

## OBSERVATIONS

## Prevalence and Risk Factors of Diabetic Foot Problems in Taiwan

A cross-sectional survey of non-type 1 diabetic patients from a nationally representative sample

About half of all nontraumatic lower extremity amputations are performed on diabetic patients (1,2), and foot ulcers precede 71–84% of all lower extremity amputations (3,4). In the Caucasian population, 15% of diabetic patients will develop a foot ulcer during their lifetime (5), and 6–43% of diabetic patients with a foot ulcer will eventually progress to lower extremity amputation (3,4,6). To this author's knowledge, there has not been any previous nationwide epidemiologic survey on diabetic foot problems in Taiwan, and the clinical outcomes of diabetic foot ulcers are still unknown.

To survey diabetic foot problems in the Taiwanese population, a total of 16,994 non-type 1 diabetic patients were randomly selected for telephone interview from a group covered by the National Health Insurance (>96% of the total population is covered by this health care system). They were questioned on whether they had diabetic foot problems, as indicated by ulcer, gangrene, or amputation on the lower extremities. Lifetime prevalence was calculated, and various risk factors were analyzed. A total of 12,531 case subjects (response rate 73.7%) were successfully interviewed. Diabetic foot problems were present in 369 patients (prevalence 2.9%) with 540 initiating events. Ulcers represented 86.7% of all initiating events. Approximately 26.9% of the ulcers progressed to gangrene or amputation, and ulcers preceded 71.9% of all amputations. In univariate analyses, diabetic foot problems were characterized by older age, male preponderance, longer duration of diabetes, smoking, poorer glycemic control, more insulin users, hypertension, hyperlipidemia, higher diastolic and systolic blood

pressure, lower education level, and living in rural areas. In logistic regression, the multivariate-adjusted odds ratios (95% CI) were significant for men 1.461 (1.063–2.008); duration of diabetes 1.048 (1.033–1.063); insulin therapy 2.921 (2.199–3.881); education level (vs. a high school education or higher) 1.450 (1.089–1.931) and 2.194 (1.543–3.121) for elementary school and illiteracy, respectively; ex-smokers <5 years versus nonsmokers 1.645 (1.030–2.627); systolic blood pressure 1.019 (1.008–1.030); and hyperlipidemia 1.478 (1.117–1.956). In conclusion, diabetic foot problems are present in 2.9% of Taiwanese non-type 1 diabetic subjects. Although foot ulcers are less common among Taiwanese than Caucasian subjects, the outcomes are not better. Conventional risk factors for atherosclerosis are important, but particular attention should be focused on patients with a lower education level and those who use insulin.

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## Nonalcoholic Fatty Liver Disease in Saudi Type 2 Diabetic Subjects Attending a Medical Outpatient Clinic

Prevalence and general characteristics

Nonalcoholic fatty liver disease (NAFLD) is a liver condition that is being recognized with increasing frequency, and it may progress to end-stage liver disease (1). NAFLD can affect any age-group and has been described in most racial groups. In most series, the typical picture is a middle-aged woman (1). Obesity has the strongest association with NAFLD, but regardless of BMI, the presence of type 2 diabetes significantly increases the risk and severity of NAFLD. The prevalence of NAFLD in the general population ranges from 13 to 15% (2). The prevalence increases in subjects with diabetes and with severe obesity and has been reported to range from 25 to 75% or even higher (3). In Saudi Arabia, a prevalence of 7–10% has been reported in the general population (4,5). The aim of our work is to determine the prevalence and characteristics of NAFLD in Saudi type 2 diabetic subjects attending King Abdulaziz University Hospital. A sample of 116 patients was randomly selected over 1 year. All participants provided informed consent before participation. The entire sample had an abdominal ultrasound examination (using an ATL HDI 5000 abdominal probe at 2.5–3 MHz) and liver enzyme measurement performed. The sonographic findings used to diagnose NAFLD were diffuse increase in echogenicity of the liver parenchyma, which is assessed by absence of hyperechoic walls

of the portal vein radicals, and absence of interface between diaphragm and liver. All radiological examinations were done by the same radiologist. The upper limit of normal liver size was 16 cm in the longitudinal plane; any measurement above this was considered hepatomegaly. Mild hepatomegaly was defined as liver size >16–18 cm in the longitudinal plane. Secondary causes of liver disease were excluded, in particular ethanol abuse (the sample studied did not drink alcohol) and use of drugs known to promote hepatic steatosis. In patients with elevated liver enzymes, those who used hepatotoxic drugs were excluded.

The mean age of the study group was  $54 \pm 12.8$  years with a male-to-female ratio of 1:2.6. The mean duration of diabetes was  $8.85 \pm 6.18$  years, mean BMI was  $30 \pm 5.5$  kg/m<sup>2</sup>, and HbA<sub>1c</sub> was  $7.9 \pm 1.1\%$ . NAFLD was diagnosed in 64 (55%) subjects. Right upper quadrant discomfort was reported in 11 of 64 (17%) subjects and elevated liver enzymes were found in 12 of 64 (19%). Mean aspartate aminotransferase level was  $23.75 \pm 10.3$  units/l (normal range 5–65 units/l), alanine aminotransferase  $71 \pm 22.04$  units/l (normal range 5–38 units/l), and alkaline phosphatase  $112.62 \pm 58.13$  units/l (normal range 35–136 units/l). Fifty-six (88%) subjects had hepatomegaly as assessed by ultrasound, which was mild in two-thirds of them. None of the patients without NAFLD had hepatomegaly. The average liver size was  $17.2 \pm 3.1$  cm in patients with fatty infiltration and  $13 \pm 2.4$  cm in non-NAFLD patients. A significant relationship was found between the presence of NAFLD and female sex ( $P = 0.05$ ). No significant relationship was found between the presence of NAFLD and age, duration of diabetes, or degree of glycemic control. Multiple regression analysis after adjustment for all factors and sex identified obesity as an independent factor associated with the development of NAFLD ( $P = 0.06$ ).

Our results agree with those reported in the literature. The natural history of NAFLD has not been well defined, but it seems to be determined by the severity of histological damage (2). Hepatomegaly with mild to moderate elevation in serum levels of transaminases has been reported; however, this doesn't correlate with liver histology (1,6). Future prospective studies need to clarify whether diabetic sub-

jects have the same natural history, i.e., whether they are affected by the same histological changes or have other additional factors that may play a role, such as insulin resistance or type of treatment.

