Bone Disease, Gestational Diabetes Mellitus, and Health Care

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This is the seventh of a series of articles based on presentations at the American Diabetes Association (ADA) Scientific Sessions held 6–10 June 2008 in San Francisco, California.

Type 2 diabetes and bone disease

Robert Josse (Toronto, Canada) discussed new concepts of skeletal homeostasis and its disorders in a symposium addressing the relationship of type 2 diabetes, and in particular that of thiazolidinedione (TZD) treatment, to bone disease. Remodeling is the process of combined osteoclast and osteoblast activity that optimizes bone structure to improve strength and mechanical function and repair microdamage, fulfills metabolic functions, and acts as an important source of growth factors. The basic multicellular units of bone contain osteoclasts that excavate bone, mononuclear cells that remove cellular debris, and osteoblasts that replace the removed bone. Receptor activator of nuclear factor-κB (RANK) ligand is a transmembrane protein belonging to the tumor necrosis factor superfamily that specifically binds RANK and osteoprotegerin and plays an important role in regulating osteoclast differentiation and activation, whereas the Wnt (related to a gene controlling wing forming in fruit flies) system controls osteoblast activity with complex signals linking osteoblasts and osteoclasts (1). An LDL receptor–related protein (LRP)5 mutation is associated with increased bone mass. The LRP5/Wnt signaling pathway increases activity of the multifunctional protein β-catenin that participates in cell adhesion and nuclear signaling and is inhibited by an osteocyte product sclerostin (defects in this are associated with sclerositis) and by the antagonist Dickkopf (DKK) proteins. DKK1 is a myeloblast product that helps explain the failure of multiple myeloma lesions to show activity on bone scan.

Osteoporosis may be caused by increased osteoclast or decreased osteoblast activity, compromising bone strength, which Josse suggested be seen as an integrated measure of bone density and bone quality, recognizing that standard bone density measurement fails to assess the latter component. Bones break when the applied load exceeds bone strength, leading to the question of whether treatment of low bone density itself fully addresses fracture risk. There is evidence that for a given bone density, with advancing age, there is an increase in fracture risk, suggesting additional factors. Josse suggested that bone density should perhaps not be used to define disease but, rather, should be considered a risk factor for fracture. He recommended use of the fracture risk calculator, available at www.shef.ac.uk/frax. Collagen is very important and can be glycosylated, perhaps occurring to an increased extent in diabetes and related to fragility. It is interesting that leptin plays a role in bone homeostasis and that abnormalities of leptin action may be related to skeletal disorders in diabetes. In addition to bone density measurement, bone formation may be inferred by measurement of bone-specific alkaline phosphatase and the vitamin K-dependent protein osteocalcin, both produced by osteoblasts, whereas resorption can be assessed by measurement of N-telopeptides that are collagen products.

Peter Vestergaard (Aarhus, Denmark) reviewed the question of whether type 2 diabetes is associated with fracture. Obesity is associated with higher bone density, which when corrected for BMI tends to be higher in type 2 diabetes and lower in type 1 diabetes. Type 2 diabetes is, however, associated with increased hip (2) and foot fractures but not with vertebral fracture, leading to the question of whether there is abnormal bone quality. Eye disease, neuropathy, and cardiovascular disease (CVD) have been shown to be risk factors for hip fracture in type 1 diabetes. Some (3) but not all (4) studies also show increased fracture rates in pre-diabetes.

Andrew Gray (Auckland, New Zealand) discussed mechanisms by which TZDs affect bone and roles of excess osteoclast and reduced osteoblast activity (5). Osteoblasts are derived from pluripotent mesenchymal stem cells in bone marrow that can produce myoblasts, chondrocytes, adipocytes, or osteoblasts. TZDs reduce osteoblast formation while increasing bone adipocytes in vitro (6) and in vivo (7). Mice heterozygous for inactivation of peroxisome proliferator–activated receptor (PPAR)γ have increased bone formation and increased bone mass (8); there also was evidence of increased osteoclast effect mediated by PPARγ, particularly in older animals (9). Healthy postmenopausal women receiving rosiglitazone versus placebo for 14 weeks had a decrease in levels of two osteoblast markers, procollagen type 1 NH_2-terminal propeptide and osteocalcin, with reduction in proximal femur and lumbar spine bone density (10); type 2 diabetic patients receiving rosiglitazone had a 20% reduction in bone-specific alkaline phosphatase (11). Both pioglitazone (12) and rosiglitazone (13) reduce bone mineral density—an effect similar to that of glucocorticoids in decreasing bone formation with inappropriately stable bone resorption (14).

