

## OBSERVATIONS

## Probing the Validity of the Probe-to-Bone Test in the Diagnosis of Osteomyelitis of the Foot in Diabetes

The ability to probe the base of a wound to periosteum or bone (the "probe-to-bone" test) is increasingly used to indicate the likelihood of underlying osteomyelitis. The original study (1) reported sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values of 66, 85, 89, and 56%, respectively. However, this work has been criticized on the grounds of the high pretest probability of the disease (2), since the prevalence of osteomyelitis in the chosen sample (in-patients with clinically overt infection) was 66%. It follows that the usefulness of the test may be very different in less-selected populations. We have therefore determined the validity of the probe-to-bone test in a consecutive series of outpatients attending our own multidisciplinary service.

A total of 81 patients (with a total 104 foot ulcers) attended the clinic over a 5-week period in May–June 2005. Ulcers were probed by one of two specialist podiatrists following debridement. The diagnosis of osteomyelitis was determined by one of two expert diabetologists, who were blind to the results of the probe to bone test. The diagnosis of osteomyelitis was based in each case on the presence of clinical signs of infection (inflammation with or without serous or purulent discharge) in association with radiologic evidence of bone destruction with interruption of the cortex (either at presentation or at any stage over the ensuing 8 weeks), supported when necessary by magnetic resonance imaging and microbiologic analysis of deep tissue samples. Those who were diagnosed with osteomyelitis included those in whom the diagnosis had already been made at the time of probing and those in whom the diagnosis was made later. Nineteen (23.5%) patients were diagnosed with osteomyelitis complicating foot ulcers, in two of whom bone infection complicated two

separate nonadjacent ulcers. Three patients had two or more nonadjacent ulcers, of which only one was associated with osteomyelitis. A total of 14 patients had osteomyelitis complicating a single ulcer. A total of 21 ulcers (20.2% of 104) were associated with osteomyelitis. The probe-to-bone test was positive in 8 of these 21 ulcers and in 7 of 83 without associated bone infection (sensitivity 38%, specificity 91%). While the NPV was 85%, the PPV (the probability that a patient with a positive test would have osteomyelitis) was only 53%. It is possible that the calculation of both sensitivity and NPV might be in part explained by the fact that some cases of osteomyelitis may already have been responding to treatment at the time of probing, but this would not have affected the calculation of either the specificity or the PPV.

These data emphasize that the predictive value of a positive probe-to bone test in the original report was influenced by the high prevalence of osteomyelitis in the population studied. The prevalence of osteomyelitis in the present population was still high at 23.5% patients (20.2% ulcers) but was only approximately one-third of that in the earlier study, and the PPV was correspondingly lower. It is likely that the PPV would be lower still in patients managed in a less-specialized service.

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## An Exploratory Study Into the Effectiveness of a Combination of Traditional Chinese Herbs in the Management of Type 2 Diabetes

While a range of drugs are used to ameliorate the effects of type 2 diabetes and its complications, they tend to slow rather than stop the progression of the disease (1). Many herbs have been used traditionally by different cultures in the management of type 2 diabetes (2); however, in general there is little scientific evidence to support their efficacy. The aim of this project was to conduct a small-scale trial to examine the effects of a commercial combination of *Trichosanthes kirilowii*, *Polygonatum sibiricum*, *Dioscorea opposita*, *Panax ginseng*, and *Stevia rebaudiana* and chromium nicotinamide (Glucostat; Health World Limited, Eagle Farm, Australia) on type 2 diabetic subjects who are not yet taking orthodox medication.

Four male and six female subjects aged between 33 and 70 years who had been diagnosed with type 2 diabetes and were on a low glycemic diet participated in this study. They were administered a 3.2-g dose three times a day over a 90-day period. Fasting blood glucose (FBG) data were collected daily using handheld glucometers, and HbA<sub>1c</sub> (A1C), cholesterol, and BMI were recorded at the start and end of the trial. This study was approved by the human ethics committee at the University of New England.

The mean FBG for all patients at the start of the study was  $9.4 \pm 1.1$  mmol/l and ranged from 7.6 to 11.3 mmol/l. Nine patients responded to the treatment showing a significant, though moderate, decrease ( $10 \pm 4\%$ ) in FBG; however, while A1C, cholesterol, and BMI also declined, this did not reach significance. When treatment stopped, FBG rose rapidly over 15–20 days to pretreatment concentrations; however, when treatment was resumed ( $n = 5$ ) FBG again declined by 14.3% (range 8–21) over the following 6 weeks.

This herbal combination may have some benefit in the treatment of type 2 diabetes, particularly perhaps in the early stages of the disease. The effects, while significant, took time to become appar-

ent, and the herbal combination appears to slowly improve the FBG concentrations over a period of continuous use. Surprisingly, this effect was rapidly reversed when the treatment ceased, as blood glucose returned to pretreatment levels within 15–20 days. Those subjects who started to take the herbal remedy again after the withdrawal period showed a more rapid decline in their FBG concentrations than when they first started the treatment. It is unclear from this study whether the FBG would return to euglycemia over a longer period of time, but it appears that the rate of decline slows and may plateau before this was reached.

