Insulin May Trigger Cell Growth

Diabetes-Cancer *from page 1*

1.52 for all cancers in one large study), with a likely role for insulin resistance and hyperinsulinemia.

Evidence also suggests that glucose-lowering medications that modulate these factors—including the thiazolidinediones and sulfonylureas as well as insulin—could therefore also have positive or negative modifying effects with regard to cancer, he said.

Craig J. Currie, Ph.D., of Cardiff (Wales) University, presented new data from a retrospective cohort study of a U.K. general practice population. In this extension study of the one published online in July (Diabetologia 2009;52:1766-77) they examined 31,421 type 2 diabetes patients on metformin monotherapy, 5,035 on insulin plus metformin, and 4,829 on insulin only.

There was a strong dose-response relationship between insulin exposure and the first solid tumor.

DR. CURRIE

There was a strong dose-response relationship between insulin exposure and first diagnosis of a solid cancer tumor. Compared with the crude rate of 10 cancers per 1,000 person-years for those taking metformin alone, the rates for those on insulin plus metformin increased from 9 for those using fewer than 7 insulin prescriptions per year to 11-12 for those using 8-14 prescriptions per year to 34 for those using more than 15 prescriptions per year), Dr. Currie reported.

Patients on insulin monotherapy showed an even greater dose-response: Those using fewer than 7 prescriptions per year had a rate of 15 per 1,000 person-years, those with 7-15 prescriptions had 19, and those with more than 15 prescriptions had three times that rate, at 60 cancers per 1,000 person-years.

After adjustment for age, sex, and smoking status, hazard ratios in the insulin plus metformin groups were 0.87 per 1,000 person-years for metformin alone, 1.0 for 8-14 prescriptions a year, and 3.2 for those with more than 15 prescriptions per year.

For those on insulin alone, hazard ratios were 1.05 for metformin alone, up to 5.73 for those with more than 15 prescriptions per year. The same pattern of association persisted after adjustment for other covariates such as weight, insulin exposure, and hemoglobin A_{1c}, he said.

Some of the risk is attenuated in those using metformin with insulin, because metformin appears to have a protective effect, he noted (see sidebar).

Dr. Ulf Smith, president of the EASD, clarified a point that has caused confusion: Insulin is not oncogenic, but rather it may promote the growth of cells that have already undergone oncogenic transformation. "I don't think anyone has suggested that insulin causes cancer, but it is a growth-promoting hormone. This has been known for some time."

The mechanism is likely to relate to insulin's binding of insulin-like growth factor receptors on tumors, noted Dr. Smith of the Salgrenska Center for Cardiovascular and Metabolic Research, Göteborg, Sweden. He had no conflicts of interest to disclose.

Dr. Johnson has been a speaker for Eli Lilly & Co. Dr. Gale and Dr. Currie stated they had no conflicts of interest.

Sanofi-Aventis has announced the launch of a research program to investigate whether there is a relationship between cancer and insulin use, including the analogues (http://en.sanofi-aventis.com/binaries/20090929_easd_lantus_en_tcm28-26400.pdf). ■

Metformin a Potential Anticancer Tx

The glucose-lowering drug metformin is increasingly showing an anticancer effect.

The data come from studies being conducted in both the diabetes and oncology research communities, according to experts who spoke at the annual meeting of the European Association for the Study of Diabetes.

The positive metformin story has been somewhat buried within the much broader and very complicated relationship between diabetes treatments and cancer.

But evidence for a protective effect of metformin did appear in one of the Diabetologia studies that caused the furor. Dr. Currie and his associates found the lowest risk for cancer among users of metformin compared with other diabetes treatments, and that adding metformin to insulin reduced the progression to cancer compared with insulin treatment alone, with a hazard ratio of 0.54 in a retrospective cohort study of more than 62,809 diabetes patients.

Several lines of investigation are now looking at metformin as a potential anticancer treatment outside of diabetes, said Dr. Gale.

The study out of Cardiff University showed that diabetes patients on insulin or insulin secretagogues were more likely to develop solid cancers than were those on metformin, while the combination with metformin abolished most of this excess risk. Metformin use was associated with lower risks of colon or pancreatic cancer, but did not affect the risk of breast or prostate cancer. Use of insulin analogues was not associated with increased cancer risk as compared with human insulin (Diabetologia 2009;52:1766-77).

