Diabetes

Insulin Glargine or Rosiglitazone as Add-On Therapies

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Triple Therapy in Type 2 Diabetes

Rosenstock J, Sugimoto D, Strange P, et al.

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In the 1999 to 2002 National Health and Nutrition Examination Survey (NHANES) from the Centers for Disease Control and Prevention, about 7% of non-institutionalized US adults reported having diabetes.[1] This percentage did not include diabetic patients who were unaware of their condition or prediabetic patients, who, with diabetic patients, are at increased risk for cardiovascular disease. Achievement of the American Diabetes Association (ADA) guidelines (Table 1) remains a lofty and as yet unrealized goal. Unfortunately, compliance with the ADA recommendations is far from ideal for a number of the parameters, in particular, attainment of optimal glycemic control. Survey data showed that less than 50% of the population achieved hemoglobin (Hb) A1c levels < 7%.[1] Nearly 30% had HbA1c levels > 8% (Table 2).

Diabetes is associated with a markedly increased prevalence of coronary artery disease—as high as 55%, compared to 2% to 4% in the general population.[2] Traditional risk factors account for only 25% to 50% of this increased risk.[3] In diabetes patients, poor glycemic control is reportedly associated with the risk of developing coronary artery disease and is likely involved with the biology of atherosclerosis. Hyperglycemia is associated with endothelial dysfunction; it reduces endothelium-dependent vasodilation and leads to modifications of coagulation factors and platelet activation, thus

Table 1
Summary of ADA Clinical Practice Recommendations That Can Be Evaluated Among Diabetic Patients in NHANES 1999–2002

Characteristic	Clinical Practice Recommendation
HbA1c	< 7%
HDL cholesterol	
Men	> 45 mg/dL
Women	> 55 mg/dL
LDL cholesterol	< 100 mg/dL
Triglycerides	< 200 mg/dL
Blood pressure	Systolic < 130 mm Hg and diastolic < 80 mm Hg
Albumin-to-creatinine ratio	< 30 μg/mg
Daily caloric intake	
Protein	10% to 20% of daily caloric intake
Saturated fat	< 10% of daily caloric intake
Unsaturated fat	< 10% of daily caloric intake
Daily fiber intake	20 g to 35 g
Smoking	Smoking abstinence and cessation among current smokers
Pneumococcal immunization	One-time vaccination for individuals younger than 65 and one-time revaccination for those 65 years or older, if first vaccination was administered more than 5 years ago
Physical activity	≥ 30 minutes of moderate exercise on most days of the week

ADA, American Diabetes Association; NHANES, National Health and Nutrition Examination Survey; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Adapted with permission from Resnick H et al.[1]

Table 2
Proportion of US Diabetic Adults Achieving Selected 2001 ADA Clinical Practice Recommendations, NHANES 1999–2002

Characteristic	Proportion Meeting Recommendation ± SE
HbA1c	
< 7%	49.8 ± 3.6
7% to < 8%	20.5 ± 1.1
≥ 8%	29.7 ± 3.4
HDL cholesterol	
Low risk (> 45 mg/dL for men, > 55 mg/dL for women)	27.4 ± 2.0
Borderline risk (35 mg/dL to 45 mg/dL for men, 45 mg/dL to 55 mg/dL for women)	35.3 ± 2.5
High risk (< 35 mg/dL for men, < 45 mg/dL for women)	37.3 ± 2.3
LDL cholesterol	
Low risk (< 100 mg/dL)	36.0 ± 4.0
Borderline risk (100 to 130 mg/dL)	30.8 ± 4.0
High risk (≥ 130 mg/dL)	33.2 ± 2.6
Triglycerides	
Low risk (< 200 mg/dL)	65.0 ± 3.8
Borderline risk (200 mg/dL to 399 mg/dL)	28.8 ± 3.4
High risk (≥ 400 mg/dL)	6.3 ± 1.7
Blood pressure (< 130 mm Hg systolic and < 80 mm Hg diastolic)	39.6 ± 2.7
Albumin-to-creatinine ratio	
Normal (< 30 mg/g)	65.8 ± 1.5
Microalbuminuria (30 mg/g to 299 mg/g)	24.0 ± 1.6
Macroalbuminuria (≥ 300 mg/g)	10.1 ± 1.2
Daily caloric intake	
Protein (10% to 20%)	64.0 ± 2.8
Saturated fat (< 10%)	48.3 ± 2.6
Unsaturated fat (< 10%)	28.3 ± 1.9
Daily fiber intake (20 g to 35 g)	18.3 ± 2.2
Nonsmokers	81.2 ± 1.4
Pneumococcal immunization (ever)	38.2 ± 3.2
Recommended physical activity	28.2 ± 2.5

ADA, American Diabetes Association; NHANES, National Health and Nutrition Examination Survey; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Adapted with permission from Resnick H et al.[1]

contributing to a hypercoaguable state. Advanced glycosylation end products that arise from the reaction of phospholipids to glucose may accelerate the oxidation of low-density lipoprotein (LDL) cholesterol by allowing it to cross the vessel wall more easily and further activate the inflammatory process and increase oxidative stresses.

Cardiologists have assumed a leadership role in the early adoption of risk reduction therapies, including the use of statins, antiplatelet drugs, beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in diabetic patients. This role will further evolve to encompass a leadership position in the treatment of hyperglycemia in diabetic patients, including the initiation and titration of insulin.