This study strongly suggests that this combination of traditional Chinese herbs, together with chromium, may be effective in improving glycemic control in people diagnosed with type 2 diabetes. The mechanism of action remains unclear and may be a combination of an increase in insulin responsiveness and glucose uptake. The relative importance of the individual component herbs is also unknown, and we are undertaking further studies to investigate this.

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## Severe Injection Site Reaction to Insulin Detemir

Insulin detemir is a new long-acting insulin analog. Though generally well tolerated, injection site reactions have been reported in 2% of insulin detemir users (1). Most commonly, these untoward reactions manifest as mild injection

site erythema or discomfort and seldom lead to discontinuation of the product. Herein, I report the case of a patient with a severe local reaction to insulin detemir necessitating its withdrawal.

A 37-year-old Caucasian woman with a 25-year history of type 1 diabetes was switched from NPH (Humulin N; Eli Lilly) to insulin detemir (Novo Nordisk) because of poor glycemic control characterized by undue variability of her blood glucose readings and an elevated HbA<sub>1c</sub>. She was also being treated with insulin lispro (Eli Lilly), which she remained on. She had no previous history of injection site problems. With both the previous and the new insulin, she maintained the same proper injection technique and injected, as was her custom, into her abdominal wall.

The patient developed injection site problems within hours of her very first injection of insulin detemir with a characteristic and reproducible pattern occurring with all subsequent injections, ultimately necessitating withdrawal of the insulin within a few days of its institution. Within 6 h of an injection of insulin detemir she would develop a slightly raised, indurated, nonerythematous, minimally uncomfortable, nonpruritic, nontender lesion of ~3 cm. Over the subsequent 6 h, a lesion would expand in size reaching a diameter of 5–6 cm and become erythematous (without central sparing), warm, and moderately tender. Over the subsequent 12 h, a lesion would enlarge further, reaching a diameter of 10 cm, and become markedly indurated, hot, and extremely painful. Over the subsequent 12 h, a lesion would gradually and spontaneously resolve. No fever, chills, rigors, or sweats were experienced. Rotating her injection site around various parts of her abdomen was of no benefit, and a trial injection into the thigh resulted in the identical sequence of events. Insulin detemir was discontinued, and the patient reverted back to her former insulin with no further injection site problems.

Recently, a patient was described who was thought to have experienced a type III allergic reaction to insulin detemir (2); however, unlike the current patient, in this previous report, the lesions encountered were said to be “small” and only “slightly painful” as well as being nonerythematous. Whether the patient described in this case report reacted to the insulin detemir per se or one of its excipients is not known.

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## A Case of Fulminant Type 1 Diabetes Associated With Painless Thyroiditis

Type 1 diabetes is classified as type 1A and type 1B diabetes, which are considered to be caused by autoimmune and nonautoimmune (idiopathic) mechanisms, respectively (1). Fulminant type 1 diabetes is characterized by a rapid-onset diabetic ketoacidosis within a short period of time, normal to near-normal HbA<sub>1c</sub> level at onset, and complete  $\beta$ -cell destruction and was originally reported as a subtype of type 1B diabetes (2). Recently, the involvement of viral infections has been suggested to be the triggering mechanism of fulminant type 1 diabetes (3,4). The involvement of T-cell autoimmunity in this disease, however, has also been reported (5–8). Thus, its etiology is still unclear. Here, we report a case of fulminant type 1 diabetes and painless thyroiditis that presented simultaneously.

A 47-year-old woman was admitted to our hospital in a diabetic ketoacidotic coma. She suffered from fatigue and fever 2 days before admission. One day before admission, she visited a clinic and was given drugs for the common cold. On the day of admission, however, she became comatose and was transferred to our emergency room. Her arterial blood pH was 6.9 and bicarbonate was 1.5 mmol/l. She had markedly increased levels of ketone bodies and serum potassium (7.6 mEq/l). Computed tomography of the brain showed no abnormal findings. After admission, she went into cardiac arrest

and was revived by cardiopulmonary resuscitation then treated in the intensive care unit. Her plasma glucose level was 56.3 mmol/l (1,013 mg/dl) and HbA<sub>1c</sub> was 6.5%. Serum and urinary C-peptide levels were very low (0.2 ng/ml and 3 μg/day, respectively). There was no increase in C-peptide following intravenous administration of 1 mg glucagon. She had no islet-associated autoantibodies (GAD antibody, islet cell antibody, or insulinoma-associated antigen-2 [IA-2] antibody). Her serum amylase was 7,492 IU/l (normal range 30–130). She had elevated lipase and trypsin levels (52 units/l [0–49] and 2,860 ng/ml [100–550], respectively). These findings were consistent with fulminant type 1 diabetes, and she was treated with intensive insulin therapy. The patient had HLA-A24, which is reported to be associated with β-cell destruction (9), and had a homozygous HLA-DR9-DQ3 haplotype, which is strongly associated with autoimmune (type 1A) diabetes (10).

