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NEJM Journal Watch

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Reprints in DIABETES

NEJM Journal Watch Reprints in Diabetes *features recent summaries and expert perspective from across NEJM Journal Watch, a literature surveillance series focused on the most critical advances in clinical medicine. Our physician-editors provide expert commentary on the most significant and clinically relevant research to help you stay informed and practice with confidence.*

High Rates of Emergency Department Visits for Insulin-Related Hypoglycemia

Rates were highest in the oldest patients, as were rates for subsequent hospitalizations.

A third of all patients with diabetes use insulin. Clinical guidelines often emphasize tight glycemic control, despite evidence of harm in some situations. In this study, CDC investigators used data from emergency departments (EDs) at 63 U.S. hospitals and population-based health surveys to assess rates of ED visits and hospitalizations for hypoglycemia among insulin-treated patients between 2007 and 2011.

Roughly 100,000 ED visits occurred annually in the U.S. for insulin-related hypoglycemia or medication errors, of which about 60% were for severe neurological events such as altered mental status and falls; 53% of cases involved blood glucose levels ≤50 mg/dL, and 29% of ED visits resulted in hospitalizations. Precipitating factors were identified in only about 20% of ED visits; of those, the most common were meal-related problems (46%) and problems with insulin doses or products (34%). Risk for ED visits was twice as high among the oldest patients (age, ≥80) as among those who were 45 to 79; the oldest patients were at five times more risk for hospitalization than were middle-aged patients (age range, 45–64).

COMMENT

These data depict a seeming epidemic of insulin-related hypoglycemia. An editorialist recommends three changes to current clinical practice: (1) set glycemic targets for diabetic patients as a range rather than a specific number; (2) develop quality measures in which overtreatment is considered to be as problematic as undertreatment; and (3) avoid insulin for most nonhospitalized older patients.

— Thomas L. Schwenk, MD

Geller AI et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. **JAMA Intern Med** *2014 May 1; 174:678.*

Lee SJ. So much insulin, so much hypoglycemia. **JAMA Intern Med** *2014 May 1; 174:686.*

Increasing Prevalence of Diabetes in American Youth

Between 2001 and 2009, the prevalence of type 1 diabetes and type 2 diabetes increased by 21% and 31%, respectively.

Diabetes is among the most common chronic diseases in children. Using the SEARCH database from four geographic regions, one healthcare based region, and selected American Indian reservations in the U.S., investigators examined the prevalence of type 1 diabetes (among >3 million youth aged <20 years) and type 2 diabetes (among 1.7 million youth aged 10–19 years) in 2001 and 2009.

Between 2001 and 2009, the prevalence of type 1 diabetes increased by an adjusted 21% — from 1.48/1000 youth to 1.9/1000. Prevalence was highest among white youth (2.66/1000) and lowest among American Indian youth (0.35/1000). The prevalence of type 2 diabetes increased by

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31% — from 0.34/1000 youth to 0.46/1000. Prevalence was highest among American Indian youth (1.2/1000), followed by black (1.07/1000), Hispanic (0.70/1000) and white youth (0.17/1000). During the same time period, the prevalence of diabetes increased in both sexes and in Hispanic, black, and white youth. Neither type of diabetes increased significantly in Asian Pacific Islander or American Indian youth.

COMMENT

Both type 1 and type 2 diabetes are important health issues for children and adolescents. We must develop models of care that are cost-efficient and provide excellent outcomes for the increasing number of children with diabetes.

— F. Bruder Stapleton, MD

Dabelea D et al. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. **JAMA** *2014 May 7; 311:1778.*

Do Mediterranean Diets Prevent Type 2 Diabetes?

A Mediterranean diet supplemented with extra-virgin olive oil was associated with 40% reduction in risk for diabetes.

Weight loss through calorie-restricted diets and exercise lowers risk for type 2 diabetes. To assess whether Mediterranean diets without caloric restriction also protect against diabetes, researchers in Spain analyzed data on the 3500 nondiabetic participants in the PREDIMED prevention trial (*N Engl J Med* 2013; 368:1279), in which adults with ≥3 cardiovascular risk factors were randomized to one of three diets: a Mediterranean diet supplemented with extra-virgin olive oil (EVOO; 3–4 tablespoons daily), a Mediterranean diet supplemented with mixed nuts (1 ounce daily), or a control diet (consisting of advice to reduce intake of all fats). No participants were advised to restrict calories or to increase physical activity.

During median follow-up of 4 years, 273 participants developed diabetes. Incidence rates were 16, 19, and 24 cases per 1000 person-years, respectively, in the EVOO group, the nut-supplement group, and the control group. After adjustment for potential confounders, the hazard ratios for diabetes were significantly lower for the EVOO group (0.60) and slightly but not significantly lower for the nut group (0.82) relative to controls. No significant changes occurred in weight, waist circumference, or physical activity levels across groups.

COMMENT

In this study, a Mediterranean diet supplemented with extra-virgin olive oil lowered diabetes incidence without associated weight loss or increased physical activity. The mechanism by which a Mediterranean diet might lower diabetes risk is unknown, but, as the authors note, such diets might alleviate inflammation, oxidative stress, and insulin resistance.

— Jamaluddin Moloo, MD, MPH

Salas-Salvadó J et al. Prevention of diabetes with Mediterranean diets: A subgroup analysis of a randomized trial. **Ann Intern Med** *2014 Jan 7; 160:1.*

Medical or Surgical Therapy for Diabetic Foot Osteomyelitis?

In selected patients with localized infections, outcomes were comparable with the two approaches.

Patients with diabetic foot infections and associated osteomyelitis can be treated medically or surgically, but randomized trials to guide this decision are lacking. In this study from Spain, 52 diabetic patients with neuropathic foot ulcers complicated by osteomyelitis were randomized to receive either a 90-day course of antibiotics or "conservative surgery" (i.e., removal of infected bone without performing amputation) followed by 10 days of antibiotic therapy. In all patients, antibiotic therapy was guided by deep soft-tissue cultures. Patients with severe soft-tissue infections, substantial peripheral arterial disease, or exposed bone at the bottom of ulcers were excluded. Forty-six patients completed the study.

Primary healing (i.e., complete epithelialization of the ulcer or surgical wound) occurred in 75% of patients in the antibiotic group and in 86% of those in the surgical group (P=0.33). During 12 weeks of observation, four antibiotic patients required surgery, and three surgery patients required reoperation; reulceration without osteomyelitis occurred in two and four patients, respectively.

