

# DIABETES IN CONTROL.com Newsletter

The Newsletter for Professionals in Diabetes Care

December 24, 2008 Issue 448

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## Top Current Diabetes News:

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**Gastric Bypass For Older Type 2's? Till What Age?\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6350>

**Research Finds Three-Quarters of Youths With Diabetes Insufficient In Vitamin D\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6349>

**Diabetes Linked To Risk Of Lymphoma\***

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**Sleep Apnea Treatment Reduces Nighttime Blood Sugar\***

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**Psoriasis, Metabolic Syndrome Linked to High Leptin Levels\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6346>

**Insulin Levels Predict Survival Odds in Colon Cancer Patients\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6343>

**Chromosome Linked to Diabetics' Heart Risks\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6340>

**Aggressive Cholesterol Lowering Has Benefits For Type 2's\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6339>

**How Important is Blood Glucose Variability In The Management Of Type 2 Diabetes?\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6338>

**Continuous Blood Pressure Monitoring, A Predictor of Future Heart Events\***

<http://www.diabetesincontrol.com/results.php?storyarticle=6336>

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**From the editor's desk:**

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This has been a very busy year for diabetes research and next year is expected to be even busier. So make sure you are registered to receive our newsletter for the new year.

**Sherri Colberg Ph.D.** has written a new book based on her experiences as an athlete and diabetes patient. The [Diabetic Athlete's Handbook: Your guide to peak performance](#) is reviewed this week by **Shannon Hart, PharmD Candidate University of Florida College of Pharmacy**

<http://www.diabetesincontrol.com/results.php?storyarticle=6351>

**Richard K. Bernstein, M.D., F.A.C.E., F.A.C.N., FCCWS** gives us an update on [Recent Developments Regarding Risk Factors For Heart Disease](#)

<http://www.diabetesincontrol.com/results.php?storyarticle=6352>

Make sure you watch for our **Special 2008 Year in Review Issue**, coming out Jan 1st. It is a summary of the most current guidelines, and breakthrough diabetes stories of 2008.

**Have a happy and safe holiday.**

**dLife TV Dec. 28, 7PM ET on CNBC**

Teenagers talk frankly about their personal diabetes challenges. Plus, young women who manipulate insulin to lose weight – the dangerous practice of diabulimia. And, *Leave it to Beaver's* Jerry Mathers opens up about his diabetes life. Be inspired by another great episode of dLifeTV: on Sundays on CNBC at 6:00 PM ET, 5:00 PM CT, and 3:00 PM PT

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***We can make a difference!***  
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***More Current News on Diabetes***

**Item #6: Next DPP-4 inhibitor (Alogliptin) Found Safe and Effective in Poorly Controlled Type 2's**

**Item #7: Atorvastatin, Fenofibrate Fixed Combo Is Effective For Mixed Dyslipidemia**

**Item #9: Arena Pharmaceuticals Announces First In Class Treatment for Type 2 Diabetes Begins Phase 1 Trial**

**Item #10: Diabetic Binge Eaters Can Still Lose Weight**

**Item #14: No-Carb Diets May Impair Memory**

Check out this weeks **["Test Your DIABETES Knowledge"](http://www.diabetesincontrol.com/results.php?storyarticle=6353)** question.  
<http://www.diabetesincontrol.com/results.php?storyarticle=6353>

**Dave Joffe, Editor-in-chief**

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**NEWS FLASH:**

**Diabetes Drugs Must Now Clear Cardiovascular Hurdle, Says FDA.**

**Click Here.**

<http://www.diabetesincontrol.com/results.php?storyarticle=6354>

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**This Week's Product:**

**Trilipix (fenofibrate extended release) by Abbott.** This is a long acting form of TriCor, and the first fibrate that the FDA has indicated for use with statins.

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**This Week's Tool:**



**Lab Tests Online:** A new public resource for understanding and learning about the different lab tests used in practice

<http://labtestsonline.org/>

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**This Week's Items:**

- 1. Gastric Bypass For Older Type 2's? Till What Age?\*

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**2. Research Finds Three-Quarters of Youths With Diabetes Insufficient In Vitamin D\***

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**15. Continuous Blood Pressure Monitoring, A Predictor of Future Heart Events\***

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**Articles For The Week:**

Item 1

**Gastric Bypass For Older Type 2's? Till What Age?**

*Recent studies showing that gastric bypass surgery extends the lives of obese patients is forcing surgeons to make tough decisions about who should go under the knife and who shouldn't.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6350>

Internists, cardiologists and endocrinologists, more than ever, are referring patients who traditionally haven't been candidates for the weight-loss surgery, also called bariatric surgery.

"I am being asked to operate on 78-year-olds with co-morbidities of heart disease and diabetes," said Dr. Edward H. Phillips, executive vice chairman of the Department of Surgery and a surgeon at the Center for Weight Loss at Cedars-Sinai Medical Center in Los Angeles. Phillips questions whether these patients will benefit, or if the damage has already been done.

"So, while it is obvious a 30-year-old will benefit, at what age is too old?" he asked.

The success of gastric bypass is also stoking debate about its use as a treatment for type 2 diabetes. Mounting evidence suggests this type of surgery may dramatically improve patients with the disease, freeing them from a lifetime of diabetes medications.

"There's more acceptance now of the concept that bariatric surgery is a truly life-saving type of therapy rather than just a way to shed pounds," said Dr. Francesco Rubino, chief of Gastrointestinal Metabolic Surgery at Weill Cornell Medical College in New York City.

Still, more long-term studies are needed, and clinicians and policymakers must reach a consensus on who should have access to this type of surgery, noted Rubino, who directed the 1st World Congress on Interventional Therapies for Type 2 Diabetes, held in New York City in September.