After admission, she had persistent sinus tachycardia. Thirteen days after admission, an echocardiogram revealed paroxysmal atrial fibrillation. At that time, her thyroid hormones were elevated (fT<sub>3</sub> 10.4 pg/ml, fT<sub>4</sub> 4.4 ng/dl) and thyroid-stimulating hormone was suppressed (<0.03 μU/ml). Thyroid-stimulating hormone receptor antibody was negative, and a 99m-Tc-labeled thyroid scan revealed a decreased uptake (Tc RI uptake ratio 0.275% [normal range 0.4–3.0]). Thyroid-stimulating hormone measured at the previous clinic 1 day before her admission was within normal limits. Thus, the onset of fulminant type 1 diabetes and painless thyroiditis appeared to be simultaneous.

Cases of fulminant type 1 diabetes with thyroid disease or with thyroid-related antibody were previously reported (11,12), and these cases were suggested to have immunogenetic characteristics. Painless thyroiditis is also generally considered to be an autoimmune disorder (13). This case also suggests participation of autoimmune mechanisms at the onset of fulminant type 1 diabetes. On the other hand, the association of a viral infection cannot be excluded because of preceding symptoms of infection. In a nationwide survey (14), fulminant diabetes comprises ~20% of Japanese type 1 diabetes with ketosis or ketoacidosis at the onset. This new subtype, however, might be a heterogeneous entity. This is the first case of fulminant type 1 diabetes associ-

ated with simultaneous painless thyroiditis. It is useful to follow such cases to elucidate fulminant type 1 diabetes etiology, and further study is required to clarify its entity.

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## Recurrence of Diabetes After Diarrhea-Associated Hemolytic Uremic Syndrome

We read with interest the article by Suri et al. (1). In this article, we find a systematic review and meta-analysis of articles assessing diabetes during diarrhea-associated hemolytic uremic syndrome (D+HUS). The 21 included studies describe 49 children who developed diabetes during acute D+HUS. Long-term outcome was reported for 44 of 49 children: 13 of 34 survivors were left with persistent diabetes requiring insulin; 11 had persistent diabetes from the outset, while 2 redeveloped diabetes at 3 and 60 months after initial apparent recovery, respectively. The remaining 21 children were reported to have made a complete recovery from diabetes. However, follow-up was <12 months or not reported for these children.

We report a boy with relapse of diabetes after 82 months (6.8 years). This boy was hospitalized with severe D+HUS when he was 6 years old. During his stay in the intensive care unit, he developed hyperglycemia and was treated with insulin during 21 days. Eighty months later he presented with nose obstruction and headache and was diagnosed with sinusitis and polyposis nasi. He was treated with antibiotics, but the complaints persisted. Two months later, he was operated on (functional endoscopic sinus surgery), and postoperatively he received 2 mg beta-methason for 5 days. On the 5th day, he presented in the emergency department with polyuria, polydipsia, and lethargy. His glycemia was 1,500 mg/dl, and his blood pH was 7.33. He was intravenously treated with insulin, and the corticosteroids were ceased.

To differentiate between type 1 diabetes, glucocorticoid-induced diabetes, and post-HUS diabetes, some additional blood tests were done. Pancreatic autoantibodies, including islet cell, insulin, GAD65, and insulinoma-associated protein 2 antibodies were all negative. Insulin was 4 mU/l for a glycemia of 1,453 mg/dl. After normalization of the glycemia, the boy was started on a basal-bolus regimen with insulin aspart and insulin glargine. Twenty months later, he still requires insulin (0.5 units · kg<sup>-1</sup> · day<sup>-1</sup>) and has an HbA<sub>1c</sub> of 6.8%.

Our report in which we describe a relapse of diabetes after 82 months confirms the conclusion of Suri et al. that survivors of D+HUS should have aggressive surveillance and treatment of hyperglycemia, not only in the acute phase but also in the long run.

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## Maternal Age and Prevalence of Gestational Diabetes Mellitus

Maternal age is an established risk factor for gestational diabetes mellitus (GDM), but there is no consensus on the age above which there is significantly increased risk of GDM. In the literature, the lowest cutoff is ≥25 years, as recommended by the American Diabetes Association (1), but there are little data to support this recommendation. To determine the age threshold for increased risk of GDM, we have reviewed the prevalence of GDM, diagnosed by the World Health Organization criteria (2), in the singleton pregnancies managed in our department from 1998 to 2001. Data on maternal anthropometric parameters, parity status, and risk factors for GDM such as booking weight ≥70 kg, BMI ≥25 kg/m<sup>2</sup>, chronic hypertension, significant medical history, and smoking, as well as risk factors identified in our population that included carrier of thalassemia trait (3) and HBsAg (4) and presence of iron deficiency anemia, which reduces the risk of GDM (5), were retrieved from a computerized database. The pregnancies were categorized according to maternal age, i.e., ≤20 years, 20–24 years, 25–29 years, 30–34 years, 35–39 years, and ≥40 years, for statistical analysis (SPSS for Windows version 11.0; SPSS, Chicago, IL) using the  $\chi^2$  test and Pearson's correlation. Multivariate analysis was used to determine the role of advancing maternal age adjusting for the other significant associated factors, and the adjusted relative risk and 95% CI was calculated for each age cohort with the 20–24 years cohort as the reference.

