OBSERVATIONS

Primary Prevention of Type 2 Diabetes Through Nutritional Counseling

Previous studies have reported convincing evidence that type 2 diabetes can be prevented by the adoption of a healthy lifestyle in overweight subjects with impaired glucose tolerance (1,2). Although intensive lifestyle intervention can result in significant improvements in a range of clinical and metabolic variables, it is uncertain whether nutritional intervention programs are feasible in the health care system of developing countries (3). The purpose of this study was to evaluate the impact of low-cost nutritional intervention in changing the lifestyle of adults attending a primary health care center in São José do Rio Preto, São Paulo State, Brazil.

We carried out a randomized controlled trial. Of the 259 volunteers (203 women and 56 men) contacted from April 2000 to March 2001, 104 eligible nondiabetic subjects (83 women and 21 men, aged 30–65 years, BMI 24–35 kg/m^2) were randomly assigned to two groups: nutritional counseling and control. Participants in the control group did not receive any individualized intervention during follow-up but received the same health check and blood sampling as the intervention group. Each subject in the intervention group received three individualized nutritional counseling sessions during the first 6 months aimed at increasing intake of fruits (at least two servings per day), vegetables (at least five servings per day), and skimmed dairy products (two or three servings per day), together with reduced intake of saturated fat (<10% of the calories by reducing red meat [less than two servings per day]) and maintaining consumption of total fat at ~30% of calories. After the second health check 6 months after baseline, the subjects did not receive any further intervention. The significance of differences between groups was tested by χ^2 analysis or Student's *t* test.

At baseline, characteristics and dietary intake of energy and macronutrients were similar between groups. After 6 months of follow-up, the mean weight reduction in the intervention group (−3.1%) was greater than in the control group (0.4%). Significantly greater improvements were seen at the 6-month follow-up in waist circumference (−2% vs. 0.2%), total cholesterol (−12.3% vs. −0.2%), LDL cholesterol (−15.5% vs. 4%), and fasting plasma glucose (−5.6% vs. 0.1%) in the intervention group compared with the control group ($P < 0.05$). At the 12-month follow-up visit, when we evaluated the maintenance of lifestyle changes, the differences in weight (−3.1% vs. 0.5%) and waist circumference (−2% vs. 0.1%) remained greater in the intervention group ($P < 0.01$). Both groups reduced serum total cholesterol after 1 year of follow-up.

The present study provides evidence for the impact of nutritional intervention programs on well-known risk factors for type 2 diabetes and related diseases among overweight subjects at primary health care centers. A second finding was the significant weight loss and decreased waist circumference, total cholesterol, and LDL cholesterol with only three individualized dietary sessions at the 6-month follow-up, suggesting that less intensive lifestyle programs, with limited resources, are effective in changing food consumption and improving metabolic control and quality of life.

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Syzygium cumini (L.) Skeels in the Treatment of Type 2 Diabetes

Results of a randomized, double-blind, double-dummy, controlled trial

Tea, extracts, solutions, and other preparations from plants with a putative antihyperglycemic effect have a worldwide utilization in the treatment of diabetes (1). Among them, the tea prepared from leaves of jambolan [*Syzygium jambos* (L.) Alst or *Syzyguium cumini* (L.) Skeels] is largely used in our city (2) and elsewhere (3). We demonstrated that the tea and extracts from different parts of the plant had no effect in normal rats (4), rats with streptozotocin-induced diabetes (5), and normal volunteers (6). An antihyperglycemic effect in patients with diabetes, however, could not be ruled out, since its mechanism of action could depend on specific abnormalities of diabetes in humans.

In this double-blind, double-dummy clinical trial, we randomized patients with type 2 diabetes to receive a tea prepared from leaves of *Syzygium cumini* (two grams per liter of water, taken as water substitute) plus placebo tablets, placebo tea (prepared with dried leaves of *Imperata braziliensis* Trinius) plus glyburide tablets (5 mg twice a day), or placebo tea plus placebo tablets.

Fasting blood glucose levels decreased significantly in participants treated with glyburide and did not change in those treated with the *Syzygium cumini*

tea and in the participants who received placebos from tea and glyburide (Table 1). BMI, creatinine, γ-glutamyl transferase, alkaline phosfatase, SGOT, SGPT, 24-h glicosuria, 24-h proteinuria, triglycerides, and total, LDL, and HDL cholesterol did not vary significantly among the groups.

With this clinical trial, we have completed a cycle of experiments showing that the tea and extracts prepared from leaves of *Syzygium cumini* are pharmacologically inert. Patients and physicians should not rely on the putative antihyperglycemic effect of this tea, and perhaps of other folk medicines, that pretend to have such an effect. The investigation of plants with potential clinical utility could start with a clinical trial testing the effect of folk preparations in order to isolate the active principles of those products that show pharmacological activity in this model.