An estimated 205,000 bariatric surgeries were performed in the United States in 2007, according to the American Society for Metabolic & Bariatric Surgery (ASMBS). That's an increase of almost 20 percent from two years earlier.

If patients commit to making necessary changes in their diet and exercise regimens, gastric bypass surgery can provide long-term, consistent weight loss, according to the Mayo Clinic.

Not only does it help shed pounds, but a pair of studies published last year in the *New England Journal of Medicine* found that it can help obese people live longer.

One study, led by Ted Adams of the University of Utah School of Medicine, tracked almost 16,000 obese people, half of whom had weight-loss surgery. After an average of seven years, the death rate was 40 percent lower for people who had the surgery compared with those who didn't. Diabetes-related deaths were cut by a whopping 92 percent.

The other study, led by a Swedish team, involved more than 6,000 obese patients. After an average follow-up of more than a decade, those who had bariatric surgery were 29 percent less likely to die than those who did not undergo surgery.

Age is not necessarily a barrier, another study suggests. In a review of 1,065 bariatric surgeries performed from 2001 to 2005, researchers at the Geisinger Medical Center in Danville, Pa., found that people 60 and older had comparable safety and effectiveness results as those under 60.

But Phillips isn't convinced it's the right thing to do for people pushing 80.

"The likelihood of extending their lives is unknown," he said, noting that they've already reached their life expectancy. "Also, if a complication occurs, they can't survive it."

And despite the life-extending benefits that the surgery may provide, every patient must proceed with caution.

"I would still strongly advise patients considering bariatric surgery to consider the risks associated with surgery in relation to the risks associated with excessive body weight," Adams said. "There should be careful assessment of the pros and cons of surgery and the pros and cons of remaining severely obese."

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Item 2

**Research Finds Three-Quarters of Youths With Diabetes Insufficient In Vitamin D**

Study urges supplementation of vitamin D to protect bones later in life for those children found to be deficient in vitamin D (75%).

<http://www.diabetesincontrol.com/results.php?storyarticle=6349>

Three-quarters of youths with type 1 diabetes were found to have insufficient levels of vitamin D, according to a study by researchers at the Joslin Diabetes Center – findings that suggest children with the disease may need vitamin D supplementation to prevent bone fragility later in life.

"To our surprise, we found extremely high rates of vitamin D inadequacy," said Lori Laffel, M.D., M.P.H., Chief of the Pediatric, Adolescent and Young Adult Section at Joslin, Investigator in the Section on Genetics and Epidemiology, and senior author of the paper. "We didn't expect to find that only 24 percent of the study population would have adequate levels."

The study, measured levels of serum 25-hydroxyvitamin D in 128 youths with type 1 diabetes ranging in age from 1.5 to 17.5 years. The study sample included subjects with recent onset of diabetes as well as those who had long-established diabetes.

It found 24 percent had sufficient levels, 61 percent with insufficient levels and 15 percent to be deficient or having the lowest levels. Generally, those with deficient levels were the oldest of the subjects. In fact, 85 percent of the adolescents in the sample demonstrated inadequate vitamin D levels.

The paper notes that diabetes itself can negatively impact bone health and is associated with a modest reduction in bone mineral density and strength and an increase in fracture risk among those middle-aged and older. At the same time, vitamin D deficiency in infants and children is associated with bone deformation, while less severe vitamin D insufficiency prevents youths from attaining their optimal bone mass and may contribute to increased fracture risk later in life, the paper adds.

For these reasons, vitamin D deficiency or insufficiency poses an increased risk for children with diabetes, the paper says. In addition to reduced sun exposure, diminished milk intake, substituted by intake of sugar-free beverages among youth with diabetes, may account for inadequate vitamin D levels.

"In addition to inadequate levels of vitamin D, adolescent patients with type 1 diabetes potentially possess multiple risk factors for increased skeletal fragility," the paper notes.

The researchers were interested in looking at vitamin D levels because of the vitamin's presumed role in immune modulation and because it is thought to possibly play a role in the occurrence of type 1 diabetes.

In addition, there has been a rise in vitamin D deficiency among children in general, mostly among those living in northern climates where sun exposure is lowest, and also in association with the increased use of sun block, recommended in efforts to prevent skin cancer. Protection from over-exposure to sunlight through use of sunscreens remains an important public health initiative, Laffel stressed.

"We need to make sure all youths in general are getting enough vitamin D in their diets," commented Britta Svoren, M.D., the primary author of the paper and a member of Joslin's Pediatric, Adolescent and Young Adult Section and the Section on Genetics and Epidemiology. "And, we need to pay particular attention to those with diabetes as they appear to be at an even higher risk of vitamin D deficiency. For children who are not drinking sufficient amounts of vitamin D fortified milk, we are encouraging them to take a vitamin D supplement of 400 IU daily. Many cereals are fortified with vitamin D as well."

*The Journal of Pediatrics, January 2009*

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## **DID YOU KNOW:**

**WHO asks India to wake up to 'diabetic' tsunami:** India is about to be hit with the Diabetes Tsunami. India has close to 41 million diabetic patients and the number is about to explode. 'The country needs to wake and fight the diabetic tsunami. India spends only three US dollars per patient to create awareness about the disease but spends not less than \$650 per person per year as medical

expenditure. And, 'Between 30 percent to 80 percent of diabetics in the Southeast Asia region do not know that they have the disease. *The World Health Organization (WHO)*

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Item 3

**Diabetes Linked To Risk Of Lymphoma**

*More cases of blood cancers classified as non-Hodgkin's lymphoma, or NHL, seem to occur among people with diabetes than those without, researchers report.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6348>

"Although the relative risk is moderate, given the rapidly increasing incidence and prevalence of diabetes, the number of incident cases of NHL attributed to diabetes can potentially be very high," Dr. Anastassios G. Pittas and colleagues point out in their report in the medical journal Diabetes Care.