There are also potential indirect effects as a result of change in adipocytokines and growth factors, with rosiglitazone decreasing IGF-I expression (15) and reducing levels of insulin that increase bone formation in vivo. Amylin inhibits bone resorption (16), and TZDs may reduce amylin levels. Interestingly, adiponectin is a potent negative regulator of bone mass, and its levels decrease with TZD treatment.

Ann Schwartz (San Francisco, CA) reviewed clinical evidence of association of TZDs with fracture risk. In A Diabetes Outcome Progression Trial (ADOPT), there were 2.74 leg and arm fractures per 100 person-years in women receiving rosiglitazone, with rates of 1.54 with metformin and 1.29 with glyburide; rates

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DOI: 10.2337/dc09-zb07

were not increased in men, and spine fracture rates were low (17). An analysis by Takeda Pharmaceutical Company of the overall experience with pioglitazone reported fracture rates of 1.9 per 100 person-years in women receiving pioglitazone but 1.1 in women receiving comparator agents (18) (again without increased risk in men), with doubling of fractures among women in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive). Fractures occurred in six women and two men receiving pioglitazone, but no fractures were reported in subjects receiving glimepiride in the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) study (19). In an epidemiological analysis of 66,696 type 2 diabetic subjects followed from 1994 to 2005 in the U.K., 6% used TZDs with a dose effect on total, hip, and wrist fractures. Fracture rates more than doubled both in men and in women, whereas there was no effect of treatment with sulfonylureas, metformin, or insulin (20). TZD bone loss does then appear to be a class effect; although with the small numbers of events, it is uncertain whether there is increased risk of hip and spine fracture. Fracture rates with TZDs may, similarly, only have been recognized to increase in women because of their higher baseline risk, and there certainly may be increased risk in older men. Older men have higher levels both of estrogens and of testosterone than postmenopausal women, potentially explaining the sex difference; however, fracture rates were increased in premenopausal women and in those receiving hormone replacement in ADOPT. Baseline risks of hip and vertebral fracture also are low in the age-group of subjects receiving TZDs in the clinical trials; thus, the apparent limitation of the effect to long bones may not be true in older subjects receiving TZDs. Schwartz concluded that fracture risk should be assessed in patients considered for TZD treatment and that treatment to prevent osteoporosis should be considered, although recognizing that the action of TZDs may be to reduce osteoblast numbers, so that the antiresorptive bisphosphonates might not be effective in reducing TZD-induced bone loss.

A number of studies presented at the ADA meeting reviewed further aspects of the relationships between diabetes and bone. Vestri et al. (abstract 93) noted that animals not expressing osteocalcin (a marker of osteoblast activity and bone formation) have insulin resistance. Adipocytes incubated with osteocalcin had three- to fourfold increase in basal and insulin-induced glucose transport. Noncarboxylated osteocalcin levels trended to be lower in 28 insulin-resistant and 16 untreated type 2 diabetic subjects than in 31 subjects who were insulin sensitive; noncarboxylated osteocalcin correlated modestly with clamp insulin sensitivity, BMI, fat mass, fasting glucose, and age, suggesting a previously unrecognized factor involved in insulin action. There is emerging evidence that low vitamin D levels are related to abnormalities of diabetes. The data of Davis et al. (abstract 891) from a 5-year follow-up study showed that vitamin D deficiency may be one factor contributing to the bone loss at the femoral neck of male type 1 diabetic patients of mean age 49 years. Ou et al. (abstract 1448) found that both insulin sensitivity and secretion during hyperglycemia in 150 subjects with normal glucose tolerance were associated with serum levels of 25-hydroxyvitamin D [25(OH)D], suggesting roles of vitamin D deficiency in the dual defects of type 2 diabetes. Sokol et al. (abstract 625) compared 28 older subjects having fasting glucose <126 and 2-h glucose level >170 mg/dl with 27 age-, sex-, and BMI-matched subjects with normal glucose tolerance and reported median 25(OH)D levels of 19 and 24 ng/ml, respectively. Reactive hyperemia–peripheral artery tonometry, a surrogate marker of endothelial dysfunction, was reduced in the impaired glucose tolerance group with vitamin D <20 ng/ml but was not associated with vitamin D status in subjects with normal glucose tolerance, suggesting that vitamin D supplementation might improve vascular function and reduce CVD risk in diabetes and in pre-diabetes. Svoren et al. (abstract 1701) reported mean 25(OH)D level of 26.8 ng/ml in 128 type 1 diabetic children with only 24% having levels of >30 ng/ml (the normal range), while 15% had levels of <20 ng/ml. Age was associated with lower vitamin D, with normal levels in 44, 31, and 15% of those aged <5, 6–11, and 12–18 years, respectively. Simpson et al. (abstract 1006) found that vitamin D intake estimated from a food frequency questionnaire was negatively associated with the likelihood of developing islet autoimmunity in 1,785 children who had a high-risk HLA genotype or who were a first-degree relative of a type 1 diabetic patient, whereas cow's milk protein ingestion was positively associated with the risk of developing such immunity. Craig et al. (abstract 1795) similarly found that vitamin D deficiency was more common among islet antibody-positive participants in a group of children having a first-degree type 1 diabetic relative.

