

DIABETES IN CONTROL.com Newsletter

The Newsletter for Professionals in Diabetes Care

July 15, 2009, Issue 477

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http://www.diabetesincontrol.com/index.php?option=com_content&id=8101

2. New Link between Elevated Insulin and Breast Cancer Risk

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3. Jumping Gene Staves Off Type 2 Diabetes

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14. CRP Not Direct Cause of Heart Disease

http://www.diabetesincontrol.com/index.php?option=com_content&id=8084

15. The Effect of Metformin on DPP-4 Activity in Type 2 Diabetes

http://www.diabetesincontrol.com/index.php?option=com_content&id=8083

From the editor's desk:

The controversy about Lantus and cancer continues to heat up. Leading experts are coming forward to share their opinions on the meta-analysis. It is too bad that the lay press will never get these expert opinions to our patients. Last week *Diabetes Technology & Therapeutics* published an outstanding editorial by three leading endocrinologists, "Insulin Glargine and Cancer – An Unsubstantiated Allegation," by **Satish K. Garg, M.D., Irl Hirsch, M.D., and Jay Skyler, M.D., M.A.C.P.** The editorial points to the many flaws in the studies that led to this controversy and is required reading for everyone in the diabetes community. You can access the editorial at

http://www.liebertpub.com/mcontent/files/dia_2009_1705_Garg_3P.pdf.

We often tell our patients to go take a walk to lower glucose after eating so the last thing we think about is supplementing exercise with food. However patient athletes need a constant supply of fuel. This week **Sheri Colberg, Ph.D., FACSM**, continues her focus on *Effective Dietary Practices of Active People with Diabetes* by discussing how we can *Supplement with Carbohydrate Before, During, and After Exercise*.

http://www.diabetesincontrol.com/index.php?option=com_content&id=8106

Thank you to all the Hospital Pharmacists who participated in our recent survey. Please check your email to see if you are the winner of the Drawing for either a Kindle, iPod, or a Flip Video Camera!

dLife: July 19, 7PM ET on CNBC

NEW! Pop superstar Nick Jonas of *The Jonas Brothers* gets up close and personal about his diabetes life in an exclusive interview with dLife. Plus, Chef Michel Nischan has a low-carb twist on a breakfast classic—the pancake. And, your vision questions answered by Dr. David Marks. Catch the **Season Premiere** of dLifeTV: Sundays on CNBC at 7 PM ET, 6 PM CT, and 4 PM PT.

We can make a difference!

Check out this week's "Test Your DIABETES Knowledge" question.

http://www.diabetesincontrol.com/index.php?option=com_content&id=8105

Dave Joffe, Editor-in-chief

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New Product: Track a healthier course to better diabetes management

TRUEmanager™

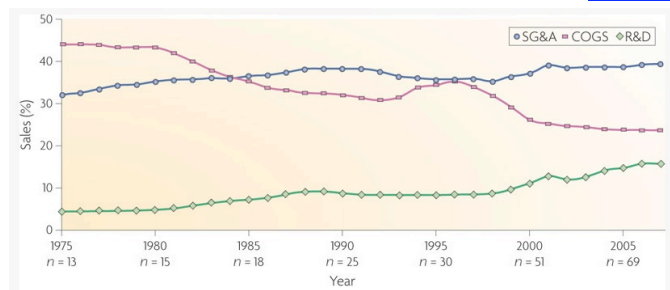


Take control of managing diabetes by setting target ranges for multiple testing times, viewing patterns and trends in glucose results and printing reports to share with your healthcare team.

Go to http://www.homediagnostics.com/our_products/ma_true_manager.aspx to learn more and download your free copy.

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New Tool for Your Practice: Proving the Value of Drug Research



Often our patients feel that pharmaceutical companies no longer do research and only spend money on advertising, dinners and conferences. This graph shows the opposite is true. [Click here to get the whole story.](#)

Articles for the Week:

Item 1

Depression Doubles Risk for Diabetic Foot Ulcers

Major depression doubles the risk of incident diabetic foot ulcers, according to the results of a large, prospective, population-based cohort study. Full Story

Lisa Williams, M.D., from the University of Washington, Seattle stated that, the findings strongly suggest screening for and treating depression to prevent this complication.

"Depression is twice as common in patients with diabetes," she said at the annual meeting of the Society for Investigative Dermatology.

"At any time, 11% to 12% of patients with diabetes have major depression, and 31% have significant depressive symptoms, which include major and minor depression."

Until now, it has not been known whether depression increases the incidence of diabetic foot ulcers, Dr. Williams said.

However, she said, "Depression is associated with more severe and larger diabetic foot ulcers, and poor healing and recurrence. Depression is also associated with a threefold increase in mortality rate among patients with their first foot ulcer."

Her analysis included data from 3,474 patients enrolled in the Pathways Epidemiologic Study -- a prospective cohort of primary care diabetes patients from nine clinics in western Washington state.

Major and minor depression was assessed, using the Patient Health Questionnaire-9 (PHQ-9), and there was a mean follow-up of approximately four years. New-onset foot ulcers were assessed during the course of the study, using ICD-9 codes, which were confirmed by chart review.

There were 401 diagnoses of major depression in the cohort, 290 diagnoses of minor depression, and 121 incident foot ulcers, said Dr. Williams. Compared to patients with no depression, the study found a significant increase in the risk of foot ulcers among patients with major, but not minor depression (HR 2.0 and 1.3 respectively). There was no difference between depressed and nondepressed patients in foot self-care, which was assessed using a validated diabetes questionnaire.

However, previous research has shown that depression in patients with diabetes is associated with poor self-care, low physical activity, unhealthy diet, nonadherence to medication regimens, nonadherence and missed doctor's appointments -- as well as hyperglycemia, smoking, and obesity, she said.

