OREGON DUR BOARD NEWSLETTER©

AN EVIDENCE BASED DRUG THERAPY RESOURCE

Controversies in Type 2 Diabetes Management

By Kathy Sentena, Pharm. D.
Clinical Assistant Professor of Pharmacy Practice, OSU College of Pharmacy

Diabetes is a common disease effecting over 7% of the United States population.[1] By 2025 it is projected that the incidence of diabetes will increase to almost 9%.[1] Mortality due to diabetes is high, accounting for the seventh leading cause of death in the general population.[1] Additionally, caring for people with diabetes consumes a large amount of healthcare resources. One out of every seven US healthcare dollars are spent on people with diabetes.[2] Currently, controversies in the area of diabetes management include how to best manage patients with impaired glucose tolerance (IGT) and if diabetes treatment should target postprandial hyperglycemia.

Impaired Glucose Tolerance

IGT is a scenario in which an oral glucose tolerance test (OGTT) demonstrates glucose values that are abnormally high but below levels used to diagnose diabetes. OGTT values that are >140mg/dL and <200mg/dL indicate IGT.[3] IGT is believed to be one of the initial defects that occur in glucose homeostasis before overt diabetes is diagnosed. IGT is a very common condition that affects approximately 20 million people in the US.[4] Not all people who have IGT will develop type 2 diabetes. The progression rate of IGT to diabetes is variable and ranges from 1 to 10 of every 100 persons.[4] Ethnicity and the presence of risk factors contribute to the development of diabetes and account for some of the variation in progression rates.[5]

Evidence supporting the treatment of IGT indicates that this pre-diabetes state predisposes individuals to complications and mortality. Epidemiological studies have suggested that IGT is associated with an increased risk of cardiovascular complications.[6,7,8,9] Some studies have also shown a relationship between IGT and an increased incidence in mortality.[10,11,12,13] Definitive, controlled trials are needed to help discern the role of IGT and its relationship to complications and mortality rates.

Although there is no concrete evidence to support initiating pharmacotherapy in individuals with IGT, some drugs have been studied in this regard. Thiazolinedinediones were shown to normalize glucose levels in people with IGT.[14,15,16] These studies were of short duration and evaluated the effects of treatment on glucose levels, but not the progression to diabetes or the development of diabetic complications. Metformin also was studied in patients with IGT. Some small studies suggested that metformin helps to improve insulin abnormalities in patients with IGT and prevents the conversion from IGT to diabetes.[17,18,25]

Lifestyle modifications show the most promise in preventing the transition from IGT to type 2 diabetes.[19,20,21,22,23,24] Many of these studies were long term, randomized controlled trials that demonstrated a decrease in the progression of diabetes with exercise and diet modifications. The most recent of these studies, the Diabetes Prevention Program, showed that diet and exercise decreased the risk of developing diabetes by 58%. Whereas, patients who took metformin 850mg twice daily, had a 31% decreased risk.[25] Although it is sometimes a challenge to get patients to adhere to diet and exercise recommendations, every attempt should be made to encourage healthy lifestyle changes in patients with IGT to delay or prevent the progression to diabetes and benefit their overall health.

Additional outcome-based, long-term studies need to be done before subjecting patients with IGT to potential adverse reactions of medications, and to justify the treatment of this population with expensive pharmacotherapeutic agents.

Postprandial Hyperglycemia

In patients with an established diagnosis of diabetes, a newer and controversial approach to patient management is targeting postprandial glucose values. Most often postprandial values are taken 2 hours after a meal, when glucose levels should have returned to normal. Time of meal, and quantity and composition of the meal affect the magnitude, time and peak of glucoses, making postprandial values difficult to consistently evaluate.

It is largely unknown if targeting postprandial values improves diabetes outcomes. Some studies have shown that abnormal postprandial glucose levels are associated with an increased prevalence of complications and mortality. [26,27,28] Studies suggest that postprandial glucoses correlate better than fasting glucoses to HbA1c levels; however, there is conflicting evidence within the literature. Since HbA1c is an average of glucose concentrations, it encompasses fasting, as well as postprandial values, and is the measurement that should be targeted when treating people with diabetes. No studies have been done to determine if targeting postprandial glucose values, independently of other glucose measurements, decreases the incidence of diabetic complications. [29,30]

Several studies have been conducted evaluating the role of drug therapy in managing postprandial hyperglycemia. Nateglinide and repaglinide are marketed for this purpose. These agents are insulin secretagogues, similar to sulfonylureas, which work quickly and have a short duration of action. [31,32,33,34,35,36] While they are effective in controlling postprandial glucoses, their overall effect on HbA1c is similar to or less than currently available therapies. Additionally, these agents are very expensive and have minimal or no advantage over sulfonylureas or metformin.

