Diabetes-Related Clinical Issues Represented by the "Faces of Diabetes"

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Members of the "osteopathic medical family" who themselves are patients with diabetes related their medical histories at the American College of Osteopathic Family Physicians symposium, "The Faces of Diabetes." The program was conducted Monday, October 7, 2002, in Las Vegas during the 107th Annual American Osteopathic Association Convention and Scientific Seminar. This article briefly discusses issues in the management of diabetes illustrated by the individual histories. Topics represented by "the faces of diabetes" include diabetes and comorbidities, hypoglycemia in diabetes mellitus, abnormalities associated with insulin-induced hypoglycemia, and diabetes in pregnancy.

The individual discussions here capture only a small amount of information based on presentations by patients with diabetes. Patients related brief histories, and they and their families provided invaluable dialogue with passion and candidness. The format here expands salient topics that may be of benefit in clinical practice.

Diabetes and Comorbidities

An osteopathic physician with diabetes relates the chronology of his medical events. A major factor in his history is the issue of diabetes and comorbidities as well as the course of diabetes with coronary artery disease.

The presence of diabetes raises the incidence of cardiovascular disease twofold to threefold and cardiovascular mortality twoford to fivefold compared with individuals without diabetes. Cardiovascular disease contributes to approximately 65% of deaths among diabetic patients.[1]

Addressing comorbidities in individuals with diabetes remains a major therapeutic focus. Several studies have addressed these issues in a variety of ways. Most recently, the Steno-2 study,[2] an intensive target-driven study, addressed cardiovascular risk.

The clinical endpoints for the intensively treated group included a blood pressure measurement of less than 130/80 mm Hg, A1c level of less than 6.5%, fasting cholesterol level of less than 175 mg/dL, and fasting triglycercide concentration of less than 150 mg/dL. All patients in the intensively treated group were treated with stepped behavior modification (diet and exercise). Hyperglycemic therapy included oral hypoglycemic agents and insulin. Hypertension was treated with angiotensin-converting enzyme inhibitors (ACE), angiotensin II–receptor blockers, diuretics, calcium-channel blockers, or β-blockers. Therapy for dyslipidemia included statins and fibrates, and, for those at risk for cardiovascular events, aspirin.

Compared with the conventionally treated group, the intensively treated group had a reduction in risk ratio of 0.47 for cardiovascular disease, 0.39 for nephropathy, 0.42 for retinopathy, and 0.37 for neuropathy. There was an overall 20% reduction in cardiovascular events in the intensively treated group versus the conventionally treated groups. The study design did not allow conclusions regarding which treatment resulted in the most critical changes in diabetes-related complications.

ACEs contribute to prevention of nephropathy in patients with diabetes (although not exclusive to drug class). The Heart Outcome Prevention Evaluation (HOPE) trial[3] involved 3500 patients with diabetes and assessed the effects of ramipril versus placebo on myocardial infarction and death due to cardiovascular disease. An observation that ramipril reduced the risk of these combined primary endpoints by 25% was noted to be independent of antihypertensive effect of ACEs. In addition to addressing glucose in the context of global risk, individuals with diabetes may require protection against myocardial infarct with aspirin, as well as β-blockers in the postinfarct period or for chronic angina.

Coronary artery revascularization remains a mainstay of surgical treatment. Several studies have compared cardiac bypass surgery (CABG) with percutaneous coronary intervention (PCI). CABG may show a mortality advantage, particularly in a population of diabetic patients with multivessel disease. However, other trials have shown similar morbidity and mortality for CABG and PCI. Methods change for coronary intervention, including coronary stenting, IIb/IIa antagonists, gamma and beta irradiation, and laser energy.

The Bypass Angioplasty Revascularization Investigation (BARI) trial[4] compared CABG with PCI. The study spanning 5 years showed reduced coronary artery disease event rates with CABG. However, several newer PCI techniques were not used.[5] Stenting and other techniques play a major role in preventing restenosis. A study by Hammoud et al[6] showed restenosis rates are no higher in the diabetic than in the nondiabetic population.

An osteopathic physician with diabetes expressed his views on the diffi-

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culty to modify lifestyle to reduce cardiac event rates. Efforts have been made to evaluate his concomitant comorbid risk factors.