"In our study, we found that compared to nondepressed patients, depressed patients were older, unmarried, had higher BMIs, were more likely to smoke, and had more diabetes complications."

Practice Pearls:

Explain that this report describes findings from an observational study, so the results should be considered hypothesis-generating and not the basis for clinical decisions.

Note that this study was published as an abstract and presented orally at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

Society for Investigative Dermatology; Williams LH et al "Depression and incident diabetic foot ulcers: a prospective cohort study" SID 2009; Abstract 365

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Item 2

New Link between Elevated Insulin and Breast Cancer Risk

Elevated insulin levels in the blood appear to raise the risk of breast cancer in postmenopausal women, according to researchers.....Full Story

Increased breast cancer risk for postmenopausal women has previously been linked to obesity and diabetes. Both conditions involve insulin resistance, which causes increases in circulating levels of insulin. Since insulin is known to promote cell division and enhance breast tumor growth in animal models, the Einstein scientists reasoned that relatively high insulin levels may contribute to breast cancer risk in women.

"Up to now, only a few studies have directly investigated whether insulin levels are associated with breast cancer risk, and those studies have yielded conflicting results," says Geoffrey Kabat, Ph.D., senior epidemiologist in the department of epidemiology and population health at Albert Einstein College of Medicine and the lead author of the paper. "Those other studies were based on just a single baseline measurement of insulin, while our study involved analyzing repeated measurements of insulin taken over several years — which provides a more accurate picture of the possible association between insulin levels and breast cancer risk."

An earlier study linking insulin levels with breast cancer risk was carried out by Einstein researchers and was published in the January 7, 2009, issue of the *Journal of the National Cancer Institute*.

In the most recent study, Dr. Kabat and his colleagues analyzed data on 5,450 women enrolled in the Women's Health Initiative, a large multicenter study investigating the influence of a number of factors on women's health. Most of the women had participated in the clinical trial portion of the study and provided fasting blood samples at the start of the study (i.e., at baseline) and then at years one, three and six. The remaining women, who were enrolled in a separate "observational" component of the study, provided fasting blood samples at baseline and at year three of the study. Among all these women, 190 cases of breast cancer were identified over eight years of follow-up.

The analysis by Dr. Kabat and colleagues revealed a strong association between elevated insulin levels and increased risk for breast cancer.

After dividing the participants into three groups based on their insulin levels, the researchers found that women in the upper third for insulin level were more than twice as likely to develop breast cancer compared with women in the bottom third for insulin level. The association between insulin level and breast cancer risk was even stronger for those women who had not received treatment in the clinical trial (i.e., the placebo participants) or were in the observational component: women in the upper third for insulin level had a more than three-fold increased risk for breast cancer compared with those in the bottom third.

Notably, the link between elevated insulin level and breast cancer was strongest among lean women and weakest among obese women (who, in general, have higher insulin levels compared with lean women). "This finding is potentially important because it indicates that, in postmenopausal women, insulin may be a risk factor for breast cancer that is independent of obesity," says Dr. Kabat. However, because the number of lean women was small, this finding is preliminary.

While these results require confirmation from other studies, Dr. Kabat notes that the current recommendations for reducing breast cancer risk in postmenopausal women — including maintaining a healthy weight and engaging in regular physical exercise — can help to reduce insulin levels.

Albert Einstein College of Medicine. Their findings are published in the online version of the International Journal of Cancer. The paper is entitled, "Repeated measures of serum glucose and insulin in relation to postmenopausal breast cancer".

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DID YOU KNOW: Diabetics are more prone to oral fungus disease. A fungal infection in the mouth (oral candidiasis) appears to occur more frequently among persons with diabetes including those who wear dentures. These infections can be treated with anti-fungals but good oral hygiene is also critical. Lichen planus is a skin disorder that produces lesions in the mouth. A more severe type of Lichen planus involves painful ulcers that erode surface tissue. Although there is no permanent cure, your dentist may prescribe a topical anesthetic or other medication to reduce and relieve the condition. Some diabetics have reported that their taste for sweets is diminished, although the taste impairment is usually not severe. Altered taste sensations, barely perceptible to most diabetic patients, may influence their food choices in favor of sweet tasting foods with highly refined carbohydrate content. This may worsen the diabetic patient's dental health and overall health. www.dentistryfordiabetics.com

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Jumping Gene Staves Off Type 2 Diabetes

New research has identified a genomic fragment, called a transposon, or "jumping gene," that diminishes the activity of the diabetes risk gene in both mice and humans..... Full Story

Transposons are sequences of DNA that can move around to different positions within the genome of a single cell, hence their nickname "jumping genes."

Researchers studied the genomes of mouse strains that were obese but had no elevated blood glucose levels and were less susceptible to diabetes. They compared these mice to other strains, which exhibited a severe malfunction of fat and glucose metabolism as they continued to gain weight, causing them to rapidly develop Type 2 diabetes.

Researchers found that the difference between the two mouse strains lies in a small fragment of genetic information, the "jumping gene." This genetic fragment is of viral origin and is localized in a non-coding segment of the risk gene for diabetes, whose effect it diminishes. Without this genetic fragment, the risk gene is fully active and, in combination with obesity, leads to Type 2 diabetes in mice. A similar risk gene is also active in the fat tissues of overweight people suffering from diabetes -- more so than in healthy people.

Stephan Scherneck, first author of the study was quoted as saying, "Our data suggest that the protein product of the risk gene in obese individuals enhances the storage of fat in fat cells.... As a result, excessive fat accumulates in the liver and this in turn contributes to the development of diabetes."