COMMENT

This study — the first such randomized trial, according to the authors — suggests that a long course of antibiotic therapy compares favorably with surgery plus short-course antibiotic therapy in highly selected patients with diabetic foot ulcers and osteomyelitis. Obvious limitations are the trial's small size and relatively brief follow-up. A recent guideline from the Infectious Diseases Society of America is an excellent resource for clinicians who care for these patients (*Clin Infect Dis* 2012; 54:e132). ***— Allan S. Brett, MD***

Lázaro-Martínez JL et al. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: A randomized comparative trial. **Diabetes Care** *2014 Mar; 37:789.*

Sex Differences in Diabetes-Associated Risk for Stroke

Excess risk for stroke was higher in diabetic women than in diabetic men.

Compared with men, women have higher relative risk for fatal coronary heart disease associated with diabetes, even after adjustment for differences in other cardiovascular risk factors. Is the same true for stroke? To find out, researchers analyzed data from 64 cohort studies (>775,000 adults with and without diabetes), conducted in various countries, in which sex-specific relative risks were reported for fatal and

nonfatal strokes; follow-up ranged from 5 to 32 years.

After adjustment for multiple other risk factors, relative risk for fatal or nonfatal stroke associated with diabetes was 2.28 in women and 1.83 in men — a significant difference. These risks were not affected significantly by study duration, year of study enrollment, region, age, smoking status, or stroke subtype.

COMMENT

Citing evidence that the liver and skeletal muscle tend to be more sensitive to insulin in women than in men and that prediabetic women have greater endothelial dysfunction and more severe hypertension than prediabetic men, the authors propose that women might accumulate more cardiovascular risk before progressing to overt diabetes. Reasons for these sex differences remain unclear, but this study calls attention to the particular importance of optimizing management of known cardiovascular risk factors in prediabetic and diabetic women.

— Bruce Soloway, MD

Peters SAE et al. Diabetes as a risk factor for stroke in women compared with men: A systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. **Lancet** *2014 Mar 7; [e-pub ahead of print] (http://dx.doi.org/10.1016/S0140-6736(14)60040-4)*

Dietary Intervention for Diabetic Gastroparesis: A Randomized Trial

A diet of easy-to-mash and pureed foods was associated with improved symptoms.

Patients with symptomatic diabetic gastroparesis are advised to eat small, frequent meals low in fat and nondigestible fiber, but controlled trials are lacking. In this study, Swedish researchers randomized 56 insulin-treated diabetic adults with symptomatic gastroparesis and delayed emptying (on gastric scintigraphy) to receive either a "small-particle-size" intervention diet or a control diet. The intervention diet consisted mainly of easy-to-mash and pureed foods, whereas in the control diet, particle size or texture of foods was not restricted. Otherwise, the diets were similar nutritionally and calorically, and both groups were asked to eat three meals and three snacks daily. All participants received seven 1-hour dietary counseling sessions. Two thirds of patients had type 1 diabetes.

On standardized symptom scales, patients in the intervention group had significantly improved nausea or vomiting, bloating, abdominal fullness, and regurgitation or heartburn compared with control patients at 20 weeks. Gastric emptying on scintigraphy also improved in the intervention group compared with the control group. Quality of life scores remained unchanged in both groups.

COMMENT

This study confirms that a dietary intervention can ameliorate at least some of the symptoms of diabetic gastroparesis. However, because many patients might find this diet to be relatively unpalatable, long-term adherence might be difficult.

— Allan S. Brett, MD

Olausson EA et al. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: A randomized controlled trial. **Am J Gastroenterol** *2014 Mar; 109:375.*

Longer-Term Follow-Up from a Bariatric Surgery Trial for Diabetic Patients

At 3 years, glycemic control and quality of life were better with surgery than with medical management.

In a previously published report from a randomized Cleveland Clinic trial, Roux-en-Y gastric bypass and sleeve gastrectomy were more likely than medical therapy (42% and 37% vs. 12%) to lower glycosylated hemoglobin (HbA_{1c}) levels to ≤6% in 150 obese diabetic patients (mean age at baseline, 48; mean body-mass index at baseline, 36 kg/m^2) at 1 year (*N Engl J Med* 2012; 366:1567). Now, the researchers present longer-term outcomes.

At 3 years, the proportions of patients whose HbA_{1c} levels were ≤6% and who no longer were taking diabetes medications remained significantly higher in the gastric-bypass and sleeve-gastrectomy groups than in the medical-treatment group (35% and 20% vs. 0%). On standardized questionnaires that reflected eight quality-of-life domains, scores improved significantly in five domains in the bypass group, two domains in the gastrectomy group, and no domains in the medical-treatment group. Four surgically treated patients required additional surgical interventions to address complications within the first year, but no patients required additional surgery thereafter.

COMMENT

The key findings here are that the improved glycemic control reported after 1 year persisted at 3 years and that quality of life improved in the surgery groups. But even-longer-term outcomes, including diabetes end-organ complications and late gastrointestinal surgical complications, will be important to track.

— Allan S. Brett, MD

Schauer PR et al. Bariatric surgery vs. intensive medical therapy for diabetes — 3-year outcomes. **N Engl J Med** *2014 Mar 31; [e-pub ahead of print]. (http://dx.doi.org/10.1056/NEJMoa1401329)*

Incretin-Based Diabetes Drugs Aren't Associated with Excess Risk for Acute Pancreatitis

Although not the final word, results of two large studies should be reassuring.

Several years ago, the FDA alerted physicians to case reports of acute pancreatitis in patients treated with the incretin-based diabetes drugs exenatide (Byetta; a glucagon-like peptide-1 [GLP-1] receptor agonist) and sitagliptin (Januvia; a dipeptidyl peptidase 4 [DPP-4] inhibitor). In two recent studies, investigators determined whether incretin-based treatment raises risk for acute pancreatitis in patients with type 2 diabetes.

In a meta-analysis of 55 randomized trials in which GLP-1 receptor agonists, DDP-4 inhibitors, or both were assessed in 33,000 patients (mean age range, 50–67; follow-up range, 12–234 weeks), only 37 participants (0.1%) experienced acute pancreatitis, and incretin-based treatment was not associated with elevated risk for pancreatitis. The same investigators analyzed data from five observational studies (320,000 patients): In only one study (a case-control study of 2500 patients) was exenatide or sitagliptin use associated significantly with increased odds for developing acute pancreatitis.

In a population-based U.K. cohort study of 73,000 patients, incretin-based drugs were compared with sulfonylureas. (Sulfonylureas were chosen as the comparator because they are used at roughly the same stage of diabetes.) After mean treatment duration of 1.4 years, no association was found between incretin-based drugs and acute pancreatitis.