We can conclude that NAFLD, as determined by ultrasound, is common in Saudi type 2 diabetic subjects. As in reports from other ethnic groups, female sex and obesity were the two predominant features of patients with NAFLD in Saudi Arabia. In this small cohort of patients, neither glycemic control nor duration of diabetes had any relationship with fatty liver infiltration. This suggests that factors other than hyperglycemia operate to cause hepatic steatosis.

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## Prospective Audit of the Introduction of Insulin Glargine (Lantus) Into Clinical Practice in Type 1 Diabetic Patients

Insulin glargine is a modified basal insulin analog that has been recently introduced, and following guidance from the National Institute for Clinical Excellence (NICE), it is now widely available in the U.K. (1). Studies in type 1 diabetes demonstrate that compared with NPH insulin, fasting blood glucose and hypoglycemic episodes are reduced and patient satisfaction is improved (2–7). To confirm whether these reported benefits are also achieved in routine clinical practice, we conducted a prospective audit of patients attending our diabetes clinic practice transferring to insulin glargine.

There were 83 patients with type 1 diabetes on multiple daily injection regimens who were transferred from NPH insulin to insulin glargine between July and November 2002. Indications for transfer were nocturnal hypoglycemia, morning fasting hyperglycemia, the use of two NPH injections, or patient request. Patient details, including glycemic control (glucose concentrations and HbA<sub>1c</sub> levels), were recorded. Patients completed a questionnaire on the frequency of hypoglycemia (requiring corrective action by patient) over the preceding month and severe hypoglycemic episodes (requiring assistance from a third party) over the 3 months preceding the initiation of insulin glargine therapy. Patient assessments on quality of life and well-being (Diabetes Treatment Satisfaction Questionnaire and Well-Being Questionnaire 28) (8,9) were also performed. Patients were reassessed after receiving insulin glargine for 3 months.

Morning blood glucose concentrations and HbA<sub>1c</sub> levels fell significantly, from  $9.63 \pm 0.44$  to  $7.15 \pm 0.28$  mmol/l ( $P < 0.001$ ) and from  $8.24 \pm 0.16$  to  $7.86 \pm 0.11\%$  ( $P = 0.006$ ), respectively. Total hypoglycemic episodes remained unchanged after transferral to insulin glargine. The number of severe hypoglycemic episodes was not statistically significantly different after transfer to glargine from baseline values (from 15 to 7) ( $P =$

0.077). Aggregate scores for the Diabetes Treatment Satisfaction Questionnaire, which reflect satisfaction with treatment, improved from 23.5 (0.68) to 28 (0.67) ( $P < 0.001$ ), whereas the score for unacceptably high blood glucose values fell from 3.53 (0.16) to 2.83 (0.17) ( $P = 0.002$ ) with no significant change for unacceptably low blood glucose values (from 2.43 [0.16] to 2.11 [0.14]) ( $P = 0.07$ ). The scores for the Well-Being Questionnaire 28 show significant improvements in patient-reported energy levels ( $P < 0.001$ ), diabetes-specific well-being ( $P = 0.044$ ), and total well-being ( $P = 0.001$ ), with significant reductions in diabetes-related stress ( $P = 0.014$ ).

Our results confirm that people with type 1 diabetes on a multiple daily insulin injection regime who transfer to insulin glargine from isophane insulin have a significant fall in their morning blood glucose concentrations and HbA<sub>1c</sub> levels as well as significant improvements in satisfaction with their treatment and subjective well-being. The use of insulin glargine appears to be advantageous for some patients with type 1 diabetes.

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## Self-Blood Glucose Monitoring Practices

Do patients know and act on their target?

**S**elf-monitoring of blood glucose (SMBG) is a major advance in diabetes care, but questions remain about its exact role in type 2 diabetes (1). Studies conducted in large clinical practices have shown a positive association between SMBG frequency and good glycemic control in patients with type 2 diabetes. However, few attempts to describe the relationship between monitoring and glycemic control have looked beyond the frequency of testing to determine whether patients clearly understood their target values and how they respond to the information obtained from monitoring (2–4).

In a collaborative effort, the Great Falls Clinic and the Montana Department of Public Health and Human Services sur-

veyed a random sample of current patients with diabetes (815 of 1,234 patients were selected) by telephone in October 2002, to assess their diabetes care. Respondents were asked if they were currently taking insulin and/or oral antihyperglycemic medications and were classified into three groups: those using insulin with or without oral antihyperglycemic agents, those taking oral therapies only, and those not currently taking any diabetes medications. Respondents were also asked about SMBG, “About how often do you check your blood for glucose or sugar?” (the response categories for this question were the number of times per day, week, month, or year, or don’t know/not sure, never, and refused to answer). Respondents reporting any SMBG were then asked, “What do you do with your blood glucose or sugar readings when they are too high? Do you adjust your medication? Do you eat less food?” Respondents who monitored were also asked, “What do you do with your blood glucose or sugar readings when they are too low? Do you adjust your medication? Do you take more food?” And finally, those who reported any SMBG were asked, “What is your target blood glucose or sugar value?”

The most recent A1c values were matched to the information collected from the telephone survey. A1c testing was performed by a central laboratory using the BioRad Variant II (BioRad, Hercules, CA), a high-pressure liquid chromatography method (normal range 4.0–6.0%). Data analyses were conducted using SPSS v10.0 software. Pearson  $\chi^2$  tests were used to compare SMBG practices by medication type, and Kruskal-Wallis tests were used to compare the median A1c value among respondents by SMBG target and medication type. Nonparametric statistical tests were used in these analyses because the A1c values were not normally distributed.