"We have therefore discovered a new diabetes gene of similar importance in mice and humans," says Hans-Georg Joost, head of the study and scientific director of German Institute of Human Nutrition, "as well as a mechanism that has not been described before in connection with the heredity of diabetes and obesity."

Joost continued, "This transposon is quite active and almost completely 'turns off' the Zfp69 [diabetes risk] gene. We have found indications that it is also active in other mouse genes. Since the human genome is full of such fragments, it is quite possible that they play a greater role than previously assumed."

PLoS Genetics, July 3, 2009

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Item 4

Using Electronic Systems to Track and Control Diabetes Care

Whatever we have been doing to help patients control their blood sugars over the last 100 years has not worked, most patients are still out of control.Full Story

Whatever we have been doing to help patients control their blood sugars over the last 100 years has not worked, most patients are still out of control but a personalized electronic health tracking system can improve diabetes patients' care and clinical outcomes, Canadian researchers say.

Their study included 511 diabetes patients and 46 family physicians and nurse-practitioners in Canada. Half the participants used internet-based tools integrated with five types of electronic health records, an automated telephone reminder system and mailings of color-coded materials. The other participants were assigned to a control group that received usual care.

The researchers found that 62 percent of diabetes patients in the intervention group showed improvement, compared with 42.6 percent of those in the control group. This is one of the first randomized trials to show that this type of electronic tracking system is effective in community-based primary care, they said.

"Despite the technical challenges for both patients and physicians, we have demonstrated that the care of complex chronic disease can be improved with electronic tracking and decision support shared by family physician and patient," wrote Dr. Anne Marie Holbrook of McMaster University in Hamilton, Ontario, and colleagues.

The findings "provide strong evidence that complex research interventions can and should be implemented in community-based practices," Dr. Richard Grant and Dr. Blackford Middleton of Harvard Medical School, wrote in an accompanying commentary.

The American Health Information Management Association has more about [personal health records](#).

Canadian Medical Association Journal, July 7, 2009

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FACT: Obesity Accounts for Greatest Jump in Healthcare Costs: Healthcare spending on obese patients in the U.S. has ballooned, growing more than 80% over a five-year period. Spending on the heaviest members of the population rose to \$303.1 billion in 2006 from \$166.7 billion in 2001 -- an 82% increase. That figure compares with a 36% increase in total expenditures for patients who were merely overweight and a 25% increase for normal-weight patients. The increase in spending on healthcare for overweight and obese Americans tracks the general rise in obesity in the U.S., as the number of obese jumped to 58.9 million from 48.2 million over the study period. Obese adults were associated with over half of the growth in healthcare spending between 2001 and 2006. The average annual healthcare expenditure for the obese population increased to \$5,148 from \$3,458 over five years and jumped to \$3,636 from \$2,792 for the overweight population. Normal-weight patients spent an average of \$3,315 in 2006 compared with from \$2,607 in 2001. *Agency for Healthcare Research & Quality.*

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Item 5

Pramlintide/Leptin Combo Shows Positive Results for Obesity

*Amylin Pharmaceuticals announced positive results, showing an average 22 pound weight loss from a 28-week study of pramlintide/leptin..... **Full Story***

Amylin Pharmaceuticals announced positive results, showing an average 22 pound weight loss from a 28-week study of pramlintide/leptin using a combination treatment comprising pramlintide, an analog of the natural hormone amylin, and metreleptin, an analog of the natural hormone leptin, in overweight and obese patients. This Phase 2 study successfully characterized patients who responded best to treatment and also provided important information to inform dose selection.

At 28 weeks, evaluable patients with a starting body mass index (BMI) less than 35 kg/m² (n=149), and treated with the highest pramlintide/metreleptin doses, experienced significantly more weight loss on average (11%; 22 pounds, p<0.01) than those receiving placebo (1.8%; 4 pounds) or either agent alone (approximately 5%; 10 pounds). Consistent with the physiologic role of leptin in regulating body fat, the weight loss in these patients was predominantly due to a reduction in fat mass (approximately 18 of the 22 pounds lost). These study results confirm previous Phase 2 results with this combination therapy and provide a solid foundation for the company's ongoing obesity development program.

In the overall evaluable study population, all of the pramlintide/metreleptin combination arms achieved more weight loss than placebo. The magnitude of weight loss was found to be dependent on dosage and baseline BMI. In a pre-specified analysis of evaluable patients with a starting BMI less than 35 kg/m², weight loss with pramlintide/metreleptin was more than additive compared to that with pramlintide and metreleptin alone, a finding that was not observed in the overall evaluable population.

Steven R. Smith, M.D., professor and assistant director of clinical research at the Pennington Biomedical Research Center, commented that, "Despite their best efforts with diet and exercise alone, most overweight or obese individuals experience progressive weight gain over time. To date, the only highly effective treatment option is surgical and limited to the minority of patients who have advanced to the most severe forms of obesity."

The combination therapy was well tolerated, and no cardiovascular or neuropsychiatric (such as anxiety or depression) safety signals were observed. Consistent with previous clinical experience, the most common side effects seen with pramlintide/metreleptin combination treatment were injection site adverse events

Lifestyle intervention was included throughout study (dietary, exercise and behavioral). Body composition was assessed at enrollment and again at study termination.

<http://www.amylin.com>

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Item 6

How Many People Request Nutritional Info at Fast Food Outlets?

Just 0.1% of people request nutritional information. So having the information listedFull Story

Just 0.1% of people request nutritional information. So having the information listed on the menu boards can be of real value in helping people make better decisions.