Gestational diabetes mellitus

David Sacks (Bellflower, CA) gave the Norbert Freinkel Lecture on gestational diabetes mellitus (GDM). For care of women with diabetes prior to pregnancy, the goal is to maintain glucose levels as near normal as possible; Sacks, however, asked, "What is normal?" He pointed out that there is a disagreement over the times for glucose testing during pregnancy, as well as over the goals for fasting, 1- and 2-h postprandial glucose, and A1C. Continuous glucose monitoring of nondiabetic women shows fasting, preprandial, and peak postprandial glucose levels averaging 72, 81, and 106 mg/dl in nonobese and 73, 90, and 117 mg/dl in obese women, with peak glucose levels somewhat later after the beginning of the meal in obese women (21). A study of diurnal glucose profiles during normal pregnancy showed progressive increase from 28 to 32 and to 38 weeks, so that there might be different glycemic targets for different stages of pregnancy (22). If one judges the adequacy of treatment by the incidence of macrosomia, one must also take into account gestational age, perhaps defining macrosomia as ≥90th percentile for gestational age. Even with such an approach, levels differ in different regions, with the 90th percentile at 40 weeks as 4,000 g in California but 3,800 g in Cleveland, Ohio. Other measures include the ponderal index (weight in grams × 100 divided by height in centimeters), which increases until the last 8 weeks of pregnancy. Furthermore, it is not altogether clear that there is a definite relationship between maternal glycemia and birth weight, with confounders including the type of diabetes, gestational age at the initiation of treatment, the number of times per day maternal glucose is tested, timing of glucose testing relative to meals, different measures of maternal glycemia, and perhaps most important, demographics, including maternal age, ethnicity, parity, prepregnancy BMI, weight gain during pregnancy, smoking, hypertension, fetal sex, and gestational age at birth. In a study of 46 women with GDM and 44 type 2 diabetic patients who tested 23 times

weekly on average during pregnancy, gestational age at first visit was 12 vs. 10 weeks, respectively, and birth weights were similar with both third-trimester glucose and maternal BMI significantly associated with birth weight, with no effect of type of diabetes (23). Moreover, neonatal birth weight might not be an optimal measure of success given that fat mass and body fat are greater in infants of women with GDM even without differences in birth weight (24).

