

Diabetic Retinopathy Occurs in Patients with Prediabetes

Diabetic retinopathy has been found in nearly 8% of prediabetic participants in the Diabetes Prevention Program (DPP), according to a report presented at the American Diabetes Association's (ADA) 65th Annual Scientific Sessions. Diabetic retinopathy was also present in >12% of participants with type 2 diabetes who developed diabetes during the DPP. No other long-term study has evaluated retinopathy in a population so carefully examined for the presence or development of type 2 diabetes, according to a news release.

"These findings reinforce the recommendation that patients with newly diagnosed type 2 diabetes should be screened for retinopathy," said Emily Chew, MD, of the National Eye Institute (NEI), the part of the National Institutes of Health under the US Department of Health and Human Services that funded the study. "We advise good control of blood glucose, blood pressure, and cholesterol as

well as regular eye exams," she said.

"Previous studies have not accurately defined when type 2 diabetes begins, so our understanding of the onset of diabetic eye disease has been limited. Now we know that diabetic retinopathy does occur in prediabetes. We're also seeing it early in the course of diabetes – within an average of 3 years after diagnosis," said Richard Hamman, MD, DrPH, professor and chair, department of preventive medicine and biometrics, University of Colorado School of Medicine, and vice chair of the DPP. "This adds to our understanding of the development of retinopathy and suggests that changes in the eye may be starting earlier and at lower glucose levels than we previously thought."

For more information visit NEI's Diabetic Retinopathy: What you should know www.nei.nih.gov/health/diabetic/retinopathy.asp.

Ruboxistaurin Improved Kidney Damage, Function

Investigators reported encouraging results from a 1-year pilot study of ruboxistaurin in patients with type 2 diabetes and kidney disease.

Speaking at the ADA meeting in San Diego, lead investigator Katherine R. Tuttle, MD, from Providence Medical Research Center and The Heart Institute of Spokane, Washington, said, "The results from this study are very encouraging for people with type 2 diabetes who suffer from diabetic nephropathy."

In patients being treated with angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists or both, ruboxistaurin significantly reduced albuminuria by 24% versus a nonsignificant 9% reduction in patients assigned placebo, according to a news release.

"The significant improvement of albuminuria with ruboxistaurin in patients already treated with ACE inhibitors or [angiotensin receptor antagonists] suggests that the drug may be helpful in further slowing the progression of kidney disease."

Reductions in albuminuria with ruboxistaurin were seen

after 1 month of treatment and remained consistent throughout the study. In addition, patients taking placebo experienced a significant loss of kidney function after 1 year, however kidney function was stable in patients treated with ruboxistaurin.

In this multicenter, randomized, double-blinded, parallel placebo-controlled trial, 123 patients were randomized at 17 clinical sites in the United States to receive either 32 mg/day of ruboxistaurin or placebo. Participants were required to be taking stable doses of either ACE inhibitors, angiotensin receptor antagonists, or both, for 6 months prior to the study and these agents were continued throughout the trial. Baseline characteristics did not differ significantly between treatment groups. Blood glucose and blood pressure control was similar at the beginning and throughout the study.

Analyses of adverse events in this trial revealed no significant differences between the ruboxistaurin (15 reported) and placebo (9 reported) groups, except in the placebo group for episodes of hypertension requiring intervention (8% of placebo participants had an episode of hypertension requiring intervention compared with 0% in ruboxistaurin treated group). The most frequently reported adverse event in this clinical trial was hypertension.

Rimonabant Treats Multiple Problems in Type 2 Diabetes

Rimonabant can help multiple problems associated with type 2 diabetes by lowering blood glucose and reducing weight and waist circumference, as well as modifying the disordered lipids associated with diabetic dyslipidemia, according to a report at the ADA.

"Results of the RIO-Diabetes (Rimonabant In Obesity) study show impressive findings in all aspects of the trial – especially in glycemic control and improvement in the lipid profile, in part explained by weight loss and in part independent of weight loss, suggesting that rimonabant may exert direct metabolic effects in type 2 diabetes," said André Scheen, MD, PhD, professor of medicine and clinical pharmacology and head of the division of diabetes, nutrition and metabolic disorders, University of Liège, Belgium, in a news release. Over 1 year, those on 20 mg rimonabant lowered HbA1c by 0.6%, lost 11.7 lbs and 2.05 inches in waist circumference, increased HDL 6.6 mg/dL, and lowered triglycerides 31.6 mg/dL. These were all significant differences ($P < .001$) from the placebo group.

