Stepwise and Combination Drug Therapy for the Treatment of NIDDM

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Pharmacological therapy for patients with non-insulin-dependent diabetes mellitus (NIDDM) is finally maturing into a rational discipline in which its primary goal is to prevent marked morbidity and increased mortality, which have been the hallmarks of this ubiquitous disease. Several major scientific advances have been responsible for this change. It has been unequivocally demonstrated that the level of glycemic control has a direct and perhaps linear relationship to the development and progression of retinopathy in both insulin-dependent diabetes mellitus (IDDM) and NIDDM patients (1–3) and to the development and progression of nephropathy and neuropathy in IDDM patients. We now know that the level of HbA_{1c} is a yardstick by which to estimate the likelihood that microvascular and neuropathic complications will occur and progress (1–3). The Diabetes Control and Complications Trial study provides us with the quantitative data shown in Table 1 (2). Similar data from the Wisconsin Eye Study in NIDDM patients provide quantitatively different but qualitatively similar data (3).

Therefore, we are able to conclude that every incremental improvement in the level of HbA_{1c} benefits patients with all types of diabetes and will reduce microvascular and neuropathic complications. As the contemporary strategy, the implication of this for the management of glycemia should be stepwise and multiple drug treatment to lower the HbA_{1c} toward normal as much as possible without causing significant side effects.

While microvascular and neuropathic complications in NIDDM patients are quite important, there are overwhelming data that in western society the major devastating chronic complications are those attributed to macrovascular disease (4–6). Between 50 and 60% of NIDDM patients' deaths are due to coronary artery disease. The reasons for the increased macrovascular disease in NIDDM patients cannot be explained solely by hyperglycemia because individuals with impaired glucose tolerance and newly diagnosed NIDDM show significant increases in macrovascular disease (7–9). This has led to the recognition that many individuals have an antecedent metabolic disease syndrome that is characterized by central obesity, hypertension, dyslipidemia (increased very-low-density lipoprotein, triglyceride [TG], and decreased high-density lipoprotein cholesterol), insulin resistance, hyperinsulinemia, abnormal levels of circulating coagulation factors (fibrinogen, PA1–1), and hyperuricemia (10,11). It is unclear how all the various cardiovascular risk factors interact to cause accelerated atherosclerosis in NIDDM patients, but it is clear that each identifiable factor should be improved if possible.

In this context of treating glycemia and the other metabolic defects in NIDDM patients, we can examine what is available now and in the near future to allow us to achieve our therapeutic goals. While diet and exercise are uniformly heralded as the panacea for the treatment of NIDDM, large long-term studies have consistently achieved adequate glycemic and metabolic control in no more than 10% of the populations treated only with dietary intervention and increased physical activity (12,13). The remainder of the patients have required pharmacological treatment.

For glycemic regulation, four classes of drugs are available worldwide. They are sulfonylurea compounds, biguanide compounds, α-glucosidase inhibitors, and insulins (14,15). These classes have different modes of actions as described in Table 2 and Fig. 1. Therefore, they can be used individually for certain types of patients or can be combined in a stepwise fashion to provide more ideal glycemic control for most patients. Additionally, each of these classes of drugs have different effects on body weight, serum lipid levels, plasma insulin levels, and perhaps even insulin resistance (16). Thus, they have the potential to alter cardiovascular risk factors as well as glycemia.

Hermann et al. (13) and Jeppesen et al. (17) are excellent examples of the points that I have discussed. Both studies confirm and extend observations that are more than 25 years old that showed that the combination of metformin and sulfonylurea compounds is able to achieve excellent glycemic control in NIDDM patients who are not adequately controlled

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; TG, triglyceride; FDA, Food and Drug Administration.

Table 1—*Glycemic control and complications in IDDM: DCCT Study*

	Rate/100 patient-years	
	HbA_{1c} ~7.2	HbA_{1c} ~9.2
Development		
≥3-step sustained retinopathy	1.2	4.7
Microalbuminuria	2.2	3.4
Clinical proteinuria	0.2	0.3
Clinical neuropathy	3.1	9.8
Progression		
Severe nonproliferative or proliferative retinopathy	1.1	2.4
Laser treatment	0.9	2.3
Clinical proteinuria	0.6	1.4
Clinical neuropathy	7.0	16.1

on either drug alone. Hermann et al. showed equal efficacy of metformin and glyburide in mildly hyperglycemic patients. More severely hyperglycemic patients experienced HbA_{1c} levels reduced by slightly >2% when the drugs were combined. An advantage of metformin over glyburide was no weight gain and no rise in plasma insulin. Jepperson et al. not only showed the efficacy of adding metformin to maximal sulfonylurea treatment in decreasing HbA_{1c} from 10.8 to 7.9%, but they also showed reductions in fasting and postprandial TGs, postprandial plasma insulin, and free fatty acids.