Another aspect of the question of whether normal glucose is necessary and desirable is the risk of hypoglycemia. Both pregnancy and type 1 diabetes may blunt the epinephrine response (25). Recurrent exposure to low glucose with tight glycemic control lowers the threshold for activation of the autonomic nervous system; a study of 84 pregnant type 1 diabetic women showed that 19 had 54 episodes of loss of consciousness and 12 had 15 seizures and that seven auto accidents occurred (26). "If we're going to subject our patients to recurrent hypoglycemia," Sacks noted, "I think we need to clearly establish that the benefit outweighs the risk." In a study of type 1 and type 2 diabetic women during pregnancy, the former had considerably higher mean glucose, averaging 110 vs. 97 mg/dl; in addition, type 1 compared with type 2 diabetic women had 19 vs. 2% of days with at least one glucose value of ≤50 mg/dl (27). A study randomizing type 1 diabetic patients to fasting and 1-h glucose levels of 60–90 and 120–140 vs. 95–115 and 155–175 mg/dl, although only including 22 patients, found mean glucose levels of 125, 127, and 131 vs. 147, 145, and 143 mg/dl during the three trimesters of pregnancy; however, on 42 vs. 25% of days at least one glucose value was ≤50 mg/dl. There were no significant differences in gestational age, birth weight, or neonatal hypoglycemia (28). Sacks reviewed a study in which the risks of birth weights large and small for gestational age were similar for fasting glucose levels between 87 and 104 mg/dl, suggesting that it may not be necessary to achieve truly normal glucose levels; however, larger studies of clinical outcomes are needed, particularly for type 1 diabetes. When asked whether 1- or 2-h postprandial glucose should be the target, he replied that "there's no resolution," but that "on a practical level" it is easier to ask women to measure 1-h levels.

Elisabeth Mathiesen (Copenhagen, Denmark) discussed the use of insulin analogs in pregnancy. Approximately half of young women with diabetes do not plan their pregnancy and often present when they have already passed the crucial 6 weeks after missed ovulation while treated with insulin analogs. Changing from insulin analogs to human insulin is typically associated with higher blood glucose levels, and Mathiesen cited a U.K. study with such treatment associated with a two- to fivefold greater likelihood of perinatal mortality, malformations, and preterm delivery. Diabetic women clearly have high risk of severe hypoglycemia during pregnancy (29,30), and here too insulin analogs might be better choices. Lispro, aspart, and glulisine and detemir and glargine all are being studied. The general consensus is that one can achieve a more physiological insulin profile with these analogs. Most patients express greater satisfaction with rapid-acting insulin analogs. There is less than half as great an increase in postprandial glucose area with insulin lispro (31) and insulin aspart (32) compared with regular insulin. However, there have been suggestions of increased malformations and acceleration of proliferative retinopathy with analogs. No evidence exists for mitogenic actions of insulin lispro, insulin aspart, and insulin detemir, but insulin glargine may have higher IGF-I binding and mitogenic potency, leading to concern that it might be less desirable during pregnancy (33).

There have been observational reports of use of insulin lispro during pregnancy (34,35,36). Glycemia achievement is typically somewhat better, with no reports of excess complications. A study of 496 women receiving insulin lispro found a malformation rate of 5.4%, comparable with that of regular insulin (37). Mathiesen performed a randomized controlled trial of 322 women randomly assigned to insulin aspart versus human insulin beginning either before pregnancy or prior to week 10, finding trends to less severe hypoglycemia and less preterm delivery with insulin aspart without differences in retinopathy, malformations, or fetal death. Insulin antibodies were not induced, and insulin aspart was not present in the fetal circulation (38,39). Based on these studies, insulin aspart and insulin lispro are approved for use during pregnancy.

Several observational studies with insulin glargine (each with ~100 patients) showed no evidence of increased malformation or fetal death, and a controlled trial of insulin detemir including 240 subjects is ongoing. Mathiesen concluded that insulin lispro and insulin aspart are safe and useful in pregnancy and that the clinical experience with long-acting insulin analogs is reassuring, although more studies are required.

Denise Feig (Toronto, Canada) discussed the use of oral agents in type 2 diabetes during pregnancy (40), commenting that "before we leap into that new paradigm we should make sure that safety issues are addressed." Preexisting diabetes during pregnancy increased 72% in Ontario, Canada, from 0.8 to 1.5% in 1996–2001 (41). Type 2 diabetes is associated with higher perinatal mortality and a malformation rate similar to that among type 1 diabetic women during pregnancy, with type 2 diabetic patients being heavier, older, more likely to have hypertension, of lower socioeconomic status, and more likely to smoke and present later for care—all associated with greater risk levels (42).