In this observational study, it was determined how frequently consumers accessed on-premises nutrition information provided at chain restaurants. The number of patrons entering and accessing nutrition information was recorded at eight locations that were part of four major restaurant chains (McDonald's, Burger King, Starbucks, and Au Bon Pain). Only six (0.1%) of 4,311 patrons accessed on-premises nutrition information before purchasing food. This very small percentage suggests that such information should be more prominently displayed, such as on restaurant menu boards, to help customers make informed decisions.

In an effort to address the obesity epidemic, New York City has required chain restaurants to post calorie information on menu boards and other cities and states are considering similar policies. The primary rationale for this mandate is that Americans eat a large proportion of meals away from home, consume excess calories in the process because of large portions, and are generally unaware of the caloric content of foods.

The restaurant industry strongly opposes menu labeling legislation, arguing that because restaurants already make nutrition information accessible to customers online and on-premises, the cost of changing and cluttering menus is not justified. However, only about half of the largest chain restaurants make nutrition information available in some form and it is unclear how often customers use this information.

In an effort to sample restaurants from both urban and suburban areas, observations at two separate locations for each restaurant chain were observed.

Nutrition information in McDonald's and Burger King was displayed on a wall poster, and the McDonald's in Manhattan, as well as both Starbucks outlets, provided nutrition pamphlets. Nutrition information at Au Bon Pain was provided via an on-premises computer. At McDonald's and Burger King, customers were categorized as accessing the nutrition information if they (1) approached the poster on the wall and turned their head toward it (because one did not have to face the poster to purchase food) or (2) picked up a nutrition pamphlet (in the McDonald's restaurant only). At Au Bon Pain, an individual had to touch the computer screen, thus turning it on. At Starbucks, a nutrition pamphlet had to be picked up.

During the observations, research personnel sat in the restaurant in a place that allowed them to count the number of people entering the restaurant and to observe who accessed nutrition information.

Of the 1,501 people who entered the McDonald's outlets, 1 woman and 1 man were observed accessing nutrition information prior to purchasing food, and 1 woman and 1 man accessed the information after making their purchases. Of the 482 people who entered the Burger Kings, only 2 men and 1 woman (0.6%) looked at the nutrition poster. Of the 1,671 customers who entered the Au Bon Pains, 1 woman (0.06%) was observed accessing nutrition information. Finally, none of the 657 people who entered Starbucks accessed information.

Overall, only 6 (0.1%) of 4,311 restaurant patrons accessed nutrition information before making their purchases at eight locations of four major restaurant chains. This finding is worrisome because people tend to underestimate the caloric content of fast-food meals which are typically higher in calories than are

meals made at home. People's inability to accurately estimate calories suggests that customers are unlikely to have looked up nutrition information online before entering the restaurant and some large chains fail to provide nutrition information on their websites. The results indicate that if on-premises nutrition information is to affect customers' purchasing behaviors, it must be displayed in a highly visible place such as on a menu board.

Obesity: Preventing and Managing the Global Epidemic. Geneva, Switzerland: World Health Organization; 1998. New York City Department of Health and Mental Hygiene. Board of health votes to require calorie labeling in some New York City restaurants [press release].

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Item 7

High-Protein, Low-Carb Diet Can Be Safe, Effective for Adolescents

Obese adolescents lost significantly more weight on a high-protein, low-carbohydrate diet than on aFull Story

Obese adolescents lost significantly more weight on a high-protein, low-carbohydrate diet than on a standard low-fat diet, according to a randomized study.

Dr. Nancy F. Krebs of the University of Colorado, Denver, said at a meeting on clinical pediatrics sponsored by the University of California, San Francisco, "At the end of 12 weeks, the teens on the high-protein, low-carbohydrate (HPLC) diet lost an average of 9.0 kg, while those on the low-fat diet lost an average of 5.6 kg, a significant difference." Moreover, adolescents in both groups tended to maintain their weight loss over an additional 24 weeks of follow-up. "My hypothesis was that [the HPLC diet] would get them to 12 weeks but they'd rebound," possibly even ending up heavier than before.

In fact, while adolescents in the HPLC group tended to gain back a little weight within the first 3 months after the end of the diet, they still weighed less than those in the low-fat group. And the HPLC group appeared to maintain that difference for another 3 months, although those differences did not reach statistical significance.

All the adolescents in the study were severely overweight, weighing at least 175% of their ideal body weight. The teens in the HPLC group were placed on a diet limiting them to 20 g/day of carbohydrates. To ensure that they were compliant with this diet, the investigators measured ketone levels twice daily. People on HPLC diets tend to become ketonic quickly, something that can be measured easily with a urine dipstick.

In terms of body composition, both groups of adolescents lost equivalent amounts of fat and protein. In this study, the HPLC diet proved not to be protein sparing.

Both groups showed similar improvements in their lipid profiles, with one exception. Adolescents on the HPLC diet lowered their triglyceride levels significantly more than the low-fat group.

Based on glucose tolerance test results, carbohydrate metabolism improved in both groups. The investigators observed no adverse effects of the HPLC diet.

"I have become a believer in this. I think it actually works for a number of kids quite well," Dr. Krebs said. "I feel pretty comfortable in using it."

Dr. Krebs said that she has submitted her study for publication. She stated that she had no relevant conflicts of interest.

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Item 8

Lower Blood Pressure Targets Offer No Benefits

Lower is not always better for blood pressure targets, according to a Cochrane review that revealed no reduction in morbidity and mortality belowFull Story

Lower is not always better for blood pressure targets, according to a Cochrane review that revealed no reduction in morbidity and mortality below the standard 140/90 mm Hg.

Treating patients to reach lower targets did drop blood pressure by a modest average of 3.9 mmHg systolic and 3.4 mm Hg diastolic more than conventional goals ($P<0.001$), according to Jose Agustin Arguedas, of the University of Costa Rica in San Pedro de Montes de Oca, and colleagues.

