treating new-onset type 2 diabetes (see *Figure 1*). These interventions should be implemented by healthcare professionals with appropriate training, usually registered dietitians, and be sensitive to ethnic and cultural differences among populations. Lifestyle interventions to promote weight loss or at least avoid weight gain should remain an underlying theme throughout the management of type 2 diabetes, even after medications are used.

The consensus group recognized that for most individuals with type 2 diabetes, lifestyle interventions fail to achieve or maintain metabolic goals, either because of failure to lose weight, weight regain, progressive disease, or a combination of factors. Therefore, the consensus was that metformin therapy

should be initiated concurrent with lifestyle intervention at diagnosis. Metformin is recommended for initial pharmacological therapy in the absence of specific contraindications for its effect on glycemia, absence of weight gain or hypoglycemia, low level of side effects, and relatively low cost. Metformin should be titrated to its maximally effective dose over 1–2 months, as tolerated.

Step 2—Additional Medications.

More than one medication will be necessary for the majority of patients over time. If lifestyle intervention and maximum tolerated dose of metformin fail to achieve or sustain glycemic goals, another medication should be added within 2–3 months of the initiation of therapy, or at any time when A_{1c} goal is not achieved. There was no strong consensus regarding the second medication added after metformin other than to choose among insulin, a sulfonylurea, or a TZD (see *Figure 1*). The A_{1c} level will determine selection in part, with consideration given to the more effective glycemia-lowering agent, insulin, for patients with A_{1c} >8.5% or with hyperglycemic symptoms. Insulin can be initiated with a basal (intermediate- or long-acting) insulin.[34]

Step 3—Further Adjustments

If lifestyle, metformin, and a second medication do not result in goal glycemia, the next step should be to start, or intensify, insulin therapy. When A_{1c} is close to goal (<8.0%), addition of a third oral agent could be considered; however, this approach is relatively more costly and potentially less effective than adding or intensifying insulin.[35] Intensification of insulin therapy consists of additional injections that might include short- or rapid-acting insulin given before meals to reduce post-prandial glucose excursions.

Special Considerations for Patients

In the setting of severely uncontrolled diabetes with catabolism (fasting plasma glucose levels >250mg/dl, random glucose levels consistently >300mg/dl, A_{1c} >10%, or the presence of ketonuria), or symptoms (polyuria, polydipsia, weight loss), insulin therapy in combination with lifestyle intervention is the treatment of choice. Some patients with these characteristics will have unrecognized type 1 diabetes; others will have type 2 diabetes but with severe insulin deficiency. Insulin can be titrated rapidly and is associated with the greatest likelihood of returning glucose levels to target levels. After symptoms are relieved, oral agents can be added and it may be possible to withdraw insulin in some cases.

Conclusions

Type 2 diabetes is an epidemic whose long-term consequences translate into enormous human suffering and economic costs. The morbidity associated with long-term complications can be substantially reduced with interventions that achieve glucose levels close to the non-diabetic range. Although new classes of medications and numerous combinations have been demonstrated to lower glycemia, current-day management often fails to achieve and maintain the glycemic levels most likely to provide optimal health outcomes for people with diabetes. The guidelines and treatment algorithm in the ADA/EASD consensus statement emphasizes: achievement and maintenance of near-normal glycemic goals; initial therapy with lifestyle intervention and metformin; rapid addition of medications, and transition to new regimens, when target glycemic goals are not achieved or sustained; and early addition of insulin therapy in patients who do not meet targets. ■

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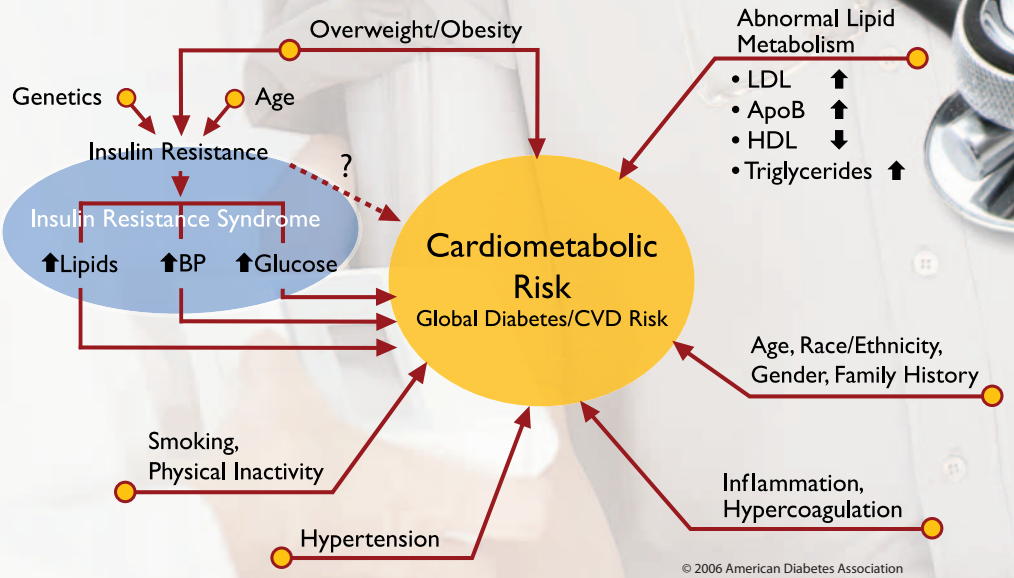

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