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Table 1—*Fasting blood glucose levels in participants treated with Syzygium cumini tea, glyburide, and placebos from tea and glyburide*

Group (*n*)	Fasting blood glucose (mmol/l)		
	Baseline	14th day	28th day
S. cumini (9)	8.7 ± 1.2	8.8 ± 2.3	9.1 ± 2.0
Glyburide (9)	8.8 ± 1.1	7.3 ± 1.2	6.8 ± 1.7
Placebos (9)	9.2 ± 1.1	10.2 ± 2.1	10.1 ± 1.9

$P = 0.015$ for the interaction of time/treatment with glyburide.

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ADHD: A Diabetic Hyperglycemic Dilemma

This report describes transient self-limiting hyperglycemia following recreational ingestion of dexamphetamine. Amphetamines are noncatecholamine sympathomimetic amines with central nervous system stimulant activity. Dexamphetamine is used to treat narcolepsy and ADHD (attention deficit/hyperactivity disorder). It may also be abused for recreational purposes. Dexamphetamine, the dextro isomer of d,l-amphetamine sulfate, can induce hyperglycemia in rats (1).

A slender 20-year-old woman presented to her family doctor with a 10-day history of dizziness, nausea, diarrhea, lethargy, and loss of 6 kg in weight over recent months. Her temperature was 37.3°C, blood pressure 120/70 mmHg, and pulse rate 120 bpm. Finger prick blood glucose was 22.9 mmol/l, with 4^+ glycosuria and 3^+ ketonuria. There was no relevant past medical history. She was taking no prescribed medications. Her great aunt had type 1 diabetes. She was referred to the emergency department with a provisional diagnosis of newly diagnosed type 1 diabetes and ketoacidosis. In the emergency department, there was 2^+ glycosuria and trace ketonuria. In venous blood, the pH was 7.45, pCO_2 30.3 mmHg, pO_2 51.2 mmHg, HCO_{3-} 20.6 mmol/l, and base excess −1.9 mmol/l. Plasma glucose was 19.8 mmol/l. Normal saline was infused intravenously, but initiation of an insulin infusion was delayed inadvertently. Two hours later, the blood glucose had fallen to 13.2 mmol/l and returned to normal over the next 10 h without insulin. A fasting blood glucose the next day was 3.9 mmol/l.

On further inquiry, she admitted to ingesting 30 mg of dexamphetamine tablets 24 h before her presentation. Plasma dexamphetamine level was 4 μg/l at baseline in the emergency department and undetectable 20 h later. Random pre- and postprandial blood glucose recordings over the next 4 days were all <6 mmol/l. The HbA_{1c} was 4.8% (<6%). The emrgency department admission plasma C-peptide was 5.2 nmol/l (0.30–1.20 nmol/l). Later, the fasting C-peptide was 0.57 nmol/l. GAD65 and islet cell autoantibodies were absent. She declined formal glucose tolerance testing.

Structural analogues of dopamine (DA), including d-amphetamine, induce transient dose-dependent hyperglycemia in rats, possibly as a result of activation of hindbrain DA receptors, inducing epinephrine release from the adrenal medulla and influencing glucoregulation via adrenergic receptors at various sites (1). Other studies (2,3) have found that stimulation of D_2 and D_3 (but not D_1) DA receptors in the brain can elevate blood

glucose in rats and support the theory of increased sympathetic adrenal activity as a mechanism. In addition, analogs of DA may directly inhibit insulin release in rat pancreatic islets through α_2-adrenergic receptors (4).

During the 1990s, a progressive decline in the perceived risk of recreational drug use was accompanied by increased recreational use of stimulants (5). Prescribed stimulant use in Australia increased fivefold (6). This patient presented with otherwise unexplained hyperglycemia. Resolution of this was associated with clearance of dexamphetamine from the blood. There is a theoretical basis for this in rat studies. Amphetamine use should be considered in the differential diagnosis of atypical hyperglycemic presentations.

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Pioglitazone Treatment of Insulin Resistance in a Patient With Werner's Syndrome

Werner's syndrome (WS) is a disease of adult progeria characterized by various phenotypical abnormalities, including prematurely graying hair, a bird-like face, slender extremities, cataracts, and endocrine dysfunction. Mutations in the DNA helicase gene *WRN* have been shown to be responsible for this disorder. The condition is associated with glucose intolerance in ~70% of patients, a complication predominantly resulting from insulin resistance. Since thiazolidinediones have been shown to enhance insulin sensitivity in patients with insulin resistance, we have treated a WS patient with pioglitazone.