Pittas, at Tufts University School of Medicine in Boston, and his team found 16 previous studies reporting an association between diabetes and NHL. Combined data from all the studies showed that the likelihood of developing NHL was 19 percent higher for subjects with diabetes than for comparison groups without diabetes.

The researchers point out that the incidence of NHL has increased since 1950. They think the immune changes associated with diabetes "may, at least in part, account for the increased risk of NHL that we found in this study."

*Diabetes Care, December 2008.*

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Item 4

**Sleep Apnea Treatment Reduces Nighttime Blood Sugar**

*Patients with type 2 diabetes and obstructive sleep apnea who used continuous positive airway pressure (CPAP) saw improved glycemic control during the night.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6347>

Mean nighttime glucose levels decreased to 102.9 mg/dL after an average of 41 days of CPAP therapy, from a baseline mean of 122.0 mg/dL in 20 patients ( $P=0.03$ ), reported Arthur Dawson, M.D., of the Scripps Clinic.

Also reduced was the mean standard deviation in nighttime glucose values for individual patients, from 20.0 to 13.0 mg/dL ( $P=0.005$ ), indicating more stable glycemia levels during sleep.

"Our findings suggest that screening type 2 diabetics for obstructive sleep apnea and treating those with moderate to severe sleep-disordered breathing could improve the management of their hyperglycemia and might favorably influence their long-term prognosis," the researchers wrote.

But they noted that the study excluded patients with poor compliance with CPAP -- a perennial problem with the treatment -- and hence may not be generalizable to all patients with sleep apnea and type 2

diabetes. The study does add, though, to the evidence that treatment of sleep apnea can lead to improvement in conditions that frequently accompany it.

Besides type 2 diabetes, sleep apnea is often associated with obesity and cardiovascular disease.

Patients in the trial were on a stable diabetic treatment regimen and had overnight oximetry data suggesting moderate to severe sleep apnea. All were newly diagnosed with sleep apnea and had never used CPAP.

A total of 28 were initially enrolled, but three were subsequently excluded because they were unable to sleep at least four hours per night with CPAP. Five others withdrew or were excluded for other reasons, leaving 20 for analysis. Patients underwent continuous glucose monitoring during sleep using an interstitial fluid sampling system. It was calibrated with blood glucose from a fingerstick in each patient. Participants also had their sleep monitored with polysomnography.

These procedures were performed once at enrollment and again after at least four weeks of CPAP therapy. In addition to lower mean nighttime glucose levels, patients also showed improvements in various measures of sleep quality and nocturnal respiration.

Mean apnea-hypopnea index values declined from 63 per hour at baseline to 7.9 per hour at the follow-up exam ( $P<0.001$ ). Daytime sleepiness, as measured by the Epworth scale, fell to 6.1 from 11.2 at baseline.

Patients' weight increased by 1 kg ( $P=0.02$ ) -- they were instructed not to try to lose weight -- and glycated hemoglobin levels remained stable. Dr. Dawson and colleagues said the latter was not surprising, because the study did not last long enough for altered daily glucose levels to be reflected in glycated hemoglobin.

Wake time after sleep onset decreased by 10 minutes from 71 minutes at baseline ( $P=0.02$ ). Sleep arousals plummeted, primarily because of almost total elimination of respiratory arousals -- from a mean of 51 at baseline to 2 at follow-up ( $P<0.001$ ).

The researchers found that daytime glucose levels were largely unchanged.

Dr. Dawson and colleagues said the finding of reduced nighttime variability in glucose levels was important because glycemic fluctuations have previously been shown to be an independent risk factor for death and microvascular complications of type 2 diabetes.

### Practice Pearls:

Explain to interested patients that the study found that when patients with type 2 diabetes and sleep apnea used continuous positive airway pressure at night, their glycemic control during sleep improved

Point out that the investigators measured interstitial glucose during polysomnography and did not demonstrate changes in hemoglobin A1c

*Journal of Clinical Sleep Medicine, Dec 15, 2008: Dawson A, et al "CPAP therapy of obstructive sleep apnea in type 2 diabetics improves glycemic control during sleep" JCSM 2008; 4: 538-43.*

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### FACT:

**Weight-Loss Surgery Increased 20% In Just 1 Year:** Almost 16,000 obese people, half of whom had weight-loss surgery participated in a survey. The survey found that after an average of seven

years, the death rate was 40 percent lower for people who had the surgery compared with those who didn't. Diabetes-related deaths were cut by a whopping 92 percent.

[See This Week's Item #1](#)

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Item 5

**Psoriasis, Metabolic Syndrome Linked to High Leptin Levels**

*Psoriasis and metabolic syndrome both are associated with high serum levels of leptin, according to a new report. "Body weight loss could potentially become part of the general treatment of psoriasis, especially in patients with obesity."*

<http://www.diabetesincontrol.com/results.php?storyarticle=6346>

Although association does not necessarily signify causation, it is possible that the proinflammatory mediators in psoriasis may stimulate leptin expression, which may in turn eventually lead to metabolic dysregulation, according to Dr. Yi-Ju Chen of the department of dermatology at Taichung (Taiwan) Veterans General Hospital, and associates.