Hypoglycemia in Diabetes Mellitus

Another patient with diabetes represented several areas of concern, but most notable is his experience with hypoglycemic increased insulin sensitivity and increased glucose utilization.

Hypoglycemia in diabetes is a common event. In the clinical setting, it is associated with morbidity and mortality. It is also partially responsible for the reluctance to achieve target A1c levels. The definition of hypoglycemia may vary from a blood glucose level of 45 mg/dL to 60 mg/dL. The symptoms of hypoglycemia may be categorized in two groups, including autonomic (adrenergic) and central glucose deprivation (neuroglycopenia).

Abnormalities Associated With Insulin-Induced Hypoglycemia

Individuals with type 1 diabetes mellitus (T1DM) have shown various abnormalities associated with insulin-induced hypoglycemia. These defects in counterregulatory responses include blunted responses to cortisol, growth hormone, glucagon, and neural activation. Impaired recovery to hypoglycemia may also stem from impaired hepatic glucose production.[7]

In patients with T1DM who have poor glycemic control, the thresholds for sympathetic activation, neuroglycopenic symptoms, and cognitive function may be at a higher setpoint than in patients with excellent glycemic control. The patient with poor glycemic control may have hypoglycemic symptoms starting at higher blood glucose levels. In contrast, patients with excellent glycemic control may have hypoglycemia at lower thresholds. Clinically, frequent episodes of hypoglycemia can be treated by raising a patient's blood glucose values for approximately 2 weeks to lower the patient's setpoints for perception of hypoglycemia.

Blunting of counterregulatory hormones results in the patient's being unaware of hypoglycemia. Neither the presence nor absence of neuropathy or autonomic neuropathy is responsible for this deterioration, but rather it is antecedent hypoglycemia. The antecedent hypoglycemia need not be prolonged or frequent episodes. It may be found after a single episode of hypoglycemia. The degree of antecedent hypoglycemia—70 mg/dl versus 50 mg/dL—may also show blunting of counterregulatory responses. This impairment of counterregulatory response, if severe, may last for 1 week after the episode.[8]

Management of Hypoglycemia

Management of hypoglycemia in patients with diabetes involves the following approaches.

■ **Avoidance—**The thresholds for hypoglycemia is higher in patients with newly diagnosed and poorly controlled T1DM. Increasing glucose levels for a short time (2 weeks) may reset the hypoglycemic threshold. Forewarning patients of the signs and symptoms of hypoglycemia is necessary. Recognize that the symptoms may vary in intensity from patient to patient. On a more fundamental basis, instructing patients to keep a schedule of mealtime without skipping or delaying meals can be helpful. It is imperative that patients match their food consumption with their insulin dose. They need to know that increased activity such as gardening and mowing grass may not be considered exercise, but such activity can result in hypoglycemia by increasing glucose utilization, also increasing insulin sensitivity. This hypoglycemia may occur even several hours after the activity period.

■ **Identification of Predisposing Factors—**Factors that predispose to hypoglycemia are important to identify, as patients may not have complete control over them. Such factors include advanced age,[9-11] hepatic or renal disease, intercurrent illness, drugs that interfere with drug metabolism, and, the most common, alcohol. Patient education and communication with the health care team are important.

■ **Gastroparesis and Malabsorption—**Other clinical entities that place patients at risk for hypoglycemia and complicate therapy are gastroparesis and malabsorption. Their presence requires careful attention to glycemic goals and the quantity and timing of food consumption.

Therapy for hypoglycemia focuses on carbohydrate ingestion. Several sources of finite amounts of carbohydrates are available. Many sources provide 20 g of glucose, including Kool-Aid with sugar (13.4 oz), orange or apple juice (12 oz), and banana (6.4 oz). Glucagon (1.0 mg intramuscularly) can be administered if oral intake is not possible. It may be useful for family, friends, or coworkers to have a glucagon kit available. Continued monitoring and serial glucose determinations may be required in more severe cases.

The issues of type 2 diabetes mellitus (T2DM) and counterregulation are not as clear. Hypoglycemia may occur in T2DM through indirect evidence. Regardless of cause, proper precautions and treatment should be implemented.