COMMENT

These analyses suggest that incretin-based treatments for patients with type 2 diabetes are not associated with excess risk for acute pancreatitis. All of the randomized trials involved in the meta-analysis were industry-funded, and none described criteria for diagnosing pancreatitis. Nonetheless, these results should be reassuring to clinicians who prescribe and patients who use these second-line drugs for type 2 diabetes.

— Paul S. Mueller, MD, MPH, FACP

Li L et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: Systematic review and meta-analysis of randomised and non-randomised studies. **BMJ** *2014 Apr 15; 348:g2366. (http://dx.doi.org/10.1136/bmj.g2366)*

Faillie JL et al. Incretin based drugs and risk of acute pancreatitis in patients with type 2 diabetes: Cohort study. **BMJ** *2014 Apr 24; 348:g2780. (http://dx.doi.org/10.1136/bmj.g2780)*

Sirolimus Is Effective in Infants with Severe Hyperinsulinemic Hypoglycemia

Sirolimus therapy resulted in normoglycemia in four infants when other medical therapies failed.

Severe infantile hypoglycemia from hyperinsulinemia, most often from genetic dysregulation of pancreatic beta cells, is a major therapeutic challenge. When infants do not respond to diazoxide and octreotide along with intravenous glucose infusions, subtotal pancreatectomy is required with inevitable diabetes mellitus later in childhood.

Investigators now report outcomes in four children (born at 33–40 weeks' gestation) with hyperinsulinemic hypoglycemia resistant to diazoxide and octreotide who were treated with sirolimus (starting dose, 0.05 mg per square meter body surface per day, increased to reach a serum trough level of 5–15 ng/mL) beginning at ages 7 to 16 weeks. All infants had symptomatic hypoglycemia with seizures, poor feeding, and irritability. Diazoxide, octreotide, and intravenous glucose infusions were discontinued by day 10 to 19 in all but one child who continued to require a small dose of octreotide. In one patient, sirolimus was discontinued without success at 7 months, and had to be reinitiated. At age 1 year, all children remained normoglycemic on sirolimus treatment. The only adverse effects noted were transient elevation in serum transaminases in one child and mild hypertriglyceridemia.

COMMENT

Sirolimus inhibits the serine-threonine protein kinase mTOR pathway, which has been shown to be abnormally activated in some cases of insulinoma. This drug proved to be effective in four infants with different genotypes, but all with hyperinsulinemia and severe hypoglycemia. Given the limited therapeutic options and high morbidity associated with both hypoglycemia and pancreatectomy, sirolimus should be considered when standard therapy is not effective. ***— F. Bruder Stapleton, MD***

Senniappan S et al. Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia. **N Engl J Med** *2014 Mar 20; 370:1131.*

Delaying Joint Replacement Surgery Until Hemoglobin A_{1c} is Less Than 7%

The benefit of this practice, which delays or prevents surgery for some diabetic patients, is unclear.

Increasingly, orthopedists are insisting that diabetic patients lower their glycosylated hemoglobin (HbA_{1c}) levels to less than 7% before they undergo total joint arthroplasty. But this is far easier said than done, particularly in older patients, in whom tight control increases risk for potentially dangerous hypoglycemia. A study from the orthopedic clinic at a U.S. Veterans Affairs hospital illustrates this problem.

During a 5-year period, 59 diabetic patients who were deemed otherwise suitable for total hip or knee arthroplasty were not scheduled for surgery because their HbA_{1c} levels were >7%. The patients were referred back to their primary care physicians to intensify glycemic control. After an average of 8 months, 35 (59%) achieved HbA_{1c} levels ≤7%, but the remaining 24 patients (41%) were unable to do so. Only 5 of those 24 patients ultimately had surgery.

COMMENT

Reluctance to perform total hip or knee arthroplasty on diabetic patients with HbA_{1c} levels >7% is based on assumptions that this threshold is a good predictor of risk for postoperative complications (especially deep infection) and that preoperative lowering of HbA_{1c} reduces that risk. But observational studies do not uniformly support the first assumption (*J Bone Joint Surg Am* 2013; 95:481), and no randomized trials have tested the second one. Indeed, it might be that glycemic control immediately after surgery is more important for preventing complications than control during the months before surgery.

— Allan S. Brett, MD

Giori NJ et al. Many diabetic total joint arthroplasty candidates are unable to achieve a preoperative hemoglobin A1c goal of 7% or less. **J Bone Joint Surg Am** *2014 Mar 19; 96:500.*

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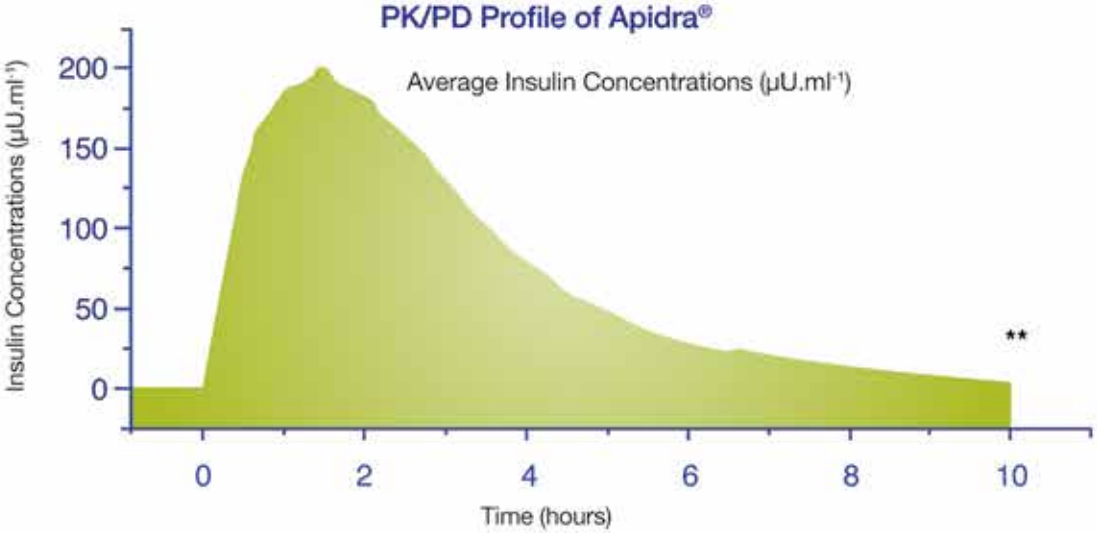
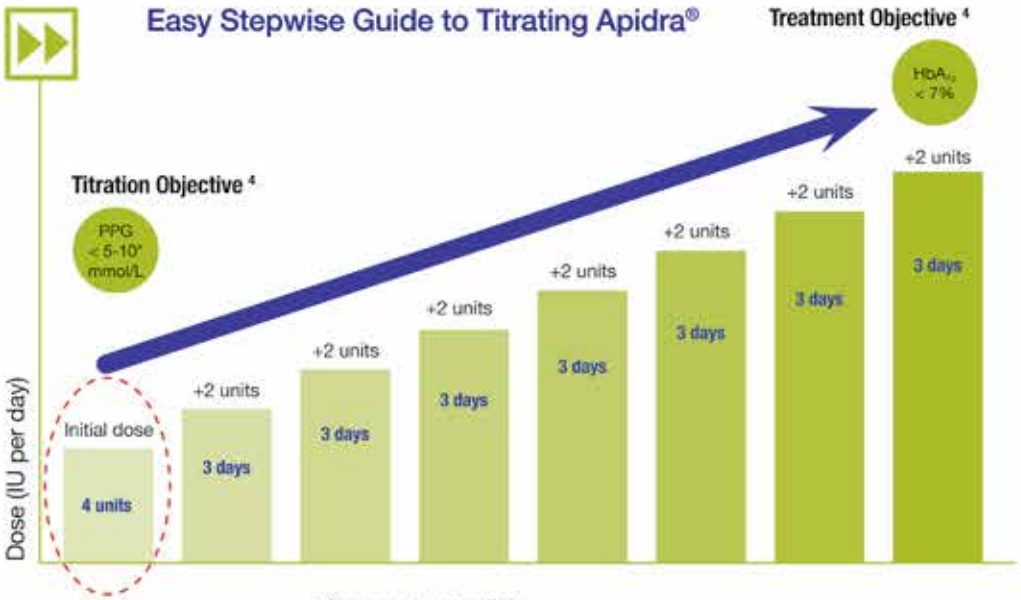
PK/PD Profile of Apidra®