Similarly, in another study, metformin use was linked with reduced risk, and insulin or insulin secretagogue use was tied to increased risk of pancreatic cancer in diabetes patients (Gastroenterology 2009;137:482-8).

Dr. Currie summarized new data from an observational U.K. study from a general practice population of more than 31,421 patients on metformin monotherapy, 5,035 on insulin plus metformin, and 4,829 on insulin only. After adjustment, there was a strong dose-response relationship between insulin use and cancer, but the risk appeared to be attenuated with the addition of metformin. Dr. Smith cited a recent study that showed a better response rate to chemotherapy among diabetic patients with breast cancer who were taking metformin (J. Clin. Oncol. 2009;27:3297-302).

—Miriam E. Tucker

Lifestyle Intervention Remains Effective at 10-Year Mark

BY DENISE NAPOLI

A follow-up to a landmark diabetes study confirms that even after 10 years, intensive lifestyle modification can prevent or delay development of the disease among high-risk adults.

Furthermore, although physical activity and lifestyle change remain the surest way to prevent type 2 diabetes, when metformin was combined with some lifestyle intervention strategies, it performed as well as did intensive lifestyle interventions alone in reducing diabetes mellitus incidence.

The new study, the Diabetes Prevention Program Outcomes Study (DPPOS) is a follow-up to the 2002 Diabetes Prevention Program (DPP) trial. That study randomized adults at high risk for diabetes to an intensive lifestyle intervention, to 850 mg of metformin twice daily, or to placebo. High risk was indicated by raised fasting plasma glucose levels, impaired glucose tolerance, or a high body mass index (24 kg/m² or higher, or 22 kg/m² or higher in Asian Americans).

After nearly 3 years, the incidence of diabetes was found to be 4.8 cases per 100 person-years in the lifestyle group and 7.8 cases in the metformin group, compared with 11.0 cases per 100 person-years among the controls.

The current study, led by Dr. William C. Knowler of the National Institute of Diabetes and Digestive and Kidney Diseases, followed up on 2,766 of these patients from the original 3,150 DPP participants for an additional 7 years, with about 900 patients coming from each of the three original cohorts.

The incidence of diabetes was 5.9 cases per 100 person-years in those who stayed on the lifestyle-only intervention.

DR. KNOWLER

This time, all three groups were offered lifestyle intervention, which encouraged 150 minutes of moderate-intensity activity per week and offered behavior reinforcement counseling sessions every 3 months. Patients who were in the lifestyle group in the original study also received two extra group classes "to reinvigorate their self-management behaviors for weight loss," the authors wrote, and patients who were originally in the metformin-only group continued on their dose of 850 mg twice daily in addition to the lifestyle intervention.

The primary outcome—just as in the original study—was a fasting plasma glucose level of 7.0 mmol/L (126 mg/dL) or higher, measured every 6 months, or a 2-hour plasma glucose level of 11.1 mmol/L (about 200 mg/dL) or higher after a 75-g oral glucose load, measured yearly.

At the current study's end, roughly 10 years from patients' randomization into the original DPP, the combined incidence of diabetes (throughout both the original and current study periods) was 4.9 per 100 person-years for patients who received metformin plus lifestyle intervention, and 5.6 per 100 person-years among patients who had originally received only placebo but now received lifestyle intervention. The incidence of diabetes was 5.9 cases per 100 person-years among those who continued on the lifestyle-only intervention to which they had originally been assigned (Lancet 2009 Oct. 29 [doi:10.1016/S0140-6736(09)61457-4]).

"These results clearly advance our reasons to make lifestyle intervention a high priority for people who are at high risk for type 2 diabetes," said Dr. R. Paul Robertson, the American Diabetes Association's president of medicine and science.

"It is our hope that health care professionals will translate the findings of this study to further motivate patients to make changes in their diet and physical activity to lower their risk," he added.

A second phase of the follow-up, scheduled to be completed in 2014, will examine longer-term outcomes such as mortality.

Dr. Knowler and coauthors in the DPP research group declared that they had no conflicts of interest related to this study, which was funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The ADA provided research funding support to the DPP and DPPOS. ■