A 58-year-old woman with WS was admitted for improvement of glycemic control. The diagnosis of WS was based on her clinical features and the reduced life-span of her fibroblasts in vitro. The genotype of this patient was heterozygote with mutation one in the WS gene, suggesting a compound heterozygote (1). Her glycemia was poorly controlled (HbA_{1c} 9.4%) without any hypoglycemic agents or insulin. Liver dysfunction was also observed (aspartate aminotransferase 123, alanine aminotransferase 108). After 1 week of treatment with dietary restriction alone, administration of 15 mg pioglitazone daily was initiated. After 16 weeks of pioglitazone treatment, fasting plasma glucose improved from 152 (before pioglitazone) to 113 mg/dl, and the ameliorating effects of pioglitazone on insulin resistance were also indicated by the decrease in immunoreactive insulin from 39 (before pioglitazone) to 17 μU/ml. HbA_{1c} fell to within the normal range from 9.4%, and liver dysfunction also normalized.

Adiponectin, a protein secreted by adipose tissue, is present at lower levels in the plasma in subjects with obesity or type 2 diabetes and is closely correlated with the degree of insulin resistance as assessed by glucose clamp technique (2). Adiponectin also has a number of vascular protective effects. Although plasma adiponectin levels were very low (1.83 μg/ml) in this patient, they increased to 9.7 μg/ml at 12 weeks and 17.4 μg/ml at 24 weeks of pioglitazone treatment. In contrast, leptin levels were initially high (20.3 ng/ml) but decreased to the high end of normal (11.2 ng/ml) following pioglitazone treatment. Interestingly, serum levels of high-sensitivity C-reactive protein were initially >0.5 mg/dl but normalized to 0.03 mg/dl at 12 weeks of pioglitazone treatment.

These results suggest that pioglitazone was effective in ameliorating impaired insulin sensitivity, thereby improving glycemic control. It may also counteract atherosclerosis by diminishing inflammatory processes. Pioglitazone activates peroxisome proliferator–activated receptor γ, which increases the triglyceride content of white adipose tissue and lessens the triglyceride content in liver and muscle, leading to amelioration of insulin resistance (3). In fact, liver dysfunction that had been seen in this patient for years returned to normal after 12 weeks of pioglitazone treatment. Pioglitazone may induce adipocyte differentiation from preadipocytes, allowing further uptake of energy overflow as fatty acids and also leading to additional production of adiponectin, which decreases insulin resistance. Additionally, the apoptosis of large adipocytes may lead to decreases in tumor necrosis factor-α, free fatty acids, and resistin (4), resulting in lowered insulin resistance and inflammation.

The insulin resistance and low adiponectinemia of WS may result from alterations in "adipocyte." Abnormalities of fat distribution have been reported in WS patients (5), and, indeed, though the present patient was thin and had lipoatrophy in the extremities, she had augmented abdominal adipose tissue. The area ratio of visceral to subcutaneous fat was 0.51 by abdominal computed tomography, though this ratio was reduced to 0.36 at 24 weeks of pioglitazone treatment, suggesting that the effects of pioglitazone on adipose tissues could have had a role in improving insulin sensitivity. Furthermore, this effect of pioglitazone might retard, at least partly, the progress of WS, though this remains to be observed in the future.

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Continuous Subcutaneous Insulin Infusion in Older Patients With Type 1 Diabetes

Insulin pump therapy has been used in patients with type 1 diabetes for 25 years (1–3). In recent years, several studies have demonstrated that continuous subcutaneous insulin infusion (CSII) is also safe and effective in adolescents and children (4–9). In the majority of studies, CSII has been shown to improve HbA_{1c} while not changing or decreasing the risk of hypoglycemia. There is little information about the optimal treatment of older adults with type 1 diabetes (10). Risk for hypoglycemia is reported to be increased in older patients with diabetes and in those with long-standing diabetes, especially in those treated with injected insulin (11). We hypothesized that switching from multiple daily injection of insulin (MDI) to CSII in older patients with type 1 diabetes would improve metabolic control of diabetes and reduce the incidence of hypoglycemia.

Thirty-four patients aged >50 years with type 1 diabetes were selected to switch from MDI to CSII from among patients followed at the Naomi Berrie Diabetes Center at the Columbia University Medical Center in New York City. MDI regimens included insulin glargine once daily in 10 patients and NPH insulin twice daily in 24 patients; all patients were additionally treated with premeal insulin analog injections. Twelve patients had a history of retinopathy, 10 had neuropathy, and 9 had nephropathy. Four patients had undergone coronary artery bypass surgery, and one had a history of myocardial infarction. Data were obtained by chart review 12 months before and after initiation of CSII.