Of the 815 patients, 61% completed the survey. There were no statistically significant differences between respondents and nonrespondents by age (mean age 62.3 vs. 61.5 years,  $P = 0.49$ ), sex (male 55 vs. 48%,  $P = 0.07$ ), or by the last A1c value (median A1c value 7.2 vs. 7.3%,  $P = 0.12$ ). Thirty-seven percent of respondents used insulin (27% insulin alone and 10% in combination with oral agents), 49% used oral medications only, and 14% were taking no antihyperglyce-



mic medications. Respondents using insulin were more likely to monitor daily (52%) compared with those taking oral medication only (30%) and those taking no medication (7%,  $P < 0.001$ ). Those using insulin were also more likely to report an SMBG target (88%) compared with respondents taking oral therapy only (70%) or those taking no medication (42%,  $P < 0.001$ ).

Among respondents using insulin, a larger proportion of those reporting a blood glucose target took some action (i.e., adjusted medication and/or ate more/less food) when their blood glucose values were low compared with those without a target (90 vs. 71%,  $P = 0.02$ ). However, there were no differences between the two groups regarding actions taken when the glucose values were high (86 vs. 77%,  $P = 0.27$ ). Among respondents taking oral medications only, those with a blood glucose target were also more likely than those without a target to take some action when their blood glucose values were low (63 vs. 46%,  $P = 0.03$ ), but not when they were high (65 vs. 64%,  $P = 0.82$ ). For respondents taking no medications, those with blood glucose targets were no more likely to take any action (i.e., eat more/less food) when their blood glucose values were high (67 vs. 33%,  $P = 0.06$ ) or low (50 vs. 40%,  $P = 0.57$ ) compared with those who did not report a target.

The median target blood glucose value reported was 120 (25th percentile = 105, 75th percentile = 130). Individuals using insulin reporting targets  $\leq 120$  had a significantly lower median A1c values (median 7.3%) compared with those with SMBG targets  $> 120$  (8.3) and those with no target (8.7,  $P = 0.02$ ). There was a small but not significant difference in the median A1c values among respondents taking oral medications in those with targets  $\leq 120$  (7.1) compared with those reporting targets  $> 120$  (7.3) or those with no target (7.0,  $P = 0.07$ ). But, there were no differences in the median A1c values regardless of a reported target or the level of the target among those taking no diabetes medications (6.1 for each medication group,  $P = 0.29$ ).

This is one of very few studies to look beyond the frequency of SMBG and ask how patients understood and utilized their values before looking at the relationship of monitoring to glycemic control. Many patients with diabetes who moni-

tored did not know their blood glucose targets. Among those taking insulin, lower targets were clearly associated with better metabolic control. The relationships between targets and metabolic control were not as clear among patients taking only oral medications or those taking no medications. However, our sample was small, and we could not distinguish recently diagnosed individuals from long-term patients. The cross-sectional design of this study precludes determining whether awareness of glycemic targets led to better glycemic control versus achievable targets that were tailored to each patient's level of glycemic control (e.g., patients in poor control were given high and more achievable glycemic targets by their provider). Longitudinal studies are needed to address this issue.

Thus, the role of SMBG in type 2 diabetes will likely depend on both the therapies used to control hyperglycemia and what both patients and health care providers do with the values. Finally, the SMBG frequency for individuals with type 2 diabetes to maintain optimal A1c levels for a given therapy may be different from the frequency needed to adjust therapy to reach a target. (5) We have previously shown that patients with diabetes did not always know their A1c value or its meaning (6). Similarly, in this study patients with diabetes did not always have a clear understanding of what blood glucose levels they should be trying to achieve.

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D.G. has received honoraria or consulting fees from NovoNordisk, Aventis, and GlaxoSmithKline.

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**Acknowledgments**— This project was supported through cooperative agreements (U32/CCU815663-05) with the Centers for Disease Control and Prevention, Division of Diabetes Translation, Atlanta, Georgia. The contents of

this report are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention.

We thank Linda Priest and the staff members of Northwest Resource Consultants for their expertise and work on the telephone survey. We also thank Susan Day for her assistance throughout this project.

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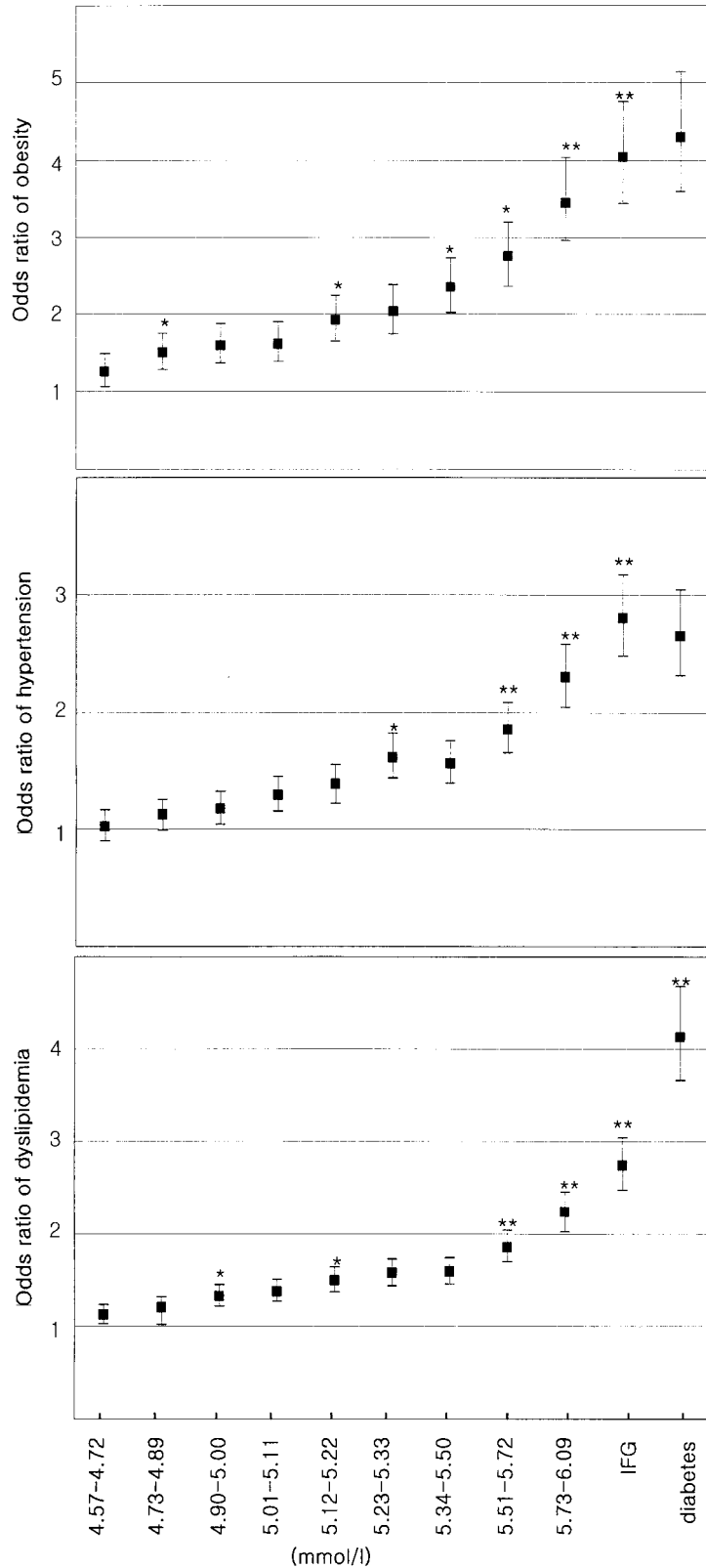
## The Cutoff Value of Fasting Plasma Glucose to Differentiate Frequencies of Cardiovascular Risk Factors in a Korean Population