The question of greatest concern is whether oral agents are teratogenic. Both tolbutamide and chlorpropamide cross the placenta, but glyburide that is highly protein bound and glipizide appear to have lower transplacental transport. Feig noted that there may be active transport of glyburide from the fetal to maternal circulation; however, in a study of 12 women who had taken glyburide during pregnancy the drug was not detectable in cord blood at delivery (43). Metformin does cross the placenta with levels of ~68% of maternal circulation, and rosiglitazone appears not to readily cross the placenta. No increase in congenital anomalies has been shown, but the number of subjects studied is small. A meta-analysis of 10 studies with 471 exposed and more than 1,000 nonexposed women showed no evidence of adverse effect. There have been few studies of TZDs that although not teratogenic in animal models do act on nuclear receptors controlling adipocyte growth and maturation, so that one would be concerned about such treatment. Meglitinides, α-glucosidase inhibitors, and incretin-based therapies have not been studied.

Certainly, oral agents should be continued until insulin is started given that hyperglycemia is well-recognized to be teratogenic. In a review of extensive clinical experience of use of sulfonylureas and metformin during pregnancy, the highest perinatal mortality was reported in untreated women (44); Feig cited a subse-

quent study by the same group that did not find association between oral agent use during the first trimester and fetal anomalies, although higher fetal mortality was reported with oral agents alone than with use of insulin either as initial treatment or subsequent to use of oral agents (45). Studies with glyburide suggest that 16–20% of treated women fail to be adequately controlled; however, no differences in glycemic control, neonatal outcome, or perinatal mortality occur when they are carefully followed (23). β-Cell stimulation is a theoretical disadvantage if transplacental passage of sulfonylureas does occur.

Metformin has the advantages of not being associated with hypoglycemia or weight gain, but it does cross the placenta. In a study of 68 sulfonylurea-treated and 50 metformin-treated women, metformin was associated with increased perinatal mortality and preeclampsia; however, the study was not randomized and metformin-treated women were more obese, so that causality was not demonstrated (46). Controlled studies with metformin have not shown adverse outcome (45,47), including a study of 109 women with polycystic ovary syndrome taking metformin in pregnancy compared with 252 healthy control subjects showing no increased perinatal mortality or preeclampsia, with potential benefits in induction of ovulation and perhaps in decreasing spontaneous abortion and reducing the development of GDM (48).

Metformin alone will likely be insufficient for many women with GDM or type 2 diabetes during pregnancy, leading to the question of whether it should be added to insulin. Hyperinsulinemia early in pregnancy is associated with development of preeclampsia months later (49). Improved glycemic control with decreased insulin dose, limited maternal weight gain, and potential reduction in preeclampsia and gestational hypertension are potential advantages. Metformin could also improve insulin sensitivity in the fetus, decreasing macrosomia and reducing neonatal hypoglycemia. In a study of 42 term Hispanic neonates 24–48 h after birth, insulin sensitivity was decreased in infants large for gestational age (50). Thus, metformin during pregnancy might reduce the likelihood of subsequent insulin resistance, obesity, and diabetes among offspring—a hypothesis being studied in coming clinical trials.

Metformin is present to a low extent in breast milk; infants of breast-feeding women taking metformin have blood levels <1% of the maternal ones (51), and there is no evidence of adverse effect in such children on follow-up testing (52). Glyburide taken during breast-feeding does not appear in breast milk, and normal blood glucose levels in small numbers of tested infants have been reported (53).