According to the ADA, rimonabant is a selective CB1 receptor endocannabinoid blocker, developed for managing cardiovascular risk factors, including intra-abdominal adiposity and its metabolic consequences. It is believed to act in the brain, where it reduces hunger and in adipose tissue, where it increases levels of adiponectin. These proteins are decreased in obese patients, a reduction associated with increased insulin resistance and a higher risk of developing type 2 diabetes. It has been demonstrated in both animal models and human studies that when rimonabant increases adiponectin, insulin sensitivity is enhanced and diabetic dyslipidemia is improved.

In RIO-Europe and RIO-North America, both 2-year trials in nondiabetic obese patients, it has already been demonstrated that rimonabant 20 mg significantly increased weight loss decreased waist circumference, reduced triglycerides, and increased HDL levels. In RIO-Lipids, a 1-year trial in obese patients with dyslipidemia, results were remarkably concordant.

The current study, RIO-Diabetes, was a multicenter, randomized, double-blind, placebo-controlled, 1-year study. Of the 1,047 participants, 51% were male, the mean age was 56 years, the mean BMI 34, the mean waist circumference 43.3 inches and the mean HbA1c was 7.5%.

Included patients had type 2 diabetes and were treated with the biguanide metformin (two-thirds of patients) or

one of several sulfonylureas for ≥ 6 months at the time of entry into the trial. All continued on these antidiabetic drugs throughout the trial but also were randomized to receive placebo or rimonabant 5 mg or 20 mg once daily in a 1:1:1 ratio. A hypocaloric diet also was prescribed.

Dr. Scheen reported intention-to-treat results. Because the differences in results for those on placebo vs 5 mg rimonabant were so minor, only placebo versus 20 mg rimonabant are reported here. The placebo group weight loss was -3.1 lbs versus -11.7 lbs for the rimonabant group. The proportion of patients who had at least a 5% body weight loss in 1 year was 14.5% in placebo and 49.4% on rimonabant 20 mg.

Changes in waist circumference paralleled weight loss. There was a 1.3 inch average difference in the loss between placebo and 20 mg rimonabant. The researchers found that 2.2 lbs of weight loss corresponded to a 0.4-inch reduction in waist circumference.

"The rimonabant trial was successful in its primary endpoint because we demonstrated that rimonabant promotes weight loss in people with diabetes," said Dr. Scheen. "It is always difficult to compare with other compounds because we don't have head-to-head studies in obesity, but these rimonabant results are at least as good as those with Orlistat or Sibutramine – the only two compounds widely used for obesity – and probably are slightly better."

HbA1c rose by 0.1% in the placebo group and dropped by 0.6% in the rimonabant 20 mg group. The percentage of patients reaching the ADA recommended treatment target of $< 7\%$ HbA1c after 1 year was 47.6% on placebo versus 67.9% on rimonabant 20 mg. There was no difference between the metformin and sulfonylurea drug groups.

HDL rose 2.7 mg/dL in those on placebo versus 6.6 mg/dL in those on rimonabant 20 mg. Triglycerides rose 3.6 mg/dL in those on placebo versus a decline of 31.2 mg/dL in those on rimonabant 20 mg.

"Again, in this and in all of the prior RIO studies, statistical analysis showed that part of the effect on lipid modification was due to the weight loss, and part due to the drug," explained Dr. Scheen.

Two-in-One Drug Treats Type 2 Diabetes, Lipids

A novel compound in a once-daily pill provides long-term lowering of blood glucose levels and improves plasma lipids in people with type 2 diabetes, according to a report presented at the ADA meeting.