It has been found that ischemic heart disease and stroke are significantly more common in psoriasis patients than in the general population. Therefore, the investigators wanted to examine the role of leptin, an adipocyte-derived hormone that helps regulate energy homeostasis, metabolism, and immune-inflammatory processes. They used serum samples from 77 psoriasis patients and 81 control patients matched for age and gender.

The median serum leptin level was found to be significantly higher in psoriasis patients (7,311 pg/mL) than in controls (4,804 pg/mL). Patient age, severity of psoriasis, presence or absence of psoriatic arthritis, and clinical subtype of psoriasis was found to have no relation to leptin levels.

In addition, psoriasis patients who also had metabolic syndrome had significantly higher leptin levels than did psoriasis patients without the metabolic syndrome, Dr. Chen and colleagues reported (Arch. Derm. 2008;144:1571-5). It seems that high circulating leptin levels in psoriasis derive not only from adipose tissue but also from an inflammation process, the authors wrote.

Since weight loss is known to decrease leptin levels, improve insulin sensitivity, and reduce the chance of developing metabolic syndrome and cardiovascular disease, "weight loss could potentially become part of the general treatment of psoriasis," the investigators concluded.

People with psoriasis have higher levels of the obesity-related hormone leptin than those without psoriasis, new research shows.

The Taiwanese study included 77 psoriasis patients and a control group of 81 people without the skin condition. The researchers gathered health information about the participants and analyzed blood samples for levels of leptin, which helps control food intake, body weight and fat stores. The hormone also plays a role in immune and inflammatory processes.

The psoriasis patients were more likely than those in the control group to be obese, to have high blood pressure, and to have elevated blood glucose levels or diabetes. High blood levels of leptin were found more often in females and in participants who were obese, had high blood pressure, had metabolic syndrome, or had psoriasis.

After the researchers adjusted for sex, body-mass index and cardiovascular risk factors, they concluded that psoriasis was independently associated with high leptin levels (hyperleptinemia). They also found that hyperleptinemia in psoriasis patients was associated with an increased risk of developing metabolic syndrome (a set of cardiovascular risk factors that includes high blood pressure and high cholesterol), a finding that links the chronic inflammation of psoriasis with metabolic disturbances.

The high blood levels of leptin in people with psoriasis may come not only from fat tissue but also from inflammation, Dr. Yi-Ju Chen, of the Taichung Veterans General Hospital and National Chung Hsing University, and colleagues, said in a university news release.

"Body weight loss has been reported to significantly decrease leptin levels and improve insulin sensitivity and may reduce the likelihood of developing metabolic syndrome and adverse cardiovascular diseases," the researchers concluded. "Body weight loss could potentially become part of the general treatment of psoriasis, especially in patients with obesity."

*Archives of Dermatology, Dec. 2008*

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Item 6

**Next DPP-4 inhibitor (Alogliptin) Found Safe and Effective in Poorly Controlled Type 2's**

*Therapy with alogliptin alone is significantly reduced glycosylated hemoglobin A1c levels in patients with type 2 diabetes and inadequate glycemic control, according to a double-blind, placebo-controlled, multicenter trial reported this month.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6345>

Alogliptin is a novel high-affinity, high-specificity inhibitor of dipeptidyl peptidase-4 (DPP-4), and has been shown to significantly reduce postprandial plasma glucose concentrations in patients with type 2 diabetes, Dr. Ralph A. DeFronzo at the University of Texas Health Science Center at San Antonio and colleagues note.

For the current study, a phase III trial, the researchers recruited 329 participants who had type 2 diabetes that was inadequately controlled with diet and exercise and who were treatment-naive. Average age of the participants was 53.4 years.

The subjects were randomized 2:2:1 to receive 12.5 mg alogliptin, 25 mg alogliptin or placebo for 26 weeks. Other antidiabetes drugs were prohibited. The study's primary endpoint was mean change from baseline in A1c levels.

Mean A1c decreased significantly more with alogliptin 12.5 mg (-0.56%) and 25 mg (-0.59%) than with placebo (-0.02%), and significant reductions were seen as soon as week 4.

In addition, decreases in fasting plasma glucose were significantly greater with alogliptin than with placebo at week 26 and as early as week 1, and the percentage of patients needing hyperglycemic rescue was significantly less with alogliptin than with placebo.

Most adverse events were mild or moderate, and rates of hypoglycemia were similar across treatment groups (1.5% - 3.0%).

Because skin and digit lesions had been seen in earlier preclinical studies of DPP-4 inhibitors other than alogliptin, Dr. DeFronzo's team monitored participants for skin-related adverse events. Although low overall, the incidence of such events was higher with alogliptin (12.8% - 15.2%) than with placebo (6.3%). One patient discontinued treatment (25 mg) because of moderate subcorneal pustular dermatosis that was judged to be possibly related to the study drug.

The researchers concluded that "the efficacy and safety of alogliptin monotherapy were comparable with those of other DPP-4 inhibitors. Alogliptin represents an effective treatment option whether given alone or in combination with antihyperglycemic agents from other classes."

*Diabetes Care, Dec. 2008.*

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Item 7

**Atorvastatin, Fenofibrate Fixed Combo Is Effective For Mixed Dyslipidemia**

*A once-daily, fixed-dose tablet combining atorvastatin and a novel micronized formulation of fenofibrate outperformed either drug alone in a phase II clinical trial in patients with mixed dyslipidemia.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6344>

This agent could fill an unmet need for a safe, convenient, and highly effective therapy for the commonplace lipid profile of high triglyceride, low HDL cholesterol, and high LDL cholesterol levels found among patients with metabolic syndrome or diabetes, Michael Rooney, Ph.D., noted at the annual scientific sessions of the American Heart Association.