Of the 16,383 women managed in this period, 15,827 (96.6%) women continued their pregnancies beyond the first trimester, and the number (% of total) from the youngest to the oldest cohort were 318 (2.0%), 1,713 (10.8%), 4,446 (28.1%), 5,457 (34.5%), 3,279 (20.7%), and 614 (3.9%), respectively. There was a significant difference and positive correlation in the prevalence of GDM, increasing from 1.3, 2.5, 6.2, 10.3, 21.7, and 31.9%, respectively, from the youngest to the oldest cohort ( $P < 0.001$ ). On multivariate analysis and adjusting for significant confounding factors that included weight ≥70 kg, BMI ≥25 kg/m<sup>2</sup>, HBsAg

carrier, thalassemia trait carrier, significant medical history, multiparity, smoker, and absence of iron deficiency anemia, the risk for the older cohorts was significantly increased as follows: 25–29 years, 2.59 (1.84–3.67); 30–34 years, 4.38 (3.13–6.13); 35–39 years, 10.85 (7.72–15.25); and ≥40 years, 15.90 (10.62–23.80). There was no significant difference for the <20 years cohort.

Our finding indicates that the risk of GDM becomes significantly and progressively increased from 25 years onwards. This supports the American Diabetes Association recommendation on the use of age ≥25 years as the cutoff for screening and the observation that maternal age ≥25 years is the factor most predictive of GDM (6). In clinical practice, maternal age of ≥25 years should be adopted instead of ≥35 years or 40 years as a risk factor for the development of GDM.

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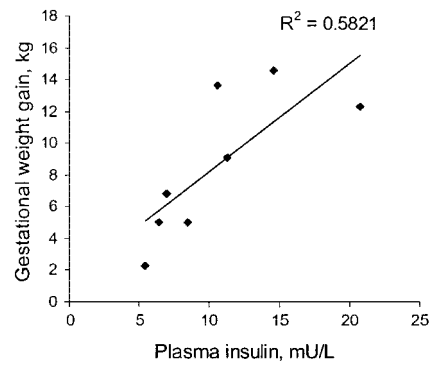
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## Maternal Weight Gain Is Associated With Infant Insulin Concentrations During the 1st Year of Life

Since hyperinsulinemia tracks from childhood to adulthood and is associated with diabetes risk, identifying modifiable conditions during gestation that may impact insulin metabolism in offspring is important. We conducted a pilot study to investigate associations between maternal weight gain and infant insulin concentrations in an underserved population at high risk for diabetes. Mexican or Native American women with an infant <1 year of age provided written consent. Infant weight-for-age Z scores (WAZ) were calculated, and nonfasting plasma samples were analyzed for insulin by standard assay. Pearson's bivariate test was used to assess relationships between variables, and the unpaired *t* test was used to examine differences between means.

A total of 16 women (means  $\pm$  SE)  $21.8 \pm 1.7$  years) and their infants ( $6.4 \pm 0.9$  months; 9 males and 7 females) completed the study, and medical records were available for 9 of these pairs. Based on combined self-reports and medical records, the mean prepregnancy weight was  $71.5 \pm 4.0$  kg, and the mean pregnancy weight gain was  $10.7 \pm 2.4$  kg. Infants were full term with birth weights ranging from 2,495 to 4,309 g ( $3,381 \pm 121.0$  g); WAZ scores averaged  $0.47 \pm 0.23$ . Blood insulin concentrations averaged  $11.5 \pm 1.6$  mU/L. Gestational weight gain was significantly correlated to infant insulin concentrations ( $r = 0.662$ ;  $P = 0.005$ ); however, for nondiabetic women with verifiable pregnancy weight gain ( $n = 8$ ), this association was strengthened ( $r = 0.763$ ,  $P = 0.028$ ; Fig. 1). Infant insulin concentrations ( $n = 16$ ) were not associated with birth weight, infant age, WAZ scores, prepregnancy weight, or maternal age.

These data show that maternal weight gain predicted infant insulin concentrations, explaining nearly 60% of the vari-



**Figure 1**—Correlation of maternal weight gain and infant insulin concentrations ( $n = 8$  mother/infant pairs;  $r = 0.763$ ,  $P = 0.028$ ).

ance in these values. Diabetes during pregnancy has been associated with cord blood insulin and with insulin concentrations in adolescence (1), and in nondiabetic pregnancies, maternal weight gain was related to cord blood insulin in macrosomic neonates (2). Currently, a weight gain of 6.8–11.5 kg is recommended for overweight women, and obese women are advised to gain a minimum of 6.8 kg. In obese, nondiabetic women, minimal gestational weight gain (<5 kg) normalized obstetric outcomes, including hypertension, cesarean section, induction of labor, and macrosomia, and did not adversely affect fetal outcomes (3). Utilizing an emerging obstetric outcome, infant insulin concentrations, our preliminary data support the contention that gestational weight gain should be carefully considered in overweight populations at high risk for diabetes. Differential analyses of our data show that minimal gestational weight gain in the nondiabetic women ( $\leq 5$  vs.  $> 5$  kg) was associated with lower infant insulin concentrations ( $7.2 \pm 0.6$  vs.  $13.4 \pm 2.0$  mU/L;  $P = 0.013$ ). Together, the available data indicate that controlling weight gain during obese pregnancies may be advantageous and that more studies of this nature are warranted.