Glucose control, as reflected by HbA_{1c}, was significantly improved with 1 year of CSII therapy ($P < 0.05$ by ANOVA). Mean HbA_{1c} was 7.64 ± 0.19% before CSII initiation, 7.23 ± 0.20 after 6 months of pump therapy, and 7.01 ± 0.10% (a significant decline, $P < 0.01$) after 1 year. Rates of severe hypoglycemia were reduced in the patients when treated with CSII. In the year before CSII initiation, seven patients on MDI required emergency room treatment for hypoglycemia. One patient was treated in the emergency room for hypoglycemia in the year following CSII initiation ($P < 0.05$ by exact one-sided P values from McNemar's test). Nine patients had hypoglycemic seizures in the year before pump start and one patient had a hypoglycemic seizure in the first 2 weeks after initiation of CSIII ($P < 0.02$). Mean BMI was 23.7 kg/m^2 (range 18.5–26) before pump start and did not change significantly after 1 year of CSII. No subjects discontinued CSII and returned to MDI.

A limitation of this study is that it was not randomized. The older patients with type 1 diabetes who were treated with pump therapy were carefully selected for CSII, and those unwilling or unable to master the technological and other features of CSII were not included.

These findings suggest that insulin pump therapy leads to decreased rates of hypoglycemia while improving glucose control in selected older adults with long-standing type 1 diabetes. CSII is an important alternative to MDI in older adults with type 1 diabetes, particularly those who experience significant hypoglycemia in association with therapy with injected insulin.

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A Korean Patient With Fulminant Autoantibody-Negative Type 1 Diabetes

Since 11 novel cases of fulminant autoantibody-negative type 1 diabetes were introduced by Imagawa and colleagues (1,2), about 150 additional cases have been reported. The development of typical fulminant autoantibody-negative type 1 diabetes is strictly confined to Japan. Although the pathogenetic mechanism still remains unclear, there is some evidence supporting the immunogenetic predisposition mechanism in the development of this subtype. A fulminant autoantibody-negative type 1 diabetic patient with insulitis and exocrine pancreatitis showed infiltration of a large number of $CD8^+$ T-cell and peripheral GAD-reactive interferon-γ–producing $CD4^+$ T-cell (3). According to previous reports, some HLA haplotypes, DRB1*0405-DQB1*0401, DQA1*0303-DQB1*0401, DQA1*0302-DQB1*0303, and DRB*0901 are closely associated with fulminant autoantibody-negative type 1 diabetes (1,4,5).

A 43-year-old man visited Gyeongsang National University Hospital complaining of nausea, vomiting, and epigastric pain, which began 1 day before admission. He was relatively healthy until several bouts of epigastric discomfort, polydipsia, and severe thirst developed 1 week before. He had lost weight: ~7 kg over the last 4 days. Levels of serum glucose (51.9 mmol/l), ketone 3+, serum amylase and lipase (368 and 632 units/l, respectively), and fructosamine (385 μmol/l) were highly elevated, but HbA_{1c} was normal at 5.4%. Arterial blood pH was 7.04. Anti-insulin, anti-GAD, and anti–islet cell antibodies were all negative. No abnormality has been observed on a simple abdominal X ray, computed tomography, and ultrasonography. We treated him with intravenous insulin injections and a large volume of intravenous normal saline administration for diabetic ketoacidosis. On the second day, nausea, vomiting, and epigastric pain had improved. Fasting serum C-peptide was below detection limit at 0.1 ng/ml, and 24-h urine C-peptide was 3.4 ng/day. Based on those clinical and laboratory observations, we concluded that this was a case of fulminant autoantibody-negative type 1 diabetes. HLA typing showed that he was a homozygous haplotype with HLA-DRB1*0901, DQA1*0302, and DQB1*0303.

Among 11 novel cases of fulminant autoantibody-negative type 1B diabetes introduced by Imagawa et al. (1), HLA-DRB1*0901, DQA1*0302, and DQB1*0303 genotypes were found in three patients, and two of them were homozygous. Most fulminant autoantibody-negative type 1 diabetes cases reported in Japan have at least one of two HLA haplotypes, DQA1*0302-DQB1*0303 and DQA1*0303-DQB1*0401 (1,5), also known as susceptible haplotypes for type 1 diabetes in Japan. In addition, they have a significantly high prevalence for heterozygous DQA1*0302, DQB1*0303 and HLA DQA1*0303, DQB1*0401 (RR13) HLA haplotypes rather than homozygous DQA1*0302, DQB1*0303 HLA haplotypes. The HLA DRB1*0901 allele is not only associated with fulminant autoantibody-negative diabetic patients but is also a highly frequent HLA DR subtype in type 1A diabetes in Korea and Japan (1,6). The homozygotes with HLA-DRB1*0901-DQB1*0303 were more frequent in type 1 diabetic than in control subjects, but there was no difference in haplotype frequency between the fulminant autoantibody-negative group and type 1A diabetes (4). In addition, the HLA-DRB1*09 has close linkage disequilibrium with the HLA DQA1*0302, DQB1*0303 haplotype in the Korean and Japanese population.

