OBSERVATIONS

Critical Evaluation of Models to Identify Individuals With Insulin Resistance

Clinical indexes of insulin resistance (IR) have acquired increasing importance with the development of various drugs that improve endogenous insulin action (1). Recently, the largest database on insulin clamp studies has been established. This database includes 2,321 subjects, of whom 2,138 are nondiabetic (92%), from 19 sites worldwide (2). Using classification trees, three models have been derived. Model 1 is based on homeostasis model assessment of insulin resistance (HOMA-IR) >4.65, BMI >28.9 kg/m^2, or HOMA-IR >3.60 and BMI >27.5 kg/m^2. Model 2 is based on BMI >28.7 kg/m^2, or BMI >27.0 kg/m^2 and a positive family history of diabetes. Model 3 is based on BMI >28.7 kg/m^2, BMI >27.0 kg/m^2 and a positive diabetes family history, or triglycerides >2.44 mmol/l and a negative family history of diabetes. These three models should all accurately identify insulin-resistant individuals (2). We have evaluated the prevalence and characteristics of subjects with IR based on these models using data from the KORA Survey 2000, an oral glucose tolerance test (OGTT)-based, population-based survey in Germany (n = 1,352 individuals aged 55–74 years without previously known diabetes) (3).

In the KORA Survey, proportions (95% CI) with IR were 47.4% (44.7–50.1), 45.8% (43.1–48.5), and 49.1% (46.4–51.8) for models 1, 2, and 3, respectively. Agreement of the models was high (κ coefficients 0.78–0.94). Although HOMA-IR significantly increased with worsening glucose tolerance (geometric means [SDF]: normal glucose tolerance 2.17 [1.83], impaired glucose tolerance [IGT] 3.39 [2.12], and newly diagnosed diabetes 4.67 [2.16]; all $P <$ 0.05), the sensitivities (0.67, 0.60, and 0.64 for models 1, 2, and 3, respectively) and specificities (0.60, 0.59, and 0.56) of the IR models for detecting IGT or diabetes were only moderate. Model 1 included HOMA-IR as a surrogate measure of IR. In multiple age-sex–adjusted logistic regression including all three models, model 1 (odds ratio 4.3, 95% CI 2.8–6.8) was more closely related to IGT/diabetes (dependent variable) than the others (model 2: 0.5, 0.2–1.1; model 3: 1.6, 0.7–3.4).

Overall, about one-third of the subjects with IGT or previously undiagnosed diabetes would not have been included when applying the proposed rules for identifying individuals with IR in our elderly population. This may indicate a limited diagnostic validity of the IR models, because a large body of evidence shows that IGT and type 2 diabetes are characterized by moderate-to-severe IR (4). On the other hand, defective insulin secretion rather than IR may be present in some subjects with IGT and type 2 diabetes (4). This could partly explain the low sensitivities of the models to detect glucose disorders in our population. In conclusion, the recently proposed IR models need to be further validated, using measures of β-cell function across the whole range of glucose intolerance, before they should be incorporated into clinical trials and clinical practice (2).

WOLFGANG RATHMANN, MD, MSPH[1]
BURKHARD HAASTERT, PHD[1]
GUIDO GIANI, PHD[1]
ROLF HOLLE, PHD[2]
WOLFGANG KOENIG, MD[3]
CHRISTIAN HERDER, PHD[4]
HANNELORE LÖWEL, MD[5]

From the [1]Institute of Biometrics and Epidemiology, German Diabetes Center, Leibniz Institute at the Heinrich-Heine-University, Düsseldorf, Germany; [2]GSF National Research Center for Environment and Health, Institute of Health Economics and Health Care Management, Neuherberg, Germany; [3]University of Ulm Medical Center, Ulm, Germany; [4]German Diabetes Clinic, German Diabetes Center, Leibniz Institute at the Heinrich-Heine-University, Düsseldorf, Germany; [5]GSF National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg, Germany.

Address correspondence to Dr. Wolfgang Rathmann, MSPH (USA), Institute of Biometrics and Epidemiology, German Diabetes Center, Auf'm Hennekamp 65 D-40225 Düsseldorf, Germany. E-mail: rathmann@ddz.uni-duesseldorf.de.

References

1. McAuley KA, Williams SM, Mann JI, Walker RJ, Lewis-Barned NJ, Temple LA, Duncan AW: Diagnosing insulin resistance in the general population. *Diabetes Care* 24:460–464, 2001
2. Stern SE, Williams K, Ferrannini E, DeFronzo RA, Bogardus C, Stern MP: Identification of individuals with insulin resistance using routine clinical measurements. *Diabetes* 54:333–339, 2005
3. Rathmann W, Haastert B, Icks A, Löwel H, Meisinger C, Holle R, Giani G: High prevalence of undiagnosed diabetes mellitus in southern Germany: target populations for efficient screening: the KORA Survey 2000. *Diabetologia* 46:182–189, 2003
4. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA: β-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab* 90:493–5 00, 2005

C-Reactive Protein for Cardiovascular Risk Assessment

Malik et al. (1) report on the usefulness of C-reactive protein (CRP) in stratifying risk in patients with the metabolic syndrome and diabetes.

Studies on normal volunteers showed intraindividual variability, which in ~50% of individuals was sufficient to change their CRP-related risk category (2).

Bogaty et al. (3) have also demonstrated what seems to be spontaneous fluctuation of CRP in stable patients with coronary artery disease (CAD).

Intraindividual biological variation data for high-sensitivity CRP (hsCRP) needs to be established for each individual before using the level to estimate risk and prognosis.

Reliance on single or even the mean of two measurements 2–4 weeks apart is clearly unacceptable, and there is conflict in the published literature regarding the number of samples that should be tested and the time span (3).

Many laboratories use conventional CRP assays, which report levels <5 mg/l as normal. These assays are obviously unsuitable for risk assessment, as it now seems that levels as low as 2 mg/l confer additional risk (3,4). Laboratories should be able to provide hsCRP assays for the purpose of cardiovascular risk stratification.

CRP seems to be an important player in the inflammatory component of atherosclerosis and an independent predic-

tor of adverse CAD outcomes (5,6). Adding it formally to risk stratification scoring methods would improve our ability to identify high-risk patients in both primary and secondary prevention. Before adopting this strategy, it is important to decide how many measurements should be checked, over what interval, and under what conditions.

Also, what weight should be given to the presence of an elevated CRP? Should it influence risk scores qualitatively, like diabetes, or quantitatively, like systolic blood pressure and cholesterol; the higher the level, the higher the risk? How should CRP level be incorporated into standard scoring systems such as the Framingham risk score?

Until these issues are addressed, CRP measurements should perhaps be reserved for problematic or borderline cases, where the decision to use an intervention, whether medical or procedural, is difficult.

MONA A. KHOLEIF, MD, FRCP, FESC

From the Department of Medicine, King Abdul Aziz Medical City, Jeddah, Kingdom of Saudi Arabia.

Address correspondence to Dr. Mona A. Kholeif, Consultant Cardiologist, Cardiology Section, Department of Medicine, King Abdul Aziz Medical City, P.O. Box 9515, Jeddah 21423, Kingdom of Saudi Arabia. E-mail: kholeifm@ngha.med.sa.

References

1. Malik S, Wong ND, Franklin S, Pio J, Fairchild C, Chen R: Cardiovascular disease in U.S. patients with metabolic syndrome, diabetes, and elevated C-reactive protein. *Diabetes Care* 28:690–693, 2005
2. de Maat MPM, de Bart ACW, Hennis BC, Meijer P, Havelaar AC, Mulder PG, Kluft C: Interindividual and intraindividual variability in plasma fibrinogen, TPA antigen, PAI activity, and CRP in healthy, young volunteers and patients with angina pectoris. *Arterioscler Thromb Vasc Biol* 16:1156–1162, 1996
3. Bogaty P, Brophy JM, Boyer L, Simard S, Joseph L, Bertrand F, Dagenais GR: Fluctuating inflammatory markers in patients with stable ischemic heart disease. *Arch Intern Med* 165:221–226, 2005
4. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E, for the Pravastatin or Atorvastatin Evaluation and Infection Therapy –Thrombolysis in Myocardial Infarction 22 (PROVE IT –TIMI 22) Investigators: C-Reactive protein levels and outcomes after statin therapy. *N Engl J Med* 352:20–28, 2005
5. Danesh J, Pepys MB: C-reactive protein in healthy and in sick populations. *Eur Heart J* 21:1564–1565, 2000
6. Ehrenstein MR, Jury EC, Mauri C: Statins for atherosclerosis: as good as it gets? *N Engl J Med* 352:73–75, 2005

Age and A1C Are Important Clinical Predictors of Continuous Subcutaneous Insulin Infusion Efficacy in Type 1 Diabetic Patients

Only a few studies have reported a long-term follow-up in a significant number of patients using continuous subcutaneous insulin infusion (CSII) (1). Who stands to benefit more from this costly insulin therapy is still unclear.