Thiazolidinediones also decrease postprandial glucoses; however, they are expensive, patients have to be frequently monitored for adverse effects and their ability to lower HbA1c is not superior to other first line agents. [37,38,39] Alpha-glucosidase inhibitors, such as acarbose, that delay intestinal absorption of carbohydrates have also been studied. These agents are effective in lowering postprandial glucose levels, however, they are plagued with bothersome side effects, such as diarrhea and flatulence. Additionally, alpha-glucosidase inhibitors only lower HbA1c by 0.2-0.5%. [40] Fast acting insulins, such as lispro and aspart, are marketed for postprandial glucose control because of their fast onset of action, which mimics first-phase insulin secretion. These insulins are effective in controlling postprandial glucose values. [41,42,43] However, regular insulin, which is less expensive, also can control postprandial

levels and may provide additional coverage by preventing loss of pre-meal glucose control.

New Consensus Guidelines

Controversies surrounding the best way to treat diabetes and other diseases are common. Using an evidence-based approach helps to ensure patients receive quality care. Recently the American Association of Clinical Endocrinologists/Amercian College of Endocrinology released new consensus guidelines for glycemic control. [44]

The HbA1c target has been reduced to 6.5%. This recommendation is based on epidemiological data from the UKPDS that demonstrated an elevated risk for microvascular and macrovascular complications beginning at HbA1c levels of 6.5%. Monitoring an HbA1c at least twice a year for patients at goal and quarterly, or more often, for those patients who are above goal or changing therapy is recommended. The panel reiterated that the HbA1c test is the best indicator of glycemic control and it should be referred to as "A1C."

The panel also states that fasting glucoses and postprandial hyperglycemia are secondary assessment markers. An increased risk of retinopathy is seen at fasting levels >110mg/dL; therefore, the target fasting and preprandial plasma glucose value of <110mg/dL is recommended. The panel recommends that a 2-hour postprandial glucose value be <140mg/dL.

Lastly, the age of screening diabetes was lowered from 45 to 30 years for high-risk groups. Risk factors include family history of diabetes, cardiovascular disease, obesity, hypertension and individuals of certain ethnicity. This recommendation was in response to a 33% increase in diabetes from 1990 to 1998. The largest increase was seen in individuals ages 30-39, in which the prevalence increased by 76%.

Conclusion

While management of patients with IGT is still being elucidated, current evidence suggests that lifestyle modifications have the most promising outcomes. Encouraging patients to make lifestyle modifications is a safe way to improve glycemic control without predisposing them to treatment risks. In patients with diabetes, drugs should be reserved for patients in whom lifestyle changes have failed and when HbA1c values exceed 6.5%. There is a lack of strong data that suggests that postprandial glucoses should be specifically targeted to improve outcomes for people with diabetes. Patients should be encouraged to target lower HbA1c values to minimize the risk of complications from glycemic abnormalities.

References

1. Engelgau M., Narayan KM, Herman W. Screening for type 2 diabetes. Diabetes Care 23:1563-1580, 2000.
2. Basile F. The increasing prevalence of diabetes and its economic burden. The Am J of Managed Care 6:S1077-1081, 2000.
3. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 20:1183-1197, 1997.
4. Diabetes Prevention Program. www.niddk.nih.gov/patient/dpp/dpp-q&a.htm. Accessed September 2001.
5. Edelstein S., et al. Predictors of progression from impaired glucose tolerance to NIDDM. Diabetes 46:701-710, 1997.
6. Barzilay J., et al. Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria. The Lancet 354:622-625, 1999.
7. Tominaga M., et al. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. Diabetes Care 22:920-924, 1999.
8. Wingard D., et al. Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. Diabetes Care 16:1022-1025, 1993.
9. Wilson P., Cupples A., Kannel W. Is hyperglycemia associated with cardiovascular disease? The Framingham Study. Am Heart Journal 121:586-590, 1991.