**D**iabetes and impaired glucose tolerance (IGT) are associated with increased cardiovascular mortality. Almost all studies, however, failed to de-

tect evidence of the presence of a fasting plasma glucose (FPG) threshold for risk of cardiovascular disease that would clearly identify groups with a low or high risk (1,2). Some studies suggested that an FPG of 5.4–5.7 mmol/l has been found to be closer to a 2-h cutoff of 7.8 mmol/l both in terms of the sensitivity for future diabetes and in defining a category of similar prevalence to IGT (3,4). The interrelationships between cardiovascular risk factors and glucose levels may vary between different populations. Therefore, these findings need to be tested in other populations with different environmental and genetic backgrounds.

The medical records of 54,623 subjects (30,435 men and 24,188 women) who attended the Health Promotion Center in the Samsung Medical Center between 1998 and 2001 were examined for this analysis. Obesity was defined as a BMI  $\geq 27$  kg/m<sup>2</sup>. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, and/or the current use of antihypertensive drugs. Dyslipidemia was defined as LDL cholesterol  $\geq 4.1$  mmol/l, triglycerides  $\geq 2.46$  mmol/l, HDL cholesterol  $< 1.04$  mmol/l, and/or current use of antilipid drugs. Cases of previous history of diabetes were excluded.

All study subjects were classified into 12 groups according to FPG (10 deciles of normal fasting glucose [NFG]: NFG 1,  $\leq 4.56$ ,  $n = 5,370$ ; NFG 2, 4.57–4.72,  $n = 4,495$ ; NFG 3, 4.73–4.89,  $n = 6,321$ ; NFG 4, 4.90–5.00,  $n = 4,655$ ; NFG 5, 5.01–5.11,  $n = 4,841$ ; NFG 6, 5.12–5.22,  $n = 4,503$ ; NFG 7, 5.23–5.33,  $n = 4,233$ ; NFG 8, 5.34–5.50,  $n = 5,236$ ; NFG 9, 5.51–5.72,  $n = 4,926$ ; NFG 10, 5.73–6.09,  $n = 4,230$ ; IFG, 6.10–6.99,  $n = 3,587$ ; and diabetes,  $\geq 7.00$  mmol/l,  $n = 2,226$ ). Those with an FPG  $\leq 4.56$  mmol/l formed the lowest group, and those with FPG  $> 7.0$  mmol/l formed the highest group. Frequencies of obesity in each group were 5.2, 6.7, 8.2, 8.9, 9.2, 10.9, 11.1, 12.9, 14.5, 17.0, 19.0, and 20.3%, respectively. Those of hypertension were 11.3, 13.2, 15.0, 16.6, 18.2, 20.1, 22.9, 23.2, 27.4, 32.8, 37.8, and 37.4%, respectively. Finally, those of dyslipidemia were 25.0, 29.0, 31.5, 34.7, 36.3, 39.3, 41.7, 42.6, 47.5, 52.8, 58.6, and 67.0%, respectively. After controlling for age and sex and odds ratio (OR) for obesity, hypertension and dyslipidemia in the IFG group were 4.04 (3.43–4.75), 2.80



**Figure 1**—ORs of obesity, hypertension, and dyslipidemia according to FPG value, with subjects with FPG  $\leq 4.56$  mmol/l as the referent group. Data are ORs and 95% CI. \*P  $< 0.05$ ; \*\*P  $< 0.01$  vs. subjects with one level lower FPG.

(2.48–3.17), and 2.74 (2.47–3.04), respectively, with FPG subjects  $\leq$ 4.56 mmol/l (NFG1) as the referent group. Those in the diabetes group were 4.29 (3.59–5.13), 2.65 (2.31–3.04), and 4.13 (3.66–4.67) (Fig. 1). Although there was no clear cutoff point to differentiate the risk of obesity, a threshold at an FPG value of 5.34–5.50 mmol/l was suggested. For hypertension and dyslipidemia, more clear threshold values were observed. The group with an FPG value of 5.51–5.72 mmol/l had a considerably greater OR of hypertension and dyslipidemia than the group with an FPG value of 5.34–5.50 mmol/l.

The data clearly showed that even in the NFG range, the level of fasting glucose was closely related to the frequencies of cardiovascular risk factors, including obesity, hypertension, and dyslipidemia, and strongly suggested the significance of a concentrated effort to reduce the cardiovascular risk factors in the earlier stage of an FPG  $<$ 6.10 mmol/l in a Korean population.

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**Safety Issues on Metformin Use**

We read with interest the letter by Faichney and Tate (1) in the May issue of *Diabetes Care*. We would like to comment on metformin and the risk of lactic acidosis; however, we do not have data to refute the hypothetical relevance of diabetic ketoacidosis to the risk of lactic acidosis (1). We believe that the aforementioned letter and relevant reports (2–4) may negatively affect the future use of metformin, not only in type 1 (1) but also in type 2 diabetic patients. In this regard, the report by Horlen et al. (2), which addressed physicians’ lack of adherence to metformin prescribing precautions, was received with strong opposition in the medical media (5) following the public support from the Associated Press (www.aace.com).