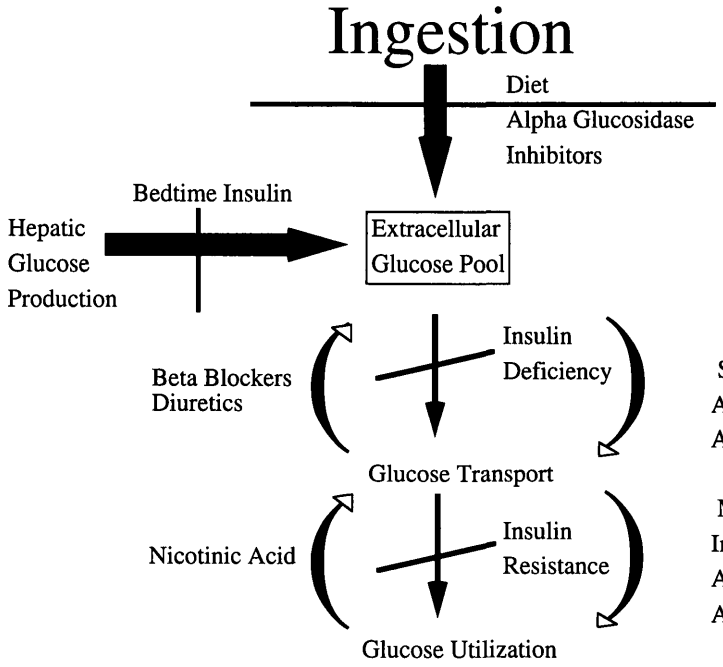

Fig. 1—*Sites of action of various antidiabetic, antihypertensive, and lipid-lowering agents on glucose metabolism in NIDDM patients. Ingestion and hepatic glucose production lead to increased flux of glucose into the extracellular pool. Diet and α-glucosidase inhibitors decrease the effects of ingestion and lower postprandial plasma glucose. Insulin administered at bedtime decreases hepatic glucose production and lowers fasting plasma glucose. Insulin deficiency and/or insulin resistance expand the pool by reducing efflux. Sulfonylurea drugs and α-adrenergic receptor antagonists can increase insulin secretion. Diuretics and β-blockers decrease insulin secretion. Metformin and α-adrenergic receptor antagonists increase insulin action. Nicotinic acid interferes with insulin action through its metabolic effects.*

Metformin, when approved by the Food and Drug Administration (FDA) for use in the U.S., will provide physicians with an important agent for controlling glycemia and lowering cardiovascular risk factors in NIDDM patients. Its ability to lower fasting and postprandial plasma glucose alone or in combination with other agents will provide improved HbA_{1c} levels for many patients (14–16,18). Its effects in decreasing body weight (1–3 kg), lowering plasma insulin, decreasing TGs and possibly low-density lipoprotein cholesterol, and reducing plasminogen activator inhibitor 1 levels may have some beneficial effects on cardiovascular disease.

Another class of drugs that specifically lowers postprandial plasma glucose, insulin, and TGs is α-glucosidase inhibitors. These drugs can be combined with sulfonylurea compounds, metformin, or both because their effect in lowering HbA_{1c} is additive (14–16,19). While approved for use in many countries, they are still being evaluated by the FDA.

The use of various oral agents alone or in combination with each other and/or insulin provides clinicians with numerous options for the treatment of NIDDM patients. Patients with mild to modest hyperglycemia who are not adequately controlled on diet and modest increases in physical activity can be treated with metformin or with α-glucosidase inhibitors when they become available. Neither would cause weight gain, and both would lower postprandial insulin and TG levels. For more severe hyperglycemia associated with modest insulin deficiency, sulfonylurea compounds might be appropriate because they increase insulin secretion. As the sulfonylurea compounds become less effective, combina-

Table 2—*Primary mode of action of antidiabetic drugs*

Sulfonylureas
Increase β-cell insulin secretion through closing the ATP-sensitive potassium ion channel
Metformin
Decreases hepatic glucose production
Increases intracellular glucose metabolism
α-glucosidase inhibitors
Decrease postprandial glycemic rise by slowing carbohydrate digestion
Insulin
Increases intracellular glucose oxidation and utilization
Decreases hepatic glucose production

tion therapy with metformin and/or an α-glucosidase inhibitor could restore glycemic control to the desired target range. As endogenous insulin deficiency increases, one could consider adding an intermediate-acting insulin at bedtime to control fasting hyperglycemia and continue oral agents during the day. And finally, with severe endogenous insulin deficiency, multiple daily injections of insulin might be necessary.

This new era of stepwise and combination therapy for the control of hyperglycemia and the other metabolic abnormalities associated with NIDDM should significantly decrease morbidity and mortality from NIDDM.

The focus of this commentary has been on antihyperglycemic agents and their associated metabolic activities. However, it is equally important to recognize that some antihypertensive and lipid-lowering agents exert specific metabolic actions on glycemic control (Fig. 1). Thus, an appropriately designed treatment program must be a symphony that plays in harmony rather than cacophony. The main goal of treatment in patients with NIDDM is to normalize as much as possible glycemia and cardiovascular disease risk factors. Only then can we reduce morbidity and mortality to nondiabetic levels.

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