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## Soluble Tumor Necrosis Factor Receptor 1 Is Strongly and Independently Associated With Serum Homocysteine in Nonobese Japanese Type 2 Diabetic Patients

The major clinical consequence of type 2 diabetes is mortality and morbidity from atherosclerotic vascular disease. With regards to the risk factors responsible for the evolution of atherosclerosis, Bierman (1) estimated that typical risk factors, including smoking, cholesterol, and blood pressure, can account for no more than 30% of excess cardiovascular risk factors in diabetic patients. Thus, other factors seem to play a key role in the progression of atherosclerosis in diabetes.

One potential factor is homocysteine. Homocysteine has been shown to contribute to the development of atherosclerosis in diabetic patients (2). Whereas the deficiencies of folate and vitamin B<sub>12</sub> lead to hyperhomocysteinemia, these deficiencies alone do not completely account for atherosclerotic changes induced by homocysteine in diabetic patients.

Tumor necrosis factor (TNF) is a potent candidate involved in the pathogenesis of atherosclerosis. Rauchhaus et al. (3) demonstrated that elevated soluble TNF receptor 1 (sTNF-R1) has shown to be predictive of cardiovascular mortality in patients with chronic heart failure. We

found that sTNF-R1 is independently associated with albuminuria in type 2 diabetic patients (4). To the best of our knowledge, however, it is not clear whether serum homocysteine is associated with TNF receptor in type 2 diabetic patients. The aim of the present study was therefore to investigate the relationships between serum homocysteine and TNF receptor in patients with type 2 diabetes.

Fifty nonobese Japanese type 2 diabetic patients were studied. Their BMI, HbA<sub>1c</sub>, and serum creatinine were  $22.6 \pm 0.3$  kg/m<sup>2</sup> (range 17.6–26.2),  $7.8 \pm 0.2\%$  (5.5–12.3), and  $0.70 \pm 0.02$  mg/dl (0.46–0.98), respectively. They had not been treated with insulin or any medications known to alter homocysteine level. In conjunction with homocysteine, systolic and diastolic blood pressure, HbA<sub>1c</sub>, glucose, lipids, serum creatinine, TNF- $\alpha$ , sTNF-R1, and sTNF-R2 were measured after an overnight fast.

With univariate analysis, serum homocysteine was positively correlated with age ( $r = 0.361$ ,  $P = 0.012$ ), diabetes duration ( $r = 0.292$ ,  $P = 0.045$ ), serum creatinine ( $r = 0.623$ ,  $P < 0.001$ ), sTNF-R1 ( $r = 0.415$ ,  $P < 0.005$ ), and sTNF-R2 ( $r = 0.371$ ,  $P < 0.01$ ). Other variables including TNF- $\alpha$ , however, were not associated with homocysteine. Multiple regression analyses showed that serum homocysteine was independently associated with serum creatinine ( $F = 20.1$ ) and sTNF-R1 ( $F = 6.9$ ), which explained 49.3% of the variability of homocysteine. Thus, TNF system activity may be responsible for the evolution of atherosclerosis induced by homocysteine in nonobese Japanese type 2 diabetic patients.

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## Phenformin-Induced Lactic Acidosis in an Older Diabetic Patient

A recurrent drama (phenformin and lactic acidosis)

*Editor's note: The authors had the following statement in their letter to me, with which I agree, "Most physicians are aware of the risk of lactic acidosis in patients taking phenformin. However, this side effect is continuously observed because phenformin is still used in Italy, Brazil, and China. We believe that the publication of our observation in an important journal like Diabetes Care may help to prompt governments of these countries to ban phenformin, just like in the rest of the world. This is the only way to prevent further cases of this avoidable, unacceptable and life-threatening complication."*

**A** 73-year-old man with diabetes presented with upper-abdominal pain and nausea. He also had a history of hypertension, a pace-maker implant, and peripheral arterial disease treated with amputation of his left leg. His therapy included ticlopidine, enalapril, omeprazole, and 2 mg glibenclamide/30 mg phenformin b.i.d. The patient was alert and cognitively intact. Blood pressure and heart rate were 120/70 mmHg and 70 bpm, respectively. Radiographs of the chest and abdomen and an abdominal ultrasound study were normal. Laboratory tests disclosed a severe lactic acidosis (pH 6.8, pCO<sub>2</sub> 14.1 mmHg, pO<sub>2</sub> 108 mmHg, HCO<sub>3</sub> 4.9 mmol/l, lactate 21 mmol/l, and anion gap 31 mmol/l). After phenformin discontinuation, the patient's conditions rapidly improved. He was treated with in-

travenous insulin and glucose (1) and discharged 7 days later in good condition.