Currently, many insulin preparations are available to control glycemia. Several choices provide individual treatment approaches to reduce hypoglycemia. Isophane insulin suspension, which has its peak effects in approximately 8 hours, may result in hypoglycemia. In contrast, insulin glargine has a relatively flat insulin profile and therefore may result in less hypoglycemia when compared with isophane insulin suspension[12,13] in both T1DM and T2DM. Short-acting insulin analogs reduce the risk of hypoglycemia 2 to 3 hours after a meal compared with short-acting insulins.[14,15]

Oral agents that stimulate insulin secretion may result in hypoglycemia. Some, particularly glyburide, may cause hypoglycemia with effects extending beyond the presence of the parent drug (due to active metabolites). Short-acting secretagogues have a reduced risk of hypoglycemia. Metformin, thiazolodinediones, and α-glucosidase inhibitors have a reduced risk for hypoglycemia unless combined with insulin or an insulin secretagogue.

Diabetes in Pregnancy

The mother of two children, aged 4 and 2 years, shared some of the everyday experiences in her care after the diagnosis of gestational diabetes during the pregancy with her first child. Her T1DM was diagnosed after her second pregnancy and within 3 months of her husband's diagnosis of T1DM. She admitted to feeling frustrated in her efforts to help her husband control his diabetes while

she managed her own diabetes during pregnancy. She was diligent in her efforts to maintain control of her diabetes during pregnancy.

The management of diabetes in pregnancy has dramatically changed since insulin was first discovered. Today new advances in genetic manipulation, stem cell research, and pancreatic islet cell capsules are being investigated. Currently, key management elements in care include the balancing of diet, exercise, and medications. The interactions between the patient and the health care team are critical. They include psychological support, fetal surveillance, and adequate postpartum follow-up.

Therapy for diabetes mellitus in pregnancy is directed to achieve fasting glucose values of less than 95 mg/dL, and postprandial levels of less than 120 mg/dL. The A1c level may be useful; however, this measurement reflects a 2-month average of ambient glucose levels.

Exogenous insulin may be used in different designs. Currently, the basal bolus approach with isophane insulin suspension prebreakfast and predinner with a premeal rapid-acting analog (insulin aspart, insulin lispro) is used frequently. Insulin glargine is used as basal insulin; however; it should be used in pregnancy only when clearly necessary as no well-controlled clinical studies of its use during pregnancy have been done.

Insulin requirements change during pregnancy:

- first trimester, 0.5 units per kilogram of weight;
- second trimester, 0.75 units per kilogram of weight;
- third trimester, 1.0 units per kilogram of weight.

Insulin is titrated to achieve the previously stated preprandial and postprandial goals and A1c levels of less than 6.5% without hypoglycemia. Insulin infusion pumps are also useful and may provide greater flexibility in lifestyle. Obviously, patients must be compliant and willing to do frequent self-monitoring. Generally, the total insulin dose is divided as a 60% basal dose and a 40% bolus dose.

Nutrition management may include three meals and mid-morning, mid-afternoon, and bedtime snacks. The diet is based on 30 kcal per kilogram of actual body weight and modified for overweight or obese patients.[16] The landmark study, the Diabetes Control and Complication Trial (DCCT),[17] involved individuals with T1DM. A total of 180 women completed 270 pregnancies between 1983 and 1993, with 191 total live births. The mean A1c level of the women was 7.4% at the time of conception for the intensively treated group and 8.1% in the conventionally treated group. Of the nine congenital malformations that occurred, eight occurred in the conventionally treated group. Thirty-two spontaneous abortions occurred. Glucose control is achievable with rates of spontaneous abortion and congenital malformations similar to those in the nondiabetic population.

The A1c level is widely used and recognized as the best marker of glycemic control.[18] A recent analysis from Denmark confirmed a clinically significant and consistent relationship between adverse fetal outcome and A1c levels in the first trimester.[18]

Preconception care of T1DM is critical. Unfortunately, many women do not take advantage of such care. A study in the United Kingdom found only 26% of women received preconception care.[19] In the United States, preconception care occurred in 7% to 34% of pregnancies.[20]

A study by Herman et al[20] compared pregnant women who had preconception care with women without such care. The women with preconception care had better A1c levels for the first prenatal visit and throughout pregnancy than women without preconception care. Preconception care when implemented can achieve better glycemic goals during fetal organogenesis and reduce major congenital malformations. Additionally, prenatal care results in fewer complications at time of delivery.