Lactic acidosis has been linked to the use of biguanides for decades. Although phenformin had been pulled from the market, metformin-associated lactic acidosis has since been believed to be the direct result of metformin use, especially in situations likely to precipitate lactic acidosis, e.g., congestive heart failure, chronic renal insufficiency, shock, etc. Although this “solid fact” of causative (etiologic) relation between metformin and lactic acidosis has not been challenged previously, recent relevant publications have appeared in the literature (6–8). Lallau and colleagues (6,7) found that metformin accumulation was not related to either lactic acidosis or the associated mortality in patients taking therapeutic doses of metformin who developed lactic acidosis in association with other precipitating conditions. Metformin overdose was an exception, they reported (6); the latter can cause genuine type B lactic acidosis, but only a few such cases have been reported (9). In the report on metformin-associated lactic acidosis published by

FDA investigators (3), metformin levels were not measured.

Rachmani et al. (8) have recently reported no lactic acidosis in diabetic patients who were continued on metformin over 4 years of follow-up; these patients had traditional contraindications (congestive heart failure, chronic renal insufficiency, or chronic obstructive pulmonary disease) to metformin use. Furthermore, a recent meta-analysis of 176 studies with  $>$ 35,000 patient-years of follow-up found no cases of lactic acidosis, although some of these studies included patients with renal insufficiency and cardiovascular conditions (4).

Finally, Jones and Macklin (10) have recently reported that evidence suggested it was time to amend the contraindication “list” of metformin prescribing. They pointed out that the limiting criteria for the use of metformin in diabetes had stemmed largely from reports in the 1970s of mortality and lactic acidosis associated with “phenformin.”

Therefore, one may wonder whether metformin is an “innocent bystander” in these clinically complex metformin-associated lactic acidosis cases.

In conclusion, in view of the aforementioned thoughts challenging the “apparently well-established” etiologic role of metformin in metformin-associated lactic acidosis, and pending further research, it is prudent to critically appraise published reports on the issue. We believe that the average dose of metformin currently used in clinical practice is reasonably safe, even in the presence of mild to moderate cases of the “traditional contraindications.” An exception to this is the safe practice of holding metformin before contrast studies and during acute, intercurrent illnesses.

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## Patient and Provider Congruence

Measures of effective diabetes management have traditionally included either provider adherence to best practice guidelines or clinical indicators such as laboratory values (1). This gives the clinical picture from the provider's viewpoint but leaves out the patient perspective. This descriptive study was designed to determine congruence between rural patient self-reported and provider-documented information on American Diabetes Association (ADA)-recommended guidelines for measurement and control of HbA<sub>1c</sub>, blood pressure, lipid levels, and preventive services (2,3).

Provider medical record information and patient questionnaires were matched for 149 patients, 45 years of age and with a diagnosis of type 2 diabetes, seen at four rural health care facilities between January 1999 and August 2000. There were significant differences ( $P < 0.05$ ) between patients' self-reports and providers in multiple areas. The aggregate percentage of patients with an HbA<sub>1c</sub> measurement was similar (57 vs. 54%) between provider documentation and patient self-report, respectively. When data were matched by individual, i.e., both patient and provider agree test was or was not done, HbA<sub>1c</sub> congruence was 47%, blood pressure measurement 79%, cholesterol check 60%, pneumovax 53%, influenza vaccination 44%, and eye examination 42%. A lack of congruence was evident in preventive services. Patients reported a significantly higher ( $P < 0.05$ ) percentage of influenza vaccinations (71 to 27%) and pneumovax rates (58 to 33%) when com-

pared with provider information. Medical records documented that 13% of patients had a dilated eye exam in the past year but 82% reported having one and named the ophthalmologist who performed it.

On chart review, 93% ( $n = 136$ ) of patients were on medication for diabetes management, but patients self-reported 81% ( $n = 110$ ). Thirty-six percent ( $n = 53$ ) of patients were on a lipid-lowering medication; 17 patients agreed, and 45% ( $n = 40$ ) of patients not on a documented lipid-lowering agent thought they were. Eighty-one percent ( $n = 72$ ) of patients with a diagnosis of hypertension were on a medication to lower their blood pressure, and 44 of these individuals (61%) agreed.

Diabetes requires a lifelong commitment to maintain control. To achieve this, providers must implement clinical practice guidelines into patient care. Patients must take an active role in their disease management. The results of this study indicate that these may not be happening in rural areas. There was suboptimal provider implementation of ADA recommended guidelines, limited patient knowledge about testing and medication use, and a disconnection between patient and provider for preventive services received. Diabetes is a complex metabolic disease in which the reasoning behind therapeutic goals can be difficult to understand. Changes in the traditional model of care that increase patient education and understanding of their disease while improving provider adherence to ADA guidelines are needed in rural areas.

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**Acknowledgments**— This study was funded by Administration on Aging Grant no. 90-AM-2304.

We thank the Deaconess Billings Clinic Center on Aging, including Connie Koch, Karen Gransbery, Betty Mulette, and Brenda Hellyer.

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## Maturity-Onset Diabetes of the Young (MODY) Mutation in Type 2 Diabetes and Latent Autoimmune Diabetes of the Adult

Owen et al. (1) reported etiologic heterogeneity among 268 subjects with type 2 diabetes, of whom ~10% had autoantibodies and ~1% had mutations in *HNF1A* (MODY3) encoding hepatic nuclear factor-1 $\alpha$ . We hypothesized that maturity-onset diabetes of the young (MODY) gene mutations would also be found in subjects with latent autoimmune diabetes of the adult (LADA) (2). We studied 37 Canadian subjects diagnosed with LADA (of whom 20 were female) and 54 control subjects with type 2 diabetes (of whom 28 were female). LADA was diagnosed when a type 2 diabetic patient concurrently had positive autoantibodies against GAD and/or the intracytoplasmic domain of tyrosine phosphatase-like protein, insulinoma-associated protein (IA)-2, using validated assays (sensitivity:specificity of 86:92% for anti-GAD and 64:86% for anti-IA-2, respectively [3,4]). Type 2 diabetic control subjects were negative for autoantibodies by the same assays. Using Student's *t* test (for means  $\pm$  SD of quantitative traits) or  $\chi^2$  analysis (for discrete traits), the LADA subjects were found to be younger ( $44.4 \pm 14.3$  vs.  $51.6 \pm 12.6$  years,  $P = 0.011$ ) and leaner (BMI  $28.7 \pm 6.5$  vs.  $32.8 \pm 6.7$  kg/m<sup>2</sup>,  $P = 0.005$ ), and despite a tendency toward shorter disease duration ( $24.8 \pm 23.8$  vs.  $34.8 \pm 27.7$  months,  $P = 0.07$ ), were more likely to





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R.C.H. has received financial support for lecturing services from Novo Nordisk, Takeda, GlaxoSmithKline, Aventis, Merck, Pfizer, Wyeth, and Novartis and has received research support from Pfizer.

