

# Use Guidelines on Calcium, Vitamin D Loosely

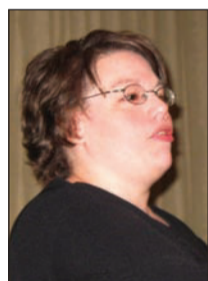
BY SHERRY BOSCHERT

EXPERT ANALYSIS FROM A MEETING ON OSTEOPOROSIS

SAN FRANCISCO – Updated national guidelines on calcium and vitamin D intake should be followed only loosely, cautioned Dr. Deborah E. Sellmeyer, director of the Metabolic Bone Center at Johns Hopkins University, Baltimore.

There's a lot of controversy surrounding the Institute of Medicine's (IOM) November 2010 report, "Dietary Reference Intakes for Calcium and Vitamin D," which updated 1997 guidelines.

Dr. Sellmeyer uses the latest IOM report as a starting point and then tailors the recommendations to meet the needs of her individual patients. And as a result, the amounts of vitamin D and calcium



Most people need about 1,200 IU per day of vitamin D to reach 'sufficient' serum levels of 30-32 ng/mL.

DR. SELLMAYER

that her patients take usually vary from the guidelines, she said at a conference on osteoporosis sponsored by the University of California, San Francisco.

There is uncertainty about the cutoff level of serum vitamin D that's considered adequate and the potential side effects from ingesting too much calcium, she said.

The IOM recommends that adults take 600 IU/day through age 50 and 800 IU/day for those aged 51 years and older, with a suggested upper tolerability limit of 4,000 IU/day. Those are the intake amounts that generally would be needed to reach a serum level of 20 ng/mL.

Many experts, however, think that physiologic and fracture data suggest that a "sufficient" serum level should be in the 30- to 32-ng/mL range, she said. "It takes most people about 1,200 IU/day to reach that" serum level, said Dr. Sellmeyer, who advises her patients to get 1,200 IU/day of vitamin D.

A 2010 study of high-dose vitamin D and fracture risk caused "a lot of consternation," she noted. The double-blind trial randomized 2,256 older women to a once-yearly oral dose of 500,000 IU cholecalciferol or placebo, and found higher rates of falls and fractures in the vitamin D group (JAMA 2010;303:1815-22).

"It's almost a moot point because you wouldn't give 500,000 IU once a year, but it did raise the idea that there may be some administration techniques, some regimens that would not be beneficial," Dr. Sellmeyer said.

The IOM committee that compiled the 2010 report expressed a great deal of concern about a potentially higher mortality risk with excessively high vitamin D serum levels.

The concern was sparked by the com-

mittee's interpretation of an analysis of data from the Third National Health and Nutrition Examination Survey. Overall, that survey documented higher mortality rates in patients in the lowest quartile of serum vitamin D levels (Arch. Intern. Med. 2008;168:1629-37). However, the IOM committee noticed a statistically nonsignificant dip in mortality risk between the highest and second-highest quartiles of serum vitamin D be-

fore the mortality risk increased in each of the two lowest quartiles, constituting what some saw as a J-shaped curve mortality risk.

Numerically, the lowest mortality was in patients with 24-32 ng/mL of serum vitamin D, but this was not significantly different than in patients with a serum level greater than 32 ng/mL.

"I'm really not sure that there is a higher mortality," Dr. Sellmeyer said. "I

think there is enough evidence to suggest that we probably ought to be a little more in the 30- to 40-ng/mL range."

The IOM recommends that adult males get 1,000 mg/day of calcium through age 70 years and 1,200 mg/day if they are older. Adult women should get 1,000 mg/day through age 50 and 1,200 mg/day at older ages. The maximum tolerability limits were set at 2,500

*Continued on following page*

## Choose Humalog and the MiniMed Paradigm® REAL-Time Revel™ Insulin Pump

For adult patients with type 1 diabetes ready to have a conversation about using an insulin pump

- Humalog® [100 units/mL] can be used in a Paradigm Revel Insulin Pump<sup>1</sup>

### Indication for Humalog

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

### Select Safety Information for Humalog

- Humalog is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.
- Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously.
- Humalog should be given within 15 minutes before or immediately after a meal.
- Hypoglycemia is the most common adverse effect of Humalog therapy. The risk of hypoglycemia increases with tighter glycemic control. Severe hypoglycemia may be life threatening and can cause seizures or death.