LifeCycle Pharma Inc., the Danish company developing the fixed-dose combination tablet, is ironing out the details of a planned pivotal phase III trial with the Food and Drug Administration, Dr. Rooney said in an interview.

The phase II study involved 220 patients with mixed dyslipidemia who were randomized double blind to 12 weeks of the investigational combination of 40 mg of atorvastatin and 100 mg of the proprietary micronized fenofibrate, 40 mg of atorvastatin alone, or 145 mg of the Tricor brand of fenofibrate. Unlike Tricor and generic fenofibrate, the novel micronized formulation of the drug need not be taken with meals.

The combination tablet lowered triglyceride levels by a mean of 49% from a baseline of 270 mg/dL, compared with reductions of 29% and 28%, with atorvastatin and the higher-dose fenofibrate monotherapy, reported Dr. Rooney of Radiant Research, Chicago, a clinical research company contracted to conduct the trial.

The fixed-dose combination also boosted HDL levels 20% from a baseline of 43 mg/dL, compared with a 19% increase with fenofibrate monotherapy and a 7% bump with atorvastatin. From a mean baseline of 164 mg/dL, LDL cholesterol was reduced by a mean of 42% with the combination, 43% with atorvastatin alone, and 14% with 145 mg/day fenofibrate. Levels of apolipoprotein B were reduced from a baseline of 145 mg/dL by 41% with the combination, 37% with atorvastatin alone, and 15% with fenofibrate.

In terms of safety end points, there were five cases of myalgia and other muscle-related problems with atorvastatin monotherapy, four cases with fenofibrate monotherapy, and none in patients on the fixed-dose combination.

*Presented at the annual scientific sessions of the American Heart Association, 2008*

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Item 8

### **Insulin Levels Predict Survival Odds in Colon Cancer Patients**

*Blood levels of two insulin-related proteins are able to predict which patients with colon cancer are most likely to die of their disease by 87%, new research suggests.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6343>

Insulin ushers blood sugar out of the bloodstream and into cells. The hormone tends to work less efficiently in people who are obese, eat heavily and don't exercise, a condition which can lead to diabetes, heart disease and other conditions.

This may explain why individuals who are obese, eat a "Western-style" diet that is high in fat, and low in fruits and vegetables, and are inactive are more likely to develop colon cancer and to have their tumors recur after surgery.

Conversely, colon cancer patients who eat a diet rich in fruits, vegetables, poultry and fish can significantly lower the risk of their cancer returning.

"This gave us further evidence that really lifestyle factors do seem to play a part in the risk of recurrence. This is another piece of the puzzle," said Dr. Brian M. Wolpin, an attending physician in medical oncology at Dana-Farber Cancer Institute. "Although this study doesn't demonstrate causation, it does start to get at the pathways that might be involved, what proteins might be involved in risk."

The magnitude of the benefit for exercise in preventing recurrences is on the same order as what we see with chemotherapy," added Dr. John Marshall, chief of hematology/oncology at Georgetown's Lombardi Comprehensive Cancer Center, in Washington, D.C. "This study is trying to find out what the science is behind that. It's not an answer. It's a lead."

Previous studies have shown that women with early breast cancer and high levels of insulin and C-peptide along with metabolic syndrome are more likely to see a recurrence of their disease and to die.

And laboratory studies had shown that insulin spurs growth of colorectal cancer cells, while IGFBP-1 inhibits their growth and spread.

This latest study involved 373 patients with non-metastatic (stage I-III) colorectal cancer diagnosed between 1991 and 2004. Researchers looked at four proteins known to have a relationship to lifestyle factors, two with a stronger association and two with a lesser association. The two with the stronger association, one harmful (C-peptide) and one protective (IGFBP-1), turned out to be key.

Participants who had the highest levels of circulating IGFBP-1 had about a 50 per cent reduced risk of dying, both overall and from colon cancer, compared with those who had the lowest levels of the protein, Wolpin said.

Meanwhile, those with the highest levels of plasma C-peptide had an 87 per cent greater chance of dying overall and a 50 per cent greater chance of dying from colon cancer than those with the lowest levels. The difference may be due to the fact that "C-peptide is basically insulin . . . and insulin clearly is correlated with heart disease and other things," Wolpin said.

"It doesn't mean we're going to give you a pill rather than tell you to exercise," Marshall said. "Instead of drug companies doing clinical trials, Nike should do them."

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## **DID YOU KNOW:**

### **Research Finds Three-Quarters of Youths With Diabetes Insufficient In Vitamin D:**

Study urges supplementation of vitamin D to protect bones later in life for those children found to be deficient in vitamin D (75%). The findings that suggest children with the disease may need vitamin D supplementation to prevent bone fragility later in life.

[See This Weeks' Item #2](#)

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Item 9

### **Arena Pharmaceuticals Announces First In Class Treatment for Type 2 Diabetes Begins Phase 1 Trial**

*Phase 1 clinical trial of APD597, a novel first in class oral drug candidate that targets the glucose-dependent insulinotropic receptor (GDIR) for the treatment of type 2 diabetes will begin shortly. The GDIR has the potential to stimulate insulin release in response to increases in blood glucose. Ortho-McNeil-Janssen Pharmaceuticals will be a partner in the program.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6342>

Ortho-McNeil's Phase 1 program will evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of APD597 in single and multiple ascending dose studies in healthy volunteers. The planned clinical studies will also include the evaluation of patients with type 2 diabetes.

The GDIR is an orphan G protein-coupled receptor (GPCR), and it is expressed in beta cells, the cells in the pancreas responsible for producing insulin in response to increases in blood glucose. The GDIR signals through a similar intracellular pathway as the GLP-1 receptor, with common downstream effects, but unlike the GLP-1 receptor, the GDIR has proven amenable to small molecule drug discovery.