**Average Insulin Concentrations following subcutaneous injection of 0.3 U/kg⁻¹ of APIDRA® in the abdominal area
6. Adapted from Nathan Becker R.H.A. et al.

Easy Stepwise Guide to Titrating Apidra®



*2hrs post-prandial
7. Adapted from Nathan D.M. et al.

SCHEDULING STATUS: S3 **PROPRIETARY NAME AND DOSAGE FORM:** APIDRA® solution for injection. **COMPOSITION:** 1 ml contains 3,5 mg insulin glulisine, corresponding to 100 U human insulin, 3.15mg of the preservative metacresol and 0.01mg of stabilising agent polysorbate 20. **REGISTRATION NUMBER:** A38/21.1/0506 **NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:** sanofi-aventis south africa (pty) ltd, 2 Bond Street, Midrand, 1685. Tel: 011 256 3700 Reg. No. 1996/10381/07.

4. Amod A. et al. 2012 SEMDSA guideline for the management of type 2 diabetes. JEMDSA. 2012;17(1):S1-S94.
5. Garg S.K. et al. Optimized Basal- Bolus Insulin Regimens in Type 1 Diabetes: Insulin Glulisine versus Regular Human Insulin in Combination with Basal Insulin Glargine. Endocrine Practice Vol 11 No. 1 January/ February 2005.
6. Becker R.H.A. et al. Insulin Glulisine, a New Rapid-Acting Insulin Analogue, Displays a Rapid Time-Action Profile in Obese Non-Diabetic Subjects. Exp Clin Endocrinol Diabetes 2005; 113: 435-443.
7. Nathan D.M. et al. Management of Hyperglycaemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, Volume 29, Number 8, August 2006.

PPG = Post-Prandial Blood Glucose

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#1 INSULIN brand worldwide[2]

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GLYCAEMIC CONTROL. ALL DAY. EVERY DAY.

Once-daily Lantus®: The one you know. It is the prescriber's first choice at the time of basal insulin initiation (T2DM)[1]. Lantus® leads to early and sustained HbA_{1c} control[3-9] with a hypoglycaemia rate comparable to that of OAD intensification[3]. With 10 years of an established efficacy and safety profile, Lantus® is the one you know[3-9].

1. Based on market data for the US, France, Italy, Spain and Japan. **2**. IMS-MAT, June 2012. **3**. Gerstein HC, et al. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study.Diabetic Med 2006;23:736-42. **4**. Rosenstock J, et al. Triple Therapy in Type 2 Diabetes:Insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients.Diabetes Care 2006;29:554-9. **5**. Ascher P, et al. Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre, randomised open-label trial. Lancet 2012;379:2262-9. **6**. Yki-Jarvinen H, et al. Insulin glargine or NPH combined with metformin in type 2 diabetes : the LANMET study. Diabetologia (2006) 49 : 442-451. **7**. Riddle MC, et al. The Treat-to-Target Trial. Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients.Diabetes Care 2003;26:3080-6. **8**. Schreiber SA, et al. The Long-Term Efficacy of Insulin Glargine Plus Oral Antidiabetic Agents in a 32-Month Observational Study of Everyday Clinical PracticeDiabetes Technol Ther 2008;10(2):121-7. **9**. DeVries JH, et al. Pooled Hypoglycemia Event Rates With Insulin Glargine Added to Metformin (IG-M) from Treat-to-Target Type 2 Diabetes Mellitus (T2DM) Trials. Diabetes 2012;61(Suppl 1):A552-3.

SCHEDULING STATUS: S3 PROPRIETARY NAME AND DOSAGE FORM: LANTUS® solution for injection. COMPOSITION: Each ml of the solution for injection contains 3.64 mg of the active ingredient insulin glargine, corresponding to 100 U human insulin; 2.7 mg of the preservative metacresol and 0.0626 mg of zinc chloride as stabiliser. 10 ml vial contains 0.02 mg polysorbate 20 as additional stabiliser. REGISTRATION NUMBER: 34/21.1/0246. NAME AND BUSINESS ADDRESS OF THE APPLICANT: sanofi-aventis south africa (pty) ltd. 2 Bond Street, Midrand, 1685. Tel: 011 256 3700. Reg. No. 1996/10301/07.