### Select Safety Information for Humalog, continued

- Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.
- Adverse reactions associated with Humalog in patients receiving continuous subcutaneous insulin infusion: In adult patients, catheter occlusions (0.09/month), infusion-site reactions (2.6%). In children and adolescents, infusion-site reactions (21%).

Reference  
1. Paradigm® REAL-Time Revel™ User Guide. Starting on Insulin. ©2009 Medtronic MiniMed, Inc. 4.7.

Please see Important Safety Information on next page and Brief Summary of Full Prescribing Information for Humalog on following pages.

For more information about Humalog, please call Eli Lilly and Company at 1-800-545-5979. For more information about Paradigm® REAL-Time Revel™, please call Medtronic at 1-888-350-3245.

*Humalog*

Paradigm REAL-Time  
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insulin lispro injection (rDNA origin)

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mg/day for adults younger than 50 years or 2,000 mg/day for older adults.

It's important to remember that the recommended level includes both dietary and supplemental sources of calcium, she emphasized. "We see a lot of women who are taking 1,200-1,500 mg/day in supplements and also drinking two glasses of milk a day," she said. "Those [are the patients who] can get into trouble."

There are no data to suggest that ingesting more than 1,200 mg/day is bet-

ter for skeletal health, and high doses of calcium increase the risk of developing kidney stones, studies show.

The most controversial aspect of calcium supplementation in recent years has been some preliminary evidence of a possible increased risk for vascular calcification with higher doses of calcium.

Initially, an analysis of data on 36,282 participants in the Women's Health Initiative (WHI) who were randomized to take 500 mg calcium carbonate with 200 IU vitamin D twice daily found no effect on risk of myocardial infarction or vas-

cular calcification (Circulation 2007; 115:846-54).

Then a randomized, controlled trial of 1,471 healthy women found that the group taking 1 g/day of calcium citrate showed a doubling in risk for MI and a trend toward higher risk of angina, compared with the placebo group (BMJ 2008;336:262-6). The investigators in that study reanalyzed the WHI data and found a 22% increase in risk for MI in women who at baseline had no personal calcium use (BMJ 2011;19:342:d2040). There were significant differences in the comparison groups in

the reanalysis, including differences in personal history of MI, Dr. Sellmeyer noted.

"Whether this truly represents an increased risk or not is unclear," Dr. Sellmeyer said.

Another study by some of the same investigators "got a ton of press" even though it was a relatively small meta-analysis, she added.

The attempted meta-analysis of 190 trials of calcium supplementation yielded 15 eligible trials, but most of the data came from 5 trials. The meta-analysis reported a 31% increase in risk for MI in

### Important Safety Information for Humalog

#### Contraindications

- Humalog® is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.

#### Warnings and Precautions

- **Dose Adjustment and Monitoring:** Closely monitor blood glucose in all patients treated with insulin. Change insulin regimens cautiously. Concomitant oral antidiabetic treatment may need to be adjusted.

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 delivery site, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require insulin dose adjustment.

- **Hypoglycemia:** Hypoglycemia is the most common adverse effect of Humalog. The risk of hypoglycemia increases with tighter glycemic control. Educate patients to recognize and manage hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or intensified diabetes control. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia. Severe hypoglycemia may be life threatening and can cause seizures or death.

Use caution in patients with hypoglycemia unawareness and who may be predisposed to hypoglycemia. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Rapid changes in serum glucose levels may induce symptoms similar to hypoglycemia in persons with diabetes, regardless of the glucose value.

Timing of hypoglycemia usually reflects the time-action profile of administered insulins. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may alter the risk of hypoglycemia.

