

Hyperglycemia Strongest Predictor of Type 2

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

STOCKHOLM – The risk for developing type 2 diabetes is not the same for everyone with metabolic syndrome, but instead varies dramatically depending on individual factors.

In fact, hyperglycemia – with or with-

out metabolic syndrome – was a much stronger predictor of incident type 2 diabetes than was metabolic syndrome without hyperglycemia in a 5-year observational analysis of 58,056 initially nondiabetic adults aged 30 years and older who were members of the managed care organization Kaiser Permanente Northwest, Gregory A. Nichols, Ph.D., said.

“In the absence of impaired fasting

glucose, the definition of metabolic syndrome may be a misleading estimator of diabetes risk,” according to Dr. Nichols, the lead investigator on the study (*Diabetes Res. Clin. Pract.* 2010;90:115-21).

He and a colleague examined the incidence of diabetes for all possible combinations of metabolic syndrome components using criteria defined in the National Cholesterol Education Program’s Adult Treatment Panel III report (ATP III) (Cir-

ulation 2004;109:433-8). The one exception was the use of body mass index as a substitute for waist circumference, which is rarely measured clinically, noted Dr. Nichols of Kaiser Permanente’s Center for Health Research, Portland, Ore.

For the study, an individual was considered to have metabolic syndrome if they met three of the following five criteria: impaired fasting glucose (greater than 100 mg/dL), hypertension (130/85 mm Hg or greater), high triglycerides (150 mg/dL or greater), low HDL cholesterol (less than 40 mg/dL for men, 50 mg/dL for women), and BMI greater than 28.8 kg/m². This BMI cut-point has been substituted for waist circumference in other published studies, he noted.

Over 5 years, 6% of the total study sample developed diabetes. Compared with those who did not develop diabetes,

Postmarketing Experience—The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Osteosarcoma:** Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing.
- **Hypercalcemia:** Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use.

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following:

- **Allergic Reactions:** Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria;
- **Investigations:** Hyperuricemia;
- **Respiratory System:** Acute dyspnea, chest pain;
- **Musculoskeletal:** Muscle spasms of the leg or back;
- **Other:** Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

USE IN SPECIFIC POPULATIONS: Pregnancy Category C—There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses \geq 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses \geq 120 times the human dose (based on surface area, mcg/m²). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

Exposure multiples were normalized based on body surface area (mcg/m²). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day).

Nursing Mothers—It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use—The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses.

Geriatric Use—Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment—No studies have been performed in patients with hepatic impairment.

Renal Impairment—In 5 patients with severe renal impairment (CrCl \leq 30 mL/min), the AUC and T_{1/2} of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

OVERDOSAGE: Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur.

FORTEO® (teriparatide [rDNA origin] injection)

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In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

Overdose Management—There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE FORMS AND STRENGTHS: Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

PATIENT COUNSELING INFORMATION: Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

PLEASE SEE FULL PRESCRIBING INFORMATION FOR ADDITIONAL INFORMATION.



In the absence of IFG, ‘the definition of metabolic syndrome may be a misleading estimator of diabetes risk.’

DR. NICHOLS

those who did were significantly older (59 vs. 57 years), and were more likely to be male (52% vs. 44%), nonwhite (10% vs. 8%), and a current smoker (15% vs. 12%).

The risk for developing diabetes was greater in the presence than in the absence of each individual component. The 5-year risk for diabetes rose with each component an individual had at baseline, from 0.3% for those with none to 1.2% with one, 3.5% with two, 8.4% with three, 16.9% with four, and 28.2% with five.

Among the five individual components, the greatest diabetes risk was associated with impaired fasting glucose (IFG; incidence of 37.4/1,000 person-years), followed by low HDL cholesterol (21.6/1,000 person-years), high triglycerides (20.6/1,000), obesity (19.5), and hypertension (16.2).

There was a clear separation between combinations of components that did and did not contain IFG. The combination of IFG and any one additional component – by definition, not meeting metabolic syndrome criteria – had a higher incidence rate of diabetes (16.5/1,000 person-years) than did any three- or four-component combination that did not include IFG (7.9 and 11.3 per 1,000 person-years, respectively), yet did meet the metabolic syndrome criteria.

The incidence of diabetes among those who had IFG and no other metabolic syndrome component was 10.2/1,000 person-years, compared with 11.3/1,000 for those with every component except IFG, Dr. Nichols reported.

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