Hyperuricemia Tied to Diabetes in Young Adults

BY MITCHEL L. ZOLER

PHILADELPHIA — Hyperuricemia in young adults was linked to a significant, roughly twofold increased risk for developing type 2 diabetes during the subsequent 13 years in an observational study with nearly 5,000 participants.

"Hyperuricemia may be a useful marker for predicting type 2 diabetes among young adults," Dr. Eswar Krishnan said at the annual meeting of the American College of Rheumatology.

But Dr. Krishnan also cautioned that it is not known whether high serum levels of uric acid play a causal role for developing type 2 diabetes, nor is it known if an intervention can prevent diabetes from developing.

This finding follows a meeting report from Dr. Krishnan earlier this year that hyperuricemia in young adults also was associated with a significantly increased risk for the development of coronary atherosclerosis, a finding made using the same database.

Both analyses used data collected from 5,115 asymptomatic men and women, aged 18-30, in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Participants enrolled in four U.S. cities: Birmingham, Ala.; Chicago; Minneapolis; and Oakland, Calif. Half were African American, half were white, their mean age was 25, and none had long-standing risk factors for coronary disease. At baseline their average body mass index was 22 kg/m^2, and they reported on average a moderate amount of regular physical activity. The new diabetes analysis used data collected during 13 years of follow-up from 4,762 of the subjects.

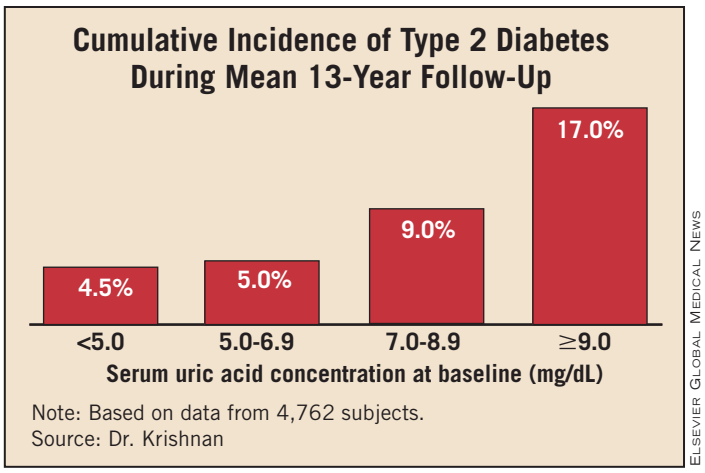
The cumulative incidence of newly diagnosed type 2

diabetes during follow-up ranged from 5% among people with baseline uric acid levels of less than 7.0 mg/dL to 17% among those with a baseline level of 9.0 mg/dL or higher. (See chart.) Type 2 diabetes was diagnosed in participants who had a fasting plasma glucose level of at least 126 mg/dL.

In a multivariate analysis that controlled for several baseline variables, people with a baseline serum uric acid level of 7.0 mg/dL or greater had a statistically significant, 94% higher risk for developing type 2 diabetes during follow-up, compared with people with a baseline level of less than 5.0 mg/dL, said Dr. Krishnan, a rheumatologist at Stanford (Calif.) University.

Only ten of the more than 4,000 people in the analysis had clinical features at baseline that met the diagnostic criteria for metabolic syndrome. When these 10 were excluded, the relationship between hyperuricemia and development of diabetes remained about the same, with a 99% increased risk for incident diabetes in those with a baseline serum uric acid of 7.0 mg/dL or higher compared with those with a level of less than 5.0 mg/dL.

Dr. Krishnan disclosed receiving research support and serving as a consultant to Takeda, a company that markets febuxostat (Uloric), a drug that lowers uric acid levels. Some of his associates on this study are employees of Takeda. Dr. Krishnan also formerly held stock in Savient, a company that is developing another uric acid–lowering drug. ■



Note: Based on data from 4,762 subjects.
Source: Dr. Krishnan

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Table 1 (contd)

