OBSERVATIONS

Remitting Diabetes

A new genetic subgroup?

We describe a previously unreported clinical scenario of remitting diabetes in two young brothers who do not fit existing diagnostic classifications. They may represent a new genetic subgroup of diabetes.

Case 1 presented at 3.6 years with poor linear growth, polyuria, and polydipsia. Diabetes was diagnosed based on a blood glucose value of 11.5 mmol/l and an elevated HbA_{1c} of 7.0% (normal 3.8–6.0). During 3 months' observation, hyperglycemia and an elevated HbA_{1c} persisted. Working diagnosis was very early type 1 diabetes, and insulin was commenced (0.2 units · kg^{-1} · day^{-1}). HbA_{1c} improved from 7.0 to 5.3%. However, linear growth did not improve.

The family also tested asymptomatic siblings and identified hyperglycemia in the 18-month-old brother. Diabetes was diagnosed on repeated blood glucose values >11 mmol/l and HbA_{1c} 9.0%. Although thriving, there was concern of early type 1 diabetes, and he commenced insulin (0.2 units · kg^{-1} · day^{-1}). HbA_{1c} normalized to 5.5% after 16 months. Two additional family members had glucose abnormalities: the 44-year-old father had impaired glucose tolerance (IGT) (glucose 6.4 mmol/l [0 min] and 10.4 mmol/l [120 min] in an oral glucose tolerance test [OGTT]; BMI 29 kg/m^2), and the 74-year-old paternal grandmother was diagnosed with type 2 diabetes at age 60 years and is on metformin (not overweight, no diabetes complications). The mother's OGTT was normal.

No evidence of autoimmunity was found in either child (insulin, islet cell, and GAD antibodies). After age 1.6 and 2.3 years, respectively, insulin was ceased, as requirements had remained low with normal HbA_{1c} and blood glucose. Both boys had OGTTs showing normal glucose tolerance. Interestingly, the older boy had hypoglycemia (glucose 2.0 mmol/l) at 120 min of OGTT, suggesting possible insulin secretion dysregulation. After 2 years off insulin, HbA_{1c} has remained normal (5.4–5.5%).

The cause of diabetes resolution in these boys remains unexplained. Transient hyperglycemia can occur during intercurrent illness, is of very short duration, and is not associated with elevated HbA_{1c}. Although type 1 diabetes was the initial diagnosis, their subsequent clinical course and absence of autoimmunity markers make this unlikely. Type 1 diabetes may have an extended honeymoon (i.e., partial remission), sometimes up to 2 years, but normal HbA_{1c} off treatment 4 years after diagnosis is very unusual. IGT in the father and type 2 diabetes in the paternal grandmother is consistent with autosomal-dominant inheritance suggesting maturity-onset diabetes of the young (MODY); however, no MODY subgroups remit (1). While glucokinase mutations could explain the adults' hyperglycemia, neither child had fasting blood glucose (>5 mmol/l) effectively excluding MODY2. Case 1 tested negative for hepatocyte nuclear factor-α (HNF-1α) mutations. Transient neonatal diabetes remits but is excluded as they presented after age 3 months (1.5 and 3.6 years). A remitting form of atypical diabetes is described in black adolescent Americans (2) but not in whites or young children.

In summary, disappearance of diabetes in these young boys is unusual and does not fit clinically recognized syndromes. Two affected siblings suggest a novel genetic syndrome probably altering β-cell function. This could be a recessive condition with coincidental hyperglycemia in adults. Alternatively, it may represent different stages in a dominant disorder, with adults having undetected hyperglycemia during childhood, suggesting that the children may later relapse. This cyclical pattern of diabetes remission and relapse occurs in transient neonatal diabetes, and we hypothesize a novel genetic mutation causing a similar process. We would welcome reports of further cases of remitting diabetes, as they could provide further insights into this potential new genetic form of diabetes.

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Seroconversion of GAD Antibody in "Unclassified" Diabetes With Long Duration of Disease

Latent autoimmune diabetes in adults (LADA) (1), or slowly progressive insulin-dependent diabetes mellitus (SPIDDM) (2), is a subtype of type 1 diabetes with a slowly progressive course. LADA, or SPIDDM, is diagnosed by the detection of islet-associated autoantibodies such as islet cell antibody (ICA) or GAD antibody (GADA) in the serum; moreover, patients with LADA are usually originally diagnosed as having type 2 diabetes. If islet-associated autoantibodies are not detected in the serum, these patients who are originally diagnosed as having type 2 diabetes cannot be diagnosed as having LADA and are followed as "unclassified" diabetes at present.