Stimulation of the GDIR is intended to more efficiently promote insulin release by beta cells in response to elevated blood glucose levels. In addition, the GDIR is expressed in cells other than pancreatic beta cells, such as endocrine cells in the gastrointestinal tract, and in preclinical studies the GDIR stimulates the release of GLP and GIP, two incretins that play an important role in insulin regulation and glucose homeostasis. GDIR stimulation has also been found to increase the levels and activity of intracellular factors thought to be involved in the preservation of beta cells, and GDIR signaling may therefore also serve to maintain beta cell mass in type 2 diabetes.

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Item 10

### **Diabetic Binge Eaters Can Still Lose Weight**

*The success of weight-loss in overweight and obese individuals with type 2 diabetes is not affected by a history of binge eating, according to a report in the Archives of General Psychiatry.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6341>

Although binge eating is often seen in those with diabetes type 2, there has been little research on its impact on weight loss, lead author Dr. Amy A. Gorin from the University of Connecticut, Storrs, and colleagues explain.

The current investigation involved 5,145 subjects, between 45 and 76 years of age, who were enrolled in the Look AHEAD (Action for Health in Diabetes) study, a weight-loss trial in which subjects were randomly assigned to an intensive lifestyle intervention or to support and education only.

At the start of the trial and 1 year later, 85.4 percent of the patients reported no binge eating at either time period. Binge eating only at the beginning of the trial was reported by 7.5 percent, binge eating

during both time periods was reported by 3.7 percent, and binge eating only after 1 year was reported by 3.4 percent.

The average weight loss for patients who had stopped binge eating at 1 year was 11.7 pounds (5.3 kilograms), which is comparable to the 10.6 pounds (4.8 kg) loss seen in subjects who reported no binge eating. By contrast, for subjects who continued binge eating or who reported it at 1 year, the average weight loss was lower, roughly 6.6 pounds (3.0 kg).

Further analysis suggested that the differences in weight loss between the groups was attributable to the difference in caloric intake, the authors note.

Patients who stop binge eating can be just as successful at losing weight as non-binge eaters, Gorin and colleagues conclude. Furthermore, they add: "This study lends further support to the recommendation that binge eating is not exacerbated by behavioral weight loss treatment and in fact may be improved by participating in a structured weight loss program targeting lifestyle changes."

*Archives of General Psychiatry, December 2008.*

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Item 11

### **Chromosome Linked to Diabetics' Heart Risks**

*Adding to earlier research, a new study has identified a genetic variation that increases the risk of coronary artery disease (CAD) in type 2 diabetes patients with poor sugar glucose (glycemic) control.*  
<http://www.diabetesincontrol.com/results.php?storyarticle=6340>

Previous research has found that genetic variations on a genetic chromosome known as chromosome 9p21 are associated with increased risk of CAD in the general population.

The team at the Joslin Diabetes Center at Harvard Medical School studied more than 1,500 people with type 2 diabetes (including 322 diagnosed with CAD) who were tested for a gene variation of chromosome 9p21 and checked for long-term glycemic control.

The findings were published in the Nov. 26 issue of the Journal of the American Medical Association.

Compared to patients with good glycemic control and no 9p21 gene risk variant, those subjects with two risk gene variants and good glycemic control were twice as likely to have CAD, while those with two risk gene variants and poor glycemic control were four times more likely to have CAD.

This association was strongest when long-term (seven years) glycemic control was measured in patients with two risk gene variants and a history of poor glycemia, and for patients with the same genotype but not long-term poor glycemia. The researchers also noted a similar interaction between the 9p21 variant and poor glycemia was associated with the death rate after 10 years.

"In conclusion, 9p21 (variant) and poor glycemic control interact in determining the odds of CAD in type 2 diabetes," Dr. Alessandro Doria and colleagues are quoted in a medical association news release. "This finding may have implications for our understanding of atherogenesis (the process of plaque forming in arteries) in diabetes and for the design of more effective prevention strategies. More broadly, it illustrates the complex etiology of multifactorial disorders and highlights the importance of accounting for gene-environment and gene-gene interactions in the quest for genetic factors contributing to these conditions."

Type 2 diabetes is one of the most significant risk factors for cardiovascular disease, and people with type 2 diabetes are two to four times more likely to suffer a major cardiac event than those without diabetes, according to background information in the article. According to the U.S. Centers for Disease Control and Prevention, more than 22 million Americans have type 2 diabetes.

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**DID YOU KNOW:**

**Insulin Levels Predict Survival Odds in Colon Cancer Patients:**

Blood levels of two insulin-related proteins are able to predict which patients with colon cancer are most likely to die of their disease by 87%, new research suggests. Insulin ushers blood sugar out of the bloodstream and into cells. The hormone tends to work less efficiently in people who are obese, eat heavily and don't exercise, a condition which can lead to diabetes, heart disease and other conditions.

[See This Weeks' Item #8](#)

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Item 12

**Aggressive Cholesterol Lowering Has Benefits For Type 2's**

*In people with type 2 diabetes, intensive drug therapy to significantly lower "bad" LDL cholesterol reduces the thickness of the carotid arteries, the major arteries in the neck that supply oxygen to the brain, research shows.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6339>

The beneficial effect on the thickness of the neck arteries is similar in people who attain equivalent LDL cholesterol reductions by taking a statin drug alone or by taking a statin plus another cholesterol medicine called ezetimibe, the researchers found. Ezetimibe (Vytorin) pairs the statin drug Zocor with cholesterol fighter Zetia.