However, the lower goals were not associated with significant reductions in any important outcome, including:

- Total mortality (relative risk 0.92, 95% confidence interval 0.86 to 1.15)
- MI (RR 0.90, 95% CI 0.74 to 1.09)
- Stroke (RR 0.99, 95% CI 0.79 to 1.25)
- Congestive heart failure (RR 0.88, 95% CI 0.59 to 1.32)
- Major cardiovascular events (RR 0.94, 95% CI 0.83 to 1.07)
- End-stage renal disease (RR 1.01, 95% CI 0.81 to 1.27)

In sensitivity analyses in diabetes and chronic renal disease, there was no statistically significant difference for any of the mortality and morbidity outcomes either.

"More trials are needed, but at present there is no evidence to support aiming for a blood pressure target lower than 140/90 mmHg in any hypertensive patient," the researchers wrote.

Over the past five years, organizations including the American Heart Association and Joint National Committee-7 have shifted to recommending targets below 130/80 mm Hg for certain high-risk populations, such as those with diabetes, cardiovascular disease, or renal impairment.

Although the blood pressure thresholds are critical for clinical practice, they are arbitrary and based on epidemiologic observations, Dr. Arguedas' group noted.

The researchers conducted a meta-analysis of all seven randomized clinical trials that have compared a target of 135/85 mm Hg or lower to a standard target in the 140-160/90-100 mm Hg range in a total of 22,089 adults who had hypertension or were taking antihypertensive medication.

Notably, none of the trials took aim at systolic blood pressure targets. All seven attempted to reduce diastolic targets only.

Attempting to achieve lower blood pressure targets required larger doses and an increased number of antihypertensive drugs, Dr. Arguedas' group said. "This has inconvenience and economic costs for patients."

But it also would increase adverse drug effects, "which, if serious, could negate any potential benefit associated with any achieved lower blood pressure," and could even increase the number of adverse cardiovascular events if blood pressure gets too low, they added.

The one trial that reported total serious adverse events found no difference in this morbidity and mortality outcome between blood pressure target groups (RR 1.03, $P=0.8$).

For side effects, the one trial that reported withdrawals due to treatment-related adverse effects showed no difference between groups either (RR 2.00, $P=0.32$).

Some studies have suggested that excessive lowering of the diastolic blood pressure increases coronary heart disease deaths -- a relationship called the "J-curve phenomenon."

But Dr. Arguedas' group noted that their meta-analysis with "acceptable confidence" indicates that the relative risk for total mortality is between a 14% decrease and a 16% increase, and that the relative risk for major cardiovascular events is between a 16% decrease and 8% increase

Still, it could not exclude the possibility of a small benefit or harm associated with lower diastolic blood pressure targets, they noted.

Sensitivity analyses showed no benefits in high-risk populations either.

In their conclusion, the authors noted that "Guidelines are presently recommending unproven lower systolic and diastolic blood pressure targets" in diabetes mellitus and chronic renal disease.

As a result, they said, "Randomized controlled trials comparing the benefits and harms associated with recommended lower targets as compared to standard targets are urgently needed in those subgroups."

They also pointed out that "The main potential bias in this meta-analysis is inevitable because the intervention of trying to achieve a target blood pressure cannot be blinded. Such open trials are subject to investigator bias for both efficacy and safety outcomes."

Practice Pearl

Explain to interested patients that blood pressure targets help determine use of pharmacologic agents for hypertension and their doses.

Cochrane Database of Systematic Reviews

[Arquedas JA, et al "Treatment blood pressure targets for hypertension" Cochrane Database of Systematic Reviews 2009; Issue 3: CD004349.](#)

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DID YOU KNOW: New Link between Elevated Insulin and Breast Cancer Risk:

Elevated insulin levels in the blood appear to raise the risk of breast cancer in postmenopausal women, according to researchers. Increased breast cancer risk for postmenopausal women has previously been linked to obesity and diabetes. Both conditions involve insulin resistance, which causes increases in circulating levels of insulin. Since insulin is known to promote cell division and enhance breast tumor growth in animal models, the Einstein scientists reasoned that relatively high insulin levels may contribute to breast cancer risk in women. [See This Week's Item 2](#)

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Item 9

New Once-daily Treatment for Type 2 Diabetes

A new treatment for Type 2 diabetes may soon be a reality in the U.S.Full Story

A new treatment for Type 2 diabetes may soon be a reality in the U.S.. Liraglutide (Victoza), a once-daily injectable treatment for Type 2 diabetes, is pharmaceutical company Novo Nordisk's latest brain child and has been approved by the E.U..

From the Glucagon-like peptide-1 (GLP-1) family of drugs, it can be taken any time of day, irrespective of meals. It helps to control Type 2 diabetes by stimulating the release of insulin when blood glucose levels are too high.

In addition, makers claim liraglutide aids weight loss by making you feel more full and delaying the rate at which your stomach empties. Studies have also shown that the drug can reduce blood pressure and improve the function of beta cells -- the cells that produce insulin in the pancreas.

Cathy Moulton, Care Advisor at leading health charity Diabetes UK, said, "Liraglutide widens the choice of treatments for people with Type 2 diabetes that not only offer improved blood glucose control but also aid weight loss. In addition, research has shown that this treatment has a positive effect on blood pressure levels."

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Item 10

New Drug Application for Exenatide LAR Accepted for Review by FDA

*It looks like it is now just a matter of time before Exenatide LAR, (once a week Byetta) gets the final approval from the FDS..... **Full Story***

Amylin Eli Lilly and Alkermes, announced that the New Drug Application (NDA) for exenatide once weekly has been accepted for review by the U.S. Food and Drug Administration (FDA).