The aim of our observational, retrospective study was to evaluate the possible predictors of the degree of improvement of metabolic control with CSII in 82 consecutive type 1 diabetic patients (age 37.9 ± 13.4 years, 42 men and 40 women, duration of diabetes 19.7 ± 9.9 years) who started CSII in the Diabetes Unit of Bergamo Hospital between June 1999 and March 2004.

The patients had been treated with multiple daily injection (MDI) therapy (regular [$n = 22$] or rapid-acting analog insulin [$n = 60$] before meals plus NPH [$n = 72$] or glargine [$n = 10$] as basal insulin) for at least 1 year. During CSII treatment, lispro or aspart analogs were used.

All patients were evaluated every 3 months both before and during CSII. The mean duration of CSII treatment was 31.9 ± 14.5 months (range 4–55).

Only three patients discontinued CSII. Every patient performed self-monitoring of blood glucose (SMBG) (four to seven daily determinations).

Data are expressed as means ± SD. The means of parametric data of the period of MDI treatment were compared with those of the CSII period using the Student's *t* test for paired data. The differences between groups were compared using the Student's *t* test for unpaired data.

Compared with MDI therapy, HbA_{1c} (A1C) significantly decreased with 3 months of CSII therapy (CSII vs. MDI: 8.35 ± 1.06 vs. 9.39 ± 1.35%, $P < 0.001$). The significant decrease of A1C was maintained over the whole CSII treatment with a mean change in A1C of 1.15 ± 0.84% ($P < 0.001$).

During CSII treatment, as compared with MDI treatment, there was a significant decrease of severe hypoglycemic episodes (0.35 ± 0.07 per patient/year during MDIs vs. 0.10 ± 0.02 during CSII, $P < 0.001$) and insulin requirement (52.1 ± 17.5 units/day vs. 38.8 ± 12.3, $P < 0.001$). CSII was not associated with any significant increase in BMI. Incidence of ketoacidosis was negligible during both MDI and CSII treatment.

To evaluate the possible predictors of CSII effect on A1C changes, multiple linear regression analysis performed on all patients revealed that age ($\beta = 0.16$, $P = 0.05$) and baseline A1C ($\beta = 0.21$, $P = 0.008$) were independently associated with A1C improvement after 3 months of CSII ($F = 5.41$, adjusted $R^2 = 0.28$). BMI, diabetes duration, insulin requirement, and frequency of SMBG were unrelated to A1C changes. Age and baseline A1C were even better predictors of the mean A1C changes during the whole follow-up period ($F = 11.87$, adjusted $R^2 = 0.48$).

This observational, clinic-based study of a significant number of type 1 diabetic patients who represent all pump-treated patients in the province of Bergamo, Italy, confirmed that CSII significantly decreased A1C levels with respect to MDIs, as reported in a recent meta-analysis of 52 CSII studies (2). The reduction of severe hypoglycemic episodes and the concomitant negligible frequency of ketaoacidosis confirmed the safety of CSII (3–4).

Although most of our patients during MDI treatment used rapid-acting analogs, only a few used glargine as basal insulin. It is possible that the extensive use of this long-term analog during MDI treatment would reduce the difference in metabolic control, as suggested (5).

There are discordant data about the persistence of initial lowering of A1C achieved with CSII (6). Our data showed that improved glucose control persisted during the whole long-term follow-up period, which was longer (mean duration 2.6 years) than most CSII studies.

Most important, our study demonstrated that CSII was particularly advan-

tageous in patients with the poorest metabolic control, as suggested by a randomized controlled trial that compared CSII and MDI treatments using a rapid-acting analog (7). In our population, those with a baseline A1C >10% ($n = 25$) had an average decline in A1C of 1.5 ± 0.6%, significantly greater ($P < 0.001$) than that observed in those with a baseline value <8% ($n = 16$; average decline 0.6 ± 0.5%).

CSII was also more advantageous in patients older than 50 years ($n = 14$; average A1C decline 1.45 ± 0.7%) than in those younger than 20 years ($n = 11$; average A1C decline 0.5 ± 0.8%; $P < 0.01$). A similar observation suggested that CSII is useful and safe in older adults with type 1 diabetes (8).

In conclusion, we suggest that in type 1 diabetic patients who have sufficient ability to master CSII therapy, a poor metabolic control, despite MDI therapy, and older age are better predictors of CSII efficacy.

GIUSEPPE LEPORE, MD
ALESSANDRO R. DODESINI, MD
ITALO NOSARI, MD
ROBERTO TREVISAN, MD, PHD

From the Diabetes Unit, Ospedali Riuniti Bergamo, Bergamo, Italy.

Address correspondence to Dr. Giuseppe Lepore, U.O. Diabetologia, Ospedali Riuniti di Bergamo, Largo Barozzi, 1, 24128 Bergamo, Italy. E-mail: glepore@ospedaliriuniti.bergamo.it.

References

1. Linkeshova R, Raoul M, Bott U, Berger M, Spraul M: Less severe hypoglycaemia, better metabolic control, and improved quality of life in type 1 diabetes mellitus with continuous subcutaneous insulin infusion (CSII) therapy: an observational study of 100 consecutive patients followed for a mean of 2 years. *Diabet Med* 19:746–751, 2002
2. Pickup J, Keen H: Continuous subcutaneous insulin infusion at 25 years. *Diabetes Care* 25:593–598, 2002
3. Bode BW, Steed RD, Davidson PC: Reduction in severe hypoglycaemia with long-term continuous subcutaneous insulin infusion in type 1 diabetes. *Diabetes Care* 19:324–327, 1996
4. Boland EA, Grey M, Osterle A, Fredrickson L, Tamborlane W: Continuous subcutaneous insulin infusion: a new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 22:1779–1784, 1999
5. Lepore G, Dodesini AR, Nosari I, Trevisan R: Both continuous insulin infusion and a multiple daily insulin injection regimen with glargine as basal insulin are equally better than traditional multiple daily insulin injection treatment (Letter). *Diabetes Care* 26:1321–1322, 2003
6. Plotnick LP, Clark LM, Brancati FL, Erlinger T: Safety and effectiveness of insulin pump therapy in children and adolescents with type 1 diabetes. *Diabetes Care* 26:1142–1146, 2003
7. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ: A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. *Diabetes Care* 25:2074–2080, 2002
8. Siegel-Czarkowski L, Herold KC, Goland RS: Continuous subcutaneous insulin infusion in older patients with type 1 diabetes (Letter). *Diabetes Care* 27:3022–3023, 2004

Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections

Modeling predicted benefits in relationship to baseline A1c

With either continuous subcutaneous insulin infusion (CSII) or multiple daily insulin injection (MDII) therapy, the optimal meal insulin is a rapid-acting analog (lispro or aspart). To date, the efficacy of CSII versus MDII therapy has been evaluated in a limited number of randomized controlled trials in which rapid-acting analogs were used for both regimens. In this context, we recently conducted a pooled analysis (1) using raw trial data from three such studies undertaken in adults with type 1 diabetes (2–4). This analysis suggested that CSII is associated with better glycemic control, particularly in those patients with poor initial control. Indeed, the relative benefit of CSII over MDII was found to increase with higher baseline A1c. To provide direct clinical context, we have now reanalyzed this data to evaluate the impact of CSII and MDII in relation to specific baseline A1c categories using the pooled dataset (139 patients representing 529 patient-months on MDII and 596 patient-months on CSII).