“Muraglitazar provided effective and durable blood glucose lowering over 2 years, and also significantly lowered triglycerides, non-HDL cholesterol, and apolipoprotein B, as well as raising HDL, all of which may reduce the risk of cardiovascular disease (CVD) in people with type 2 diabetes,” said David Kendall, MD, chief of clinical services and medical director of the International Diabetes Center and associate professor of medicine at the University of Minnesota Medical School, in a news release.

“Further, muraglitazar achieved these goals with only one pill a day, which makes it easier for people with type 2 diabetes to manage multiple health problems and may enhance patient compliance,” he said.

Muraglitazar targets the peroxisome proliferator-activated receptors (PPARs). Activator drugs that target PPAR-gamma (glitazones), which is associated with improvements in insulin sensitivity and glycemic control, have long been successfully used to treat type 2 diabetes.

Muraglitazar targets PPAR-gamma as well as PPAR-alpha, which is associated with regulation of lipids. As a dual PPAR activator, muraglitazar becomes the first of a novel “glitazar” class.

Dr. Kendall reported on several studies with muraglitazar. Initially, a double-blind dosing trial was done. It involved 985 patients given one of five different once-daily doses of muraglitazar (0.5 - 20 mg.) or pioglitazone 15 mg by random selection. All participants were in their mid-50s, generally obese and had diabetes for 5 to 6 years. The group was roughly balanced between men and women. At the initiation of the study, all had inadequate blood glucose control on diet and exercise. Based on this study, the 5 mg dose was selected for further study. This short-term, 24-week dosing trial also was the base from which the subjects for the next trial were extracted.

A group of 88 participants who continued on 5 mg for the 2-year trial achieved very tight control of blood glucose levels. “The patients on muraglitazar went from poor control – an average HbA1c of 8.0% – to an excellent level of control – an average of 6.5% by the 20th week – and then maintained that level of control over two years,” said Dr. Kendall.

“It is well known that type 2 diabetes is a progressive disease and deterioration in control is commonly observed in people who are treated with conventional glucose-lowering therapies, such as the sulfonylureas and metformin,” noted Dr. Kendall. “However, medications that target insulin resistance, such as the PPAR-gamma activators, may improve the ability of the beta cells in the pancreas to secrete insulin which helps patients to achieve their glucose control goals and sustain them over time.”

Often people with type 2 diabetes is a cluster of lipid abnormalities including: elevated triglycerides, reduced levels of HDL cholesterol, and a shift toward smaller and denser LDL-cholesterol particles, although total and LDL cholesterol levels may be normal or elevated. A number of these problems seemed to be improved by muraglitazar.

Dr. Kendall reported on another study in which the drug was evaluated in 1,159 patients with type 2 diabetes, all of whom were taking metformin. All continued to take metformin but were also randomized in double-blind fashion to either 5 mg muraglitazar or 30 mg pioglitazone once daily. After 24 weeks, the muraglitazar group lowered blood glucose by 1.14% versus 0.85% for the pioglitazone group.

The differences in lipids were also greater for muraglitazar versus pioglitazone (respectively: triglycerides -28.4% vs -13.4%; HDL +19.2% vs +13.6%; non-HDL -5.9% vs -1.2%; apolipoprotein B -11.8% vs -6.0%).

“Muraglitazar treatment resulted in greater improvement in glucose control and lipids when added to metformin when compared to pioglitazone plus metformin,” Dr. Kendall said. Both glucose control and dyslipidemia may play an important role in the greater risk of myocardial infarctions and strokes seen in people with diabetes.

Antibiotic May Limit, Prevent Diabetic Retinopathy

The antibiotic minocycline, used to treat acne, may slow or prevent diabetic retinopathy, according to animal studies.

“Our studies in rats suggest that this antibiotic may be a strong candidate for further consideration as a therapeutic drug in reducing the retinal complications of diabetes,” said Kyle Krady, PhD, assistant professor of neural and behavioral sciences, Penn State College of Medicine, Penn State Milton S. Hershey Medical Center. “Further studies are necessary to test the prediction that minocycline will reduce damage to the retina.”

The team found that minocycline limits by about 50% the retinal damage caused by microglia. Microglia are cells that clean up the central nervous system, according to a news release from Penn State University. They destroy damaged cells by releasing toxins and then engulf them, much like a Pacman. Should they become activated and release their toxins in the retina, those toxins will kill the healthy neurons critical for normal vision.