Exenatide once weekly is an investigational sustained release medication for Type 2 diabetes that is injected subcutaneously and administered only once a week. Exenatide is the active ingredient in BYETTA® (exenatide) injection, which is currently available in the U.S. and in many countries worldwide for people with Type 2 diabetes who are unable to achieve good glycemic control with common oral therapies.

"Acceptance of the NDA submission for exenatide once weekly is an important milestone both in the exenatide development program and in the treatment of Type 2 diabetes," said Orville G. Kolterman, M.D., senior vice president of research and development at Amylin Pharmaceuticals. "If approved, this therapy could fill an important unmet need for treating patients with Type 2 diabetes with just one dose per week."

BYETTA is the first and only FDA-approved incretin mimetic for the treatment of Type 2 diabetes. BYETTA exhibits many of the same effects as the human incretin hormone glucagon like peptide-1 (GLP-1). GLP-1 improves blood sugar after food intake through multiple effects that work in concert on the stomach, liver, pancreas and brain. BYETTA is approved by the FDA for use by people with Type 2 diabetes who are unsuccessful at controlling their blood sugar levels. BYETTA is an add-on therapy for people currently using metformin, a sulfonylurea, or a thiazolidinedione. BYETTA provides sustained A1c control and low incidence of hypoglycemia when used with metformin or a thiazolidinedione, with potential weight loss. BYETTA is not a weight loss product. BYETTA was approved in April 2005 and has been used by more than one million patients since its introduction.

Amylin News Release.

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Item 11

New Culprit Behind Obesity's Ill Metabolic Consequences

*Obesity very often leads to insulin resistance, and now researchers have uncovered another factor behind that ill consequence. The newly discovered culprit - a protein known as**Full Story***

Obesity very often leads to insulin resistance, and now researchers have uncovered another factor behind that ill consequence. The newly discovered culprit -- a protein known as pigment epithelium-derived factor (PEDF for short) -- is secreted by fat cells.

They also report evidence to suggest that specifically blocking that protein's action may reverse some of the health complications that come with obesity.

Matthew Watt of Monash University in Australia, states that, "With obesity, PEDF release is increased from fat, leading to higher levels of PEDF in the bloodstream.... PEDF sends a signal to other body tissues, causing insulin resistance in muscle and liver, a major defect that leads to the development of Type 2 diabetes."

Elevated PEDF is also associated with increased release of fatty acids from fat stores, which cause blood lipid levels to rise. That "dyslipidemia" may be associated with other complications including cardiovascular disease.

What's more, they found that treatments designed to block the action of PEDF in obese mice lowered the animals' blood lipid levels and reversed some of their insulin resistance, Watt said.

In recent years, scientists have come to appreciate fat cells as important regulators of metabolism, at least in part through the hormones and other chemicals they secrete. Changes in fat-cell size are also accompanied by reprogramming of the fat-cell secretory profile, a shift that is thought to play an important role in the link between obesity and insulin resistance, the researchers said. That has led scientists in search of all the chemicals issued by fat tissue -- the so-called adipocyte secretome -- in hopes of identifying regulatory players with as-yet-unidentified roles in whole-body metabolism.

In the current study, a screen of molecules secreted by fat cells turned up PEDF as one of the most abundant. Watt said they took particular note of the protein because prior evidence from their lab and others had shown that PEDF rises in the bloodstream of patients with Type 2 diabetes more than in those who remained insulin sensitive. "We also observed in a separate study that, when mice lost weight by calorie restriction or pharmaceutical intervention, PEDF in fat cells was reduced," he explained.

Indeed, they now report that PEDF levels in fat and blood are higher in rodents who are obese for different reasons. PEDF levels dropped when the animals lost weight. Lean mice injected with PEDF also become less responsive to insulin and show signs of inflammation in both muscle and liver. In the long term, PEDF contributes to elevated fatty acids in the blood, they found.

"These fatty acids are then transported into muscle and liver, where they accumulate," Watt said. "Fat accumulation in muscle and liver is a bad thing as it can cause insulin resistance."

The findings identify PEDF as a "bona fide adipocyte secretory factor," the researchers concluded. The observations made in mice are particularly exciting, they said, given that circulating PEDF was recently found to be high in people with metabolic syndrome -- a collection of risk factors including too much belly fat, high cholesterol, high blood pressure, and insulin resistance -- and in those with Type 2 diabetes.

Cell Metabolism, July 8, 2009

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Item 12

Researchers Find Environmental Causes for Alzheimer's, Diabetes

*A new study by researchers at Rhode Island Hospital have found a substantial link between increased levels of nitrates in our environment and food, with increased deaths from**Full Story***

A new study by researchers at Rhode Island Hospital have found a substantial link between increased levels of nitrates in our environment and food, with increased deaths from diseases, including Alzheimer's, diabetes and Parkinson's.

Led by Suzanne de la Monte, MD, MPH, of Rhode Island Hospital, researchers studied the trends in mortality rates due to diseases that are associated with aging, such as Alzheimer's, Parkinson's, diabetes and cerebrovascular disease, as well as HIV. They found strong parallels between age adjusted increases in death rate from Alzheimer's, Parkinson's, and diabetes, and the progressive increases in human exposure to nitrates, nitrites and nitrosamines through processed and preserved foods as well as fertilizers. Other diseases including HIV-AIDS, cerebrovascular disease, and leukemia, did not exhibit those trends. De la Monte and the authors propose that the increase in exposure plays a critical role in the cause, development and effects of the pandemic of these insulin-resistant diseases.