There are a number of potential theoretical and practical advantages of metformin, with potential adverse (as well as beneficial) effects of the agent crossing the placenta. Janet Rowan (Auckland, New Zealand) presented rather disappointing results of a recently reported large randomized controlled trial of the use of metformin in type 2 diabetes during pregnancy (54). The investigators hypothesized that similar perinatal outcomes and greater patient acceptability would be seen with metformin, using neonatal morbidity as the primary outcome measure quantitated with a multiple outcome score based on recurrent hypoglycemia, respiratory distress, phototherapy, birth trauma, and 5-min Apgar score <7. Women with GDM were randomized at 20–33 weeks (363 to metformin vs. 370 to insulin), stratified by gestational duration and site, baseline data, maternal glucose, and fetal ultrasound. The median metformin dose was 2,500 mg daily, with 7.6% of women discontinuing prior to delivery (1.9% because of gastrointestinal side effects). The dose was limited by side effects for 8.9%, and 46.3% received supplementary insulin at a median dose of 42 units daily. In the insulin arm, the median dose was 50 units, with greater weight gain seen as expected. Some adverse outcome was seen in 32% of each group, with recurrent hypoglycemia occurring in 15% of those receiving metformin and 18% of those receiving insulin, although profound hypoglycemia was significantly less frequent in those treated with metformin. Respiratory distress, phototherapy, birth trauma, and 5-min Apgar <7 rates were similar with the two strategies. Birth at <37 weeks occurred in 12.1% of women receiving metformin but in 7.6% of those receiving insulin. There was a trend to increased spontaneous preterm birth with metformin, and mean gestational date was 1.7 days shorter with the drug. Cesarean section was performed with similar frequency in 36 and 38% of the two groups. Glycemic control was identical during the first week and remained identical through the pregnancy. Women who needed insulin in addition to metformin had somewhat higher baseline glucose and BMI levels. Women who started at ≤27 and >27 weeks had similar outcomes, and there was a trend to less preeclampsia with metformin. Weight gain was 0.8 kg with metformin plus insulin but 2.0 kg in women receiving insulin alone.

Glucose control appeared to be more important than treatment choice. Dividing the population by fasting glucose tertile <88, 89–97, and >97 mg/dl, the primary outcome occurred in 23, 33, and 39%, respectively. Preliminary analysis of outcome for 2-year-old offspring shows no treatment effect on weight, height, head or abdominal circumference, or other parameters. Subscapular-to-triceps thickness ratio showed an ethnicity effect and was greater in offspring of mothers with higher blood glucose during pregnancy. Rowan suggested that metformin should not be used with fetal growth restriction and should be discontinued if fetal size is small on ultrasound. In a sense, the trial does show overall safety of metformin use during pregnancy and leaves open the question of whether there would be benefit from a strategy of its use in the important group of women with polycystic ovarian syndrome when the agent is begun pregestation and continued through the entire pregnancy.

Several studies presented at the ADA meeting addressed additional aspects of the relationships between pregnancy and diabetes. Correa et al. (abstract 1829) analyzed diabetes-associated birth defects among 12,238 case and 4,608 control subjects and reported pre-GDM in 2.4 and 0.5% of case and control mothers, respectively. For 14 of 18 noncardiac defects and 17 of 26 cardiac defects, however, the elevated risk was limited to offspring of mothers with pre-GDM who did not consume a multivitamin, prenatal vitamin, or folic acid supplement prior to conception. Overall, pre-GDM women who did not take folate had 5.6- and 9.5-fold increase in the likelihood of combined noncardiac and combined cardiac defects, whereas these risks among diabetic women taking folate were increased 1.9- and 3.4-fold, respectively. Retnakaran et al. (abstract 28) compared 487 women in late second/early third trimester who had GDM, gestational impaired glucose tolerance, abnormal screening glucose challenge, or normal glucose tolerance and glucose challenge, finding glucose intolerance at 3 months postpartum

in 33, 17, 10, and 3% of the women, respectively, with the increased risk remaining significant after adjustment for age, ethnicity, family history of type 2 diabetes, prepregnancy BMI, and gestational weight gain, and progressive reduction in insulin sensitivity and insulin secretion, suggesting that pregnancy screening offers an important opportunity to identify pre-diabetic women.

Costacou et al. (abstract 1835) studied 296 type 1 diabetic women, with 16-year follow-up beginning at mean age 28 years and diabetes duration 19 years. Having more than two early pregnancy losses (miscarriage, tubal/ectopic pregnancy, or abortion) increased the likelihood of coronary disease and overt nephropathy 3.1- and 3.9-fold, respectively, whereas there was no increase in risk among women having full-term pregnancy. Shah et al. (abstract 27) studied all 351,685 women who delivered in Ontario, Canada, between April 1994 and March 1997, excluding those with preexisting diabetes or CVD, and compared 8,194 subjects who had GDM with 81,262 control subjects, followed on average for 11.5 years. The risk of having myocardial infarction, stroke, or coronary or cerebral vascular intervention was 1.7-fold higher among women who had GDM; however, adjustment for subsequent development of type 2 diabetes reduced this risk to 1.1-fold, suggesting that diabetes prevention might have worthwhile benefit in this group.