The study, published in *Diabetes*, showed that in early

diabetes elevated levels of cytokines activate microglia that produce neurotoxins and kill nerve cells. The neuron death causes progressive vision loss characteristic of diabetic retinopathy. After establishing that microglia are activated early in the course of diabetes, the team compared the mRNA levels of cytokines in the retinas of rats with diabetes to healthy rats. Increasing mRNA levels are an indicator of increasing cytokine production.

The team found that there was a four- to sixfold increase in cytokines present in the retinas of diabetic rats. Because cytokines activate microglia, the investigators established that, indeed microglia in the retinas of diabetic rats were activated. Then, the team treated diabetic rats with minocycline and the mRNA levels of cytokines were subsequently measured.

"Minocycline reduces the neuroinflammation in the retina caused by cytokines, which reduces microglia activation, and hence, reduces their production of neurotoxins with the net result being that there is less retinal nerve death," said Steve Levison, PhD, professor of neural and behavioral sciences, Penn State College of Medicine, and professor of neurology and neuroscience, University of Medicine and Dentistry, New Jersey, in a news release. "Results confirm studies that showed that diabetes causes an early increase in the expression of inflammatory mediators within the retina, and it shows that minocycline reduces this inflammatory component."

To determine whether the toxins from activated microglia kill the retinal cells, the team grew active microglia with retinal cells. Some cultures were treated with minocycline while others were not. Activated microglia caused a 2.5-fold increase in retinal cell death. By contrast, in co-cultures treated with minocycline, nearly all retinal cells survived. An additional study in rats confirmed the results.

Better Outcomes with Kidney Transplant

According to a study in the *Journal of the American Society of Nephrology*, successful kidney transplantation provides a better outcome compared to dialysis, and doubles the life expectancy of patients with renal failure.

A longitudinal study of 4,532 patients, conducted by Gabriel C. Oniscu and investigators at The Royal Infirmary of Edinburgh, showed that 38% of patients were listed for a first cadaveric transplant between January 1989 and December 1999. Of these, 24% received a transplant, and they had a 54% lower mortality rate compared to patients

who remained on dialysis. They also had a 17.19-year projected life span compared to a 5.84-year span for dialysis patients.

Patients who remained on dialysis had twice the incidence of myocardial infarction, angina, had a higher prevalence of smoking and a better chance of developing gastrointestinal disorders and cerebrovascular diseases. Initially, transplant recipients had an increased risk of death, however, the risk decreased after 1 year. Investigators found that the risk of mortality was 68% less for transplant recipients than dialysis patients.

Displaced Weight Bearing May Signal Peripheral Neuropathy

Type 2 diabetic patients experiencing plantar pressure while walking on a level surface may develop peripheral neuropathy, according to a study in *Diabetic Medicine*.

Type 2 diabetes patients (n=15), were free from any microvascular or macrovascular complications, were measured for plantar pressure to determine the distribution of pressure across the heel, big toe and first, third and fifth metatarsal heads. Force Sensing Resistors determined the distribution, and these results were compared to results from 15 control patients, all of which were nondiabetic.

Peak plantar pressure in the big toe and fifth metatarsal head was higher in the diabetic group. This also indicated a prolonged duration of plantar pressure through each step, investigators wrote. Alternately, pressure was lower across the heel of diabetic patients compared to nondiabetic controls. The diabetic group also experienced a lower level of contact with the plantar surface in the right and left feet.

"We observed an anterior displacement of weight bearing during walking on a level gradient as well as a reduced static contact plantar surface in diabetic patients ... compared with the nondiabetic control group," the investigators concluded. "This could be a premature sign of peripheral neuropathy."

Most Patients Do Not Know about Diabetic Neuropathy

According to a national survey by the ADA, 56% of diabetes patients do not know what diabetic neuropathy is.

"These study results are alarming because, [if] left untreated, diabetic neuropathy always progresses," said Aaron I. Vinik, MD, PhD, director of the Strelitz Diabetes Research Institute and Associate Medical Editor of *Diabetic*

Microvascular Complications Today. “Not knowing you have diabetic neuropathy doesn’t mean that the condition will not progress. It will still get you.”