De la Monte, who is also a professor of pathology and lab medicine at The Warren Alpert Medical School of Brown University, says, "We have become a 'nitrosamine generation.' In essence, we have moved to a diet that is rich in amines and nitrates, which lead to increased nitrosamine production. We receive increased exposure through the abundant use of nitrate-containing fertilizers for agriculture." She continues, "Not only do we consume them in processed foods, but they get into our food supply by leeching from the soil and contaminating water supplies used for crop irrigation, food processing and drinking."

Nitrites and nitrates belong to a class of chemical compounds that have been found to be harmful to humans and animals. More than 90 percent of these compounds that have been tested have been

bacon, cured meats and cheese products as well as beer and water. Exposure also occurs through manufacturing and processing of rubber and latex products, as well as fertilizers, pesticides and cosmetics.

Nitrosamines are formed by a chemical reaction between nitrites or other proteins. Sodium nitrite is deliberately added to meat and fish to prevent toxin production; it is also used to preserve, color and flavor meats. Ground beef, cured meats and bacon in particular contain abundant amounts of amines due to their high protein content. Because of the significant levels of added nitrates and nitrites, nitrosamines are nearly always detectable in these foods. Nitrosamines are also easily generated under strong acid conditions, such as in the stomach, or at high temperatures associated with frying or flame broiling. Reducing sodium nitrite content reduces nitrosamine formation in foods.

Nitrosamines basically become highly reactive at the cellular level, which then alters gene expression and causes DNA damage. The researchers note that the role of nitrosamines has been well-studied, and their role as a carcinogen has been fully documented. The investigators propose that the cellular alterations that occur as a result of nitrosamine exposure are fundamentally similar to those that occur with aging, as well as Alzheimer's, Parkinson's and Type 2 diabetes mellitus.

De la Monte comments, "All of these diseases are associated with increased insulin resistance and DNA damage. Their prevalence rates have all increased radically over the past several decades and show no sign of plateau. Because there has been a relatively short time interval associated with the dramatic shift in disease incidence and prevalence rates, we believe this is due to exposure-related rather than genetic etiologies."

The researchers recognize that an increase in death rates is anticipated in higher age groups. Yet when the researchers compared mortality from Parkinson's and Alzheimer's disease among 75 to 84 year olds from 1968 to 2005, the death rates increased much more dramatically than for cerebrovascular and cardiovascular disease, which are also aging-associated. For example, in Alzheimer's patients, the death rate increased 150-fold, from 0 deaths to more than 150 deaths per 100,000. Parkinson's disease death rates also increased across all age groups. However, mortality rates from cerebrovascular disease in the same age group declined, even though this is a disease associated with aging as well.

De la Monte notes, "Because of the similar trending in nearly all age groups within each disease category, this indicates that these overall trends are not due to an aging population. This relatively short time interval for such dramatic increases in death rates associated with these diseases is more consistent with exposure-related causes rather than genetic changes." She also comments, "Moreover, the strikingly higher and climbing mortality rates in older age brackets suggest that aging and/or longer durations of exposure have greater impacts on progression and severity of these diseases."

The researchers graphed and analyzed mortality rates, and compared them with increasing age for each disease. The findings indicate that while nitrogen-containing fertilizer consumption increased by 230 percent between 1955 and 2005, its usage doubled between 1960 and 1980, which just precedes the insulin-resistant epidemics the researchers found. They also found that sales from the fast food chain and the meat processing company increased more than eight-fold from 1970 to 2005, and grain consumption increased five-fold.

The authors state that the time course of the increased prevalence rates of Alzheimer's, Parkinson's and diabetes cannot be explained on the basis of gene mutations. They instead mirror the classical trends of exposure-related disease. Because nitrosamines produce biochemical changes within cells and tissues, it is conceivable that chronic exposure to low levels of nitrites and nitrosamines through processed foods, water and fertilizers is responsible for the current epidemics of these diseases and the increasing mortality rates associated with them.

De la Monte states, "If this hypothesis is correct, potential solutions include eliminating the use of nitrites and nitrates in food processing, preservation and agriculture; taking steps to prevent the formation of nitrosamines; and employing safe and effective measures to detoxify food and water before human consumption."

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Item 13

Etanercept Can Benefit New-Onset Type 1's

Treatment with etanercept in pediatric patients with newly diagnosed Type 1 diabetes lowers A1c and increases ... Full Story

Treatment with etanercept in pediatric patients with newly diagnosed Type 1 diabetes lowers A1c and increases endogenous insulin production, according to new published findings.

Dr. Teresa Quattrin, of State University of New York at Buffalo, states that, "Type 1 diabetes is a T-cell-mediated autoimmune disease characterized by selective destruction of insulin-producing beta-cells within the pancreatic islet.... Tumor necrosis factor-alpha (TNF-alpha) and other cytokines play a role in the autoimmune process leading to pancreatic destruction.... Etanercept is a recombinant soluble TNF-alpha receptor fusion protein that binds to TNF-alpha."

The researchers conducted a 24-week, double-blind, placebo-controlled study to determine the ability of etanercept to prolong endogenous insulin production in 18 newly diagnosed Type 1 diabetes patients between 3 and 18 years old. The children were randomized to either etanercept or placebo.

Inclusion criteria for the study included GAD-65 and/or islet cell antibody positivity, A1c >6% at diagnosis, three insulin injections per day, a white blood cell count of 3,000 to 10,000, platelets >100,000, and normal liver and renal function.

At week 24, A1c values were significantly lower in the etanercept group compared with the placebo group (5.91% versus 6.98%; $p < 0.05$). The percent decrease from baseline was higher in the etanercept group than in the placebo group (0.41 versus 0.18; $p < 0.01$).

The etanercept group showed a greater percent change in C-peptide area under the curve from baseline to week 24 (39% increase in etanercept group versus 20% decrease in placebo group; $p < 0.05$). Insulin use decreased by 18% in the etanercept group and increased by 23% in the placebo group ($p < 0.05$).