In conclusion, this case is very similar to those reported in Japan in terms of genetic and clinical characteristics. This finding suggests that the haplotype (DRB*0901-DQA1*0302-DQB1*0303) might be a considerable risk allele for fulminant autoantibody-negative type 1 diabetes as well as type 1 diabetes in Far East Asia, although the immunogenetic mechanism of this novel disease entity remains to be clarified further.

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The American Cancer Society, American Diabetes Association, and American Heart Association Joint Statement on Preventing Cancer, Cardiovascular Disease, and Diabetes

Where are the social determinants?

By focusing on shared causes of diabetes, cardiovascular disease, and cancer, the recent joint statement (1) from the American Diabetes Association, American Cancer Society, and American Heart Association is to be welcomed. However, while the statement draws attention to the importance of influencing lifestyle behaviors, treatments, health systems, and the law, these diseases also share social causes that the statement does not address or acknowledge. The social determinants of these diseases are well recognized and documented in the research literature. These include social inequalities related to income differences and social exclusion, insecure and poor quality employment, lack of social support, poor literacy and lack of education opportunities, and addictions that result from all of the preceding (2).

Not surprisingly, people from socioeconomically deprived communities are more likely to be exposed to these social risk conditions, such that these risk conditions swamp the effects of lifestyle choices. The primary modifiable behavioral risk factors for diabetes and cardiovascular disease are also heavily determined by social conditions (3), while individual and social risk factors tend to compound each other by clustering together (4). In effect, lifestyle choices may be more appropriately referred to as lifestyle chances for the proportion of the population with inadequate access to resources for initiating changes. Compounding this, people from socioeconomically deprived communities tend to benefit least from existing and new health services and treatments (5).

Thus, due to the clustering of these behavioral, systems-related, and poor social conditions, people living in socioeconomically deprived communities are more likely to develop diabetes and cardiovascular disease, are at considerably higher risk of further and more rapid disease progression, and have the least resources and most barriers to subsequent health improvement.

In addition to recommending steps to support willingness to change modifiable behavioral and system risk factors, governments, decision makers, and clinicians need to promote individual and community capacity to live healthier lives and support health policies and legislation that tackle both individual and societal or structural causes of the social conditions that give rise to these common diseases.

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COMMENTS AND RESPONSES

Effectiveness of Diabetic Therapeutic Footwear in Preventing Reulceration

Response to Maciejewski et al.

The report by Maciejewski et al. (1) concerning the three quoted articles from our institution (2–4) is flawed. Our 1990 article is one of the first ever to attempt to assess custom-made "diabetic" footwear in a scientific manner. It was an observational study (not a trial), which could serve for generating hypotheses concerning technical features of diabetic footwear, the selection of patients for footwear studies, etc., rather than for settling the issue of the effectiveness of whatever kind of diabetic footwear.

Our second article is from 1994 (3) and was an observational study as well (as was stated explicitly several times, even in the title). It reported that patients who differed significantly in compliance toward both footwear and footcare (which Maciejewski et al. failed to mention) differed in outcome (e.g., the incidence of

foot lesions). This article should have been included in Table 2 (multifactorial studies) rather than in Table 3 (studies of footwear) of the Maciejewski et al. (1) report.

Regarding our third article from 2003 (4), the internal validity was rated "poor" by Maciejewski et al., who criticized "uncertainty on whether insurance denial [of footwear coverage] was a proxy for insurance differences or lower incomes" (1). Had the authors of this article been asked for additional information, as is common practice of writers of metanalyses, Maciejewski et al. would have learned that in Germany, every citizen is obliged to be member of a health insurance, either legal or private. The vast majority of citizens belongs to one of the several hundreds of legal health insurances. While the legal insurances have to follow all the same governmental standards in terms of fees and benefices irrespective of the income of the insured person, the private insurances do not. In our article (4), patients belonging to a private health insurance were not included.