Treatment effect on A1c was studied using a mixed linear modeling approach (MIXED procedure in SAS 9.1.3), with an isotropic exponential spatial covariance structure used to model intrasubject correlation of the repeated measurements and random effects used to model patient, patient*treatment, study, and study*month effects. All fixed and random effects were initially allowed to differ between studies, with the Akaike Information Criterion (AIC) approach used to reduce model complexity. Fixed effects in the final model included the following: *1*) baseline A1c, *2*) treatment modality, and *3*) the interaction between baseline A1c and treatment effect.

These models predicted that, with both MDII and CSII, the reduction in A1c will progressively increase as baseline A1c rises (Fig. 1). Importantly, however, CSII

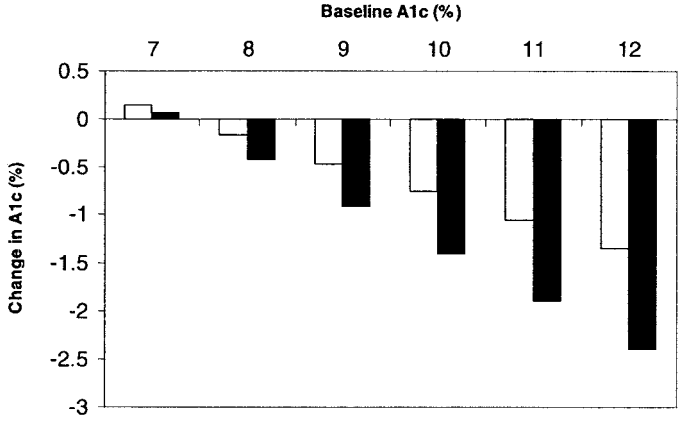

Figure 1—*The predicted relative benefit of CSII over MDII in lowering A1c increases as baseline A1c rises.* □, *MDII;* ■, *CSII.*

is predicted to achieve a greater reduction in A1c at each level of initial glycemia. Moreover, the relative benefit of CSII over MDII in lowering A1c (i.e., difference in treatment effect between the two modalities) increases as baseline A1c rises. Indeed, for a patient with an A1c of 12%, CSII would be expected to reduce A1c by a full 1% more than MDII.

In summary, this analysis extends our earlier work by providing a quantitative estimate of the anticipated reduction in A1c associated with CSII and MDII therapy, respectively, in relation to baseline A1c. Importantly, the relative benefit of CSII over MDII in lowering A1c increases as baseline A1c rises. This analysis has significant clinical implications in that *1*) it provides an anticipated response to intensive insulin regimens in adults with type 1 diabetes, and *2*) it highlights the importance of baseline glycemic control as a factor to consider when choosing between CSII and MDII therapy.

It should be noted that NPH insulin provided basal replacement in MDII therapy in the current analysis. Given the superior basal pharmacokinetics of long-acting analogs, future clinical trial comparison between CSII and MDII using both rapid- and long-acting analogs will be of great interest. Based on the current findings, comparison of these treatment modalities across a broad range of baseline glycemic control would be particularly relevant.

Ravi Retnakaran, MD[1,2]
J. Hans DeVries, MD[3]
Helene Hanaire-Broutin, MD[4]
Robert J. Heine, MD, PhD[5]
Vincent Melki, MD[4]
Bernard Zinman, MD[1,2]

From the [1]Division of Endocrinology, University of Toronto, Toronto, Ontario, Canada; [2]Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Ontario, Canada; the [3]Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands; [4]Service de Diabetologie, Hospital de Rangueil, CHU de Toulouse, Toulouse, France; and the [5]Department of Endocrinology, Diabetes Center, VU University Medical Center, Amsterdam, the Netherlands.

Address correspondence to Dr. Bernard Zinman, Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Lebovic Building, 5th Floor, Room L5-024, 600 University Ave., Toronto, ON, Canada, M5G 1X5. E-mail: zinman@mshri.on.ca.

R.J.H. is a member of an advisory board for Novo Nordisk, Denmark. B.Z. has received consulting fees from Smiths Medical Canada.

References

1. Retnakaran R, Hochman J, DeVries JH, Hanaire-Broutin H, Heine RJ, Melki V, Zinman B: Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. *Diabetes Care* 27:2590–2596, 2004
2. DeVries JH, Snoek FJ, Kostense PJ, Masurel N, Heine RJ: A randomized trial of continuous subcutaneous insulin infusion and intensive injection therapy in type 1 diabetes for patients with long-standing poor glycemic control. *Diabetes Care* 25:2074–2080, 2002
3. Tsui E, Barnie A, Ross S, Parkes R, Zinman B: Intensive insulin therapy with insulin lispro: a randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. *Diabetes Care* 24:1722–1727, 2001
4. Hanaire-Broutin H, Melki V, Bessieres-Lacombe S, Tauber JP: Comparison of continuous subcutaneous insulin infusion and multiple daily injection regimens using insulin lispro in type 1 diabetic patients on intensified treatment: a randomized study. *Diabetes Care* 23:1232–1235, 2000

The Effect of Blood Sample Volume on 11 Glucose Monitoring Systems

The effect of variable blood sample volume on the accuracy of 11 glucose meters was studied to verify the reliability of self-monitoring of blood glucose. A total of 11 meters were assessed: OneTouch FastTake, OneTouch Basic, OneTouch Profile, and SureStep (LifeScan Canada, Burnaby, B.C., Canada); AccuSoft Advantage and AccuSoft Manager (Roche, Hoffman-LaRoche, Laval, P.Q., Canada); Precision Pen and Precision QID (MediSense Canada, Mississauga, ON, Canada); and Glucometer Elite, Glucometer Elite XL, and Glucometer DEX (Bayer, Toronto, ON, Canada). Venous blood collected from 16 fasting patients with diabetes was used to test each meter brand in triplicate. Sample volumes tested were of 1, 2, 3, 4, 5, 10, and 20 μl. Each patient contributed to the 5-μl sample plus two other sample volumes. The 5-μl volume, which is the usual volume required by the manufacturer of most meters, was considered the reference for comparison with other volumes tested, thus excluding the confounding effects of hematocrit, humidity, hypotension, and hypoxia. Several replicates of each volume size were tested. The number of times meters gave no result or an error message was recorded. Results were then calculated as percentages of the reference value and considered accurate if within 20% of the reference, as recommended by the Food and Drug Administration/National Committee for Clinical Laboratory Standards (1). It has been recognized that most current meters do not comply with the 5% accuracy recommended by the American Diabetes Association (2–4).

All meters gave mostly nonmisleading

Table 1—*Meter brands ranked by performance as estimated by Somers' d statistic*

Meter brand	Percentage of misleading results at 2 μl* (*n*/*N*)†	Percentage of misleading results at 1 μl (*n*/*N*)†	Somers' *d* statistic‡
Precision QID	0 (0/14)	0 (0/12)	−0.01
Precision Pen	7 (1/14)	0 (0/10)	0.02
AccuSoft Advantage	13 (2/16)	0 (0/16)	0.03
AccuSoft Manager	13 (2/16)	6 (1/16)	0.05
Glucometer Elite	0 (0/16)	31 (5/16)	0.13
SureStep	11 (2/18)	44 (8/18)	0.14
Elite XL	19 (3/16)	25 (4/16)	0.14
OneTouch Profile	75 (12/16)	6 (1/16)	0.17
Glucometer DEX	69 (11/16)	19 (3/16)	0.20
OneTouch Basic	81 (13/16)	19 (3/16)	0.22
OneTouch FastTake	22 (4/18)	44 (8/18)	0.22

*Results >20% from the reference value. †Number of misleading results divided by the number of samples tested. ‡Measures the degree to which more blood volume decreases the chance of a misleading result. Calculation is based on all volumes tested (1, 2, 3, 4, 5, 10, and 20 μl).

results (accurate result or error message) at the 3-μl volume or above. However, below the 3-μl volume, most meters gave misleading results (Table 1). At the 1-μl volume, the mean calculated as a percentage from the 5-μl reference volume varied between 40 and 68%. OneTouch Basic and FastTake were the most likely to give a misleading result for a smaller blood volume as shown by Somers' *d* statistic. Only four meters were reliable at all volumes showing no association with the Jonckheere tests: Precision QID, Precision Pen, AccuSoft Advantage, and AccuSoft Manager (data not shown).

Our results confirm that insufficient blood sample volume remains potentially a major source of user error with many of the current meters, including those with built-in detection of insufficient blood sample. Inaccurate results underestimated the real glucose value. Patients should be aware of this phenomenon since falsely low readings may result in unnecessary treatment of hypoglycemia and weight gain.