10. The Decode Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The Lancet 354:617-21, 1999.
11. Balkau B., et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. Diabetes Care 21:360-367, 1998.
12. Curb J., et al. Sudden death, impaired glucose tolerance, and diabetes in Japanese American men. Circulation 91:2591-2595, 1995.
13. Lowe L., et al. Diabetes, asymptomatic hyperglycemia, and 22-year mortality in black and white men. Diabetes Care 20:163-169, 1997.
14. Antonucci, T. et al. Impaired glucose tolerance is normalized by treatment with the thiazolidinedione troglitazone. Diabetes Care 20:188-193, 1997.
15. Berkowitz K., et al. Effect of troglitazone on insulin sensitivity and pancreatic beta-cell function in women at high risk for NIDDM. Diabetes 45:1572-1579, 1996.
16. Cavaghan M., et al. Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance. J Clin Invest 100:530-537, 1997.
17. Li C., et al. Effect of metformin on patients with impaired glucose tolerance. Diabetic Medicine 16:477-481, 1999.
18. Scheen A., Letiexhe M., Lefebvre J. Effects of metformin in obese patients with impaired glucose tolerance. Diabetes Metabolism 11:S69-80, 1995.
19. Eriksson K., Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. Diabetologia 34:891-898, 1991.
20. Pan X, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. Diabetes Care 20:537-544, 1997.
21. Baan C., et al. Physical activity in elderly subjects with impaired glucose tolerance and newly diagnosed diabetes mellitus. Am J of Epidemiology 149:219-27, 1999.
22. Uusitupa M., et al. The Finnish diabetes prevention study. British J of Nutrition 83:S137-S142, 2000.
23. Marshall J., et al. Dietary fat predicts conversion from impaired glucose tolerance to NIDDM. Diabetes Care 17:50-56,1994.
24. Long S., et al. Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type 2 diabetes. Diabetes Care 17:372-375, 1994.
25. Charatan F. Exercise and diet reduce risk of diabetes, US study shows. BMJ 323:359, 2001.
26. Monnier L. Is postprandial glucose a neglected cardiovascular risk factor in type 2 diabetes? European J of Clin Investigation 30:S3-11, 2000.
27. Beks P., et al. Peripheral arterial disease in relation to glycaemic level in an elderly Caucasian population: the Hoorn study. Diabetologia 38:86-96, 1995.
28. Hanefeld M., et al. Risk factors for myocardial infarction and death in newly detected NIDDM; the Diabetes Intervention Study, 11-year follow-up. Diabetologia 39:1577-1583, 1996.
29. Avignon A., Radauceanu A., Monnier L. Nonfasting plasma glucose is a better marker of diabetic control than fasting plasma glucose in type 2 diabetes. Diabetes Care 20:1822-1826, 1997.
30. Bastyr E., et al. Therapy focused on lowering postprandial glucose, not fasting glucose, may be superior for lowering HbA1c. Diabetes Care 23:1236-1241, 2000.
31. Kalbag J., et al. Mealtime glucose regulation with nateglinide in healthy volunteers. Diabetes Care 24:73-77, 2001.
32. Hirschberg Y., et al. Improved control of mealtime glucose excursions with coadministration of nateglinide and metformin. Diabetes Care 23:349-353, 2000.
33. Uchino H., et al. Impairment of early insulin response after glucose load, rather than insulin resistance, is responsible for postprandial assessment using nateglinide, a new insulin secretagogue. Endocrine Journal 47:639-641, 2000.
34. Horton E., et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. Diabetes Care 23:1660-1665, 2000.
35. Nattrass M., Lauritzen T. Review of prandial glucose regulation with repaglinide: a solution to the problem of hypoglycemia in the treatment of type 2 diabetes? International Journal of Obesity 24:S21-S31, 2000.
36. Landgraf R., Frank M., Dieken M. Prandial glucose regulation with repaglinide: its clinical and lifestyle impact in a large cohort of patients with type 2 diabetes. International J of Obesity 24:S38-S44, 2000.
37. Frias J., et al. Metabolic effects of troglitazone therapy in type 2 diabetic, obese, and lean normal subjects. Diabetes Care 23:64-69, 2000.
38. Miyazaki Y., et al. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. Diabetes Care 24:710-719, 2001.
39. Raskin P., et al. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type 2 diabetes. Diabetologia 43:278-284, 2000.
40. Landgraf R. Approaches to the management of postprandial hyperglycemia. Exp Clin Endocrinol Diabetes 107:S128-S132, 1999.
41. Setter S., et al. Insulin aspart: a new rapid-acting insulin analog. The Annals of Pharmacotherapy 34:1423-1431, 2000.
42. Raskin P., et al. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 23:583-588, 2000.
43. Lindholm A., McEwen J., Rus A. Improved postprandial glycemic control with insulin aspart. Diabetes Care 22:801-805, 1999.
44. American Association of Clinical Endocrinologists. ACE consensus conference on guidelines for glycemic control. www.aace.com/pub/press/release/diabetesconsuswhitepaper.php. Accessed October 2001.