Finally, reproducing a picture of an unattractive diabetic shoe and claiming that this is an example of the "Chantelau study shoe" (Fig. 1, [1]) is highly unfair. The picture was taken from our 1990 study and shows an admittedly unattractive custom-made shoe. In 2003, we have been studying industrially manufactured LucRo shoes, which are depicted in our publication (4) and which appear even more attractive than the "Reiber study shoe" that Maciejewski et al. have chosen to depict for comparison (Fig. 1, [1]).

Anyone who wants to disprove our data are invited to repeat our study in a more sophisticated trial design (e.g., with step monitors incorporated into the footwear) (5). All relevant technical features of the LucRo shoe have been outlined in detail in our publication (4) to ease further studies in this field.

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Effectiveness of Diabetic Therapeutic Footwear in Preventing Reulceration

Response to Chantelau

We thank Chantelau for his thoughtful comments (1) on our study (2), and we recognize his pioneering work on the influence of patient compliance on the effectiveness of diabetic footwear. We characterized his 1990 and 1994 studies (3,4) as descriptive studies of footwear in the text and in Table 3 of our article on the basis of whether additional interventions were provided to patients. The 1994 study was characterized as a footwear study instead of a multifactorial study because the study had "no regular planning of visits" (4) as a study provision. If foot care had been scheduled at regular intervals in the intervention protocol, Chantelau and Haage's study would have been classified as a multifactorial descriptive study.

We made our internal validity assessment of Busch and Chantelau's 2003 study (5) and all other studies based on the information in the published literature in the English language. We did not contact any authors for additional information because all relevant information for the assessment of study validity should be available in the publications. Treatment allocation in Busch and Chantelau's 2003 study was based on the determination of the insurance provider, an inappropriate strategy for ensuring randomization and balance in observed covariates across treatment arms. This approach to treatment allocation reduced internal validity and did not merit classification as a randomized trial. Finally, we agree that the footwear used in Busch and Chantelau's 2003 study (5) reflects advances in therapeutic footwear design. We hope that this dialogue furthers reulceration prevention research and care for patients with a history of foot ulcers.

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Comparative Roles of Microvascular and Nerve Function in Foot Ulceration In Type 2 Diabetes

Response to Krishnan et al.

We have read the article by Krishnan et al. (1) with much interest. The article found that there was a difference between foot microcirculation in subjects with and without diabetes, but there was no difference between patients with diabetes with or without foot ulceration. There are points in the methodology and conclusions regarding the microcirculatory investigations that we would like to raise with the authors and would be grateful for their opinion. In the methodology, their assessment of the presence of macrovascular disease comprised ankle pressures and clinical evaluation. These assessments are unreliable in diabetes (2,3). As macrovascular disease could have profound effects on microvascular perfusion, might a more robust arterial evaluation, such as toe pressures or color duplex imaging, have been more appropriate? The groups were not all matched for age or BMI. It has been previously demonstrated that TcPo2 is influenced by both these variables and may confound comparative analyses (2). Further, microvascular assessments are likely to be vulnerable to the influence of local ulceration, compromising the validity of comparison with nonulcerated limbs. Microvascular tests should be performed, therefore, at locations on the foot or distal leg less likely to be influenced by adjacent ulceration. Was an attempt made to limit the local influence of ulceration in those individuals included in the ulcer group that had current ulceration? Regarding medication, although the effect on cutaneous perfusion may be relatively small, their reduction or omission in the diabetic groups would have reduced their potential to influence results. Finally, although the groups were relatively small, further subdivision of the ulcer group into those with active disease and those with healed ulcers may have been more informative.

The presence or absence of ulceration in this study was demonstrated to be associated with worsening neuropathy but not with differences in microvascular function. However, the methodology may have confounded the accurate comparison of microcirculatory function. In the conclusions, the microvascular dysfunction demonstrated in the diabetic groups was compatible with the findings of other workers. Although the reduction in cutaneous perfusion in the groups with diabetes was relatively small, preexisting microvascular dysfunction, when exacerbated by increased tissue pressures consequent to local inflammation and sepsis, may be critical to the development of local ischemia and subsequent delayed healing in diabetic foot disease.

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Comparative Roles of Microvascular and Nerve Function in Foot Ulceration In Type 2 Diabetes

Response to Williams, Norman, and Stacey

We value the comments of Williams, Norman, and Stacey (1) in their letter regarding our article (2) on the comparative roles of microvascular and nerve function in foot ulceration in type 2 diabetes. We agree that ankle brachial pressure indexes (ABPIs) should be interpreted with caution in people with diabetes, as medial calcification is common. However, Brooks et al. (3) have shown that toe brachial pressure index does not convey any advantage over ABPI in determining perfusion pressure of the lower limbs except in those with overt calcification, i.e., an ABPI >1.3. We were thus careful not to include any subjects with ABPI >1.3. Moreover, if there were subjects with peripheral vascular disease in the ulcer group, it would have lowered the microvascular response, whereas our study demonstrated no difference. In fact, there were slightly higher responses in those with ulceration. Thus, the key finding of our study was that microvascular studies may not differentiate between people with and without foot ulceration.