ZEINA YARED, MD[1,2]
KHALED ALJABERI, MD[1,2]
NANCY RENOUF[1,2]
JEAN-FRANÇOIS YALE, MD[1,2]

From the [1]Royal Victoria Hospital Metabolic Day Centre, McGill University, Montreal, Quebec, Canada; and the [2]McGill Nutrition Centre, Royal Victoria Hospital, MUHC, McGill University, Montreal, Quebec, Canada.

Address correspondence and reprint requests to Dr. Jean-François Yale, MD, McGill Nutrition Centre, Royal Victoria Hospital, 687 Pine Ave. West, Montreal, Quebec, Canada, H3A 1A1. E-mail: jean-francois.yale@mcgill.ca.

References

1. Chen ET, Nichols JH, Show-Hong D, Hortin G: Performance evaluation of blood glucose monitoring devices. *Diabetes Technol Ther* 5:749–768, 2003
2. Böhme P, Floriot M, Sirveaux MA, Durain D, Ziegler O, Drouin P, Guerci B: Evolution of analytical performance in portable glucose meters in the last decade. *Diabetes Care* 26:1170–1175, 2003
3. Trajanoski Z, Brunner GA, Gfrerer RJ, Wach P, Pieber TR: Accuracy of home blood glucose meters during hypoglycemia. *Diabetes Care* 19:1412–1415, 1996
4. American Diabetes Association: Standards of medical care in diabetes. *Diabetes Care* 27 (Suppl. 1):S15–S35, 2004

Anticraving Effects of Topiramate in a Diabetic Patient

Topiramate is an effective antiepileptic medication. It holds promise in the care of diabetic patients by virtue of its effect on weight loss (1). It is also reported efficacious as an adjunct in the treatment of alcohol dependence (2) and in the management of binge-eating disorder (3). We report a case illustrating the potential anticraving effects of topiramate against chocolate, leading to significantly improved glycemic control in an epileptic patient with concurrent diabetes.

A 67-year-old woman presented to the epilepsy clinic in September 2003 for evaluation of "possible seizures" and was subsequently treated with topiramate. She also had an 11-year history of poorly controlled diabetes and was a recovered alcoholic for 30 years. Medications included levothyroxine, repaglinide, acetylsalicylic acid, and atorvastatin. General examination was remarkable for an obese woman with clinical features of hypothyroidism. She weighed 194 pounds, and neurological examination was significant for symmetrical peripheral neuropathy. Subsequent follow-ups were remarkable for a moderate improvement in seizure control, a total of 34 pounds weight loss, and significant amelioration of her diabetes. She ascribed the improved glycemic control to her recent aversion to chocolates and sweets, which she claimed had occurred since starting the topiramate.

Initial blood work was remarkable for a fasting blood glucose of 14.3 mmol/l (normal 3.3–6.0 mmol/l) and HbA_{1c} (A1C) of 8.9% (normal 4.3–6.1%). Eight months after starting the topiramate, her fasting blood glucose was 6.1 mmol/l, and A1C dropped from 8.9 to 6.1%. We checked fasting blood glucose and A1C every 3–4 months after initiating the topiramate. Average fasting blood glucose and A1C before introduction of topiramate were 10.2 mmol/l and 8.4%, and 8 months later were 8.7 mmol/l and 6.7%, respectively. The dosage of repaglinide was unchanged over the last 2 years. The patient reported a significant aversion to chocolate after starting the topiramate.

Topiramate is one of the preferred agents in obese epileptic patients, and this was one of the reasons for prescribing this agent to our patient. The 34-pound weight loss was most likely related to the use of topiramate. Our patient reported a very strong craving for chocolate in previous years, which together with her obesity was apparently responsible for her poor glycemic control. Topiramate is known to cause weight loss in 15–20% of patients, but the precise mechanism is unknown. There is a possibility that the anticraving effect may in part be responsible for the weight loss.

Topiramate is known to be efficacious as an adjunct treatment for alcohol dependence and in the treatment of binge-eating disorder. The proposed mechanism is facilitation of γ-amino-butyric acid activity and inhibition of glutamate function in the mesocorticolimbic dopamine pathways (2). Similar mechanisms may be responsible for the anticraving effects noted in our patient. Dietary noncompliance can adversely affect glycemic control. Although some patients are aware of this fact, they are unable to avert this craving without pharmacological support, thus leading to failure of oral hypoglycemic agents. By virtue of its potential to cause weight loss, topiramate deserves consideration when treating diabetic patients with epilepsy. Our case illustrates the possibility of another potential mechanism, its anticraving effect, which would support topiramate as a useful adjuvant in the treatment of diabetes.

SYED NIZAMUDDIN AHMED, MD, FRCPC[1]
YASMIN RASHID, MD[2]

From the [1]Division of Neurology, University of Alberta Hospital, Edmonton, Alberta, Canada; and the [2]All Well Primary Care Centre, Edmonton, Alberta, Canada.

Address correspondence to S. Nizam Ahmed, MD, FRCPC, 2E3.12. University of Alberta Hospital, Edmonton, AB T6G 2B7, Canada. E-mail: snahmed@ualberta.ca.

References

1. Astrup A, Toubro S: Topiramate: a new potential pharmacological treatment for obesity (Review). *Obes Res* 12:167S–173S, 2004
2. Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ: Oral topiramate for treatment of alcohol dependence: a randomized controlled trial. *Lancet* 361: 1677–1685, 2003
3. Shapira NA, Goldsmith TD, McElroy SL: Treatment of binge-eating disorder with

topiramate: a clinical case series. *J Clin Psychiatry* 61:368–372, 2000

COMMENTS AND RESPONSES

Diabetes Is the Main Factor Accounting for the High Ferritin Levels Detected in Chronic Hepatitis C Virus Infection

Response to Lecube et al.

We read with interest the article by Lecube et al. (1) regarding the strong association they observed between diabetes and serum ferritin in chronic hepatitis C. We sought to analyze the contribution of biochemical, metabolic, and histological parameters to high ferritin levels detected in hepatitis C.

We investigated a large consecutive series of 177 patients with chronic hepatitis C who underwent a diagnostic liver biopsy. Serum ferritin was tested in a univariate analysis against demographics, biochemical parameters, and histological features. Patients with cirrhosis or with any alcohol intake were excluded. The median age of the patients was 48.4 years (range 19–71) and 97 (54.8%) were men. Using the same cutoff values of Lecube et al., serum ferritin was raised in 92 cases (52.0%). The prevalence of impaired glucose tolerance or diabetes was 9.6% (17 cases) in our series. Overall, 66 patients (37.3%) had mild fibrosis (F0–F1) and 111 patients (62.7%) had moderate to severe fibrosis (F2–F3) according to METAVIR. Hepatic iron deposits were found in 68 patients (38.4%). Hepatic steatosis was detected in 132 patients (74.6%). Serum ferritin correlated by univariate analysis with male sex ($P = 0.05$), BMI ($P = 0.0001$), aspartate aminotransferase and alanine aminotransferase levels ($P = 0.003$ and $P = 0.0009$, respectively), γ-glutamyl transferase levels ($P < 0.00001$), hepatic iron ($P < 0.00001$), and hepatic steatosis ($P = 0.01$). No correlation between serum ferritin and fasting glucose could be observed. Moreover, no significant difference in serum ferritin was observed in patients with impaired glucose tolerance or diabetes in comparison with other patients.

The following considerations arise from the comparison of our data with those reported by Lecube et al. First, mean serum ferritin in our study was much higher than that observed by Lecube et al. even if we excluded cirrhosis and alcohol consumption. Second, prevalence of diabetes was much higher (21.7%) in the Spanish series compared with our own cohort, probably because Lecube et al.'s study was conducted in a tertiary reference center for both diabetes and hepatitis C. Third, we did not observe any association between raised serum ferritin and diabetes. In chronic hepatitis C there are many conditions that could elevate serum ferritin such as necroinflammation, steatosis, and hepatic iron deposition (2). In our series, we found an association with metabolic factors and with markers of inflammation. On the other hand, there was also a strong association with proper hepatic iron deposition.

We can therefore conclude that the increase of serum ferritin in chronic hepatitis C could be linked to diabetes, as Lecube et al. have clearly suggested, but the pathogenesis is multifactorial. The weight of different determinant factors on the elevation of ferritin depends on their prevalence in the analyzed series of patients.