Prenancy provides an opportunity for patients to upgrade their diabetes treatment status and potentially establish a generally improved lifestyle.

Comment

"The Faces of Diabetes" program provided a forum for individuals with diabetes and their families to share their experiences with health care professionals. It provided an opportunity in every way to enlighten the health care personnel of the adjustments to daily life, the day-to-experiences people with diabetes must face. This forum also provided the opportunity for individuals with diabetes to candidly speak out about their individual experiences, concerns, fears, and frustrations that they face on a daily basis. Perhaps most important, the program provided an opportunity to share success stories, which are helpful in promoting overall well-being.

References

1. Kannel WH, McGee DL. Diabetes and cardiovascular disease: The Framingham Study. *JAMA.* 1979;241(19):2035-2038

2. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med.* 2003;348:383-393.

3. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. *Lancet.* 2000;355:253-259.

4. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med.* 1996; 335:217-225.

5. Niles NW, McGrath PD, Malenka D, Quinton H, Wennberg D, Shubrooks SJ, et al for the Northern New England Cardiovascular Disease Study Group. Survival of patients with diabetes and multivessel coronary artery disease after surgical or percutaneous coronary artery disease revascularization results of a large regional prospective study. Northern New England Cardiovascular Disease Study Group. *J Am Coll Cardiol.* 2001;37:1008-1015.

6. Hammoud T, Tanguay JF, Bourassa MG. Management of coronary artery disease: therapeutic options in patients with diabetes. *J Am Coll Cardiol.* 2000;36:355-365.

7. Mevorach M, Kaplan J, Chang CJ, Rossetti L, Shamoon H. Hormone-independent activation of EGP during hypoglycemia is absent in type 1 diabetes mellitus. *Am J Physiol.* 2000;278:E421-E429.

8 George E, Harris N, Bedford C, Macdonald IA, Hardisty CA, Heller SR. Prolonged but partial impairment of the hypoglycaemic physiological response following short-term hypoglycaemia in normal subjects. *Diabetologia.* 1995;38:1183-1190.

9. Shorr RI, Ray WA, Daugherty JR,Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med.* 1997;157:1681-1686.

10. Seltzer HS. Drug-induced hypoglycemia. A review of 1418 cases. *Endocrinol Metab Clin North Am.* 1989;18:163-183.

11. Ben-Ami H, Nagachandran P, Mendelson A, Edoute Y. Drug-induced hypoglycemic cima in 102 diabetic patients. *Arch Intern Med.* 1999;159:281-284.

12. Pieber TR, Eugene-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study group of HOE 901 in type 1 diabetes. *Diabetes Care.* 2000;23:157-163.

13. Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care.* 2000;23: 1666-1671.

14. Setter SM, Corbett CF, Campbell RK, White JR. Insulin aspart: a new rapid acting insulin analog. *Ann Pharmacother.* 2000;34:1423-1431.

15. Horton ES, Clinkingbeard C, Gatlin M, Foley J, Mallows S, Shen S. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care.* 2000;23:1660-1665.

16. Gonzalez JL. Management of diabetes in pregnancy. *Clin Obstet Gynecol.* 2002;45:165-169.

17. The Diabetes Control and Complications Trial Research Group. Pregnancy outcomes in the Diabetes Control and Complications Trial. *Am J Obstet Gynecol.* 1996;174:1343-1353.

18. Nielsen GL, Sorensen HT, Nielsen PH, Sabroe S, Olsen J. Glycosylated haemoglobin as predictor of adverse fetal outcome in type 1 diabetic pregnancies. *Acta Diabetol.* 1997;34:217-222.

19. Dunne FP, Brydon P, Smith T, Essex M, Nicholson H, Dunn J. Preconceptive diabetes care in insulin-dependent diabetes mellitus. *QJM.* 1999;92:175-176.

20. Herman WH, Janz NK, Becker MP, Charron-Prochownik D. Diabetes and pregnancy. Preconception care, pregnancy outcomes, resource utilization and cost. *J Reprod Med.* 1999;44:33-38.