As described in our article (2), diabetic subjects were recruited consecutively from the outpatient clinic. The diabetic groups had higher BMIs compared with the control group. We would remind the correspondence that the important comparison was between the diabetic groups. There was no difference in BMI between the diabetic groups, and, thus, BMI would not influence the findings. Again, with regards to age, there was no statistically significant difference between the diabetic groups.

In those diabetic subjects with an active ulcer, the laser studies were performed on the contralateral foot; thus, there was no influence of local inflammation on the microvascular studies. As suggested, the effect of vasoactive medication on maximum blood flow is minimal, and, moreover, similar numbers of subjects in

the two groups were on medication for cardiovascular protection.

We believe that our study design and methodology are robust and conclude that these microvascular tests may not be of additional value in discriminating those with and without ulceration. However, we agree with the correspondents that microvascular dysfunction may play a role in delayed wound healing, as stated in our article.

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Real World Effectiveness of Rosiglitazone Added to Maximal (Tolerated) Doses of Metformin and a Sulphonylurea Agent

Response to Roy et al.

I read with interest the article by Roy et al. (1) regarding the use of triple oral therapy in their minority population. I would like to point out our similar experience in the U.K. with a few take-home messages.

We studied 32 consecutive patients with type 2 diabetes (18 men and 14 women, aged 53 ± 10.6 years [means ± SD], diabetes duration 7.2 ± 5.4 years) in an inner city teaching hospital. Sixteen were South Asians, 8 Afro-Carribeans, and 8 Caucasians. All were on maximal doses of metformin (1,000 mg b.i.d.) and a sulfonylurea (gliclazide, 160 mg b.i.d.) with A1C of 9.20 ± 1.4%.

Our target A1C was also <7.5%, as recommended by the National Institute of Clinical Evidence in the U.K. (2). We used triple oral therapy in all patients, using either 4 mg rosiglitazone (14 patients) or 30 mg pioglitazone (18 patients) in a random fashion. After triple oral therapy, A1C (measured at 4 months) was 8.2 ± 1.6. Thirteen of 32 patients (41%) responded with an A1C <7.5% and remained at this level at 1 year. Nine of these 13 respondents (69%) were South Asians; therefore, this was not surprising given that they are usually more insulin resistant (3). Despite the success of glitazones, the majority of our patients have needed insulin (15 of 19; 4 patients unwilling). Glitazone use was particularly successful in those with a prestart mean A1C of 9.1 (±2.0%), in keeping with suggestions that glitazones work best if used early in the course of the disease process in type 2 diabetes (4).

Thus, our experience in an inner-city ethnic population (where a lot of patients are disinclined to use insulin) is that triple oral therapy can be successful with proper patient selection, but with a precondition that if A1C is not <7.5% after 6 months of use, then the patient will need insulin. We would recommend a trial of triple oral therapy for *1*) taxi/heavy goods vehicle drivers (with obvious implications if insulin commenced) and *2*) individuals in whom prestart A1C is no higher than 9.0%, particularly in the minority population.

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Real World Effectiveness of Rosiglitazone Added to Maximal (Tolerated) Doses of Metformin and a Sulfonylurea Agent

Response to De

We were very interested to learn of Dr. De's (1) experience with triple oral therapy in a population that was comparable to that in our study (2). We observed, in 48 patients, a fall in A1C levels from 9.3 to 7.5% in 4 months, while De saw a decrease from 9.2 to 8.2% in the same time period. Perhaps the difference in the final values was due to the fact that we used a maximal dose of rosiglitazone, whereas he used submaximal doses. Sixty-five percent of our patients reached a goal A1C level of <7.5% at 4 months compared with 41% of his patients; once again, this difference was perhaps due to the differing glitazone doses. Sixty-one percent of our patients, as opposed to all of his, remained at goal at 1 year.

We would disagree with limiting glitazones in patients failing maximal doses of a sulfonylurea and metformin to those

with A1C levels of ≤9.0%. Twenty-four of our 48 patients had initial A1C levels >9.0%. Their average initial value of 10.6% fell to 8.0% at 4 months, with 13 achieving the target level of <7.5%. Of these 13, 6 were not taking rosiglitazone at 1 year, 4 because of failure to maintain the target level, 1 because of edema, and 1 due to loss at follow-up. Even though only approximately half of those with A1C levels >9.0% responded, why not give these patients the opportunity to reach the A1C target level with triple oral therapy? Insulin administration requires much more of a lifestyle change for patients (as well as increased demands on conscientious providers). If the A1C target is not achieved (or once reached, not maintained), patients should then have insulin added to their regimen. Treating to target remains the crucial goal.