This report confirms that phenformin-induced lactic acidosis (PLA) is still a public health problem (1,2). To our knowledge, phenformin is still used in Italy, China, and Brazil. In a Medline search, we found 12 cases that occurred in Italy between 1981 and 1998 (2). In two patients phenformin was even brought back into use soon after, thereby questioning the belief that PLA is adequately recognized (2). More importantly, according to data by Intercontinental Marketing Services ([www.imshealth.com](http://www.imshealth.com)), 838,000 preparations of phenformin and a sulfonylurea have been sold in Italy between January and October 2005. Because PLA occurs in 1 of 4,000 patients (3) with a mortality rate of ~50%, these data raise worrying health care considerations. In fact, diabetic patients often have comorbid conditions known to favor PLA.

Phenformin was removed from the U.S. market in 1977, but, surprisingly, cases of patients who have been prescribed the drug abroad are continuously reported (1). Phenformin can also be illegally obtained online or through mail orders to replace metformin, which is more costly. Furthermore, herbal medicines containing phenformin are also consumed in developed countries. In February 2000, the Food and Drug Administration recalled five Chinese herbal medications containing phenformin (4), while Health Canada is currently warning consumers not to take "Shortclean," a phenformin-based Chinese "natural" medicine (5).

Phenformin can always be replaced by metformin, which should not be associated with a higher risk of lactic acidosis compared with nonbiguanide therapies (6). Despite most clinicians being aware of PLA, the only way for preventing further cases is to forbid phenformin in countries where it is still used.

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COMMENTS AND RESPONSES

**Patient Self-Management of Insulin Doses in the Hospital**

*This letter may seem “far out,” but in my experience and that of some of my colleagues, with select patients, usually type 1’s, patient self-management (with physician oversight) yields better glycemic results (and less patient and physician anxiety) than if insulin dosing is left to the vagaries of the busy floor staff. Getting the hospital administration to allow this is often the biggest challenge.*

Reading the exchange of letters in the December 2005 issue regarding the management of inpatient hyperglycemia made me reflect on personal experiences as a hospital patient (1,2). In past years, as surgeons and cardiologists tended to their more immediate tasks, my diabetes was often relegated to a secondary and sometimes seemingly nonexistent

concern. I was frustrated and angered by substitution of the sliding-scale for my normal insulin regimen, especially as my blood glucose spiraled out of control. It is encouraging that this critical issue is receiving increased attention.

My own bouts with surgeries at the University of Pittsburgh Medical Center this past winter highlight the benefits of focusing on inpatient diabetes management. Not only did I demand a consult with my endocrinologist and her staff to develop and implement a treatment plan for my hospital stay, I requested intravenous insulin infusions during surgery and in the recovery room and intensive care unit. The growing evidence supporting the value of infusions is overwhelming.

It is sometimes easy, however, to overlook another effective tool for in-hospital diabetes management—the patient. Undoubtedly, the most helpful step for me was continuing to manage my own insulin pump therapy while in the hospital. Clearly, every patient demonstrating proficiency, whether using a pump or multiple insulin injections, should be encouraged to continue self-management on the nursing floor. For me, this alleviated the anxieties often felt by patients when their diabetes management routines have been disrupted. And the results were phenomenal. My blood glucose stayed within normal ranges almost the entire time! With the help and oversight of my consulting endocrinologist and certified diabetes educators, self-management presented few difficulties for me and relieved the surgical staff of this additional responsibility. Many of the nurses and other hospital staff were actually curious to learn more about insulin therapy and, particularly, pump therapy.

I kept my own glucose monitor and a supply of strips with me, as well as replacement batteries and other pump supplies. While staff would routinely check my blood glucose levels, the timing was somewhat irregular and did not always correlate with meals. I carefully recorded monitor readings, food intake, and insulin dosing to review with my consulting diabetes specialists. I also maintained a cache of glucose tablets and fruit juice to treat inevitable lows. Although these were available on the hospital floor, I was concerned about getting the immediate attention of the nursing staff during a sudden hypoglycemic episode. Nevertheless, I reported every incident and the actions taken for entry into my medical records.

In addition, I reminded every hospital

staff member about my diabetes and my treatment plan, and I always had a family member available to do this when I was unable to speak for myself. While this information was contained in my chart, it is unreasonable to expect that everyone remembers every detail all the time. These approaches kept my diabetes in the forefront and dramatically enhanced each hospitalization.

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**Acute Neuropathic Joint Disease: A Medical Emergency?**

Response to Tan et al.

We read with some interest the commentary by Tan et al. (1) on the management of the Charcot foot in diabetes. While we agree entirely that this condition should be ranked as a medical emergency, because failure to act quickly can lead to irreversible adverse consequences, we do not agree that the evidence is available to support uncritical use of bisphosphonates. The only blinded trials conducted so far did not demonstrate any overt improvement in long-term prognosis (2,3). There is much suggestive evidence to favor the consideration of bisphosphonate use, but it is not currently accepted by all authorities that this therapy is essential.

