

Formula Links HbA_{1c} to Average Plasma Glucose

BY MIRIAM E. TUCKER

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AMSTERDAM — Data from an international trial have yielded a formula that accurately converts hemoglobin A_{1c} values to an estimated average blood glucose.

The results of the A_{1c}-Derived Average Glucose (ADAG) study, comprising 4 months' worth of glucose data from 643 diabetic and nondiabetic subjects from 10 centers around the world, provided this

“simple, linear” equation to obtain glucose values in mmol/L: $(1.583 \times \text{HbA}_{1c}) - 2.52$. Thus, when multiplied by 18 to get the value in the American units mg/dL, a hemoglobin A_{1c} of 6% is converted to approximately 126 mg/dL, 7% is converted to 155 mg/dL, and 8% is converted to 182 mg/dL.

“The results are even better than we expected or could have hoped for. There's a linear correlation between the HbA_{1c} and the calculated mean glucose over a wide range of A_{1c} values. ... The results should apply to the majority of patients with diabetes,” study leader Dr. Robert Heine of Vrije University, Amsterdam, said at a press briefing held during the annual meeting of the European Association for the Study of Diabetes (EASD), where the study results were presented later that day at a special symposium.

No need to pull out your calculator for every diabetic patient, though. In August, a joint consensus statement from the EASD, the American Diabetes Association (ADA), the International Diabetes Federation, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the International Diabetes Federation advised that—pending the results from the ADAG study—clinical laboratories begin reporting both the HbA_{1c} percentage and the ADAG, along with a third number, the “true” HbA_{1c} value expressed in mmol/mol (Clin Chem. 2007;53:1562-4 and Diabetes Care 2007;30:2399-400).

Clinically, these developments provide an opportunity for physicians to begin shifting discussions with diabetic patients away from hemoglobin A_{1c} and toward average glucose, two representatives from the ADA said at the briefing. “The clinician has the choice to use one, two, or three values when communicating with the patient. The diabetes organizations would encourage physicians to use the estimated average glucose,” said Richard Kahn, Ph.D., ADA's chief scientific officer.

The reason, explained ADA president Dr. John Buse, is that “[The HbA_{1c}] has always been kind of confusing for patients. At home they measure their glucose, then

every 3 months they visit the doctor and get something that has the word ‘hemoglobin’ in it ... There's always been a disconnect.” In contrast, “The estimated average glucose is expressed in numbers that people are used to looking at all day every day,” said Dr. Buse, director of the Diabetes Care Center of the division of general medicine and clinical epidemiology at the University of North Carolina at Chapel Hill.

It's not yet clear what will happen with point-of-care HbA_{1c} machines that many physicians currently have in their offices, but it's likely that the manufacturers can provide some sort of simple software adjustment or Internet link that won't be excessively burdensome or costly, Dr. Kahn noted at the briefing.

The shift to ADAG was initially spurred by the 2002 IFCC publication of a new reference method that measures the concentration of only one molecular species of glycated hemoglobins (the A_{1c}), as opposed to the mixture that had previously been measured. Recognizing that the IFCC's adoption of the new reference method would cause confusion in the clinical setting, an international working group decided in 2004 to launch the ADAG study. Although there already were data that provided a rough estimate of average glucose from HbA_{1c}—and indeed, many labs currently report those numbers—they were generated from old studies using infrequent fingerstick monitoring. The ADAG study, in contrast, utilized both frequent fingerstick and continuous glucose monitoring (CGM) to gather “thousands of data points” in order to derive a precise average, Dr. Heine explained.

Dr. Judith Kuenen, who works with Dr. Heine at Vrije University, presented the study data at the symposium. The entire group of 643 patients was about half men and half women. Half had type 1 diabetes, 36% had type 2 diabetes, and the other 14% did not have diabetes. Three-fourths were

Caucasian. A total of 38% of participants, including all the nondiabetics, had hemoglobin A_{1c} values of 4%-6.5%. Another 44% had values between 6.6% and 8.5%, while 18% had HbA_{1c} levels about 8.5%.

A total of 427 patients had completed the study at the time of the meeting; the addition of the other 216 subjects is not expected to change the results. Of the 427 patients, 224 had type 1 diabetes and 125 had type 2 diabetes; the rest did not have diabetes. They had a mean age of 46 years; 53 were women, and 82% were white. (More minority subjects are among the other 216 patients who had not yet completed the study.) Approximately 2,400 CGM and 300 fingerstick glucose measurements were collected per subject, “an enormous amount of data,” Dr. Kuenen remarked.

Despite such frequent monitoring, HbA_{1c} levels remained stable in most patients during the course of the study, with only 4% showing improvement of more than 1 percentage point.