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COMMENTS AND RESPONSES

**Glimepiride and Serum Adiponectin Level in Type 2 Diabetic Subjects**

Response to Nagasaka et al.

We read with interest the article by Nagasaka et al. (1) reporting that glimepiride, a new agent of sulfonylurea, has an increasing effect on circulating adiponectin concentration, which may play a role in mediating insulin sensitivity. The authors demonstrated that serum adiponectin concentration increased significantly from  $22.1 \pm 2.7$  to  $28.5 \pm 2.8 \mu\text{g/ml}$  after 3 months' glimepiride treatment. However, their baseline level of serum adiponectin was markedly higher than that of the Japanese type 2 diabetic subjects reported by Tsunekawa et al. (2) ( $22.1 \pm 2.7$  vs.  $6.61 \pm 3.06 \mu\text{g/ml}$ ) in spite of higher BMI ( $26.5 \pm 0.9$  vs.  $21.2 \pm 2.2 \text{ kg/m}^2$ ) and greater homeostasis model assessment of insulin resistance ( $5.0 \pm 0.8$  vs.  $2.54 \pm 2.25$ ), although both groups measured serum adiponectin levels with Linco radioimmunoassay kits (St. Charles, MO).

Recently, Hara et al. (3) reported the association between single nucleotide polymorphism (SNP) 276 of the adiponectin gene and plasma adiponectin levels, showing that the G allele at position 276 was linearly associated with

lower plasma adiponectin levels (G/G:  $10.4 \pm 0.85 \mu\text{g/ml}$ ; G/T:  $13.7 \pm 0.87 \mu\text{g/ml}$ ; and T/T:  $16.6 \pm 2.24 \mu\text{g/ml}$ ) in Japanese subjects with higher BMIs. Here, we measured serum adiponectin concentrations by human adiponectin enzyme-linked immunosorbent assay kits (Otsuka Pharmaceutical, Tokyo, Japan) in Japanese diabetic patients and investigated the influence of SNP 276 of the adiponectin gene. A total of 101 type 2 diabetic subjects (70 men and 31 women, aged  $55.5 \pm 8.7$  years) were studied (data are means  $\pm$  SD). Twenty-eight subjects (20 men and 8 women, aged  $55.2 \pm 6.5$  years) had been treated with glimepiride (daily dosage  $1.5 \pm 0.6 \text{ mg}$ ) and 31 subjects (22 men and 9 women, aged  $60.2 \pm 6.3$  years) with gliclazide (daily dosage  $39.3 \pm 18.4 \text{ mg}$ ) for  $>6$  months. The remaining 42 subjects (28 men and 14 women, aged  $51.4 \pm 10.3$  years) had been treated with diet therapy alone and without any hypoglycemic agents. BMI (glimepiride group:  $24.6 \pm 3.4 \text{ kg/m}^2$ ; gliclazide group:  $24.3 \pm 3.1$ ; and diet group:  $24.5 \pm 5.3$ ), HbA<sub>1c</sub> (glimepiride group:  $7.2 \pm 1.2\%$ ; gliclazide group:  $6.7 \pm 0.5$ ; and diet group:  $6.8 \pm 1.4$ ), homeostasis model assessment of insulin resistance (glimepiride group:  $3.3 \pm 2.3$ ; gliclazide group:  $2.5 \pm 1.4$ ; and diet group:  $3.1 \pm 2.0$ ), and serum lipid levels (data not shown) were not significantly different among the groups. Serum adiponectin levels in subjects with glimepiride ( $5.34 \pm 2.82 \mu\text{g/ml}$ ) and gliclazide ( $5.38 \pm 2.61 \mu\text{g/ml}$ ) were significantly lower than that of the diet group ( $7.31 \pm 4.87 \mu\text{g/ml}$ ). The G allele frequency of SNP 276 of the adiponectin gene was 0.70. The serum adiponectin levels were not different among the genotypes at position 276 of the adiponectin gene (G/G,  $n = 54$  [53.5%]:  $6.43 \pm 5.54 \mu\text{g/ml}$ ; G/T,  $n = 34$  [33.7%]:  $6.31 \pm 4.25 \mu\text{g/ml}$ ; and T/T,  $n = 13$  [12.8%]:  $5.70 \pm 2.00 \mu\text{g/ml}$ ). After various treatments were started, SNP 276 of the adiponectin gene did not associate with significantly different serum adiponectin levels.

Again, the serum adiponectin levels after glimepiride therapy reported by Nagasaka et al. (1) were quite higher than our results. Although cautious interpretation of our results is necessary because the present study is cross-sectional and the number of subjects is small, multiple factors such as glycemic control per se, obesity (4), polymorphisms of the adi-

ponectin gene (3), or peroxisome proliferator-activated receptor- $\gamma$ 2 gene (5) may affect serum adiponectin concentration. In addition, therapy with sulfonylureas, such as glimepiride (1) and gliclazide, is a possible affecting factor for serum adiponectin level. Prospective and large-scale studies are needed to clarify the interactions between environmental factors or therapeutic interventions and genetic factors on serum adiponectin concentrations.