A number of other treatments also deserve consideration (4,5). For example, intranasal calcitonin and tumor necrosis factor- $\alpha$  antagonists may prove useful, although the efficacy of both has yet to be established in controlled trials. In the absence of evidence to support the use of

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specific treatments, it is accepted by all with a specialist interest in this field that the mainstay of emergency management is the immediate institution of effective offloading, preferably in a total contact cast. Offloading results in protection of the bones and joints of the foot, as well as amelioration of the underlying inflammatory process.

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## Acute Neuropathic Joint Disease: A Medical Emergency?

Response to Jeffcoate et al.

We thank Jeffcoate et al. (1) for their comments on our article (2). To summarize, they agree that neuropathic joint disease (NJD) is in-

deed a medical emergency, but they disagree that bisphosphonates are of proven efficacy. One of the major problems for clinicians at the moment is the failure to recognize early NJD based on several considerations, including other possible diagnosis at presentation, the presence of pain, normal radiographs, and patients presenting to nonendocrinological specialists. Therefore, at the time of initiation of therapy, damage may already be well established and, furthermore, joint offloading with prolonged casting has several drawbacks (3).

It was not the intention of our article to convey the idea that the very early initiation of bisphosphonate therapy before radiographic damage would definitely halt disease. We agree with Jeffcoate et al. that further work needs to be done in this regard. However, given the data from trials in NJD, the safety profile and costs of bisphosphonate therapy, and ease of administration, it would seem reasonable to prescribe these.

It is interesting to note that bisphosphonates may have some structural modification properties in the more common garden variety of osteoarthritis (4) and also some evidence of symptom control (4,5). However, based on the magnetic resonance imaging (MRI) observations that the earliest stages of NJD is strikingly associated with bone edema, which is also a predictor of progressive osteoarthritis joint deterioration in other sites (6), besides the ankle and foot, then it would seem prudent that attempts to inhibit osteoclast function may be of use.

To summarize, we feel that the MRI features of early NJD will allow for early intervention, including those suggested by the authors, at a stage before irreversible joint damage to see whether ultimately progressive joint damage can be prevented. We feel that the MRI observations in early disease have broad implications for raising awareness of the potential for early NJD diagnosis and for monitoring potential therapies.

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## Resistance to Insulin Therapy Among Patients and Providers: Results of the Cross-National Diabetes Attitudes, Wishes, and Needs (DAWN) Study

Response to Peyrot et al.

The recent article by Peyrot et al. (1) concerning the attitudes of both patients and providers with respect to insulin therapy raises some potentially important issues about barriers to an important treatment in diabetes. However, their statement that “U.S. physicians were significantly more disposed to delay insulin therapy than physicians in all other countries . . .” (1) appears to contradict



differences in cited prescribing patterns between type 2 diabetic patients in America, Australia, and Europe. For example, results from the National Health and Nutrition Examination Survey 1999–2000 cohort (2,3) and a large western U.S. study (4) are consistent in finding that ~34% of type 2 diabetic patients on medication are using insulin. However, a more recent study (5) in the Canadian primary care setting reported only a 14% use of insulin, while two independent Australian studies (6,7) and our own results show an insulin prevalence of 16–18%. Studies in Denmark (8) and France (9) establish an insulin prescription rate of 24 and 17%, respectively. It therefore appears that physicians in U.S. are more likely to initiate insulin therapy for type 2 diabetic patients than their colleagues in other Western countries. The discrepancy between physicians' attitudes, as reported by Peyrot et al. (1), and actual practice may represent a lack of generalizability of their findings or that the such "attitudes" are not the principal determinants of prescribing behavior.

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mine physician prescribing behavior. Also important is the level of perceived need for insulin. The relevance of the attitude identified in our study depends explicitly on the level of perceived need for insulin treatment (delay of insulin “until it is absolutely essential”). If the need is perceived as greater in the U.S. than in other countries, U.S. physicians might be more likely to prescribe insulin even if they have a higher threshold for making that choice. The level of perceived need might itself be a function of attitudes or it could be a result of actual differences in need, e.g., higher BMI, worse glycemic control, patient unwillingness to change lifestyles, etc.

We believe that finding out how all of these factors combine to influence physicians' insulin-prescribing behaviors would be a major contribution to the field. We hope that others will continue the study of this issue.

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## Resistance to Insulin Therapy Among Patients and Providers: Results of the Cross-National Diabetes Attitudes, Wishes, and Needs (DAWN) Study

### Response to Phillipov and Phillips

Phillipov and Phillips (1) suggest that our finding (2) that U.S. physicians were significantly more disposed to delay insulin therapy than were physicians in all other countries surveyed contradicted reports from other studies of the proportion of patients with type 2 diabetes taking insulin in the U.S., Australia, and some European countries. Phillipov and Phillips conclude that either our findings cannot be generalized or that attitudes are not the key determinant of prescribing behavior.

We thank Phillipov and Phillips for providing additional information regarding international differences in insulin-prescribing attitudes and behaviors. We agree that attitudes alone do not deter-

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## Beneficial Effects of a Dietary Approaches to Stop Hypertension Eating Plan on Features of the Metabolic Syndrome

Response to Azdbakht et al.