GIADA SEBASTIANI, MD
ALESSANDRO VARIO, MD
ALFREDO ALBERTI, MD

From the Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy.

Address correspondence to Prof. Alfredo Alberti, MD, Department of Clinical and Experimental Medicine, University of Padova, Via Giustiniani 2, 35100 Padova, Italy. E-mail: alfredo.alberti@unipd.it.

References

1. Lecube A, Hernández C, Genescà J, Esteban JI, Jardí R, García L, Simó R: Diabetes is the main factor accounting for the high ferritin levels detected in chronic hepatitis C virus infection. *Diabetes Care* 27:2669–2675, 2004
2. Metwally MA, Zein CO, Zein NN: Clinical significance of hepatic iron deposition and serum iron values in patients with chronic hepatitis C infection. *Am J Gastroenterol* 99:286–291, 2004

Diabetes Is the Main Factor Accounting for the High Ferritin Levels Detected in Chronic Hepatitis C Virus Infection

Response to Sebastiani et al.

After reading the comments by Sebastiani et al. (1) on our article (2) regarding the association between diabetes and ferritin in chronic hepatitis C virus (HCV) infection, we would like to make the following comments. In contrast to our results, the authors did not find any relationship between serum ferritin levels and glucose abnormalities in HCV-infected patients. However, it should be noted that the number of patients included in our study was much larger and, thereby, a statistical multivariate analysis considering sex (a major confounding factor) could be performed. In addition, because in our study a group of diabetic patients without HCV infection and a group of anti–HCV-negative nondiabetic control subjects were analyzed, we were able to conclude that the increase in ferritin levels detected in HCV patients was closely related to the presence of diabetes (2). Another concern of Sebastiani et al. is the high prevalence of diabetes in our population (21.7%). Although some influence could be attributed to the tertiary reference center setting of our study, it is more important to note that the HCV-infected patients included in our study were ~10 years older that those reported by Sebastiani et al. In addition, our results agree with a previous study by our group that specifically addressed this issue (3). Concerning the higher serum ferritin levels detected in Sebastiani et al.'s population, it should be emphasized that most of the patients included in their study appear to have been in more advanced stages of chronic hepatitis than those in our study. Moreover, we are unaware whether they had ruled out hemochromatosis. Finally, we did not deny that there are other factors apart from diabetes accounting for the high serum ferritin levels detected in HCV-infected patients. In fact, the relationship between alanine aminotransferase and serum ferritin levels

observed by Sebastiani et al. in univariate analysis was also observed by us in a multiple regression analysis (2). However, in light of our results, it would appear that diabetes is not only associated with higher serum ferritin levels but also is a significant factor accounting for the higher ferritin levels detected in HCV-infected patients.

ALBERT LECUBE, MD[1]
CRISTINA HERNÁNDEZ, MD[1]
JOAN GENESCÀ, MD[2]
RAFAEL SIMÓ, MD[1]

From the [1]Diabetes Research Unit, Endocrinology Division, Hospital Universitari Vall d'Hebron, Barcelona, Spain; and the [2]Liver Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain.

Address correspondence to Dr. Rafael Simó, Diabetes Research Unit, Endocrinology Division, Hospital General Vall d'Hebron, Pg. Vall d'Hebron 119-129, 08035 Barcelona, Spain. E-mail: rsimo@vhebron.net.

References

1. Sebastiani G, Vario A, Alberti A: Diabetes is the main factor accounting for the high ferritin levels detected in chronic hepatitis C virus infection (Letter). *Diabetes Care* 28:1838, 2005
2. Lecube A, Hernández C, Genescà J, Esteban JI, Jardí R, García L, Simó R: Diabetes is the main factor accounting for the high ferritin levels detected in chronic hepatitis C virus infection. *Diabetes Care* 27:2669–2675, 2004
3. Lecube A, Hernández C, Genescà J, Esteban JI, Jardí R, Simó R: High prevalence of glucose abnormalities in patients with hepatitis C virus infection: a multivariate analysis considering the liver injury. *Diabetes Care* 27:1171–1175, 2004

Glycemic Index, Glycemic Load, and Glycemic Response Are Not the Same

The paper by Hodge et al. (1) published in the November 2004 issue of *Diabetes Care* aptly contrasts the potential benefits of moderately high-carbohydrate diets with a low glycemic index (GI) versus diets that have a lower glycemic load (GL) by virtue of a low carbohydrate content. In their prospective analysis of a cohort of ~36,000 adults followed for 4 years, Hodge et. al found that higher-carbohydrate diets were associated with a lower risk of development of type 2 diabetes. However, the type of carbohydrate was equally important: low-GI carbohydrates reduced the risk, while high-GI carbohydrates increased the risk. Thus, low GI and low GL are not equivalent and produce different clinical outcomes.

Because this issue may be confusing to some readers, it is important to clarify the difference between GI and GL. Both the quality and quantity of carbohydrate determines an individual's glycemic response to a food or meal (2). By definition, the GI compares equal quantities of available carbohydrate in foods and provides a measure of carbohydrate quality. Available carbohydrate can be calculated by summing the quantity of available sugars, starch, oligosaccharides, and maltodextrins. As defined (3), the GL is the product of a food's GI and its total available carbohydrate content: glycemic load = [GI × carbohydrate (g)]/100.

Therefore, the GL provides a summary measure of the relative glycemic impact of a "typical" serving of the food. Foods with a GL ≤10 have been classified as low GL, and those with a value ≥20 as high GL (4). In healthy individuals, stepwise increases in GL have been shown to predict stepwise elevations in postprandial blood glucose and/or insulin levels (5).

It can be seen from the equation that either a low-GI/high-carbohydrate food or a high-GI/low-carbohydrate food can have the same GL. However, while the effects on postprandial glycemia may be similar, there is evidence that the two approaches will have very different metabolic effects, including differences in β-cell function (6), triglyceride concentrations (7), free fatty acid levels (7), and effects on satiety (8). Hence, the distinction has important implications for the prevention and management of diabetes and cardiovascular disease. Our concern is that the use of the GL or "glycemic response" in isolation may lead to the habitual consumption of lower-carbohydrate diets.

The simplest way to consume a moderately high-carbohydrate, but low-GI diet is to follow the new 2005 Dietary Guidelines for Americans (9) and to incorporate the recommendations of the World Health Organization/Food and Agriculture Organization (10); that is, the GI should be used to compare foods of similar composition within food groups. By choosing the lower-GI options within a food category (breads, breakfast cereals, etc.), an individual automatically chooses those with a lower GL. Because most fruit and vegetables, other than potatoes, are not major contributors to carbohydrate intake, their GI should not be the basis for restriction.

The important message for clinicians, nutritionists, and food industry professionals is that the evidence, as it stands, suggests that for preventing type 2 diabetes, we ought to encourage low-GI carbohydrate foods but not those that simply have low "net carbs," low GL, or produce a low glycemic response.

ALAN W. BARCLAY, BSC, GRADDIPDIET,[1]
JENNIE C. BRAND-MILLER, PHD[1]
THOMAS M.S. WOLEVER, MD, PHD[2]

From the [1]School of Molecular and Microbial Biosciences, University of Sydney, Sydney, Australia; and the [2]Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to Alan Barclay, Diabetes Australia, GPO Box 9824, Sydney, NSW, 2001, Australia. E-mail: awbarclay@optusnet.com.au.

T.M.S.W. is president of the Board of Directors of, holds stock in, and has received grant/research support from G.I. Testing. T.M.S.W. also holds stock in G.I. Laboratories.