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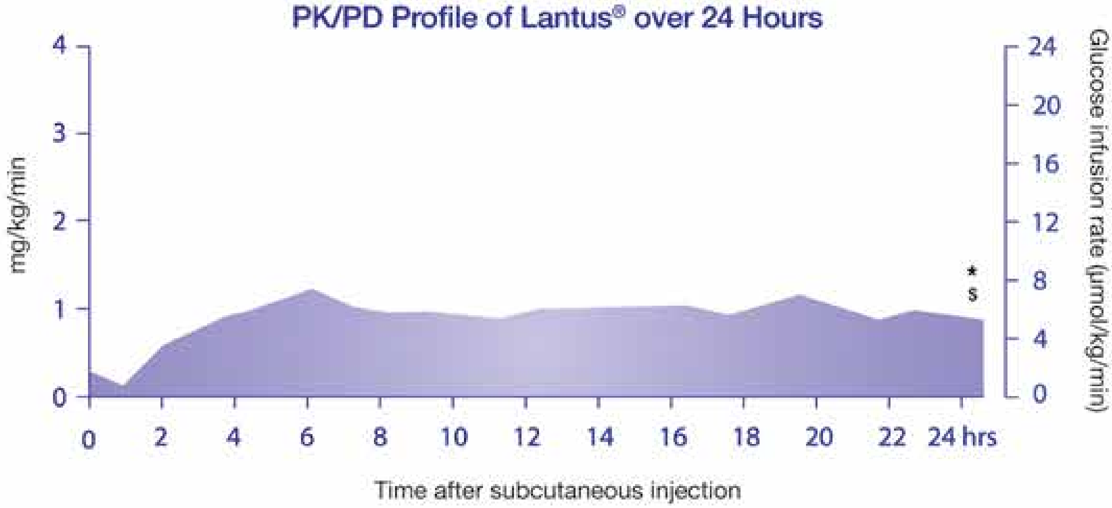
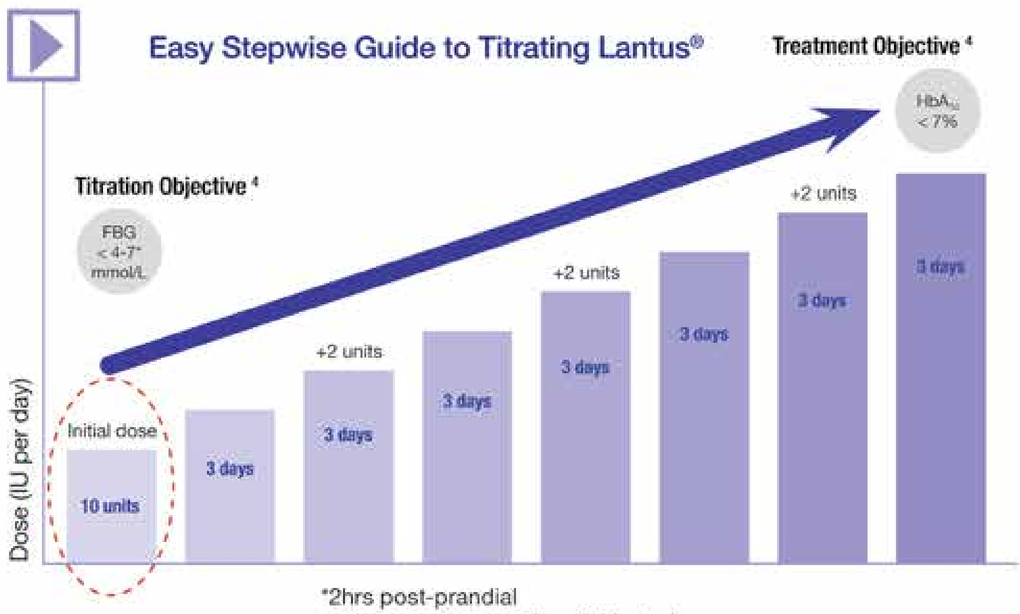


* PK/PD Data referenced are from Type 1 DM patients

$ Rates of Glucose infusion needed to maintain plasma glucose at target value of 7.2 mmol/L after subcutaneous Lantus® injection

1. Adapted from Lepore M et al.



*2hrs post-prandial

7. Adapted from Nathan D.M. et al.

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1. Lepore M et al. Pharmacokinetics and Pharmacodynamics of Subcutaneous Injection of Long-Acting Human Insulin Analog Glargine, NPH Insulin, and Ultralente Human Insulin and Continuous Subcutaneous Infusion of Insulin Lispro. Diabetes 2000; 49: 2142-2148.
2. Mooradian A.D. et al. Narrative Review: A Rational Approach to Starting Insulin Therapy. Ann Intern Med. 2006; 145: 125- 134.
3. Riddle M.C et al. The Treat-to-Target Trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care, Volume 26, Number 11, November 2003: 3080-3086.
4. Amod A. et al. 2012 SEMDSA guideline for the management of type 2 diabetes. JEMDSA. 2012;17(1):S1-S94.
7. Nathan D.M. et al. Management of Hyperglycaemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care, Volume 29, Number 8, August 2006.

FBG = Fasting Blood Glucose

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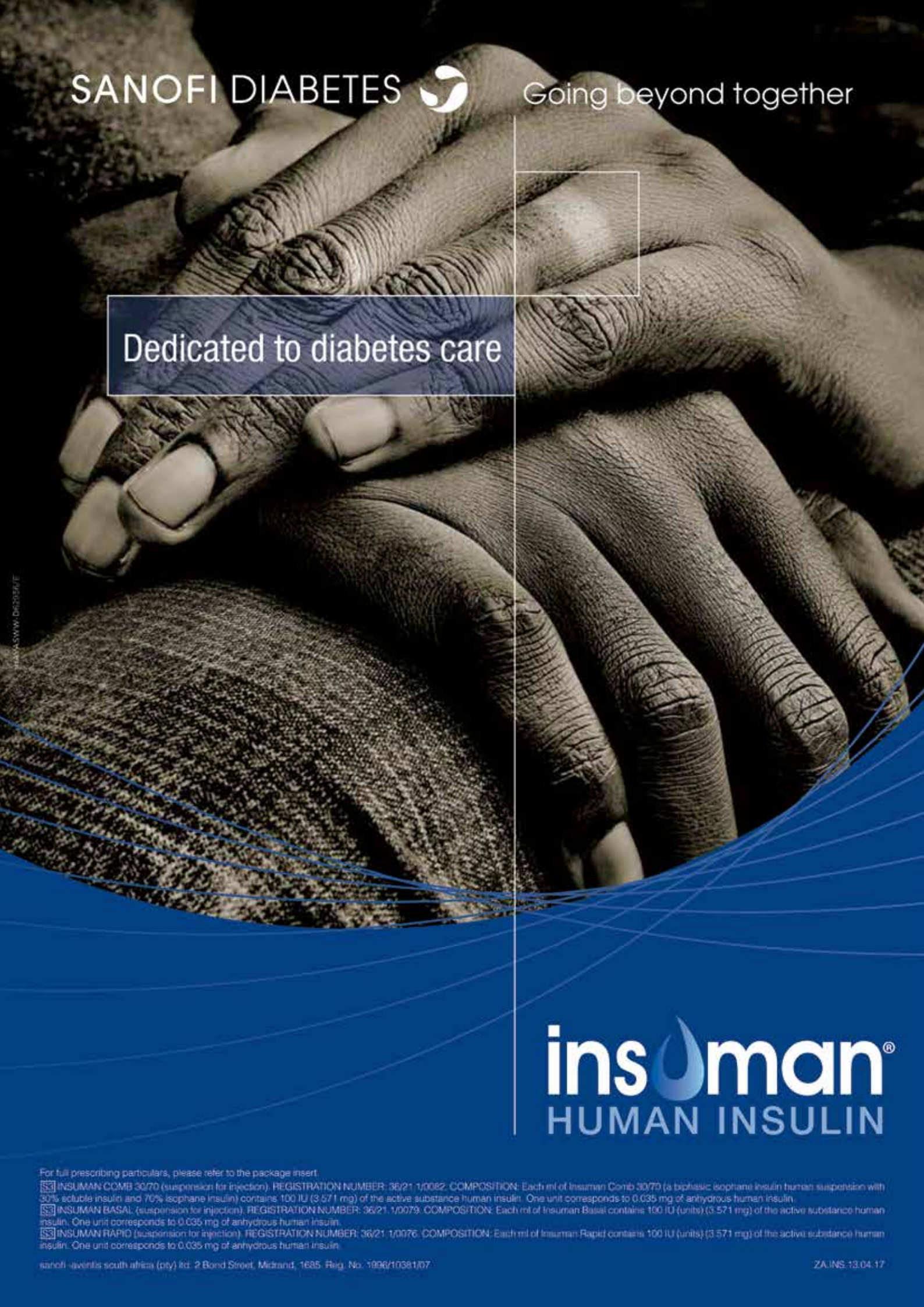