In clinical situations, if islet-associated autoantibodies are not initially detected in the serum, these cases are usually followed as type 2 diabetes or "unclassified diabetes" without reevaluation of autoantibodies because it is unknown whether islet-associated autoantibodies will appear later in the disease course. It has been reported that islet-associated autoantibodies are detected within 1 year after onset in ~15% of cases of "classical" type 1 diabetes without islet-associated autoantibodies at the onset of disease (3).

The following case patient, who was confirmed as not having GADAs at 31 years after the onset of diabetes and was followed as having "unclassified diabetes," is a rare case in whom GADA was detected at 36 years.

The patient was diagnosed as having type 2 diabetes at age 47 years, had an HbA_{1c} level of ~7%, and was being treated with a sulfonylurea (glibenclamide). However, glycemic control subsequently worsened despite being treated with 8.75 mg/day of glibenclamide, 150 mg/day of buformin, and 0.9 mg/day of voglibose, and she was admitted to the hospital at age 78. On admission, her height was 155 cm and her body weight was 38.8 kg (BMI 16.1 kg/m^2), with no history of obesity. According to laboratory findings, her fasting plasma glucose level was 338 mg/dl and her HbA_{1c} level was 10.1%. Her insulin secretion was also low (serum C-peptide level 0.3 ng/ml on fasting, 0.9 ng/ml at 2 h after breakfast, and 24-h urine C-peptide level 10.5 μg/day), thus requiring insulin therapy (total 16 units/day at discharge). Based on these findings, it was possible that she had SPIDDM; however, GADA was negative (detection limit <0.4 units/ml; 100% sensitivity and 100% specificity of the assay in the GADA proficiency test [Immunology of Diabetes Workshop], lab ID no. 305), resulting in the diagnosis of "unclassified diabetes."

At age 83, she was again admitted to the hospital because of acute myocardial infarction. On the second admission, her body weight was 39.4 kg (BMI 16.4 kg/m^2). Laboratory results indicated that her fasting plasma glucose level was 198 mg/dl, her HbA_{1c} level 7.2%, and her 24-h urine C-peptide level 12.5 μg/day. Surprisingly, GADA, which was negative at the time of her first admission, was now positive (144 units/ml), although insulinoma-associated protein 2 antibody was negative. Furthermore, HLA typing detected DR4, which is considered to be a susceptible HLA type for type 1 diabetes (other HLA types: A24, A26, B35, B55, DR8). Based on these observations, she was diagnosed as having SPIDDM.

The frequency of seroconversion of GADA in diabetic patients who were originally diagnosed as having type 2 diabetes is not known, and a more extensive large-scale study is needed to clarify the frequency of seroconversion in this type of diabetes. Based on this case, however, we would like to emphasize that it is essential to measure islet-associated autoantibodies such as GADA periodically for the precise diagnosis of diabetes, especially in patients given the diagnosis of "unclassified diabetes," even if the patient has suffered from diabetes for a long period of time.

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Normal β-Cell Function in Post–Liver Transplantation Diabetes Treated With Tacrolimus

Use of immunosuppressive agents is mandatory after organ transplantations but may be complicated by the development of hyperglycemia or diabetes. The prevalence of diabetes after liver transplantation in adulthood ranges from 13.6 to 33% (1,2) with a progressive increase in risk that parallels the time after transplant (3). Tacrolimus, a calcineurin inhibitor, is a recent immunosuppressive agent largely used to prevent and treat transplant rejections often following other immunosuppressive failures (4–5). The incidence of post-transplant diabetes mellitus (PTDM) in tacrolimus-treated patients was significantly higher than in those treated with cyclosporine (6,7) and in pediatric-age patients (8). Usually PTDM refers to renal recipients, and only one pediatric case has been reported after liver transplantation (9). PTDM in tacrolimus-treated patients has been related to reduced pancreatic β-cell function and is generally reversed by dose reduction (10–11).