A total of 8,119 people were asked via telephone about their awareness of diabetic neuropathy. Questions screened for diabetes diagnosis, awareness of diabetic neuropathic symptoms, insight into how to prevent or manage the symptoms and how patients and doctors are communicating about the condition. The survey was part of the ADA’s new Diabetic Neuropathy Campaign.

Some significant findings include:

- About 62% of survey respondents who experienced symptoms of diabetic neuropathy believe that their symptoms are associated with diabetes. However, 42% have been told by their doctor that diabetes is the cause.
- Only 25% of respondents who experience symptoms of diabetic neuropathy have been diagnosed.
- The majority of respondents with symptoms of diabetic neuropathy are unaware of the term diabetic neuropathy.

“There is no doubt that with proper attention, management and treatment, diabetic neuropathy can be prevented or its progress delayed,” said Dr. Vinik. “Knowing about it gives you the opportunity to take care of yourself and prevent serious consequences.”

Duloxetine Appears Safe for Patients with Hypertension

Duloxetine (Cymbalta, Eli Lilly and Company) appears to be safe for use with diabetic neuropathic pain and hypertension, according to findings presented at the American Geriatrics Society Annual Scientific Meeting in Orlando.

Michael J. Robinson, MD, a clinical investigator with Lilly said: “We know that studies have shown duloxetine to be safe and effective for treating diabetic peripheral neuropathic pain. Many patients with diabetes are predisposed to hypertension – the most common comorbidity – so our study looked at safety when that comorbidity is present. “We found that safety is not impacted by the presence of hypertension in this population.”

In their analysis, Dr. Robinson and colleagues pooled data from two double-blind, placebo-controlled studies of patients with diabetic peripheral neuropathic pain. The 568-patient cohort was randomized duloxetine or placebo for 12 to 13 weeks. Investigators assessed safety data, discontinuation rates, adverse events and changes in patients’ vital signs. The most common comorbidities among this population were hypertension, hypercholesterolemia, gas-

troesophageal reflux disease and erectile dysfunction.

Dr. Robinson reported no significant difference in terms of dropout rates due to adverse events between patients with versus those without hypertension (13.5% and 14.5%, respectively). Hypertensive patients assigned duloxetine had blood pressures similar to those in the placebo group (-9.3 mm Hg for duloxetine vs -8.4 mm Hg for placebo; $P = .639$).

Duloxetine produces marginal changes in blood pressure for hypertensive patients in this population, researchers concluded.

BMD, Temperature and VDT Higher in Type 2 Diabetes

Comparing the bone mineral density (BMD) in diabetic patients, investigators reporting in *Diabetic Medicine* have shown that type 1 diabetic patients experience a high temperature threshold, while patients with type 2 diabetes had high temperature and vibration detection thresholds (VDT).

Investigators from King’s College Hospital, London, studied the Charcot and non-Charcot feet of 130 patients. Patients were broken into four groups: type 1 diabetic patients with and without osteoarthropathy and type 2 diabetic patients with and without osteoarthropathy.

In respect to the non-Charcot foot of type 1 diabetic patients, BMD was further reduced than in the Charcot feet. This trend was not seen among the type 2 diabetic patients. In Charcot feet, BMD was lower than in non-Charcot feet. This was seen in both type 1 and 2 diabetes.

“Bone density was reduced in the non-Charcot foot in type 1 but not in type 2 diabetes,” investigators wrote. “Type 2 patients had high temperature and [VDT] in contrast to type 1 patients who had a high temperature threshold only.”

Cholesterol-carrying Proteins Affect Cardiovascular Risk

Lipoprotein levels and the size of apolipoprotein are important risk factors for cardiovascular events, especially for patients on kidney dialysis.

According to a study published in the *Journal of the American Society of Nephrology*, led by J. Craig Longenecker, 297 of the 833 enrolled patients had an atherosclerotic cardiovascular event over an average of 2 years. Investigators enrolled the patients, who started dialysis at 81 United States clinics, and determined the occurrence of atherosclerosis, focusing on how specific lipoproteins affect the risk of cardiovascular events.