For full prescribing particulars, please refer to the package insert.

SS INSUMAN COMB 30/70 (suspension for injection). REGISTRATION NUMBER: 36/21.1/0082. COMPOSITION: Each ml of Insuman Comb 30/70 (a biphasic isophane insulin human suspension with 30% soluble insulin and 70% isophane insulin) contains 100 IU (3.571 mg) of the active substance human insulin. One unit corresponds to 0.035 mg of anhydrous human insulin.

SS INSUMAN BASAL (suspension for injection). REGISTRATION NUMBER: 36/21.1/0079. COMPOSITION: Each ml of Insuman Basal contains 100 IU (units) (3.571 mg) of the active substance human insulin. One unit corresponds to 0.035 mg of anhydrous human insulin.

SS INSUMAN RAPID (suspension for injection). REGISTRATION NUMBER: 36/21.1/0076. COMPOSITION: Each ml of Insuman Rapid contains 100 IU (units) (3.571 mg) of the active substance human insulin. One unit corresponds to 0.035 mg of anhydrous human insulin.

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Is Anything the Matter with White Matter in Insulin-Resistant Patients?

Brain microstructures may be abnormal even in individuals without cognitive symptoms.

Higher fasting glucose and glycosylated hemoglobin levels, even within the normal range, are associated with cognitive problems and hippocampal abnormalities (*Neurology* 2013; 2013; 80:1557). Extending these findings, researchers have examined white-matter integrity on diffusion tensor imaging in 127 cognitively healthy individuals (age range, 41–86) who were divided into high and low insulin-resistance levels on the homeostasis model of assessment of insulin resistance (HOMA-IR), which is calculated from fasting levels of serum insulin and glucose.

Patients with high HOMA-IR had higher triglyceride concentrations, higher glycosylated hemoglobin levels, and greater use of hypoglycemic medications. Independent of confounding factors, patients with high HOMA-IR had widespread lower values on two measures, fractional anisotropy and axial diffusivity, indicating microstructural irregularities. Across all subjects, diffusion measures were linearly associated with HOMA-IR levels.

COMMENT

This study adds to the data connecting insulin resistance with abnormalities in brain structure and function. To appropriately monitor and counsel our patients, we need to know more — which interventions minimize insulin resistance (e.g., diet, exercise, sleep), which factors increase it (e.g., atypical antipsychotics), and whether monitoring fasting insulin levels is more sensitive than glycosylated hemoglobin or fasting glucose levels for indicators of glucose resistance in patients treated with atypicals. ***— Jonathan Silver, MD***

Ryu SY et al. Effects of insulin resistance on white matter microstructure in middle-aged and older adults. **Neurology** *2014 Apr 25; [e-pub ahead of print]. (http://dx.doi.org/10.1212/WNL.0000000000000452)*

MEDICAL NEWS

Rare, Diabetes-Sparing Gene Mutation Identified

A rare mutation is associated with a 65% reduced risk for type 2 diabetes.

Researchers mined genetic data on 150,000 people and found 70 in Iceland and Sweden with the gene variant, according to a *New York Times* report. The researchers report in a a letter to *Nature Genetics* that the variant, in a gene known as *SLC30A8*, truncates a protein — ZnT8 — that transports zinc in the islet cells of the pancreas. The faulty protein results in lower glucose levels and lower diabetes risks.

The *Times* says a vice president for one of the two drug-company sponsors "cautioned it can take 10 to 20 years to get a drug to market after discovering something new about human genetics and disease." ***— Joe Elia,*** **Physician's First Watch**

Flannick J et al. Loss-of-function mutations in SLC30A8 protect against type 2 diabetes. **Nature Genet** *2014 Mar 2; 46:357.*

Kolata G. Rare mutation kills off gene responsible for diabetes. **New York Times.** *Mar 2, 2014. (http://www.nytimes.com/2014/03/03/health/rare-gene-protects-against-type-2-diabetes-even-in-obese-people.html)*

ACE Inhibitors Linked to Better CV Outcomes Than ARBs in Patients with Diabetes

Angiotensin-converting-enzyme (ACE) inhibitors are associated with reduced mortality and cardiovascular events in patients with diabetes, while angiotensin-receptor blockers (ARBs) have little effect, according to a meta-analysis in *JAMA Internal Medicine*.

Researchers assessed the results of 35 randomized, controlled studies comprising some 56,000 patients. Participants had been randomized to either the active group (ACE inhibitors or ARBs) or a comparator group (placebo, no treatment, or other antihypertensive drugs).

Use of ACE inhibitors was associated with a 13% to 17% risk reduction in all-cause mortality, cardiovascular mortality, and major cardiovascular events. ARB users did not see a similar benefit. However, ARBs were associated with a 30% risk reduction in heart failure.