No severe adverse events were observed in either group. The frequency of events was generally similar between the two groups.

Dr. Quattrin stated that, "There are many ongoing studies that are trying to test new therapies that could preserve or improve the endogenous insulin production in patients newly diagnosed with Type 1 diabetes.... By achieving this goal, patients with new-onset diabetes could maintain optimal blood sugar control for a longer time," she explained.

"Our data indicate that etanercept has the potential to be a therapy that could be used alone or in combination to preserve or improve endogenous insulin production," Dr. Quattrin said. "Moreover, since the process leading to pancreatic islet cell destruction takes many years, it is possible that etanercept may be of help for patients who are known to be at high risk for developing Type 1 diabetes, to slow down the islet cell production."

Diabetes Care 2009;32:1244-1249.

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FACT: Diabetes Causes Skin Problems: The skin is the largest organ in the body. And like every other organ it can be affected by diabetes. One in three diabetics will have a problem with their skin, when their blood sugars are not in control. The most common skin problem in diabetes is acanthosis nigricans. That's the raised and velvety discoloration of skin most often found along areas of the body which bend

and flex such as the neck, elbows and knuckles or which are exposed to frequent friction such as the waist and groin. Bacterial skin infections are more common in diabetics largely because of poor control of blood sugar levels. Staph is the common bacterial cause for diabetic skin infections. Boils are infections located within the hair follicles. A typical boil is hot, inflamed and painful to touch. Fungal infections are much more common in diabetics. The most common infection is caused by a fungus called Candida albicans. Itching is one of the most common diabetic skin symptoms and has many causes, including dry skin, fungal infection or poor circulation. Getting blood sugars to normal can reduce your risk of skin problems.

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Item 14

CRP Not Direct Cause of Heart Disease

*A protein that is widely used as an indicator of a person's heart disease risk does not actually cause heart disease, **Full Story***

A protein that is widely used as an indicator of a person's heart disease risk does not actually cause heart disease, new research reveals. The findings are important because until now many researchers have viewed C-reactive protein (CRP) as a possible target for heart disease drugs.

Coronary heart disease is the leading cause of death worldwide. All stages of the disease are characterized by inflammation, and CRP levels in a person's blood are a good indicator of inflammation. Observational studies have also shown that high levels of CRP in the blood are associated with a higher risk of heart disease.

However, it was not clear whether CRP was causing heart disease in some way, or whether it was simply a marker of the inflammation involved in heart disease.

In this latest study, an international team of researchers studied the genes that control the levels of CRP in the blood and their effect on heart disease. In total they looked at different gene variants in 28,112 people with heart disease and 100,823 people who did not have heart disease.

They found that the gene variants linked with different CRP levels are not associated with an increased risk of heart disease, indicating that CRP is unlikely to be directly involved in causing heart disease.

In addition, the researchers identified genetic variants in three other genes that affect CRP levels.

"Coronary heart disease is a common cause of death, especially in the UK and other western countries, and scientists have been looking for new ways to treat the disease and reduce mortality," commented the lead author of the paper, Professor Paul Elliott of the Department of Epidemiology and Public Health at Imperial College London, UK.

"Some researchers thought C-reactive protein would be a good molecule to target, as raised levels of this protein in the blood are associated with increased risk of coronary heart disease. However our research suggests that the association may not be causal, so attempts to target this protein to reduce the risk of the disease are unlikely to be fruitful."

"We have also discovered new genetic variations that are associated with coronary heart disease. If confirmed in other studies, these might give clues to identify new targets to treat the disease," he added.

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Item 15

The Effect of Metformin on DPP-4 Activity in Type 2 Diabetes

DPP-4 activity suppressed by metformin Full Story

Glucagon-like peptide-1 (GLP-1) is an insulinotropic hormone and major component of the enteroinsular axis. Its therapeutic potential in human diabetes is limited by rapid degradation and inactivation by the enzyme dipeptidylpeptidase-4 (DPP-4).

The study investigated the acute effects of metformin with and without food on DPP-4 activity in Type 2 diabetes.

Ten subjects with Type 2 diabetes (6 male/4 female, age 65.8 +/- 2.6 years, body mass index 30.0 +/- 1.2 kg/m², glycated haemoglobin (HbA(1c)) 6.3 +/- 0.2%, mean +/- SEM) received metformin 1 g orally or placebo together with a standard mixed meal (SMM) in a random crossover design. Six subjects re-attended fasting and received metformin 1 g without a SMM.

The results showed that DPP-4 activity was not suppressed by metformin compared with placebo (area under curve (AUC)(0-4 h) 1574 +/- 4 vs. 1581 +/- 8 micromol/ml/min, respectively). Plasma glucose, insulin and active GLP-1 were not different.

However, DPP-4 activity was suppressed with metformin following fasting compared with a SMM (n = 6) (AUC(0-4 h) 1578 +/- 4 vs. 1494 +/- 9 micromol/min, P < 0.02). Metformin serum levels were significantly lower (P < 0.001) after SMM than fasting (AUC(0-4 h) 350 +/- 66 vs. 457 +/- 55 mg/ml/min).

In conclusion, metformin inhibits DPP-4 activity in Type 2 diabetic patients in the fasting state but not when taken with a standard mixed meal. Metformin serum concentrations are lower if the drug is taken with food. These findings should be taken into account in establishing how to maximize efficacy of the drug.

[Research Support, Non-U.S. Gov't](#)
[Diabet Med.](#) 2009 Jun;26(6):649-54. PMID: 19538242 [PubMed - in process]

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Quote of the Week

"An early morning walk is a blessing for the whole day."

.....Henry David Thoreau

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