- **Allergic Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog.
- **Hypokalemia:** Humalog can cause hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Use caution in patients who may be at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).

### Important Safety Information for Humalog, continued

#### Warnings and Precautions, continued

- **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 insulins 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.

- **Subcutaneous Insulin Infusion Pump:** Humalog should not be diluted or mixed when used in an external insulin pump. Change Humalog in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days.

Malfunction of the insulin pump or infusion set or insulin degradation can rapidly lead to hyperglycemia and ketosis. Prompt correction of the cause of hyperglycemia or ketosis is necessary. Interim subcutaneous injections with Humalog may be required. Train patients using an insulin pump to administer insulin by injection and to have alternate insulin therapy available in case of pump failure.

- **Drug Interactions:** Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required.

#### Adverse Reactions

- Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

#### Use in Specific Populations

- **Pediatrics:** Humalog has not been studied in children with type 1 diabetes less than 3 years of age or in children with type 2 diabetes.

#### Dosage and Administration

- Humalog should be given within 15 minutes before or immediately after a meal.

Please see following pages for Brief Summary of Full Prescribing Information for Humalog.

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insulin lispro injection (rDNA origin)

calcium supplement users, with possibly a higher risk in those taking more than 1,600 mg/day (BMJ 2010; 341:c3691).

“It’s really hard to know at this point” whether the risk of vascular calcification from supplementation is significant, Dr. Sellmeyer said.

“I think it does behoove us to be judicious with our calcium and not let people consume more calcium than we think is really beneficial.”

Calcium citrate probably is a little better absorbed than calcium carbonate and may be a little less con-

stipating, “but for a lot of people it doesn’t matter,” she said.

As always, physicians should be alert for conditions in their patients that might warrant higher intakes of calcium or vitamin D, she said, including malabsorption (as in patients who underwent gastric bypass surgery), healing osteomalacia, fracture healing, anabolic therapy, postoperative hyperparathyroidism, hypoparathyroidism, or adolescence.

Dr. Sellmeyer said she has no relevant conflicts of interest. ■

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### MiniMed Paradigm REAL-Time Revel Insulin Pump Indications for Use

#### Pump

The Paradigm Revel insulin pump is indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin.

### MiniMed Paradigm REAL-Time Revel Insulin Pump Important Safety Information

#### Contraindications

Pump therapy is not recommended for people who are unwilling or unable to perform a minimum of four blood glucose tests per day and to maintain contact with their healthcare professional. Successful insulin pump therapy requires sufficient vision or hearing to allow recognition of the pump signals and alarms.

#### Warnings

The pump is not suitable for use in the presence of a flammable anaesthetic mixture with air, oxygen or nitrous oxide.

Standard Luer sets are not compatible with the Medtronic MiniMed Paradigm pump. Medtronic Diabetes Paradigm reservoirs and Paradigm-compatible infusion sets are specifically designed for use with the pump.

Do not modify your Paradigm reservoir or Paradigm-compatible infusion set.

Do not put any other drugs/medications inside your reservoir to use with this pump. Only insulin that has been prescribed by your physician can be used in this pump.

Do not use pump cases that have a magnetic clasp.

Do not expose your insulin pump to MRI equipment or other devices that generate very strong magnetic fields. The magnetic fields in the immediate vicinity of these devices can damage the part of the pump’s motor that regulates insulin delivery, possibly resulting in over-delivery and severe hypoglycemia. Your pump must be removed and kept outside the room during magnetic resonance imaging (MRI) procedures.

If your pump is inadvertently exposed to a strong magnetic field, discontinue use and contact our 24 Hour HelpLine for further assistance.

**Please visit <http://www.medtronicdiabetes.com/about/safety.html> for complete safety information.**

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The MiniMed Paradigm Revel Insulin Pump does not include optional continuous glucose monitoring (CGM) technology available from Medtronic Diabetes. For information on the MiniMed Paradigm Revel Insulin Pump integrated with CGM, please contact your Medtronic Diabetes representative.

**Please see Important Safety Information for Humalog on opposite page.**