However, the addition of ezetimibe may be required if a statin alone fails to lower LDL levels to target levels, they report in the Journal of the American College of Cardiology.

The Stop Atherosclerosis in Native Diabetics Study, or SANDS, trial, tested the value of aggressively lowering LDL cholesterol to 70 milligrams per deciliter (mg/dL) or lower, and non-HDL cholesterol to 100 mg/dL or lower, versus lowering levels of these harmful lipids merely to "standard goals" (i.e., 100 mg/dL or lower for LDL and less than 130 mg/dL for non-HDL-C).

If the LDL goal was not reached with a statin alone in the aggressive group, ezetimibe was added.

The study involved 427 type 2 diabetic Native Americans who were age 40 or older and who had no history of heart attack or other heart-related event. There were 204 people in the standard treatment group and 223 in the aggressive treatment group -- 154 treated with statins alone and 69 who received statin plus ezetimibe.

Ultrasound tests showed that neck artery thickness got worse, or progressed, in the standard treatment group and regressed, to a similar degree, in the two aggressive treatment groups.

Nearly identical proportions of patients in the two aggressive subgroups demonstrated no change or a decrease in neck artery thickness during follow-up, Dr. Wm. James Howard at MedStar Research Institute in Hyattsville, Maryland, and colleagues report.

Comparable LDL and non-HDL cholesterol lowering accomplished with a statin plus ezetimibe versus a statin alone resulted in similar benefit, they say.

Ezetimibe "remains a viable therapeutic option for patients who fail to reach their LDL cholesterol target on a statin alone," they conclude.

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Item 13

**How Important is Blood Glucose Variability In The Management Of Type 2 Diabetes?**

*A group of researchers conducted a study to investigate the role of blood glucose (BG) variability in glycemic control in patients with type 2 diabetes.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6338>

A total of 117 participants, 48 with normal glucose regulation and 69 with newly diagnosed type 2 diabetes, were monitored using the continuous glucose monitoring system; a subset of 23 patients with type 2 diabetes characterized by poor glycemic control (reflected by HbA<sub>1c</sub> levels > 8.5%) were monitored a second time following 2 to 3 weeks of daily insulin injections. BG variability was calculated using the mean amplitude of daily excursions (MAGE), mean of daily differences (MODD), and the incremental areas above preprandial glucose values (AUCpp), and expressed as intra-day, inter-day, and postprandial BG variability.

The researchers found that MAGE, MODD, and AUCpp levels were significantly higher in patients with type 2 diabetes compared with participants with normal glucose regulation ( $p < 0.001$ ), resulting in greater blood glucose variability in those patients. However, significant decreases were observed in the subset of patients that underwent intensive insulin therapy (MAGE, 41%; MODD, 29%; AUCpp, 49%;  $p < 0.001$ ).

Postprandial hyperglycemia was most prominent following breakfast; peak intra-day values occurred at an average of 103 minutes after breakfast in 65.2% of the participants.

The researchers concluded that minimizing BG variability in patients with type 2 diabetes could be an important aspect of glucose management.

*Med Sci Monit. 2008;14:CR552-8.*

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**FACT:**

**Sleep Apnea Treatment Reduces Nighttime Blood Sugar:** Patients with type 2 diabetes and obstructive sleep apnea who used continuous positive airway pressure (CPAP) saw improved glycemic control during the night. Mean nighttime glucose levels decreased to 102.9 mg/dL after an average of 41 days of CPAP therapy, from a baseline mean of 122.0 mg/dL in 20 patients ( $P=0.03$ ).

[See This Weeks' Item #4](#)

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Item 14

**No-Carb Diets May Impair Memory**

*Memory improved when carbs reintroduced to diet. Eliminating carbohydrates from your diet may help you lose weight, but it could leave you fuzzy headed and forgetful, a new study suggests.*

<http://www.diabetesincontrol.com/results.php?storyarticle=6337>

One week after starting a weight loss diet that severely restricted carbohydrates, participants in the Tufts University study performed significantly worse on memory tests than participants who followed a low calorie, high-carbohydrate diet.

The low-carb dieters' memory-test performances improved in the following weeks after they began eating some carbohydrates.

study co-author and cognitive psychologist Holly A. Taylor, PhD stated that, "The connection between the foods we eat and how we think doesn't really enter into most people's minds." "But this study demonstrates that the foods we eat can have an immediate impact on brain function."

The body breaks carbohydrates into glucose, which it uses to fuel brain activity. Proteins break down into glycogen, which can also be used for fuel by the brain, but not as efficiently as glucose.

So it stands to reason that eliminating carbohydrates from the diet might reduce the brain's source of energy and affect brain function. But there has been little research examining this hypothesis in people following low-carb weight loss diets.

The study by Taylor and colleagues included 19 women between the ages of 22 to 55 who were closely followed after beginning a low-carb weight loss plan similar to the Atkins diet or the low-calorie diet recommended by the American Dietetic Association that includes plenty of fruits, vegetables, and whole grains.

Before starting the diets, the women underwent testing designed to measure long- and short-term memory and attention. The tests were repeated one, two, and three weeks after the diet began.

Low-carb dieters ate virtually no carbohydrates during their first week on the diet. In testing conducted after week one, they performed worse on memory-based tasks than the women following the ADA diet.

Reaction times for those on the low-carb diet were slower and their visual-spatial memories were not as good as the low-calorie dieters.

They did perform better than the low-calorie dieters in testing that measured attention and the ability to stay on task, however. And their performance on the memory tests improved after week one, when limited carbohydrates were reintroduced into their diets.