Health care delivery for type 2 diabetes

John Buse (Chapel Hill, NC) delivered the ADA presidential lecture and reviewed evidence showing that diabetes treatment has improved over time, with lower levels of A1C, blood pressure, and cholesterol. In 1999, just 37% of diabetic patients had A1C <7%; however, in 2003–2004 this was seen in 56% of patients with a 0.5% reduction in mean A1C over the 4-year period (55), although some of the apparent benefit might be explained by changes in diabetes diagnosis patterns. End-stage renal disease rates among diabetic patients increased by 86% from 1984 to 1995 but then decreased by 25% to 2002. CVD rates in the Framingham studies decreased in diabetic as well as in nondiabetic subjects over the past 50 years (56), Buse noted, concluding that "the face of diabetes is being transformed."

He contrasted the roles of evidence and marketing in health care delivery. Evidence-based medicine refers, he said, to a "set of principals and methods intended to ensure that to the greatest extent possible population-based policies and individual medical decisions are consistent with evidence of effectiveness and benefit" (57). Perfect evidence is not, however, always available. Furthermore, there often are differences between population-based and individual-based outcomes, and no clinical trial can address all the complex potential interactions of conditions, so that clinical judgment is required. Effectiveness and benefit of various strategies should be taken into account to incorporate ideas of cost and value in decision making of evidence-based medicine. There are multiple potential benefits and potential adverse effects of various treatment approaches for different clinical states, so that "evidence-based" treatment does not imply use of a single cookbook approach.

As Buse suggested, one can think of clinicians as marketers of drugs, devices, and services including education and examinations. In turn, he continued, these "were marketed to us" not only by industry but in an important sense by teaching institutions, political bodies, and organizations such as ADA, which are considered an authoritative source of recommendations. As an example, ADA recommends home glucose monitoring at least three times daily for patients using insulin pumps or taking multiple daily insulin doses but finds the level of evidence for intensive monitoring to be weaker for patients using less frequent insulin injections or other treatment approaches. Buse reviewed recent studies that imply that, in fact, there is no benefit of home glucose monitoring for the latter group. Although he criticized the design of these trials, he noted that a Roper group study reported that in the U.S. 84% of non–insulin-treated patients test capillary glucose levels on average twice daily and that 45% of health care practitioners recommend this. Buse stated, "Perhaps at some level industry marketing has effectively targeted both health care professionals and patients." He continued with a second example of the ADA's recommendations on achieving glycemic goals pointing out that these are not directly addressed by the Diabetes Control and Complications Trial (DCCT), Kumamoto, and UK Prospective Diabetes Study (UKPDS) that show, rather, that more intensive treatment strategies were associated with better outcome. Microvascular complications increase, but hypoglycemia decreases with increasing A1C levels, so the studies do not allow across-the-board definition of optimal A1C. Buse characterized the benefit of lowering A1C below 7% as modest, so that the choice to pursue such a goal should be individualized based on patient characteristics, costs, and risks.

More research is warranted. We do not yet know whether (or under what circumstances) glucose lowering does reduce CVD. It is still not clear whether there is benefit to targeting postprandial glucose, whether patients should be screened for asymptomatic heart disease, whether 130 mmHg is an appropriate systolic blood pressure target, whether HDL cholesterol and triglyceride levels should routinely be treated, and whether aspirin is useful for primary CVD prevention in middle-aged diabetic patients. Buse pointed out, "The primary push [for new studies] comes from marketing, . . . from industry, . . . health care professionals, and professional societies," which he termed "entirely appropriate . . . and . . . the process by which knowledge occurs." Diabetes treatment costs 174 billion USD per year, and we need to develop approaches that will reduce ineffective and increase effective treatment.

Acknowledgments— Z.T.B. has served on speaker's bureaus of Merck, Novo Nordisk, Lilly, Amylin, Daiichi Sankyo, and GlaxoSmithKline; has served on advisory panels for Medtronic, Takeda, Merck, AtheroGenics, CV Therapeutics, Daiichi Sankyo, BMS, and AstraZeneca; holds stock in Abbott, Bard, Medtronic, Merck, Millipore, Novartis, and Roche; and has served as a consultant for Novartis, Dainippon Sumitomo Pharma America, Forest Laboratories, and Nastech. No other potential conflicts of interest relevant to this article were reported.

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