Thiazolidinediones Appear Safe for Diabetic Eyes

BY KATE JOHNSON

A study of nearly 3,500 patients indicates no link between thiazolidinedione use and diabetic macular edema, but given case reports of such an association, the findings still must be interpreted with some caution, researchers say.

The authors of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial Eye Substudy say the findings are reassuring yet inconclusive.

"We cannot rule out the possibility of either a modest protective or deleterious association," wrote Walter T. Ambrosius, Ph.D., of Wake Forest University, Winston-Salem, N.C., and his colleagues in the ACCORD Study Group, explaining that the cross-sectional analysis found an adjusted odds ratio (OR) of 0.97 with a wide confidence interval (0.67-1.40), and did not account for duration of thiazolidinedione exposure, past exposure, or type of exposure.

"A more definitive answer may be provided from the 4-year follow-up data, which will enable us to examine prospectively the relationship between thiazolidinedione exposure and [diabetic macular edema] incidence."

The ACCORD Eye Substudy is the largest study to date to examine the association between diabetic macular edema (DME) and thiazolidinedione, the authors noted (Arch. Ophthalmol. 2010;128:312-8).

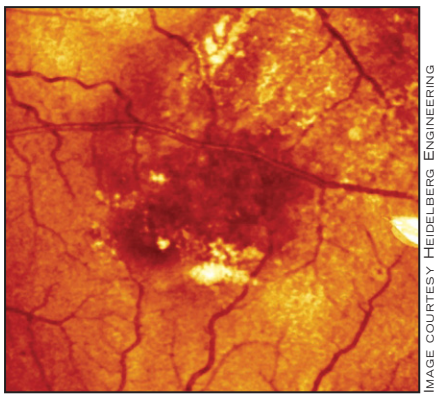

IMAGE COURTESY HEIDELBERG ENGINEERING

Reflectance map shows edema associated with diabetic retinopathy.

The Eye Substudy involved 3,473 participants from the larger ACCORD trial. Subjects were eligible only if they had no previous laser photocoagulation or vitrectomy for diabetic retinopathy in either eye. Participants had a mean age of 62 years.

DME was scored separately for each eye on a scale of 0 (none) through 3 (retinal thickness or adjacent hard exudates within 500 mcm of the center of the macula). A score of 1 was considered questionable, while 2 was defined as a zone of retinal thickness 1 disk area or greater and within 1 disk diameter or less from the center of the macula. Eyes graded at level 2 or 3 were considered to have clinically significant macular edema.

Thiazolidinedione use was defined as self-reported current use of rosiglitazone or pioglitazone at baseline. The duration of exposure before baseline was not known, however inclusion criteria for the main ACCORD trial required an antihyperglycemic washout period of 3 months before the start of the study.

Among the 3,473 participants, 695 (20%) had used thiazolidinediones, and 217 (6.2%) had DME. In the adjusted analysis, thiazolidinedione use was not significantly associated with DME (OR 0.97), nor were hemoglobin A_{1c}, duration of diabetes, gender, or ethnicity. Significant association was found between thiazolidinedione and both retinopathy and age.

Former and current smokers had lower prevalence of DME than did those who had never smoked, a finding that "is perhaps attributable to chance or the inclusion process," wrote the authors, citing a previous study that contradicts this finding (Invest. Ophthalmol. Vis. Sci. 1998;39:233-52).

Thiazolidinedione use was also associated with marginally better visual acuity ($P = .009$), although "we do not know whether this finding is clinically significant," they wrote.

The authors pointed out several limitations to the findings, including the possibility that "perhaps longer-term exposure to a thiazolidinedione is necessary for risk to develop." ■

Disclosures: *The study was funded by the National Eye Institute and the National Heart, Lung, and Blood Institute. Dr. Ambrosius disclosed no conflicts. Among his associates, Dr. Hertzel C. Gerstein has received honoraria and grants from GlaxoSmithKline for speaking, consulting, and research related to thiazolidinediones and/or rosiglitazone. Since 2005, the University of North Carolina, Chapel Hill, has contracted with pharmaceutical companies for Dr. John B. Buse's research or consulting on thiazolidinediones and related compounds. Dr. David C. Goff Jr. has received research funding from Merck and Co. for a trial involving the glucose-lowering medication sitagliptin.*

Some PCOS Treatments Can Reduce Cardiovascular Risk

BY SHERRY BOSCHERT

SAN FRANCISCO — Metformin and some oral contraceptives used to treat polycystic ovary syndrome can decrease the associated cardiovascular risk, but other oral contraceptives increase cardiovascular risk, studies suggest.

