

Estrogen Therapy Linked to Brain Atrophy in Women With Diabetes

BY MICHELE G. SULLIVAN

WASHINGTON — Women with type 2 diabetes who take estrogen therapy showed lower total gray matter volume, with atrophy particularly evident in the hippocampus.

A new analysis of the Women's Health Initiative Memory study suggested that these hormone therapy-related decrements in brain volume seem to stabilize in the years after

treatment ends. However, said Christina E. Hugenschmidt, PhD, of Wake Forest University, Winston-Salem, NC, the findings also suggested caution when considering a prescription for estrogen therapy for a woman with emerging or frank diabetes.

"The concern is that prescribing estrogen to a woman with diabetes could increase her risk of brain atrophy," she said at the Alzheimer's Association International Conference 2015.

Dr. Hugenschmidt reviewed data from the Women's Health Initiative Memory Study–MRI (WHIMS-MRI). The parallel placebo-controlled trial randomized women 65 years and older to placebo, or 0.625 mg conjugated equine estrogen with or without 2.5 mg progesterone. They were all free of cognitive decline at baseline.

Dr. Hugenschmidt focused on 1,400 women who underwent two MRI brain scans: one 2.5 years after beginning the

study and another about 5 years after that. The primary outcomes were total brain volume, including any ischemic lesions, total gray matter, total white matter, frontal lobe and hippocampal volume, and ischemic white matter lesion load.

At enrollment, the women were a mean age of 70 years old; 124 had type 2 diabetes. About 42% had long-standing disease of 10 years or longer. Not surprisingly, there were some significant differences between the diabetic and nondiabetic groups: Body mass index, waist girth, and waist/hip ratio were all significantly larger in the women with diabetes.

Diabetes = Less Brain Volume

At the first scan, women with diabetes who had been randomized to estrogen therapy had about 18 cc less total brain volume than those without diabetes. The brain volumes of women with diabetes who were taking placebo were nearly identical to those of the nondiabetic women, regardless of what treatment they were taking.

The difference seemed to be driven by a loss of gray matter, Dr. Hugenschmidt said. There was no significant effect on white matter. The hippocampus appeared to have a similar amount of shrinkage. However, she added, there were no differences in cognitive scores on the Mini Mental State Exam.

Insulin use didn't appear to ameliorate the findings of smaller brain volume among those with diabetes. Atrophy didn't progress, however; findings at the same scan were similar.

Interrupted Brain Metabolism

The findings may be linked to the suppression of a natural process that occurs during the perimenopausal transition, Dr. Hugenschmidt said. Estrogen is crucial in maintaining the brain's energy metabolism. It works by increasing glucose transport and aerobic glycolysis. But during this time of life, as estrogen wanes, it becomes uncoupled from the glucose metabolism pathway. The female brain then begins to use ketone bodies as its primary source of energy. Intact estrogen levels normally down-regulate the use of alternative energy sources before menopause; supplementing them seems to prevent this transition from occurring.

"Among older women with diabetes for whom the glucose-based energy metabolism promoted by estrogen is already compromised, this downregulation of alternative energy sources may lead to increased atrophy of gray matter, which has a greater metabolic demand relative to white matter," Dr. Hugenschmidt and her colleagues wrote in an article published online ahead of print in *Neurology* (2015 July 10 [doi:10.1212/WNL.0000000000001816]).

Dr. Hugenschmidt reported having no relevant financial disclosures.

MICHELE G. SULLIVAN is with the Mid-Atlantic bureau of *Frontline Medical News*.

Humalog® (insulin lispro injection, USP [rDNA origin]) Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

Humalog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

ADMINISTRATION

Humalog has a rapid onset of action and should be given within 15 minutes before a meal or immediately after a meal.

CONTRAINDICATIONS

Humalog is contraindicated:

- During episodes of hypoglycemia.
- In patients who are hypersensitive to Humalog or to any of its excipients.

WARNINGS AND PRECAUTIONS

Never Share Pens, Cartridges, Syringes or Needles Between Patients —

Humalog KwikPens, cartridges, and reusable pens compatible with Lilly 3 mL cartridges must never be shared between patients, even if the needle is changed. Patients using Humalog vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

Dose Adjustment and Monitoring — Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for Humalog may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

Hypoglycemia—Hypoglycemia is the most common adverse effect associated with insulins, including Humalog. The risk of hypoglycemia increases with tighter glycemic control. Patients must be educated to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may be different for each person and may change from time to time. Severe hypoglycemia can cause seizures and may be life threatening or cause death.