Here we describe the β-cell function in a 15-year-old male liver transplant recipient treated with tacrolimus at the onset of PTDM and 1 year after remission. He underwent liver transplantation at age 7 years for Alagille Syndrome and was subsequently treated with steroids and cyclosporine. Because of acute rejection at age 15, treatment with cyclosporine was switched to tacrolimus and mycophenolate mofetil. One month later, he presented symptomatic hyperglycemia (42 mmol/l) without ketoacidosis; his BMI was 21.3 kg/m^2, and his HbA_{1c} was 9.4% (normal values 3.3–6.0). Initially, the patient required 1.8 units · kg^{-1} · day^{-1} of insulin. β-Cell function was investigated by glucagon stimulation—basal C-peptide levels were 0.90 nmol/l (normal values 0.165–0.993) and 1.67 nmol/l after 6 min (relative increase 186%, normal values 130–377%). Tacrolimus was substituted by cyclosporine while continuing other immunosuppressive agents. This allowed a gradual decrease of insulin and its withdrawal within 5 weeks. One year later, an oral glucose tolerance test showed normal glucose tolerance (basal levels 4.5 mmol/l, peak 7.7). In addition, stimulated C-peptide response was normal (relative increase 231%), fasting insulin level was 54.6 pmol/l, and HbA_{1c} was 5.6%.

The absence of ketoacidosis and the presence of normal C-peptide levels during tacrolimus treatment indicate that β-cell function was normal in our patient, not confirming the β-cell impairment ascribed to tacrolimus (9,10). The high insulin dose required suggests that insulin resistance, which was not due to steroids

since they were never withdrawn from therapy, may have played a role. Furthermore, because proneness to diabetes depends on several genetic mechanisms, it is possible that immunosuppressive agents play only a triggering role in PTDM. In addition, since most PTDM cases were described after renal transplantations, we cannot exclude a putative role of the transplanted liver itself on the abnormal peripheral insulin action. With the spreading use of tacrolimus in liver transplantation, pediatric diabetes practitioners will probably face many new cases of PTDM.

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Definition of Microalbuminuria in First-Morning and Random Spot Urine in Diabetic Patients

Measurement of albumin excretion in a 24-h urine collection has long been the "gold standard" for quantitative evaluation of albuminuria in diabetic patients; however, collection errors due to improper timing and missed samples may lead to significant over- and underestimation of albuminuria. For convenience and consistency, the American Diabetes Association (1) and the National Kidney Foundation (2) have recently recommended measurement of albumin-to-creatinine ratio (ACR) in a random spot urine collection for diagnosis of microalbuminuria. Microalbuminuria is diagnosed if ACR ranges between 30 and 300 mg/g creatinine. The guidelines recommended using a first-morning sample because of the potentially higher correlation with 24-h albumin excretion, but a random sample is considered acceptable if a first-morning specimen is not available. Measurement of ACR using a first-morning or random urine sample may differ significantly, as exercise stress, diurnal variation, and other factors may affect urinary albumin excretion. We provide data from a cross-sectional study evaluating potential differences in ACR obtained from first-morning and random spot urines collected on the same day.

A total of 717 adult diabetic patients with and without nephropathy were recruited from the outpatient clinic of the Diabetes Center, Tokyo Women's Medical University Hospital, Tokyo, Japan. Patients were instructed to bring a first-morning urine specimen to the clinic and then provide a random urine specimen immediately upon arriving at the clinic on the same day. ACR was calculated from urinary albumin and creatinine concentrations determined using radioimmunoassay and Jaffe's method, respectively. Paired samples with a random urinary ACR of more than 1,000 mg/g were excluded to provide a more accurate range for estimating the relationship between measurements.

Paired samples were analyzed from 668 patients (289 women and 379 men, mean age 58 ± 12 years, 95% with type 2 diabetes). The majority (75%) of random spot urine was collected during a morning visit (8:30 A.M. to 12:00 P.M.). There was a strong relationship between ACRs measured from first-morning and spot urine samples, yielding a linear correlation on a logarithmic scale: $\log_{10}$ ACR (first-morning sample) = 0.8589 · $\log_{10}$ ACR (random spot sample) −0.0604 (r = 0.871). Applying this equation, ACR values of 30–300 mg/g in a first-morning urine specimen would correspond to values of 51–391 mg/g in random spot collection. Using the ACR cutoff value of 30–300 mg/g, 135 patients (20%) would receive a diagnosis of microalbuminuria based on first-morning urine, whereas 234 patients (35%) would receive this diagnosis based on a random spot collection.

This rather large discrepancy between ACR from first-morning and random spot urine may have important implications in the diagnosis of microalbuminuria in diabetes. We advocate strict adherence to the use of first-morning urine or possibly an upward adjustment of the range for diagnosis of microalbuminuria using ACR from random spot urine. Further analysis of the relationship of ACR in first-morning and random spot urines to 24-h urinary albumin excretion, as well as their value in predicting future development of clinical proteinuria, is required.