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**Acknowledgments**— This work was supported by a Grant-in-Aid for Scientific Research (no. 14571106) (to T. Yoshida) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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## Glimepiride and Serum Adiponectin Level in Type 2 Diabetic Subjects

Response to Yoshioka, Yoshida, and Yoshikawa

We thank Yoshioka, Yoshida, and Yoshikawa for their comments on our article (1) in this issue of *Diabetes Care* (2). We reported that serum adiponectin concentration increased after 3 months' glimepiride treatment in type 2 diabetic patients (1). They indicated that baseline values of serum adiponectin ( $22.1 \pm 2.7 \mu\text{g/ml}$ , mean  $\pm$  SE) seem to be higher than those expected from subjects with greater BMI ( $26.5 \pm 0.9 \text{ kg/m}^2$ ) and homeostasis model assessment of insulin resistance ( $5.0 \pm 0.8$ ) levels. First, we must apologize for not having corrected the final results of serum adiponectin concentration by using the ratio of sample dilution. The correct results of our study (1) are as follows: serum adiponectin concentration increased from  $11.1 \pm 1.3$  to  $14.2 \pm 1.4 \mu\text{g/ml}$  (29%,  $P = 0.015$  by Wilcoxon's sign-rank test) in the glimepiride-treated patients ( $n = 28$ ), and the concentration also increased from  $9.4 \pm 1.5$  to  $10.3 \pm 1.7 \mu\text{g/ml}$  (10%,  $P = 0.034$ ) by metformin treatment in another group of type 2 diabetic patients ( $n = 12$ ) matched with the glimepiride group for sex, age, BMI, glycemia, and insulinemia. Statistical analysis and data interpretation remained unchanged despite the changes in absolute values of serum adiponectin concentration.

Along with glimepiride (1,3), insulin-sensitizing thiazolidinediones are known to increase mRNA and circulating levels of adiponectin (4,5). We have also confirmed that serum adiponectin concentration increased from  $9.1 \pm 2.3$  to  $19.6 \pm 2.0 \mu\text{g/ml}$  (123%,  $P < 0.001$ ) in 15 type 2

diabetic patients (10 men and 5 women, aged  $61 \pm 2$  years, BMI  $27.2 \pm 0.4 \text{ kg/m}^2$ ) after 4 months' pioglitazone treatment, which was concomitant with improvements in fasting glucose from  $161 \pm 6$  to  $137 \pm 6 \text{ mg/dl}$  ( $P = 0.023$ ), HbA<sub>1c</sub> from  $7.9 \pm 0.2$  to  $7.2 \pm 0.2\%$  ( $P = 0.002$ ), and homeostasis model of insulin resistance from  $5.9 \pm 3.0$  to  $3.8 \pm 0.4$  ( $P = 0.025$ ). Very recently, blockade of the renin-angiotensin system was also shown to increase serum adiponectin concentration (15% by temocapril and 30% by candesartan, respectively) as well as insulin sensitivity in hypertensive men (6). Therefore, at least three kinds of therapeutic interventions are known to increase both adiponectinemia and insulin sensitivity in men. The mechanisms responsible for increased adiponectinemia by glimepiride and blockade of the renin-angiotensin system await further investigation. In addition, we agree with Yoshioka, Yoshida, and Yoshikawa in that further clinical study is also necessary to establish the long-term beneficial effects of such pharmacological interventions to increase adiponectinemia in type 2 diabetic patients.

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## Comparison of Repaglinide and Nateglinide in Combination With Metformin

Response to Raskin et al.

I believe there are significant limitations in the study by Raskin et al. (1) in the June issue of *Diabetes Care* that preclude broad conclusions about the relative efficacy of nateglinide and repaglinide. They presented the results of a "head-to-head assessment of the relative efficacy and safety of repaglinide versus nateglinide, under conditions of combination therapy with metformin."

The authors concluded that when both agents were compared in combination with metformin, repaglinide lowered fasting plasma glucose and HbA<sub>1c</sub> significantly better than nateglinide and with a similar safety profile. The design of the study precludes drawing conclusions about the comparable efficacy of these



agents. Patients were titrated to 2 g/day of metformin (if they were currently taking metformin) or switched from either a sulfonylurea or Glucovance to metformin, which was titrated to 2 g/day. Titration to the final metformin dose occurred over 4 weeks, at which point either repaglinide or nateglinide was added.

Combination therapy is usually initiated as either first-line therapy in drug-naïve patients or added to stable doses of current therapy if glycemic goals are not met. This study was neither a head-to-head comparison of initial combination therapy with repaglinide/metformin versus nateglinide/metformin nor a true comparison of repaglinide and nateglinide added to metformin. In order to compare the efficacy of these agents as add-on therapy to metformin over a 16-week period, patients should have been maintained on the final dose of metformin for a sufficient period to allow their glycemic control to stabilize and establish a clear baseline.

The most important limitation of the study is that the nateglinide/metformin treatment arm was biased by including patients recently treated with sulfonylureas. The nateglinide label states that patients should not be switched from a sulfonylurea to nateglinide. Over one-third (33 of 96) of patients receiving the nateglinide/metformin combination had been on sulfonylurea monotherapy or Glucovance before being switched to the combination and were therefore treated outside of product labeling.

In addition, the underlying assumptions and relevant background information whereby the imputation method was chosen to handle missing data are not provided. Imputation is generally considered exploratory in nature, whereas the last observation carried forward approach is conservative and appropriate when reductions in the parameter under consideration reflect the improvement of disease.

Finally, the authors conclude that repaglinide achieved improved glycemic control with no difference in safety compared with nateglinide; however, there was a 3.5-fold increase in the incidence of hypoglycemia with repaglinide compared with nateglinide.

We believe that for the appropriate patient, nateglinide is a valuable treatment option to control postmeal glucose and reduce HbA<sub>1c</sub> and trust that physi-

cians will continue to exercise discretion in evaluating product comparisons before making clinical decisions.

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## Comparison of Repaglinide and Nateglinide in Combination With Metformin

Response to Baron

We have seen Baron's letter in this issue of *Diabetes Care* (1) regarding our recent clinical research trial (2) and wish to point out the following facts for readers.

Regarding the matter of whether sufficient time was allowed to develop a response to metformin therapy, the duration of metformin treatment in this trial reached 20 weeks, which is more than enough time for metformin effects to stabilize. As shown in Fig. 1B of the arti-

cle, fasting plasma glucose values showed little or no change for either therapy group in the times from 4 to 16 weeks of therapy. The final fasting plasma glucose values achieved during repaglinide/metformin or nateglinide/metformin therapy were clearly different, and HbA<sub>1c</sub> values reflected this difference.