Triple Therapy

A 24-week, multicenter, randomized, open-label, parallel trial evaluated the safety and efficacy of insulin glargine

Table 3
Forced Insulin Titration Schedule

Titrated Weekly According to Fasting Plasma Glucose and Monitored Blood Glucose Meter Levels for the Previous 2 Consecutive Days, With No Severe Hypoglycemia or Blood Glucose < 72 mg/dL	Increase in Insulin Dose (IU)
≤ 100 mg/dL (≤ 5.5 mmol/L)	0
≥ 100 mg/dL and ≤ 120 mg/dL (≥ 5.5 mmol/L and ≤ 6.7 mmol/L)	0-2
≥ 120 mg/dL and ≤ 140 mg/dL (≥ 6.7 mmol/L and ≤ 7.8 mmol/L)	2
≥ 140 mg/dL and ≤ 160 mg/dL (≥ 7.8 mmol/L and ≤ 8.9 mmol/L)	4
≥ 160 mg/dL and ≤ 180 mg/dL (≥ 8.9 mmol/L and ≤ 10 mmol/L)	6
≥ 180 mg/dL (≥ 10 mmol/L)	8

IU, International Units. Adapted with permission from Rosenstock J, et al.[4]

(Lantus®) or rosiglitazone (Avandia®) as add-on therapies in patients with type 2 diabetes who have chronic hyperglycemia despite maximized combination therapy with metformin and a sulfonylurea.[4] Insulins lower blood glucose levels by stimulating peripheral glucose uptake by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulins inhibit lipolysis in the adipocyte, inhibit proteolysis, and enhance protein synthesis. Insulin glargine is a human insulin analog that has been designed to have low aqueous solubility at neutral pH. After it is injected into the subcutaneous tissue, the acidic solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 hours, with no pronounced peak. This profile allows once-daily dosing as a patient's basal insulin.

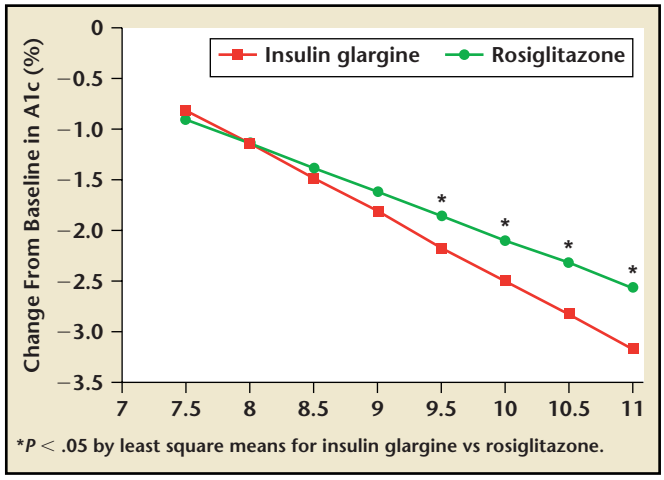
The 217 study subjects had HbA1c levels ≥ 7.5% and ≤ 11%, and they had a body mass index > 25 kg/m^2. The subjects randomized to insulin glargine started with a bedtime subcutaneous injection of 10 IU/d for 7 days and had a weekly dose titration schedule, based on self-monitored fasting plasma glucose (FPG) levels, to meet the target FPG of 100 mg/dL to 120 mg/dL (Table 3). Patients randomized to rosiglitazone received a starting dose of 4 mg/d for 6 weeks and then were titrated to 8 mg for an FPG > 100 mg/dL.

There was no difference in the final HbA1c levels between the treatment groups in patients with baseline HbA1c levels < 9.5%. However, for patients with baseline HbA1c levels ≥ 9.5%, treatment with insulin glargine was able to achieve lower HbA1c levels (Figure 1). Insulin glargine reduced total cholesterol levels, LDL-cholesterol levels, and triglycerides to a greater extent than did rosiglitazone. High-density lipoprotein cholesterol levels were not affected by insulin glargine but increased 4.4% with rosiglitazone.

Adverse Events

Adverse events were more common in patients treated with rosiglitazone than with insulin glargine (28.6% vs 6.7%; $P < .0001$). Peripheral edema occurred only in the patients receiving rosiglitazone. Weight gain was greater in the rosiglitazone group. Confirmed hypoglycemia (plasma glucose < 70 mg/dL) occurred at a slightly higher incidence in the insulin-treated patients (in 57 patients receiving insulin and 47 patients receiving rosiglitazone). The cost of improved glycemic control was lower among

Figure 1. *Change from baseline HbA1c with insulin glargine or rosiglitazone in those studied with baseline HbA1c levels ≥ 9.5%. Adapted with permission from Rosenstock J, et al.[4]*



patients receiving insulin glargine. The estimated mean cost for every 1% lowering of the HbA1c level was $824 with insulin glargine and $1,062 with rosiglitazone.

Conclusion

The development of improved formulations of insulin will modify the approach to the treatment of hyperglycemia in the type 2 diabetic patients who present to our clinics, emergency departments, and cardiac catheterization laboratories. Undertreatment of hyperglycemia is associated with poorer outcomes in a variety of cardiovascular conditions, including the development of coronary artery disease in diabetic patients. It will be important for cardiologists to take an aggressive approach to glycemic treatment at the point of contact with the patient, as they do with blood pressure and lipid therapies. It is likely that a multi-drug approach will be required in many patients. Based on safety, efficacy, and cost, it seems that the use of newer insulin formulations, such as the long-acting insulin glargine and the rapid-acting insulin glulisine (Apidra®), should be considered a part of this multi-drug regimen, therefore making it important for cardiologists to become familiar with them. ■

References

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