

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 non-diabetic (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/m², or HOMA-IR >3.60 and BMI >27.5 kg/m². Model 2 is based on BMI >28.7 kg/m², or BMI >27.0 kg/m² and a positive family history of diabetes. Model 3 is based on BMI >28.7 kg/m², BMI >27.0 kg/m² 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).

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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.

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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 \pm 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. $9.39 \pm 1.35\%$, $P < 0.001$). The significant decrease of A1C was maintained over the whole CSII treatment with a mean change in A1C of $1.15 \pm 0.84\%$ ($P < 0.001$).

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 ketoacidosis 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 advanced

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.

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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 re-analyzed 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

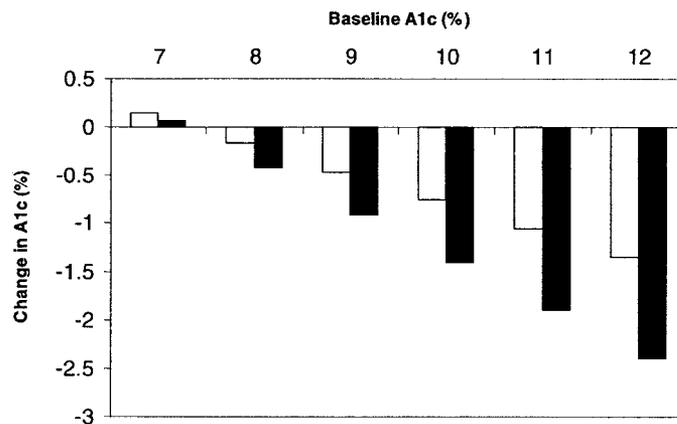


Figure 1—The predicted relative benefit of CSII over MDII in lowering A1c increases as baseline A1c rises. □, MDII; ■, CSII.

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.

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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 glu-

cose. 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- μ l volume or above. However, below the 3- μ l volume, most meters gave misleading results (Table 1). At the 1- μ l volume, the mean calculated as a percentage from the 5- μ l 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.

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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.

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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.

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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 than 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.

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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: $\text{glycemic load} = [\text{GI} \times \text{carbohydrate (g)}]/100$.

Therefore, the GL provides a summary measure of the relative glycemic impact of a "typical" serving of the food. Foods with a $\text{GL} \leq 10$ 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.

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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.

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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.

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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 assay-ing 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.

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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.

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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-