The issue of the possible effects of prior treatment is a consideration that is not unique to our study. This is precisely what the randomization procedure was intended to address. Statistical testing for imbalance between the treatment groups for previous oral antidiabetic drug therapy yielded a *P* value of 0.86 (any imbalances were insignificant).

Regarding concerns that a subset of patients previously treated with a sulfonylurea may have been unresponsive to nateglinide/metformin therapy, combination therapy enrollment of a patient population entirely lacking previous sulfonylurea therapy would be a doubtful reflection of clinical practice reality. When patients from this clinical trial were analyzed based on prior therapy, repaglinide/metformin produced significantly greater reductions of HbA<sub>1c</sub> values than nateglinide/metformin for patients who had previously received metformin, as well as for those who had previously received sulfonylureas (including Glucovance). The comparison of Table 1 makes it clear that the overall study conclusions were not solely determined by the nateglinide/metformin response of patients previously treated with sulfonylureas. While patients having prior sulfonylurea therapy had a lesser response to nateglinide/metformin than those previously treated with metformin, the majority of enrolled patients in this study had received prior metformin therapy. Both patient subsets showed significant HbA<sub>1c</sub> reductions from baseline for both treatment regi-

Table 1—Change in HbA<sub>1c</sub> values by prior therapy

| Previous therapy subset          | Repaglinide/<br>metformin |   | Nateglinide/<br>metformin |   | <i>P</i> (repag/met<br>vs. nateg/met) |
|----------------------------------|---------------------------|---|---------------------------|---|---------------------------------------|
|                                  | <i>n</i>                  | Change in<br>HbA <sub>1c</sub> from<br>baseline | <i>n</i>                  | Change in<br>HbA <sub>1c</sub> from<br>baseline |                                       |
| Total study population           | 92                        | −1.28 (0.1)                                     | 89                        | −0.67 (0.1)                                     | <0.001                                |
| Prior metformin                  | 56                        | −1.29 (0.16)                                    | 60                        | −0.77 (0.11)                                    | 0.002                                 |
| Prior sulfonylurea or glucovance | 36                        | −1.27 (0.16)                                    | 29                        | −0.47 (0.19)                                    | 0.006                                 |

Date are means ± SE.





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## Meta-Analysis of Low-Glycemic Index Diets in the Management of Diabetes

### Response to Franz

In her editorial (1) accompanying the meta-analysis carried out by Brand-Miller et al. (2), Dr. Franz describes the glycemic index as “not the most effective nutrition therapy intervention.” Her conclusion appears principally based on the fact that the reduction in HbA<sub>1c</sub> by 0.4–0.6% units (a 7.4% decrease in glycated protein is equivalent to ~0.6% HbA<sub>1c</sub> units) when comparing high- and low-glycemic index diets is less than that seen when considering other dietary manipulations, which may achieve decreases in HbA<sub>1c</sub> of 1–2% units (a 15–22% decrease in HbA<sub>1c</sub>). Franz appears to have missed a pivotal issue clearly discussed by Brand-Miller et al. in their article (2). The observed improvement in glycemic control is the net improvement over and above that of standard current best practice nutrition therapy (and medication) in the institutions where the studies were conducted. By failing to acknowledge the additional benefit that may be achieved by the choice of low-glycemic index foods and emphasizing only the importance of total carbohydrate, the American

Diabetes Association may be depriving people with diabetes of the full benefit of nutrition therapy. It is noteworthy that the recommendations of the Nutrition Study Group of the European Association for the Study of Diabetes (3) and the Food and Agriculture Organization/World Health Organization Expert Consultation on Carbohydrates (4) include advice to use the glycemic index as a means of determining the most appropriate choices of carbohydrate-containing foods.

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## Meta-Analysis of Low-Glycemic Index Diets in the Management of Diabetes

### Response to Brand-Miller et al. and Mann

Mann (1) and Brand-Miller et al. (2) state in this issue of *Diabetes Care* that study subjects have been on previous nutrition therapies before the implementation of low- versus high-

glycemic index diets. Although this may be the case, in reviewing the studies included in the meta-analysis, only two studies state this clearly. The first is the study by Fontvieille et al. (3), in which the low- compared with high-glycemic index diet did not improve HbA<sub>1c</sub> levels over 5 weeks but did result in a decrease in fructosamine ( $P < 0.05$ ). The second is the study by Heilbronn et al. (4), wherein subjects participated in 12 weeks of energy restriction. After 4 weeks on a weight loss diet similar in composition to the average Australian diet, the subjects were randomized to a low- versus high-glycemic index diet for 8 weeks. At week 12 there was no statistically significant difference in improving glycemic control or weight loss between the low- and high-glycemic index groups. However, if subjects in the reported trials had been on previous food/meal planning approaches, it supports the position of the American Diabetes Association, which holds that there is not evidence “to recommend use of low-glycemic index diets as a primary strategy in food/meal planning,” (5) but as is suggested in the editorial, “glycemic responses of foods can best be used for fine-tuning glycemic control” (6).

There are three questions that need answering in order to assist clinicians in deciding on an intervention approach. First, have two different approaches been compared and which approach has the better outcome? This is the question that Brand-Miller et al. addressed in their meta-analysis (7). They determined that low-glycemic index diets compared with high-glycemic index diets resulted in a small but significant improvement in glycemia (7.4% reduction in glycated proteins). Although Brand-Miller et al. (2) state in their letter that the change in HbA<sub>1c</sub> is >0.6%, they also state in their conclusion that “after an average duration of 10 weeks, subjects who were following low-glycemic index diets had HbA<sub>1c</sub> levels ~0.4% lower than those ingesting a high-glycemic index diet.” But regardless if it is 0.4 or 0.6%, it is still less than other nutrition intervention outcomes cited in the editorial, which report decreases in HbA<sub>1c</sub> of ~1–2% and, therefore, are better choices for primary nutrition therapy interventions (8,9).

The second question is of equal importance. What is the expected outcome from the intervention? Table 1 lists the studies included in the meta-analysis with