The authors conclude that ACE inhibitors "should be considered as first-line therapy to limit the excess mortality and morbidity in this population." ***— Kelly Young,*** **Physician's First Watch**

Cheng J et al. Effect of angiotensin-converting enzyme inhibitors and angiotensin ii receptor blockers on all-cause mortality, cardiovascular deaths, and cardiovascular events in patients with diabetes mellitus: A meta-analysis. **JAMA Intern Med** *2014 May; 174:773.*

Diabetes Prevalence Continues to Rise, Especially Among Minorities

About 6% of the U.S. population had diabetes in 1988; that fraction was 9% in 2010.

Using data from >15,000 people (age, ≥20) that were collected as part of the U.S. National Health and Nutrition Examination Survey (NHANES), researchers evaluated trends in diabetes during the past 2 decades (1988–1994 and 1999–2010). Laboratory data included glycosylated hemoglobin (HbA_{1c}) and fasting plasma glucose levels. Participants who reported physician-diagnosed diabetes were classified as confirmed diabetic; participants without diagnosed diabetes were categorized as undiagnosed diabetic (HbA_{1c}, ≥6.5%; or fasting glucose, ≥126 mg/dL), prediabetic (HbA_{1c}, 5.7%–6.4%; or fasting glucose, 100–125 mg/dL), or normal glycemic.

The prevalence of obesity among people without confirmed diabetes increased from 21% in 1988–1994 to 32% in 2005–2010. During the same time, prevalence of diabetes (confirmed plus undiagnosed) increased from 5.5% to

9.3%, whereas prevalence of undiagnosed diabetes remained stable at approximately 1%. Prevalence of prediabetes increased from 5.8% to 12.4% based on HbA_{1c} values or from 25% to 29% based on fasting glucose values. Among patients with confirmed diabetes, the proportion of individuals with HbA_{1c} <7% increased from 51% to 59%. Finally, racial disparities persisted: Hispanics and non-Hispanic blacks had significantly higher rates of diabetes overall and of undiagnosed diabetes, and good glucose control among confirmed diabetics in these cohorts was lower.

COMMENT

This cross-sectional study confirms that rates of obesity and diabetes are rising significantly, and these rates are even higher among minorities.

— Jamaluddin Moloo, MD, MPH

Selvin E et al. Trends in prevalence and control of diabetes in the United States, 1988–1994 and 1999–2010. **Ann Intern Med** *2014 Apr 15; 160:517.*

Metformin Might Reduce Gastric Cancer Risk

In a retrospective analysis, using metformin for >3 years reduced gastric cancer risk by 43% in patients with type 2 diabetes who did not use insulin.

The oral antidiabetic drug metformin has demonstrated anticancer activity in limited studies. To investigate whether metformin use is associated with reduced risk for gastric cancer, researchers in Korea used national insurance claims data to retrospectively assess cancer incidence in metformin users versus nonusers among 40,000 patients with type 2 diabetes.

Among a total of 7000 regular insulin users, 5900 had used metformin, and among 33,000 insulin nonusers, 27,000 had used metformin.

Gastric cancer incidence was lower in patients taking metformin compared with those not taking metformin among insulin nonusers (P=0.047) but not among regular insulin users. In a multivariate regression model, longer duration of metformin use was associated with reduced risk for gastric cancer (adjusted hazard ratio, 0.88; 95% confidence interval, 0.81–0.96). In a second model that assessed duration of use in blocks of time, metformin use >3 years was associated with reduced risk for gastric cancer (adjusted HR, 0.57; 95% CI, 0.38–0.87).

COMMENT

A few study limitations should be noted. The overall and annual data analyses barely achieved statistical significance. Also, because of inherent confounding in retrospective database studies, results should be interpreted with caution. Compared with the main findings, those showing reduced cancer risk with long-term use of metformin are more compelling and consistent with reduced risks for cancers in other studies. However, perhaps most compelling was the finding that gastric cancer risk was doubled in insulin users versus nonusers, regardless of metformin use. Understanding the mechanisms by which both insulin and metformin might affect cancer risk requires additional study.

— David J. Bjorkman, MD, MSPH (HSA), SM (Epid.)

Kim Y-I et al. Long-term metformin use reduces gastric cancer risk in type 2 diabetics without insulin treatment: A nationwide cohort study. **Aliment Pharmacol Ther** *2014 Apr; 39:854.*

Do Specific DSM Disorders Increase the Risk for Diabetes?

In a 19-country, community-based survey, adult-onset diabetes mellitus was associated with increased rates of prior depression, impulse control disorders, and two eating disorders.

Patients with complications of diabetes mellitus have elevated rates of mood and cognitive disorders. Concomitantly, some psychiatric disorders might be associated with increased risk for subsequent diabetes. To study these relationships, investigators in a study with some industry funding used World Health Organization data from 19 countries based on household surveys assessing respondents for 16 DSM-IV diagnoses (mood, anxiety, impulse control, and substance use disorders); respondents also self-reported the presence of select physician-diagnosed chronic health conditions. Among 52,095 surveys, 2580 cases of adult-onset diabetes were identified (onset age, ≥21 years; mean, 50 years). Rates of all mental disorders studied, except obsessive-compulsive disorder and agoraphobia without panic, were elevated in respondents with self-reported diabetes (odds ratios for bivariate associations, 1.3–3.8). After adjustments for psychiatric comorbidity, age, sex, illness duration, and country, four psychiatric disorders remained associated with subsequent development of diabetes: binge-eating disorder (OR, 2.6), bulimia nervosa (OR, 2.1), intermittent explosive disorder (OR, 1.6), and major depression (OR, 1.3).

COMMENT

This study didn't differentiate between type I and type II diabetes and offered no data on lifestyle factors potentially linking psychiatric disorders, how individuals cope with them (e.g., dietary habits, body-mass index, psychiatric medications), and the subsequent development of diabetes. The strong association of binge-eating disorder (which commonly leads to obesity) with subsequent diabetes is unsurprising. Mechanisms linking other disorders to later diabetes are less evident, but might include common genetic predispositions or, more likely, other stress-related neurohumoral, inflammatory, or other psychosocial and lifestyle factors. Certainly, some psychiatric medications increase insulin resistance. Because associations between psychiatric disorders and diabetes are bidirectional, clinicians treating these psychiatric disorders should know that their patients are at increased risk for diabetes and require suitable monitoring and intervention.

— Joel Yager, MD

de Jonge P et al. Associations between DSM-IV mental disorders and diabetes mellitus: A role for impulse control disorders and depression. **Diabetologia** *2014 Apr; 57:699.*

Prematurity Linked with Elevated Insulin Levels

Premature infants exhibit long-lasting elevations of plasma insulin levels.

Growing evidence indicates that fetal and early life events lay the foundation for metabolic health or disease later in life. During the last decade, a link has been established between preterm birth and development of insulin resistance and type 2 diabetes in childhood and adulthood. However, whether alterations in insulin homeostasis are detectable at birth is not known.