References

1. Hodge AM, English DR, O'Dea K, Giles GG: Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diabetes Care* 27:2701–2706, 2004
2. Sheard NF, Clark NG, Brand-Miller JC, Franz MJ, Pi-Sunyer FX, Mayer-Davis E, Kulkarni K, Geil P: Dietary carbohydrate (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association. *Diabetes Care* 27:2266–2271, 2004
3. Salmeron J, Manson JAE, Stampfer MJ, Colditz GA, Wing AL, Jenkins DJ, Wing AL, Willett WC: Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* 277: 472–477, 1997
4. Brand-Miller JC, Holt SHA, Petocz P: Reply to R. Mendosa. *Am J Clin Nutr* 77: 994–995, 2003
5. Brand-Miller JC, Thomas M, Swan V, Ahmad ZI, Petocz P, Colagiuri S: Physiological validation of the concept of glycemic load in lean young adults. *J Nutr* 133:2728–2732, 2003
6. Wolever TMS, Mehling C: High-carbohydrate/low-glycaemic index dietary advice

improves glucose disposition index in subjects with impaired glucose tolerance. *Br J Nutr* 87:477–487, 2002
7. Wolever TMS, Mehling C: Long-term effect of varying the source or amount of dietary carbohydrate on postprandial plasma glucose, insulin, triacylglycerol, and free fatty acid concentrations in subjects with impaired glucose tolerance. *Am J Clin Nutr* 76:5–56, 2002
8. Ball SD, Keller KR, Moyer-Mileur LJ, Ding YW, Donaldson D, Jackson WD: Prolongation of satiety after low versus moderately high glycemic index meals in obese adolescents. *Pediatrics* 111:488–494, 2003
9. Dietary Guidelines for Americans 2005 [article online]. Department of Health and Human Services and the U.S. Department of Agriculture. Available from www.healthierus.gov/dietaryguidelines. Accessed 16 January 2005
10. Food and Agriculture Organization/World Health Organization: Carbohydrates in human nutrition: report of a Joint FAO/WHO expert consultation. *FAO Food and Nutrition Paper* 66:1–140, 1998

α-Glucosidase Inhibitors for Patients With Type 2 Diabetes

Response to van de Laar et al.

The authors of the Cochrane systematic review carefully analyzed all available studies that fulfilled the criteria of randomized clinical trials of at least 12 weeks' duration (1). With the exception of one study (2), all registered mortality and morbidity as secondary objectives. Glycemic control was the primary objective in 40 of 41 of these trials. Thus, the major legitimate conclusion of this careful analysis was that "AGIs [α-glucosidase inhibitors] have clear beneficial effects on glycemic control" mainly through their dose-dependent effect on postprandial hyperglycemia.

However, the authors also state as one of their main conclusions that they "found no evidence for an effect on mortality or morbidity." Although this statement may be mathematically correct, it is misleading as it purports to be based on a solid analysis of the data from the 41 studies. This is not the case in their meta-analysis. Most of the selected trials had a treatment period of ≤24 weeks; many were of 3-month duration only and were therefore not designed and powered to investigate hard clinical end points such as morbidity or mortality. This is well reflected by the fact that, as reported by the authors, information on morbidity or mortality could only be retrieved in 3 of the 41 trials. While one study showed a significant treatment effect regarding cardiovascular events, the others presented only general statements without providing any detail. It is well known that sample sizes of individual clinical trials are often too small to detect clinically important effects reliably and that this is one of the reasons why meta-analysis is employed (3,4). However, hard end points such as cardiovascular mortality are going to be very rare in short-term duration studies unless compensated for by a huge population sample. Therefore, including short-term duration studies in their meta-analysis dilutes the cases of cardiovascular mortality. That biases the interpretation of the data analyzed.

The MERIA (MEta-analysis of Risk Improvement under Acarbose) analysis of seven placebo-controlled, long-term, randomized studies examining the effect of acarbose on cardiovascular-related mortality and morbidity showed a reduction of cardiovascular events in patients with type 2 diabetes (5). This analysis is based on all available acarbose studies with a minimum treatment duration of 52 weeks from a database including individual patient data. Because of this, publication and selection bias were already ruled out, as discussed in the response (6) to the criticism raised by van de Laar and Lucassen. Unfortunately, the same criticism voiced previously is repeated in their meta-analysis without taking the detailed response into consideration. In summary, the MERIA analysis showed a beneficial effect on cardiovascular complications in patients with established type 2 diabetes, a finding which is in accordance with the results from the STOP-NIDDM trial in subjects with impaired glucose tolerance (7).

We fully agree with the authors' statement that prospective trials with the primary objective of investigating cardiovascular events and mortality are required to confirm the beneficial effect of acarbose on cardiovascular events in these high-risk populations. However, the combined data from the STOP-NIDDM trial and the MERIA meta-analysis are highly suggestive of the preventive effects of acarbose on cardiovascular complications in subjects with glucose intolerance.

MARKOLF HANEFELD, MD, PHD[1]
ROBERT G. JOSSE, MBBS[2]
JEAN-LOUIS CHIASSON, MD[3]

From the [1]Centre for Clinical Studies, Science and Technology Transfer–Technical University Dresden, Dresden, Germany; the [2]Department of Medicine, St. Michael's Hospital, University of Toronto, Toronto, Canada; and the [3]Centre Hospitalier de l'Ùniversite de Montreal-Hotel-Dieu and Department of Medicine, Montreal University, Montreal, Canada.

Address correspondence to Markolf Hanefeld, MD, PhD, Science and Technology Transfer–GWT TU Dresden, Centre for Clinical Studies, Fiedler Str. 34, Dresden 01307, Germany. E-mail: hanefeld@gwtonline-zks.de.

References
1. van de Laar FA, Lucassen PL, Akkermans RP, von de Lisdonk EH, Rutten GE, van Weel C: α-Glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes Care* 28:154–163, 2005
2. Holman RR, Cull CA, Turner RC: A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes Care* 22:960–964, 1999 (erratum in *Diabetes Care* 22: 1922, 1999)
3. Thompson SG: *Biostatistics in Clinical Trials*. Redmond CK, Colton T, Eds. Chichester, NY, Wiley, 2001
4. Committee for Propietary Medicinal Products: *Points to Consider on Application With 1: Meta-analyses, 2: One Pivotal Study*. London, European Agency for the Evaluation of Medicinal Products, 2001
5. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M: Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 25: 10–16, 2004
6. Hanefeld MG: Meta-analysis of long-term studies to assess the effect of acarbose on cardiovascular risk reduction scientifically credible: reply (Letter). *Eur Heart J* 25:1179–1180, 2004
7. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003

α-Glucosidase Inhibitors for Patients With Type 2 Diabetes

Response to Hanefeld et al.

Hanefeld et al. (1) assert that the conclusion ("no evidence for an effect on mortality or morbidity") from our systematic review on the effects of α-glucosidase inhibitors for patients with type 2 diabetes was biased. Furthermore, they claim to have found evidence for such an effect based on their own meta-analysis. We disagree with both statements.

First, we would like to underline that the solid basis of our results is a systematic review and that meta-analyses were only applied when this was methodologically sound. The extensive search for all possible trials investigating α-glucosidase inhibitor monotherapy yielded only one study with prospectively collected data on morbidity or mortality (2), so a meta-analysis could not be done with these end points; therefore, we concluded that no evidence for an effect on mortality and morbidity could be found (which is essentially different from "evidence for no effect"). In the above-mentioned study, it was reported that for the entire treatment group (α-glucosidase inhibitors given both as monotherapy and as additional therapy), no effects of acarbose on cardiovascular end points were found.

This makes it quite remarkable that this particular study (2) was not included in the MERIA (MEta-analysis of Risk Improvement under Acarbose) study (3). Hanefeld et al. assert that this meta-analysis shows a beneficial effect of acarbose on the occurrence of myocardial infarctions. If it had been included in the MERIA study, it would have been the study with the second longest duration, it would have nearby doubled the number of patients, and it would have been the only study with a sound method of collecting end points. This points to the fact that the sole use of a manufacturer's database is not a reliable method for the selection of studies for a meta-analysis and that an extensive systematic review is necessary to reduce the risk of selection bias.

Other differences between the conclusions of MERIA and our Cochrane review can be explained by differences in inclusion and methodological robustness. Three of the seven studies in MERIA were also included in our Cochrane review, but no reliable data on cardiovascular outcomes could be obtained. The four other publications were excluded from our review, mainly because no data on α-glucosidase inhibitor monotherapy were available or accessible. Moreover, it should be noted that there was no quality assessment of the studies included in MERIA. Other serious concerns about the MERIA study were expressed in our previous letter and remain largely unresolved (4).

In conclusion, there is currently no evidence for an effect on cardiovascular morbidity and mortality of monotherapy with α-glucosidase inhibitors in patients with type 2 diabetes. In the near future, indirect evidence may be derived from another Cochrane review on the effects of α-glucosidase inhibitors for patients with glucose intolerance (5). We are pleased that the authors of the main studies in this field already have assured their cooperation.