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulations. Other factors such as changes in food intake (eg, amount of food or timing of meals), injection site, exercise, and concomitant medications may also alter the risk of hypoglycemia (see Drug Interactions).

As with all insulins, use caution in patients with hypoglycemia unawareness and in patients who may be predisposed to hypoglycemia (eg, the pediatric population and patients who fast or have erratic food intake). The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. This may present a risk in situations where these abilities are especially important, such as driving or operating other machinery.

Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value. Early warning symptoms of hypoglycemia may be different or less pronounced under certain conditions, such as longstanding diabetes, diabetic nerve disease, use of medications such as beta-blockers (see Drug Interactions), or intensified diabetes control. These situations may result in severe hypoglycemia (and, possibly, loss of consciousness) prior to the patient's awareness of hypoglycemia.

Hypersensitivity and Allergic Reactions—Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including Humalog (see Adverse Reactions).

Hypokalemia—All insulin products, including Humalog, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia.

Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Renal or Hepatic Impairment—Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.

Mixing of Insulins—Humalog for subcutaneous injection should not be mixed with insulin preparations other than NPH insulin. If Humalog is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing.

Do not mix Humalog with other insulins for use in an external subcutaneous infusion pump.

Subcutaneous Insulin Infusion Pumps—When used in an external insulin pump for subcutaneous infusion, Humalog should not be diluted or mixed with any other insulin. Change the Humalog in the reservoir at least every 7 days; change the infusion sets and the infusion set insertion site at least every 3 days. Humalog should not be exposed to temperatures greater than 98.6°F (37°C).

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt identification and correction of the Humalog® (insulin lispro injection, USP [rDNA origin]) HI HCP BS 25MAR2015

cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with Humalog may be required. Patients using continuous subcutaneous insulin infusion pump therapy must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure (see Dosage and Administration and How Supplied/Storage and Handling).

Drug Interactions—Some medications may alter insulin requirements and the risk for hypoglycemia and hyperglycemia. Some medications may mask the signs of hypoglycemia in some patients. Therefore, insulin dose adjustments and close monitoring may be required.

Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists—Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin, including Humalog. Fluid retention may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure and consider discontinuation or dose reduction of the PPAR-gamma agonist.

ADVERSE REACTIONS

Hypoglycemia and hypokalemia are discussed in Warnings and Precautions.

Clinical Trial Experience—Because clinical trials are conducted under widely varying designs, the adverse reaction rates reported in one clinical trial may not be easily compared with those rates reported in another clinical trial, and may not reflect the rates actually observed in clinical practice.

The frequencies of treatment-emergent adverse events during Humalog clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in the tables below.

Table 1: Treatment-Emergent Adverse Events in Patients with Type 1 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=81)	Regular human insulin (n=86)
Flu syndrome	28 (34.6)	28 (32.6)
Pharyngitis	27 (33.3)	29 (33.7)
Rhinitis	20 (24.7)	25 (29.1)
Headache	24 (29.6)	19 (22.1)
Pain	16 (19.8)	14 (16.3)
Cough increased	14 (17.3)	15 (17.4)
Infection	11 (13.6)	18 (20.9)
Nausea	5 (6.2)	13 (15.1)
Accidental injury	7 (8.6)	10 (11.6)
Surgical procedure	5 (6.2)	12 (14.0)
Fever	5 (6.2)	10 (11.6)
Abdominal pain	6 (7.4)	7 (8.1)
Asthenia	6 (7.4)	7 (8.1)
Bronchitis	6 (7.4)	6 (7.0)
Diarrhea	7 (8.6)	5 (5.8)
Dysmenorrhea	5 (6.2)	6 (7.0)
Myalgia	6 (7.4)	5 (5.8)
Urinary tract infection	5 (6.2)	4 (4.7)

Table 2: Treatment-Emergent Adverse Events in Patients with Type 2 Diabetes Mellitus (adverse events with frequency ≥5%)

Events, n (%)	Lispro (n=714)	Regular human insulin (n=709)
Headache	63 (11.6)	66 (9.3)
Pain	77 (10.8)	71 (10.0)
Infection	72 (10.1)	54 (7.6)
Pharyngitis	47 (6.6)	58 (8.2)
Rhinitis	58 (8.1)	47 (6.6)
Flu syndrome	44 (6.2)	58 (8.2)
Surgical procedure	53 (7.4)	48 (6.8)

Insulin Initiation and Intensification of Glucose Control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

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