"Although this study only tracked dieting participants for three weeks, the data suggest that diets can affect more than just weight," Taylor notes in a news release. "The brain needs glucose for energy and diets low in carbohydrates can be detrimental to learning, memory, and thinking."

Australian research scientist Grant D. Brinkworth, PhD, mentioned that the findings, while intriguing, do not prove that low-carbohydrate weight loss diets affect memory.

In a study published in 2007, Brinkworth and colleagues performed cognitive function testing on dieters after they had been on either a low-carb or high-carb weight-loss diet for eight weeks. Both groups lost weight and showed improvements in mood.

The low-carbohydrate dieters showed slight impairments in cognitive processing speed, but no difference was recorded between the two groups in working memory.

Brinkworth says if eliminating carbohydrates from the diet does affect memory, the effect may only be temporary.

"What (Taylor and colleagues) recorded may be an acute, transient effect that may just be the body readjusting to an unfamiliar diet," he says. "We really need studies that examine the long-term impact of these diets on cognition."

*D'Anci, K.E. Appetite, February 2009; vol 52: pp 96-103.: Holly A. Taylor, PhD, professor of psychology, Tufts University, Medford, Mass. Grant D. Brinkworth, PhD, research scientist, Commonwealth Scientific and Industrial Research Organization, Human Nutrition, Adelaide, Australia.*

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Item 15

## **Continuous Blood Pressure Monitoring, A Predictor of Future Heart Events**

*In the largest study of its kind to date, researchers have shown that continually monitoring blood pressure (BP) — called ambulatory BP monitoring (ABPM) — is a predictor of future cardiovascular events in patients with resistant hypertension, but office BP is not .*

<http://www.diabetesincontrol.com/results.php?storyarticle=6336>

Resistant hypertension is defined as the failure to control office BP despite optimal treatment with at least 3 antihypertensive drugs in full dosages, always including a diuretic. Its prevalence ranges from 10% to almost 30% of patients with general hypertension. ABPM has become increasingly important in the management of patients with hypertension, especially in patients with resistant hypertension to differentiate from white-coat resistant hypertension. Currently, the prognostic value of office and ABPM in patients with resistant hypertension is uncertain.

The aim of this study was to evaluate the prognostic importance of ABPM for the future occurrence of fatal and nonfatal cardiovascular events.

Salles et al explain that about 10% to 30% of individuals with high BP have resistant hypertension. In these patients, BP remains high despite treatment with at least three antihypertensive drugs, including a diuretic. ABPM — which measures blood pressure at regular intervals throughout the day — is increasingly important in managing patients with this condition because of the possibility of a white-coat effect, when an individual only has high BP at the physician's office.

In their prospective study, they followed 556 patients with resistant hypertension who attended an outpatient clinic between 1999 and 2004. Participants underwent a clinical examination and had their blood pressure monitored continuously during a 24-hour period (every 15 minutes throughout the day and every 30 minutes at night). They were followed-up at least three or four times a year until December 2007.

The primary end point was a composite of fatal and nonfatal cardiovascular events and all-cause and cardiovascular mortalities. Multiple Cox regression was used to assess associations between BP and subsequent end points.

After a median follow-up period of 4.8 years, 109 participants (19.6%) had had a cardiovascular event or had died of cardiovascular disease. This included 44 strokes, 21 myocardial infarctions, 10 new cases of heart failure, and five sudden deaths. Seventy patients (12.6%) died, 46 (8.3%) of cardiovascular causes.

After multivariate adjustment, office BP did not predict any of these events, whereas higher mean ambulatory BPs (both systolic and diastolic) were independent predictors of the composite end point.

Ambulatory systolic and diastolic BPs were equivalent predictors and both were better than pulse pressure; nighttime BP was superior to daytime BP.

But ABPM did not predict cardiovascular deaths alone or coronary heart disease (CHD) events, although it did predict some outcomes, such as stroke.

"The relatively few cardiovascular deaths and CHD events probably contributed to the failure to demonstrate the prognostic value of ambulatory BPs for these end points, owing to insufficient statistical power," the researchers observe.

"This study has important clinical implications," the authors write. "First, it reinforces the importance of ABPM performance in resistant hypertensive patients . . . , [which] should be performed during the whole 24 hours, with separate analyses of the daytime and nighttime periods, because it seems that nighttime blood pressures are better cardiovascular risk factors than are daytime blood pressures."

Salles notes: "In this particular subgroup of hypertensives, those with resistant hypertension, the antihypertensive treatment should be based on ambulatory BP levels, with particular attention to nighttime BP, instead of on office BPs."

The work raises the question of whether therapeutic interventions directed specifically at controlling nighttime hypertension will be able to improve cardiovascular prognosis compared with the traditional approach of controlling daytime blood pressure levels, he adds. "This important clinical question should be addressed in future prospective interventional studies."

The researchers also point out that a simple ABPM diagnosis of true or "white coat" resistant hypertension at baseline "provides useful independent prognostic information for cardiovascular morbidity and for all-cause mortality."

**Practice Pearls**

- ?? Resistant hypertension is defined as the failure to control office BP despite optimal treatment with at least 3 antihypertensive drugs in full dosages, always including a diuretic.
- ?? Higher ABPM predicts cardiovascular morbidity and mortality in patients with resistant hypertension, whereas office BP has no prognostic value.

Salles GF, Cordoso CRL, Muxfeldt ES. Prognostic influences of office and ambulatory blood pressures in resistant hypertension. Arch Intern Med. 2008;168:2340-2346. (University Hospital Clementino Fraga Filho, Rio de Janeiro, Brazil)

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**Quote of the Week**

*“Mistakes are part of the dues one pays for a full life.”*

.....Sophia Loren

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