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Variability in Activity May Precede Diabetic Foot Ulceration

Response to Armstrong et al.

The study by Armstrong et al. (1), investigating the effect of weight-bearing activity on diabetic foot ulcer risk, provides new information on the role of activity variability in foot ulcer risk and confirms the results of a cohort study published last year. In that study (2), which used 24-h physical activity diaries, every additional hour of daily weight-bearing activity was associated with a 23% reduction in the risk of subsequent foot ulceration.

The approach used by Armstrong et al. to assess "the number of steps taken over a period of time," may not have sufficiently captured the critical elements of weight-bearing activity that place those with diabetic peripheral neuropathy at increased risk of foot ulcers. Waist-mounted accelerometers, such as the Biotrainer they used, may not detect short shuffling steps characteristic of this population (3). Other important parameters include time per day spent weight bearing, the intensity of activity during the day, or the combination of weight bearing and dynamic plantar pressure (the "pressure-time integral," an indicator of plantar tissue stress) (4). Secondly, while they excluded those with peripheral vascular disease, their use of nonparametric statistical tests made it impossible to adjust statistically for the effect of other characteristics that could potentially confound the association between activity and foot ulceration risk (5).

This study nonetheless should provoke a re-examination of the effect of weight-bearing activity on diabetic foot ulcer risk, in particular questioning the traditional clinical belief that weight-bearing activity should be discouraged categorically in this population. While we agree with the speculation by Armstrong et al. that "modulating the 'peaks and valleys' of activity in this population through some form of feedback might prove to reduce the risk for ulceration in this very-high-risk population," another approach to reduce foot ulcer risk may be to promote a carefully "dosed" increase in weight-bearing activity that allows plantar tissues to adapt to increasing loads gradually (6). Further studies are needed to test this hypothesis and investigate the role of weight-bearing activity in plantar tissue adaptation, using technology (which needs to be developed and validated) that measures the pressure-time integral continuously.

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Variability in Activity May Precede Diabetic Foot Ulceration

Response to LeMaster, Mueller, and Sinacore

We greatly appreciate the opportunity to reply to the very thoughtful and insightful letter by LeMaster, Mueller, and Sinacore (1). We believe that the comments raised are very important and deserve this sort of forum.

As to the first suggestion that waist-mounted accelerometers may not be robust enough to capture short shuffling steps taken by many of our less active pa-

tients with diabetes, our only response is that we agree. While the devices we used were highly sensitive and could be very finely calibrated, they do not approach the ability of ankle-worn devices to capture very fine movements of the lower extremity. Our decision to use waist-mounted devices was based on practicality. Waist-mounted pedometers and accelerometers (rather than ankle-worn devices) are highly acceptable to our patients and, we believe, led to a great deal of study adherence and acceptability. One outstanding study that we discuss in our manuscript, that of Maluf and Mueller (2), lasted several days (rather than several months). Many of our patients have a good deal of trouble applying their shoes and stockings in the morning secondary to their morphology and limited joint mobility. Applying an ankle-worn accelerometer (or activity monitors worn on multiple sites) over a prolonged period might not be all that attractive in this setting. That said, we may be entirely incorrect in this assumption. We have more recently begun using ankle-mounted devices with some success. The other fine study discussed by LeMaster et al. (3), used daily activity diaries, which, it might be argued, might be somewhat less accurate than a waist-mounted accelerometer in detecting subtle activity.

As to the second point made by the authors, we completely agree that assessment of total force per day or continuous measurement of pressure-time integral may be a critical factor in assessing risk for reulceration. We look forward to larger trials that can incorporate this metric.

The issue as to the potential for confounding factors affecting activity is a compelling one. It is entirely possible that this was the case in this study. However, the truly profound difference that was noted in variability of activity is a compelling finding and worthy of further investigation.

Finally, it (again) seems entirely reasonable, following the work from Mueller and Maluf (4) and, to a lesser extent, our unit, that modulating activity might have the potential to either increase or lower risk based on dose and duration. Perhaps a slowly applied (with continuous feedback to the patient and clinician) steady increase in activity could reduce risk by improving the quality of plantar tissue and its response to stress. Conversely, we believe, based on these aforementioned works, too little (and perhaps too much) activity might leave the patient outside of a zone of safety. Discovering the upper and lower limits of this zone will be a goal, we are sure, for many investigators in this most fascinating area of inquiry.

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