The study was supported by grants from several pharmaceutical and glucose monitoring device manufacturers. Among its limitations were the inclusion of only small numbers from various ethnic minority groups, and the lack of any data on children, pregnant women, or patients with renal impairment, Dr. Kuenen noted.

Independent commentator Dr. Philip Home, professor of diabetes medicine at the University of Newcastle-upon-Tyne (England), cautioned that it will take time to transition to using new numbers that don't correlate with a huge amount of published literature on data using the HbA_{1c} measurement to predict diabetes complications and other important clinical values. “The problem we have as a result of all this is that we have to re-standardize all our guidelines to align with this [ADAG], and that means a bit of re-education.”

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%); Anorgasmia (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=225 Lexapro; N=188 placebo). §Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 ADAG patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). **TABLE 3. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Lexapro (N=429) and Placebo (N=427)).** **Autonomic Nervous System Disorders:** Dry Mouth (3% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Parosmia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder[†] (14% and 2%); Anorgasmia[‡] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). §Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of \geq 5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4. Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125).** **Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%). *Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual performance. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). (In Females Only: Lexapro (N=737) and Placebo (N=636)):** Libido Decreased (3% and 1%); Anorgasmia (3% and <1%). There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligam has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. **Cardiovascular - Frequent:** palpitation, hypertension. **Infrequent:** bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. **Central and Peripheral Nervous System Disorders - Frequent:** light-headed feeling, migraine. **Infrequent:** tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased, gastrointestinal disorder. **Frequent:** heartburn, abdominal cramp, gastroenteritis. **Infrequent:** gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. **General - Frequent:** allergy, pain in limb, fever, hot flashes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Infrequent:** bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. **Metabolic and Nutritional Disorders - Frequent:** increased weight. **Infrequent:** decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. **Musculoskeletal System Disorders - Frequent:** arthralgia, myalgia. **Infrequent:** jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. **Psychiatric Disorders - Frequent:** appetite increased, lethargy, irritability, concentration impaired. **Infrequent:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. **Reproductive Disorders/Female* - Frequent:** menstrual cramps, menstrual disorder. **Infrequent:** menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. **N= 905 Respiratory System Disorders - Frequent:** bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. **Infrequent:** asthma, breath shortness, laryngitis, pneumonia, tracheitis. **Skin and Appendages Disorders - Frequent:** rash. **Infrequent:** pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodules. **Special Senses - Frequent:** vision blurred, linnitus. **Infrequent:** taste alteration, sarcoma, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. **Urinary System Disorders - Frequent:** urinary frequency, urinary tract infection. **Infrequent:** urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, chorea-thetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hyposaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.
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Carbs Often Undercounted by Diabetic Patients

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AMSTERDAM — Patients with type 1 diabetes often underestimate the amount of carbohydrates in their meals, Dr. Guido Freckmann reported at the annual meeting of the European Association for the Study of Diabetes.

The ability to accurately estimate the carbohydrate content is key to a patient's efficacy in making appropriate therapy decisions with insulin pump or basal-bolus insulin injection regimens. It is therefore of concern that underestimation by about 25% was typical in this study of 74 such patients, with warm meals and large meals presenting even greater potential for error, said Dr. Freckmann, of the Institute for Diabetes Technology in Ulm, Germany.

The study included 38 men and 36 women with a mean age of 44 years and mean diabetes duration of 21 years. Their mean hemoglobin A_{1c} level was 7.2%. Twenty-six were on multiple daily injections and 48 were on insulin pump therapy.

Patients were given 24 different test meals—11 warm and 13 cold—in random order, including 8 breakfasts, 8 lunches, and 8 dinners ranging in carbohydrate content from 55 g to 164 g. Among the meals were a breakfast of rye bread, roll, margarine, ham sausage, Camembert, and yogurt containing 82 g of carbohydrate; a pizza lunch including mozzarella, basil, olive oil, and fruit, adding up to 138 g of carbs; and a dinner of baguette, tomato, mozzarella, and olive oil totaling 101 g of carbs.

Patients estimated the carbohydrate content of the meals to be a median of 75%

compared with the actual content; estimates ranged from 53% to 127%. Warm meals prompted even more carb underestimation than cold (72% vs. 77%), and large meals were underestimated to a greater degree than were smaller meals, Dr. Freckmann reported.

Possible reasons include the fact that patients often don't count the carbs of vegetables and other low-carb items. It's also possible that some patients might compensate for the underestimation by adapting their individual insulin-to-carb ratio, thereby giving themselves sufficient insulin doses despite the carb underestimation, he said.

On the positive side, the degree of correct estimation was significantly improved—from 73% to 83%—among 35 patients who received training in carb counting.