Floris A. van de Laar, MD
Peter L. Lucassen, MD, PhD

From the Department of General Practice, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands.

Address correspondence to Floris van de Laar, Radboud University Nijmegen Medical Centre, Department of General Practice, 229 HAG, P.O. Box 9101, 6500 HB Nijmegen, Netherlands. E-mail: f.vandelaar@hag.umcn.nl.

References

1. Hanefeld M, Josse RG, Chiasson J-L: α-Glucosidase inhibitors for patients with type 2 diabetes (Letter). *Diabetes Care* 28: 1840, 2005
2. Holman RR, Cull CA, Turner RC: A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years (U.K. Prospective Diabetes Study 44). *Diabetes Care* 22:960–964, 1999 (erratum in *Diabetes Care* 22: 1922, 1999)
3. Hanefeld M, Cagatay M, Petrowitsch T, Neuser D, Petzinna D, Rupp M: Acarbose reduces the risk for myocardial infarction in type 2 diabetic patients: meta-analysis of seven long-term studies. *Eur Heart J* 25: 10–16, 2004
4. van de Laar FA, Lucassen PL: No evidence for a reduction of myocardial infarctions by acarbose (Letter). *Eur Heart J* 25:1179, 2004 (reply 1179–1180)
5. van de Laar FA, Lucassen PLBJ, Akkermans RP, Van de Lisdonk EH, De Grauw WJC: Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose (Protocol). *Cochrane Database Syst Rev* 2004. Issue 4. Art. no. CD005061. DOI: 10.1002/14651858

Chromium Supplementation Does Not Improve Glucose Tolerance, Insulin Sensitivity, or Lipid Profile: A Randomized, Placebo-Controlled, Double-Blind Trial of Supplementation in Subjects With Impaired Glucose Tolerance

Response to Gunton et al.

We read the recent article by Gunton et al. (1) with great interest and feel that it warrants comment. In this study, the authors stated that they "found no beneficial effect of chromium supplementation in the treatment of people with IGT [impaired glucose tolerance]." The results are in conflict with other clinical studies that showed chromium picolinate can enhance or normalize impaired glucose metabolism, as described in a recent review (2). The lack of effect described by the authors may be explained by the apparent low dose of elemental chromium used in the study.

The authors stated that the chromium picolinate "dose (at 800 μg/day) was at the higher end of the ranges used in previous studies" (1). However, chromium picolinate administered at 800 μg per day yields a daily dose of 100 μg per day of elemental chromium (i.e., chromium picolinate contains 12.4% elemental chromium). An elemental chromium dose of 100 μg a day is half of the suggested minimum amount (200 μg) of elemental chromium previously shown to exhibit

efficacy in glucose and lipid metabolism (2). A daily dose of 200–1,000 μg of elemental chromium, as chromium picolinate, is the efficacious dosage range used in previous studies.

Bullivants Natural Health Products, the supplier of the study products used by the authors, stated that 400 μg of the chromium picolinate product they produce yields 50 μg of elemental chromium. The study was conducted in Australia, and the 50-μg elemental chromium dose is also the maximum daily dose allowed by the Australian Therapeutic Goods Administration (3).

It was also interesting to note that although the serum chromium levels significantly rose in the active group, the serum chromium levels were not significantly higher in the active group than in the placebo group after 3 months of supplementation (active group 5.2 ± 8.9 nmol/l, placebo group 4.4 ± 4.0 nmol/l). For these reasons, we believe study subjects in the active group may have been administered daily doses of 50 μg elemental chromium, twice daily.

We recommend future studies be conducted in people with impaired glucose tolerance (following criteria defined by the American Diabetes Association) using daily doses of chromium picolinate providing ≥200–1,000 μg of elemental chromium for at least 90 days. We also recommend evaluating efficacy using the 75-g oral glucose tolerance test with calculation of the area under the curve using the trapezoidal method.

JAMES KOMOROWSKI, MS
VIJAYA JUTURU, PHD

From the Technical Services & Scientific Affairs Department, Nutrition 21, Inc., Purchase, New York.

Address correspondence to Vijaya Juturu, PhD, Nutrition 21, Inc., 4 Manhattanville Rd., Purchase, NY 10577. E-mail: vjuturu@nutrition21.com.

The authors are employees of Nutrition 21, Inc., which manufactures products containing chromium.

References

1. Gunton JE, Cheung NW, Hitchman R, Hams G, O'Sullivan C, Foster-Powell K, McElduff A: Chromium supplementation does not improve glucose tolerance, insulin sensitivity, or lipid profile: a randomized, placebo-controlled, double-blind trial of supplementation in subjects with impaired glucose tolerance. *Diabetes Care* 28:712–713, 2005
2. Cefalu WT, Hu FB: Role of chromium in human health and in diabetes. *Diabetes Care* 27:2741–2751, 2004
3. Complementary Medicines Evaluation Committee (CMEC), meeting 41, 1 August 2003, public recommendation summary [summary online]. Available at http://www.tga.gov.au/docs/html/cmec/cmecdr41.htm. Accessed 1 August 2003

Chromium Supplementation Does Not Improve Glucose Tolerance, Insulin Sensitivity, or Lipid Profile: A Randomized, Placebo-Controlled, Double-Blind Trial of Supplementation in Subjects With Impaired Glucose Tolerance

Response to Komorowski and Juturu

We thank Komorowski and Juturu (1) for their interest in our study, and we agree that it is possible that higher doses of chromium may show some effects. The subjects in this study received 100 μg of elemental chromium daily, administered as 800 μg of chromium picolinate, for 3 months. The small increase in serum chromium in the active group is probably appropriate for this dose. It is worth noting that significant uncertainty remains regarding how best to measure whole-body chromium status, as there are no well-defined outcomes to allow determination of a therapeutic range. This unfortunately includes assaying of serum.

The Australian Therapeutic Goods Administration daily dose recommendation was adopted in 2004 and is based on concerns about the safety of higher doses as raised by the Complementary Medicines Evaluation Committee (2), including two reports of renal failure (3,4). Our study commenced before 2003 and was scientifically reviewed by our local ethics committee.

We do not agree that the results of the study conflict with the literature. Studies of chromium supplementation in nondiabetic subjects and people with normal glucose tolerance, insulin resistance, and/or impaired glucose tolerance (IGT) have not produced any consistent benefits, as reviewed by Cefalu et al. (5), Yeh et al. (6), Althuis et al. (7), and Gunton et al. (8). In contrast, some studies in subjects with diabetes have shown significant benefits (5,8), and further studies in this group will be of great interest.

Our study was conducted in people diagnosed with impaired glucose tolerance according to the American Diabetes Association criteria. Efficacy was also evaluated using area under the curve during glucose tolerance testing, but this was also nonsignificant (data not shown). We feel that at this dose, chromium picolinate supplementation in subjects with impaired glucose tolerance is ineffective.

We note that Komorowski and Juturu are affiliated with Nutrition 21, Inc., which markets chromium picolinate.

JENNY E. GUNTON, MBBS, FRACP, PHD[1,2]
N. WAH CHEUNG, MBBS, FRACP[3]
ROSEMARY HITCHMAN, RNCM[1]
GRAHAM HAMS, MAPPSC[4]
CHRISTINE SULLIVAN, RNDEC[3]
KAYE FOSTER-POWELL, BSC, MNUTR, DIETAPD[3]
AIDAN MCELDUFF, MBBS, FRACP[1]

From the [1]Department of Endocrinology, Royal North Shore Hospital, St. Leonards, Sydney, Australia; [2]Cellular and Molecular Physiology, Joslin Diabetes Center, Boston, Massachusetts; the [3]Department of Diabetes and Endocrinology, Western Sydney Area Health Service, Westmead and Nepean Hospitals, Sydney, Australia; and [4]Pacific Laboratory Medical Services, Royal North Shore Hospital, Sydney, Australia.

Address correspondence to Jenny Gunton, c/o Kahn Laboratory, Level 6, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215. E-mail: jenny.gunton@joslin.harvard.edu.