A statistical analysis that accounted for other factors, patients who had high levels of lipoprotein had a 38% increase in the risk of cardiovascular events. It should be noted that patients with end stage renal disease on dialysis have elevated lipoprotein levels.

However, investigators wrote that the risk of a cardiovascular event was more strongly affected by very small low molecular weight forms of apolipoprotein. For patients in the smallest category of apolipoprotein size, the cardiovascular event rate was increased by 58%. A further analysis showed that apolipoprotein size was more of a risk factor than lipoprotein, and the cardiovascular event rate was highest (73% elevation) for patients with both high lipoprotein levels and small apolipoprotein size.

Pioglitazone May Improve Cardiovascular Risk Predictors

Results published in *Circulation* have shown that the diabetes medication pioglitazone HCl reduced carotid artery intima-media thickness (IMT), insulin resistance, C-reactive protein (CRP) and blood pressure. These are all contributors of CVD.

"These study results support the growing body of evidence that – beyond its effects on blood glucose – pioglitazone may keep blood vessels healthy and prevent hardening of the arteries," said Thomas Forst, principal investigator and professor of internal medicine at the Institute for Clinical Research and Development, Germany, in a news release. "We are encouraged by these results because the benefits seen with pioglitazone could, theoretically, lead to an overall reduction in the incidence of heart attack and stroke for people with type 2 diabetes."

Investigators performed a randomized, controlled study to examine the effects of oral therapy with either pioglitazone (89 patients, 45 mg/day) or glimepiride (84 patients, 2.7 ±1-6 mg) for 12 and 24 weeks on HbA1c, insulin resistance, and carotid artery thickness. All of the patients were type 2 diabetic, aged 62.6 ±7.9 years and had a mean body mass index of 31.8.

Treatment was generally well tolerated. Despite similar improvements in metabolic control after 24 weeks, carotid IMT was reduced from baseline only in the pioglitazone group after both 12 weeks and after 24 weeks of treatment. Additionally, insulin resistance was significantly improved in the pioglitazone group versus the glimepiride group (-2.2 ±3.4 vs -0.3 ±-3.3, $P<.0001$). Changes in IMT correlated with improvement in insulin resistance were found to be independent from the

improvement in metabolic control.

Patients in the pioglitazone group also improved their CRP blood and blood pressure levels at 24 weeks, while the glimepiride group was unchanged from baseline. This difference was statistically significant.

Pioglitazone treatment, however, was associated with a higher number of cases of increased body weight and edema. Two patients in the pioglitazone arm experienced a clinically significant deterioration in their preexisting cardiac insufficiency.

Control Glucose After Myocardial Infarction

Results from DIGAMI 2 indicate that glucose level, and not long-term insulin treatment, may predict long-term mortality in type 2 diabetic patients.

Reporting their study in the *European Heart Journal*, investigators based DIGAMI 2 on findings from their previous study that indicated glucose levels managed with insulin were better controlled in diabetic patients who had an acute myocardial infarction. The glucose management caused an upsurge in survival rates among those who used insulin.

In the follow-up study, patients were all suspect to acute myocardial infarction, and were randomly treated with one of the following insulin therapies: acute insulin-glucose infusion with a long-term insulin-based glucose control program afterwards (group 1); insulin-glucose infusion with glucose control that is standardized (group 2); or routine metabolic management (group 3), the investigators wrote. A total of 1,253 patients, mean age 68 years, were studied for a median of 2.1 years. Investigators were interested in discovering the all-cause and total mortality.

Overall, investigators found the mortality to be 18.4%, and when broken down in groups the rates were 23.4% in group 1, 22.6% in group 2 and 19.3% in group 3. The difference between groups 1 and 2 was not significant, but it was significant between groups 1 and 3, the investigators wrote. There was no significant difference in HbA1c levels between any of the groups.

"DIGAMI 2 did not support the fact that an acutely introduced, long-term insulin treatment improves survival in type 2 diabetic patients following myocardial infarction when compared with a conventional management at similar levels of glucose control," investigators wrote. "However ... the glucose level is a strong, independent predictor of long-term mortality in this patient category." ■