	Titration	Maintenance	
System Organ Class Preferred Term	**EMBEDA (N=547) n (%)[1]**	**EMBEDA (N=171) n (%)**	**Placebo (N=173) n (%)**
Vomiting	46 (8.4%)	7 (4.1%)	2 (1.2%)
General disorders and administration site conditions	39 (7.1%)	9 (5.3%)	10 (5.8%)
Fatigue	16 (2.9%)	1 (0.6%)	2 (1.2%)
Nervous system disorders	135 (24.7%)	12 (7.0%)	11 (6.4%)
Dizziness	42 (7.7%)	2 (1.2%)	2 (1.2%)
Headache	22 (4.0%)	4 (2.3%)	2 (1.2%)
Somnolence	76 (13.9%)	2 (1.2%)	5 (2.9%)
Psychiatric disorders	34 (6.2%)	10 (5.8%)	9 (5.2%)
Insomnia	7 (1.3%)	5 (2.9%)	4 (2.3%)
Skin and subcutaneous tissue disorders	46 (8.4%)	7 (4.1%)	7 (4.0%)
Pruritus	34 (6.2%)	0	1 (0.6%)
Vascular disorders	4 (0.7%)	5 (2.9%)	2 (1.2%)
Flushing	0	4 (2.3%)	1 (0.6%)