We read with interest the article by Azdbakht et al. (1), showing that a nutritional approach based on a Dietary Approaches to Stop Hypertension (DASH) diet reduced the prevalence of the syndrome by about one-third. This study adds to the mounting evidence that fighting metabolic and cardiovascular disease with diet is possible (2). As the DASH diet is very similar to the Mediterranean diet, these results confirm in the short term (6 months) previous findings obtained over a longer period of time (24 months) (3). The authors did a fine job obtaining such a significant weight loss (13 kg on the average in the weight-control arm and 15 kg on the average in the DASH arm), as the change in body weight expected with a program of intensive lifestyle changes may be less impressive ( $-6.7 \pm 7.9$  kg at 12 months) (3). Perhaps one would have expected a larger resolution of features of the metabolic syndrome in the weight-control arm (19% resolution). To give more strength to their work, the authors should also comment on some inconsistency in Table 2. Fasting blood glucose (FBG) was only 3 mg/dl at baseline in the control group (obviously a mistake); however, it seems difficult to imagine that the DASH diet increased FBG by 15 and 8 mg/dl on the average at 6 months (men and women), as in the RESULTS section the opposite is stated (obviously a mistake). As the table seems imprecise (the reason why values for men are reported as median and for women as mean is unclear), the authors should also check the huge SD of basal FBG. Lastly, there is an important thing missing: the starting and posttreatment quantity of energy consumed by participants is not reported, leaving the reader to assume that all subjects in both arms ate a diet with 500 kcal less than their caloric needs, without any check. The findings of Azdbakht et al. (1) confirm that diet is at least equivalent to drugs in reducing the prevalence of the metabolic syndrome (3–5).

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## Beneficial Effects of a Dietary Approaches to Stop Hypertension Eating Plan on Features of the Metabolic Syndrome

Response to Esposito and Giugliano

We thank Esposito and Giugliano (1) for their attention to our study, in which we showed the beneficial effects of a Dietary Approaches to Stop Hypertension (DASH) eating pattern on components of the metabolic syn-

drome (2). DASH diet is similar to the Mediterranean diet; both have high levels of fiber and isoflavones and a large number of low-glycemic index foods such as vegetables and whole grains (3,4). We agree with Esposito and Giugliano that in the short term, our study (2) confirms the results reported by them previously (3). However, we discussed differences between DASH and Mediterranean diet in the CONCLUSIONS section of our study (2).

We reported a 13-kg weight reduction in the weight-reducing diet and a 15-kg reduction in the DASH diet (2). As it had been mentioned in the RESEARCH DESIGN AND METHODS section of our study, subjects on both weight-reducing diet and DASH diet ate 500 kcal less than their caloric needs. Despite intensive lifestyle changes in the study by Esposito et al. (3), patients did not consume a diet with 500 calories less than their needs. However, the patients reduced dietary caloric intake (if needed) by 170 kcal in the intervention group.

Regarding Esposito and Giugliano's expectation about the larger resolution of features of the metabolic syndrome in the weight-reducing diet, it should be kept in mind that the metabolic syndrome is a constellation of risk factors (high blood pressure, lipid abnormalities, and elevated blood glucose). Although the amount of weight reduction in the weight-reducing diet and DASH group in our study was not significantly different, the decrement of the prevalence of the metabolic syndrome in the DASH and the weight-reducing group was significantly different ( $-35$  vs  $-19\%$ ,  $P < 0.05$ ). Therefore, the nutrient content of the DASH diet may be important. The DASH diet has larger amounts of dairy and calcium that are inversely related to the metabolic syndrome and its components (5). Also, its sodium content is restricted, which could regulate blood pressure. Some studies (6) also have shown no significant effect of weight-reducing diet on some metabolic risks.

Unfortunately, Table 2 in our study (2) has some inconsistencies due to a typing error in the fasting blood glucose (FBG) values in women (the last row). The baseline FBG in the control group was actually 93 mg/dl and in the DASH group 91 and 86 mg/dl after 3 and 6 months, respectively. As it has been stated in Fig. 2, DASH diet decreased FBG by 15 and 8 mg/dl in men and women, respectively. By correcting the mentioned typing error, there would be a logical SD in FBG.

The variables did not have normal distributions in men but were normally distributed in women; this is the reason we have reported medians in men and means in women.

Regarding the amount of energy consumed by subjects, the baseline energy intake in the control, weight-reducing diet, and DASH groups was 2,023, 2,009, and 2,017 kcal/day, respectively. After 6 months, the corresponding energy intakes were 1,997, 1,573, and 1,549 kcal, respectively. It had been mentioned in the RESEARCH DESIGN AND METHODS section that we prescribed a diet with 500 kcal less than caloric needs in the weight-reducing and DASH groups, and we checked the subjects' intake by means of dietary records for 3 days in a month. Nutrients and food group values that have been shown in Table 1 are based on a 2,000-kcal diet; therefore, we could not report the mean of the energy intake in this Table.

Finally, our study (2) and that of Esposito et al. (3) showed that diet could be an important factor in the prevention or

treatment of the metabolic syndrome. However, the effects of a DASH diet on metabolic risks need to be compared with those of other diets (e.g., Mediterranean diet) in future studies.

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