Researchers prospectively evaluated plasma insulin levels from birth and to age 6.5 years in 1358 singleton children without major birth defects from an urban minority population (the Boston Birth Cohort). Each child had at least two insulin levels obtained (a cord blood sample at birth and a subsequent sample between ages 6 months and 6.5 years). About 30% of the population was born prematurely (<36 weeks).

Cord blood insulin levels were strongly and inversely associated with gestational age, independent of birth weight for gestational age ($P<0.001$ for linear trend). Compared with cord blood insulin levels in full-term infants, insulin levels were 1.13-fold higher in early term infants (37–38 weeks' gestation), 1.45-fold in late preterm infants (34–36 weeks), and 2.05-fold in early preterm infants (<34 weeks). Adjustment for covariables (including maternal race, cigarette smoking, parity, birth weight for gestational age, maternal diabetes, and leptin levels at birth) did not alter the association. In addition, cord blood insulin levels at birth were significant predictors of insulin levels in early childhood.

COMMENT

This population of predominantly urban and minority children had a high incidence of prematurity accompanied by long-lasting, gestational age-dependent elevations in plasma insulin levels. The findings suggest that preterm birth is an independent risk factor for later development of insulin resistance and could pave the way for identifying vulnerable populations that could benefit from preventive strategies. ***— Robin Steinhorn, MD***

Wang G et al. Preterm birth and random plasma insulin levels at birth and in early childhood. **JAMA** *2014 Feb 12; 311:587.*

MEDICAL NEWS

FDA Advisers Back New Inhaled Insulin

By Kelly Young

An advisory committee to the FDA has voted to recommend approval of Afrezza, a new inhaled form of insulin for types 1 and 2 diabetes, the *New York Times* reports.

The *Times* says that the votes were surprising, given the FDA's own critical review of the drug. In clinical trials, lung cancer diagnoses were more common among patients receiving Afrezza than in the comparator group, but the absolute numbers were small.

Pfizer's inhaled insulin drug, Exubera, which was pulled from the market in 2007 for low sales, also carried an increased lung cancer risk. The Exubera inhaler was roughly the size of a tennis ball can. The Afrezza inhaler, meanwhile, can fit in the palm of the hand.

MannKind, which developed Afrezza, says that its insulin takes effect faster than rapid-acting injected insulin. The FDA could decide whether to approve the drug by the middle of April.

— Kelly Young,
Physician's First Watch

Pollack A. Inhaled insulin clears hurdle toward F.D.A. approval. **New York Times.** *Apr 1, 2014. (http://www.nytimes.com/2014/04/02/health/inhaled-insulin-clears-advisory-hurdle-toward-fda-approval.html?_r=0)*

2014 Meeting Materials, Endocrinologic and Metabolic Drugs Advisory Committee. Silver Spring, MD: Food and Drug Administration; Apr 1, 2014. (http://jwat.ch/1gQruDZ)

Improving Six Risk Factors Could Delay 37 Million Deaths

By Kelly Young

Achieving global targets for six modifiable risk factors could delay or prevent roughly 37 million deaths over 15 years, according to a *Lancet* study.

Researchers used country data on mortality to estimate the effects of achieving the following targets:

1. Reducing prevalence of tobacco use by 30%
2. Reducing per-person alcohol consumption by 10%
3. Reducing mean population consumption of salt by 30%
4. Reducing prevalence of hypertension by 25%
5. Stopping the increase in diabetes prevalence
6. Stopping the increase in obesity prevalence

If all six targets are achieved by 2025, it could lead to a roughly 20% reduction in the probability of premature death (ages 30 to 70) from four noncommunicable diseases. The largest benefits, the authors write, would come from reducing tobacco use and blood pressure.

A commentator writes: "These are remarkable potential health gains in view of the highly cost-effective interventions available, which could be readily scaled up in all countries."

— Kelly Young,
Physician's First Watch

Kontis V et al. Contribution of six risk factors to achieving the 25×25 non-communicable disease mortality reduction target: a modelling study. Lancet 2014 May 3 [epub ahead of print]. (http://dx.doi.org/10.1016/S0140-6736(14)60616-4)

Atun R. Decisive action to end apathy and achieve 25×25 NCD targets. Lancet 2014 May 3 [epub ahead of print]. (http://dx.doi.org/10.1016/S0140-6736(14)60728-5)

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New Quality Measures for Distal Symmetric Neuropathy Care

How useful are new quality measures likely to be?

In a special article, a committee of experts reports American Academy of Neurology measures of quality of healthcare in distal symmetric polyneuropathy (DSP). The six measures came from a systematic review of the medical literature and a consensus process.

The authors note that "Measuring quality of health care is a central part of current concepts of health care plans and physician reimbursement." My paraphrase of these measures is as follows:

1. The percentage of DSP patients who had their specific signs and symptoms documented in the initial evaluation (The report lists specific symptoms and signs.),
2. The percentage who had electrodiagnostic studies "conducted, documented and reviewed" within 6 months of their evaluation,
3. The percentage who had been screened for diabetes mellitus (DM) and impaired glucose tolerance,
4. The percentage screened for abnormal alcohol use,
5. The percentage queried about pain, and
6. The percentage queried annually about number of falls.

COMMENT

These measures appear to be sensible and implementable. The following concerns should be considered. First, the emphasis is on retrospective rather than point-of-care surveillance. Second, the measures regarding evaluation and treatment are perhaps too narrowly focused on DM and alcoholism. The differential diagnosis of DSP should probably include other varieties of DSP: those caused by malnutrition and vitamin deficiency or infections (HIV and other), metabolic disorders (hypothyroidism, hepatic and kidney disease, amyloidosis, and other), industrial and medicinal toxins and other causes, as well as hereditary sensory and autonomic neuropathies (increasingly recognized as more frequent than generally appreciated), and neoplastic and paraneoplastic disorders. Also, patients with DM and alcoholism frequently have another cause for their DSP. Third, prevalence of causes of DSP are ever-changing, making it important that surveillance measures not be too rigid and unchanging. Fourth, regulatory rules should not inhibit development of better methods of assessment, differential diagnosis, and management. Therefore, although the present measures probably are useful, great care should be taken in how they are implemented and administered.

— Peter James Dyck, MD

Dr. Dyck reports that his laboratory receives support from ISIS, Inc., Alnylam, Inc. and Pfizer, Japan for quality assessment of abnormal neurological signs and nerve tests in transthyretin amyloid polyneuropathy.

England JD et al. Quality improvement in neurology: Distal symmetric polyneuropathy quality measures. **Neurology** *2014 May 13; 82:1745.*