[1]Adverse reactions are classified by System Organ Class and Preferred Term as defined by the Medical Dictionary of Regulatory Affairs (MedDRA) v9.1. If a subject had more than one AE that codes to the same Preferred Term, the subject was counted only once for that Preferred Term. *Long-Term Open-Label Safety Study:* In the long-term open-label safety study, 465 patients with chronic non-malignant pain were enrolled and 124 patients were treated for up to 1 year. The distributions of adverse events were similar to that of the randomized, controlled studies, and were consistent with the most common opioid related adverse events. Adverse reactions, defined as treatment-related adverse events assessed by the investigators, reported by ≥ 2.0% of subjects are presented immediately below. **Adverse Reactions Reported by ≥2.0% of Subjects in Long-Term Safety Study – Safety Population (N=465):** Any Related AE 288 (61.9%); Gastrointestinal disorders 219 (47.1%); Constipation 145 (31.2%); Diarrhoea 10 (2.2%); Dry mouth 17 (3.7%); Nausea 103 (22.2%); Vomiting 37 (8.0%); General disorders and administration site conditions 51 (11.0%); Fatigue 19 (4.1%); Nervous system disorders 99 (21.3%); Dizziness 19 (4.1%); Headache 32 (6.9%); Somnolence 34 (7.3%); Psychiatric disorders 42 (9.0%); Anxiety 10 (2.2%); Insomnia 13 (2.8%); Skin and subcutaneous tissue disorders 52 (11.2%); Hyperhidrosis 16 (3.4%); Pruritus 26 (5.6%). Adverse reactions are classified by System Organ Class and Preferred Term as defined by the Medical Dictionary of Regulatory Affairs (MedDRA) v9.1. If a subject had more than one AE that codes to the same Preferred Term, the subject was counted only once for that Preferred Term. *Adverse Reactions Observed in the Phase 2/3 Studies:* **Most common (≥10%):** constipation, nausea, somnolence **Common (≥1% to <10%):** vomiting, headache, dizziness, pruritus, dry mouth, diarrhea, fatigue, insomnia, hyperhidrosis, anxiety, chills, abdominal pain, lethargy, edema peripheral, dyspepsia, anorexia, muscle spasms, depression, flatulence, restlessness, decreased appetite, irritability, stomach discomfort, tremor, arthralgia, hot flush, sedation. *Adverse Reactions Observed in the Phase 2/3 Studies:* **Most common (≥10%):** *Gastrointestinal disorders:* constipation, nausea; *Nervous system disorders:* somnolence. **Common (≥1% to <10%):** *Gastrointestinal disorders:* abdominal pain, diarrhea, dry mouth, dyspepsia, flatulence, stomach discomfort, vomiting; *General disorders and administration site conditions:* chills, edema peripheral, fatigue, irritability; *Metabolism and nutrition disorders:* anorexia, decreased appetite; *Musculoskeletal and connective tissue disorders:* arthralgia, muscle spasms; *Nervous system disorders:* dizziness, headache, lethargy, sedation, tremor; *Psychiatric disorders:* anxiety, depression, insomnia, restlessness; *Skin and subcutaneous tissue disorders:* hyperhidrosis, pruritus; *Vascular disorders:* hot flush. **Less Common (<1%):** *Eye disorders:* vision blurred, orthostatic hypotension; *Gastrointestinal disorders:* abdominal distension, pancreatitis, abdominal discomfort, fecaloma, abdominal pain lower, abdominal tenderness; *General disorders and administration site conditions:* malaise, asthenia, feeling jittery, drug withdrawal syndrome; *Hepatobiliary disorders:* cholecystitis; *Investigations:* alanine aminotransferase increased, aspartate aminotransferase increased; *Musculoskeletal and connective tissue disorders:* myalgia, muscular weakness; *Nervous system disorders:* depressed level of consciousness, mental impairment, memory impairment, disturbance in attention, stupor, paraesthesia, coordination abnormal; *Psychiatric disorders:* disorientation, thinking abnormal, mental status changes, confusional state, euphoric mood, hallucination, abnormal dreams, mood swings, nervousness; *Renal and urinary disorders:* urinary retention, dysuria; *Reproductive system and breast disorders:* erectile dysfunction; *Respiratory, thoracic and mediastinal disorders:* dyspnea, rhinorrhoea; *Skin and subcutaneous tissue disorders:* rash, piloerection, cold sweat, night sweats; *Vascular disorders:* hypotension, flushing. **USE IN SPECIFIC POPULATIONS: Pregnancy:** *Teratogenic Effects:* Pregnancy Category C: Teratogenic effects of morphine have been reported in the animal literature. High parental doses during the second trimester were teratogenic in neurological, soft and skeletal tissue. The abnormalities included encephalopathy and axial skeletal fusions. These doses were often maternally toxic and were 0.3 to 3-fold the maximum recommended human dose (MRHD) on a mg/m^2 basis. The relative contribution of morphine-induced maternal hypoxia and malnutrition, each of which can be teratogenic, has not been clearly defined. Treatment of male rats with approximately 3-fold the MRHD for 10 days prior to mating decreased litter size and viability. *Nonteratogenic Effects:* Morphine given subcutaneously, at non-maternally toxic doses, to rats during the third trimester with approximately 0.15-fold the MRHD caused reversible reductions in brain and spinal cord volume, and testes size and body weight in the offspring, and decreased fertility in female offspring. The offspring of rats and hamsters treated orally or intraperitoneally throughout pregnancy with 0.04- to 0.3-fold the MRHD of morphine have demonstrated delayed growth, motor and sexual maturation, and decreased male fertility. Chronic morphine exposure of fetal animals resulted in mild withdrawal, altered reflex and motor skill development, and altered responsiveness to morphine that persisted into adulthood. There are no well-controlled studies of chronic *in utero* exposure to morphine sulfate in human subjects. However, uncontrolled retrospective studies of human neonates chronically exposed to other opioids *in utero,* demonstrated reduced brain volume which normalized over the first month of life. Infants born to opioid-abusing mothers are more often small for gestational age, have a decreased ventilatory response to CO_2, and increased risk of sudden infant death syndrome. There are no adequate and well-controlled studies of naltrexone in pregnant women. EMBEDA should only be used during pregnancy if the need for strong opioid analgesia justifies the potential risk to the fetus. **Labor and Delivery:** EMBEDA is not recommended for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor. Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific opioid antagonist, such as naloxone or nalmefene, should be available for reversal of opioid-induced respiratory depression in the neonate. **Nursing Mothers:** Morphine is excreted in the maternal milk, and the milk to plasma morphine AUC ratio is about 2.5:1. The amount of morphine received by the infant depends on the maternal plasma concentration, amount of milk ingested by the infant, and the extent of first pass metabolism. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Because of the potential for adverse reactions in nursing infants from EMBEDA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and efficacy of EMBEDA in individuals less than 18 years of age have not been established. **Geriatric Use:** Clinical studies of EMBEDA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. The pharmacokinetics of EMBEDA have not been investigated in elderly patients (>65 years) although such patients were included in clinical studies. In a long-term open label safety study, the pre-dose plasma morphine concentrations after dose normalization were similar for subjects <65 years and those ≥65 years of age. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **Neonatal Withdrawal Syndrome:** Chronic maternal use of opiates or opioids during pregnancy coexposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration, and severity of the disorder differ based on such factors as the addictive drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn. Approaches to the treatment of this syndrome have included supportive care and, when indicated, drugs such as paregoric or phenobarbital. **Race:** Pharmacokinetic differences due to race may exist. Chinese subjects given intravenous morphine in one study had a higher clearance when compared to Caucasian subjects (1852 ± 116 mL/min versus 1495 ± 80 mL/min). **Hepatic Failure:** The pharmacokinetics of morphine was found to be significantly altered in individuals with alcoholic cirrhosis. The clearance was found to decrease with a corresponding increase in half-life. The morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) to morphine plasma AUC ratios also decreased in these patients indicating a decrease in metabolic activity. **Renal Insufficiency:** The pharmacokinetics of morphine is altered in renal failure patients. AUC is increased and clearance is decreased. The metabolites, M3G and M6G, accumulate several fold in renal failure patients compared with healthy subjects. Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted. **Breakthrough Pain/ Adverse Experiences:** Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication. **Mental and/or Physical Ability:** Patients should be advised that EMBEDA may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on EMBEDA or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected *[see Warnings and Precautions]*. **Avoidance of Alcohol or Other CNS Depressants:** Patients should be advised that EMBEDA should not be taken with alcohol, prescription or non-prescription medications containing alcohol, or other CNS depressants (sleeping medication, tranquilizers) except by the orders of the prescribing healthcare provider because dangerous additive effects may occur resulting in serious injury or death *[see Warnings and Precautions]*. **Pregnancy:** Women of childbearing potential who become or are planning to become pregnant, should consult their prescribing healthcare provider prior to initiating or continuing therapy with EMBEDA *[see Use in Specific Populations]*. **Cessation of Therapy:** Patients should be advised that if they have been receiving treatment with EMBEDA for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the EMBEDA dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their prescribing healthcare provider should provide a dose schedule to accomplish a gradual discontinuation of the medication. **Drug of Abuse:** Patients should be advised that EMBEDA is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed *[see Warnings and Precautions]*. **Constipation:** Patients should be advised that severe constipation could occur as a result of taking EMBEDA and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy. **Storage/Destruction of Unused EMBEDA:** Patients should be instructed to keep EMBEDA in a secure place out of the reach of children. When EMBEDA is no longer needed, the unused capsules should be destroyed by flushing down the toilet.