References

1. Komorowski J, Juturu V: Chromium supplementation does not improve glucose tolerance, insulin sensitivity, or lipid profile: a randomized, placebo-controlled, double-blind trial of supplementation in subjects with impaired glucose tolerance: response to Gunton et al. (Letter). *Diabetes Care* 28:1841–1842, 2005
2. Complementary Medicines Evaluation

Committee (CMEC), meeting 41, 1 August 2003, public recommendation summary [summary online]. Available at http://www.tga.gov.au/docs/html/cmec/cmecdr41.htm. Accessed April 2005
3. Wasser WG, Feldman NS: Chronic renal failure after ingestion of over-the-counter chromium picolinate. *Ann Intern Med* 126: 410, 1997
4. Cerulli DW, Grabe I, Gauthier M, Malone and McGoldrick MD: Chromium picolinate toxicity. *Ann Pharmacother* 32:428–431, 1998
5. Cefalu WT, Hu FB: Role of chromium in human health and in diabetes. *Diabetes Care* 27:2741–2751, 2004
6. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS: Systematic review of herbs and dietary supplements for glycemic control in diabetes (Review Article). *Diabetes Care* 26:1277–1294, 2003
7. Althuis MD, Jordan NE, Ludington EA, Wittes JT: Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr* 76:148–155, 2002
8. Gunton JE, Hams G, Hitchman R, McElduff A: Serum chromium does not predict glucose tolerance in late pregnancy. *Am J Clin Nutr* 73:99–104, 2001

The Case for Biennial Retinopathy Screening in Children and Adolescents

Response to Maguire et al.

I have read the article by Maguire et al. (1) with interest. In a large, longitudinal cohort of type 1 diabetic children and adolescents, the study describes the natural history and prevalence of retinopathy. Although not the main focus of the article, their data also highlight two important points. First, Maguire et al. highlight the relationship between puberty and microvascular complications, as evidenced by the significantly increased incidence of retinopathy after 2 years' follow-up in subjects aged >11 years and after 5 years' follow-up in subjects aged <11 years. These findings were independent of glycemic control. Second, the study reveals that in 136 subjects with evidence of retinopathy at outset, 64 (47%) regressed, after a median of 3.1 years, to either lower-grade retinopathy or to normal at the end of follow-up, although the median age at which this occurs is not given.

These data are comparable to the natural history of microalbuminuria as described in longitudinal studies of children and adolescents, including the Oxford Regional Prospective Study in the U.K. (2). In this study, puberty (using age 11 years as a surrogate marker for onset of puberty) conferred a threefold increased risk of microalbuminuria, independent of poor glycemic control, and these data have been in part confirmed by previous studies from Couper et al. (3). This may relate in part to pubertal hormonal variables, as recent evidence suggests that microalbuminuria risk in this age-group is associated with growth hormone hypersecretion and insulin resistance, particularly in females (4). Furthermore, in ~60% of subjects, microalbuminuria subsequently regressed, and in these subjects compared with those with persistent microalbuminuria, mean HbA_{1c} levels were similar before onset of microalbuminuria (median age 15.8 years) but were lower thereafter. Thus, adolescent subjects with regression may be individuals in whom microalbuminuria initially manifests during the poor glycemic control and insulin resistant state associated with puberty but demonstrate regression when glycemic control improves in the postpubertal period. One may hypothesize that microalbuminuria may subsequently reappear in these "at risk" subjects in later life; however, this remains unproven.

These same mechanisms may apply to the pathogenesis and natural history of retinopathy during adolescence. We hope Maguire et al. will further detail the demographic details and risk factors for progression and regression of retinopathy, as adequate longitudinal data in this age-group are currently lacking.

RAKESH AMIN, MBCHB, MRCP

From the Department of Paediatric Endocrinology and Diabetes, Royal Manchester Children's Hospital, Manchester, U.K.

Address correspondence to Rakesh Amin, MBCHB, MRCP, Royal Manchester Childrens Hospital, Department of Paediatric Endocrinology, Hospital Road, Manchester, M27 4HA U.K. E-mail: amnrk@aol.com.

References

1. Maguire A, Chan A, Cusumano J, Hing S, Craig M, Silink M, Howard N, Donaghue K: The case for biennial retinopathy screening in children and adolescents. *Diabetes Care* 28:509–513, 2005
2. Schultz CJ, Konopelska-Bahu T, Dalton RN, Carroll TA, Stratton I, Gale EA, Neil A, Dunger DB: Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study: Oxford Regional Prospective Study Group. *Diabetes Care* 22:495–502, 1999
3. Couper JJ, Clarke CF, Byrne GC, Jones TW, Donaghue KC, Nairn J, Boyce D, Russell M, Stephens M, Raymond J, Bates DJ, McCaul K: Progression of borderline increases in albuminuria in adolescents with insulin-dependent diabetes mellitus. *Diabet Med* 14:766–771, 1997
4. Amin R, Williams RM, Frystyk J, Umpleby M, Matthews D, Orskov H, Dalton RN, Dunger DB: Increasing urine albumin excretion is associated with growth hormone hypersecretion and reduced clearance of insulin in adolescents and young adults with type 1 diabetes: the Oxford Regional Prospective Study. *Clin Endocrinol (Oxf)* 62:137–144, 2005

The Case for Biennial Retinopathy Screening in Children and Adolescents

Response to Amin

In response to the letter from Amin (1), we provide further details on the risk factors for progression and regression of retinopathy in our natural history study (2). Of 136 patients with retinopathy at baseline, 72 progressed or persisted compared with 50 patients (37%) who regressed to no retinopathy and 14 who regressed to a lower grade of retinopathy after a median follow-up of 3.1 years in both groups. Those who progressed or persisted had longer duration (7.8 vs. 5.9 years, $P = 0.0086$) and higher HbA_{1c} (9.1 vs. 8.5%, $P = 0.034$) at baseline and were older at follow-up (18.1 vs. 17.4 years, $P = 0.037$). In multivariate logistic regression analysis of baseline factors, glycemic control ($P = 0.0057$) and duration of diabetes ($P = 0.017$) were significant predictors of progression/persistence versus regression of retinopathy to normal; these data are consistent with the Diabetes Control and Complications Trial. Neither high baseline BMI nor blood pressure per-

centiles were significant contributors to the incidence or progression/regression of retinopathy.

We agree that our data support a relationship between puberty and microvascular complications (using age ≥11 years as a surrogate marker for puberty). In this cohort, however, we did not find a relationship between pubertal staging and progression/regression of retinopathy, but the small number (n = 13) of prepubertal patients with retinopathy prevented us from answering this question. In addition, the permissive effect of puberty, growth hormone, and IGF-1 may be more pronounced in the pathogenesis of microalbuminuria than retinopathy. When we studied an incident cohort after 6 years' duration, we found that higher pubertal stage (Tanner stage 4–5 vs. 1–3) had a larger effect on elevation of albumin excretion than retinopathy (odd ratios 5.2 vs. 3.4). The effect on albumin excretion rate was independent of HbA_{1c} (3).

ANN M. MAGUIRE, MB, BAO, BCH[1]
ALBERT K.F. CHAN, MAPPSTAT[1]
JANINE M. CUSUMANO[1]
STEPHEN J. HING, MBBS[1]
MARIA E. CRAIG, PHD[1,2,3]
MARTIN SILINK, MD[1,2]
NEVILLE J. HOWARD, MBBS[1]
KIM C. DONAGHUE, PHD[1,2]

From the [1]Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, Australia; the [2]Department of Paediatrics and Child Health, University of Sydney, Sydney, Australia; and the [3]School of Women's and Children's Health, University of New South Wales, Sydney, Australia.

Address correspondence to Dr. Ann Maguire, Institute of Endocrinology and Diabetes, The Children's Hospital at Westmead, Locked Bag 4001, Sydney, NSW 2145, Australia. E-mail: annm4@chw.edu.au.

References

1. Amin R: The case for biennial retinopathy screening in children and adolescents (Letter). *Diabetes Care* 28:1843, 2005
2. Maguire A, Chan A, Cusumano J, Hing S, Craig M, Silink M, Howard N, Donaghue K: The case for biennial retinopathy screening in children and adolescents. *Diabetes Care* 28:509–513, 2005
3. Donaghue KC, Craig ME, Chan AKF, Fairchild JM, Cusumano JM, Verge CF, Crock PA, Hing SJ, Howard NJ, Silink M: Prevalence of diabetes complications six years after diagnosis in an incident cohort of childhood diabetes. *Diabet Med*. In press