Dr. Andrea Dunaif summarized the data on cardiometabolic risk in the treatment of polycystic ovary syndrome (PCOS) at a meeting sponsored by the American Diabetes Association.

Previous evidence that estrogen therapy can increase triglyceride levels and that certain oral contraceptives can exacerbate insulin resistance raised concern that oral contraceptives may have adverse metabolic consequences in women with PCOS, explained Dr. Dunaif, professor of endocrinology at Northwestern University, Chicago.

One study randomized 48 hirsute women with PCOS to 6 months of treatment with a common oral contraceptive (Yasmin) containing 3 mg of drospirenone and 20 mcg of ethinyl estradiol or the same therapy plus either metformin 1,500 mg/day or cyproterone acetate (12.5 mg/day, 10 days per cycle), a progesterone used outside the United States (Fertil. Steril. 2009 Nov. 19 [doi:10.1016.j.fertnstert.2009.10.016]).

Insulin sensitivity improved in patients on Yasmin alone or Yasmin plus metformin but significantly worsened with Yasmin plus cyproterone acetate in the open-label trial, Dr. Dunaif said.

A separate open-label trial randomized 100 overweight women with PCOS to 6 months of oral therapy with 35 mcg of ethinyl estradiol and 2 mg of cyproterone acetate (a formulation known in Europe as Diane-35), a low-dose oral contraceptive regimen (20 mcg of ethinyl estradiol and 100 mcg of levonorgestrel) plus the antiandrogen drug spironolactone 50 mg b.i.d., or metformin 1 g b.i.d.

Each of the treatment arms showed similar, significant improvements in PCOS symptoms and menstrual cycle length. Insulin resistance improved significantly in the metformin group, but insulin resistance and arterial stiffness worsened in the ethinyl estradiol/cyproterone acetate group (Diabetes Care 2007;30:471-8).

"Cyproterone acetate looks to be a bad actor in these studies," she said.

Several studies of metformin therapy in women with PCOS have shown that the drug can improve risk factors for cardiovascular disease such as endothelial dysfunction, she noted. Compared with placebo, 12 weeks of metformin significantly decreased arterial stiffness and improved endothelial function in 30 women with PCOS in a randomized, double-blind crossover trial (J. Clin. Endocrinol. Metab. 2010;95:722-30). ■

Disclosures: *Dr. Dunaif has been a consultant for Bristol-Myers Squibb Co., which makes metformin.*

Treatment of Sleep Apnea May Improve Glucose Control

BY SHERRY BOSCHERT

SAN FRANCISCO — The presence and severity of obstructive sleep apnea were associated with worse glucose control in a study of 60 patients with type 2 diabetes.

Polysomnography and hemoglobin A_{1c} tests showed that participants with no obstructive sleep apnea (OSA) had an average HbA_{1c} level of 5.7%. HbA_{1c} levels averaged 7.2% in participants with mild OSA, 7.7% in those with moderate OSA, and 9.4% in those with severe OSA, Dr. Esra Tasali reported.

'These effect sizes are comparable to some medications we use to treat A_{1c} levels.'

DR. TASALI

"These effect sizes are comparable to some medications we use to treat A_{1c} levels," she said, suggesting that "treatment of obstructive sleep apnea may improve glucose control as much as widely used pharmacologic agents."

The linear trend for poorer glucose control with increasingly severe OSA was highly significant ($P < .0001$) after adjustment of the data for the effects of age, gender, race, body mass index, level of exercise, duration of diabetes, number of diabetes medications being taken, and total sleep time, she said at a meeting sponsored by the American Diabetes Association.

Previous studies have shown a high prevalence of OSA in people with type 2 diabetes and shown that in nondiabetic people OSA is associated with alterations in glucose metabolism and reduced insulin sensitivity independent of age, sex, or degree of obesity. The current study is the first to identify the relationship between OSA severity and glycemic control in a diabetic population (Am. J. Respir. Crit. Care Med. 2010;181:507-13).

Overall, 77% (46 of 60) of the study cohort had OSA. Three previous studies of diabetic populations found OSA prevalences of 58%, 71%, and 86%, said Dr. Tasali of the University of Chicago.

Six trials of treating OSA in patients with type 2 diabetes using continuous positive airway pressure (CPAP) produced conflicting results, with some showing improvements in HbA_{1c} levels, insulin sensitivity, or glucose levels, some showing no change, and others with split results. The only randomized clinical trial among them found no effect of CPAP therapy on HbA_{1c} or insulin sensitivity. All the studies were small (ranging from 9 to 44 patients), she noted.

Dr. Tasali said that she had no conflicts of interest to disclose. ■