FDA-Approved Patient Labeling

[See separate leaflet.]

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Breastfeeding Lowers Metabolic Syndrome Risk

The longer a woman breastfeeds, the less likely she will develop metabolic syndrome over time, even if she has a history of gestational diabetes, according to the results of a prospective study that followed almost 1,400 women for 20 years.

Having breastfed for more than 1 month was associated with a 39%-46% lower incidence of metabolic syndrome (depending on duration of breastfeeding) among women with no history of gestational diabetes, and with a 44%-86% lower incidence among those with gestational diabetes."The findings indicate that breastfeeding a child may have lasting favorable effects on a woman's risk factors for later developing diabetes or heart disease," the lead author, Erica P. Gunderson, Ph.D., said in a statement released by Kaiser Permanente. The study was published online, [doi.org/10.2337/db09-1197]), and will appear in print in Diabetes in February.

Their findings did not appear to be caused by differences in weight gain, physical activity, or other health behaviors, but less abdominal fat and higher levels of high-density lipoprotein were characteristic of women who did not develop metabolic syndrome, added Dr. Gunderson of the division of research, epidemiology and prevention at Kaiser Permanente, Oakland, Calif.

The study followed 1,399 women enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study, who were aged 18-30 years when they were enrolled, had never delivered a baby, and did not have metabolic syndrome at baseline. Of these women, 704 had at least one singleton live birth in 1986-2006, including 84 who had gestational diabetes; over 20 years, 120 cases of metabolic syndrome were diagnosed among these women. The overall incidence of metabolic syndrome was 12.0 cases/1,000 person years. The incidence was significantly higher among those who had been diagnosed with gestational diabetes during pregnancy, than those who had not (22.1 cases/1,000 person years, compared with 10.8 cases/1,000 person years.)

The study was funded by the National Institutes of Health.

—Elizabeth Mechcatie