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Lipid Levels in Black South Africans With Type 2 Diabetes

Dispelling misconceptions

Dyslipidemia in type 2 diabetes typically comprises hypertriglyceridemia and reduced HDL cholesterol, usually associated with hypercholesterolemia (1). Relatively little is known about its occurrence in developing African communities, where the prevalence of type 2 diabetes may escalate dramatically (2). This is important because dyslipidemia constitutes a major risk factor for coronary artery disease (CAD) in type 2 diabetes (3). We therefore assessed serum lipids of South African blacks with type 2 diabetes of differing socioeconomic status and compared levels with those of patients two decades earlier. Our initial expectations were that dyslipidemia would be substantially greater in the higher socioeconomic group due to affluence and that lipids would have risen considerably over time because of increasing urbanization.

Our low socioeconomic community comprised 445 black African patients (241 women and 204 men) with recently diagnosed type 2 diabetes studied between 1994 and 1996. They attended the diabetes clinic at Johannesburg Hospital and were mostly domestic workers, laborers, and pensioners who were overweight and not undergoing lipid-lowering therapy. The higher socioeconomic cohort consisted of 82 patients (32 women and 50 men), also with recently diagnosed type 2 diabetes studied during 2001–2003. They attended a private diabetes clinic in the same city and were mainly civil servants, clerks, and executives. Again, the majority was overweight and not receiving hypolipidemic drugs. Finally, we reevaluated lipid data from 47 African patients (mainly women, mean age 55 years) with type 2 diabetes who attended Johannesburg Hospital complex in 1976; they were predominantly domestic workers.

Venous blood was collected at ~0800, and although not formally fasting, most subjects had not eaten overnight. Serum was analyzed for total cholesterol, HDL cholesterol, and triglycerides by automated enzymatic methods (4). LDL cholesterol was calculated using the Friedewald formula. (These differed from the 1976 automated techniques [5].) Long-term diabetes control was assessed by HbA_{1c} concentrations. Statistical analysis of data between patient groups utilized the unpaired *t* test, with $P < 0.05$ after Bonferonni adjustment being significant.

Biochemical data (Table 1) showed unimpressive dyslipidemia in women with no significant differences, although total and LDL cholesterol tended to be lower and triglycerides higher in the higher socioeconomic cohort. For men, similar trends emerged ($P < 0.05$ for triglycerides). In both sexes, diabetes control was significantly worse in the Johannesburg Hospital setting.

Comparing mean total cholesterol and triglyceride concentrations in African diabetic patients (three-quarters of them women) from the 1976 survey with African diabetic women attending the same clinic two decades later, serum cholesterol had risen from 4.8 ± 1.1 to 5.3 ± 1.3 mmol/l ($P < 0.01$). Serum triglycerides, however, had not changed significantly (1.2 ± 0.5 to 1.5 ± 1.1 mmol/l).

Dyslipidemia in the higher socioeconomic cohort of South African blacks with type 2 diabetes was unimpressive and not substantially greater than in their less sophisticated counterparts, apart from mild hypertriglyceridemia; importantly, total and LDL cholesterol tended to be lower. This was our first misconception to be corrected and is explainable by two factors: tighter metabolic control and the likeli-

Table 1—*Demographic, anthropometric, and biochemical characteristics of black South African patients with type 2 diabetes of differing socioeconomic status*

	Johannesburg hospital 1994–1996 (Low socioeconomic community)	Private diabetes clinic 2001–2003 (Higher socioeconomic cohort)
Women		
n	241	32
Age (years)	53.6 ± 5.4	53.9 ± 10.8
BMI (kg/m^2)	31.7 ± 6.6	30.1 ± 5.9
Total cholesterol (mmol/l)	5.3 ± 1.3	4.9 ± 1.0
LDL cholesterol (mmol/l)	3.3 ± 1.4	3.1 ± 1.0
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.4 ± 0.5
Triglycerides (mmol/l)	1.5 ± 1.1	1.9 ± 2.4
HbA_{1c} (%)	9.6 ± 3.2*	7.9 ± 1.5
Men		
n	204	50
Age (years)	52.6 ± 4.9*	49.5 ± 9.0
BMI (kg/m^2)	27.6 ± 4.9	28.3 ± 4.6
Total cholesterol (mmol/l)	4.9 ± 1.3	4.6 ± 1.2
LDL cholesterol (mmol/l)	3.0 ± 1.1	2.8 ± 1.0
HDL cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.7
Triglycerides (mmol/l)	1.6 ± 1.2*	2.2 ± 1.2
HbA_{1c} (%)	9.3 ± 3.3*	8.5 ± 2.1

Data are means ± SD. *$P < 0.05$ compared with private diabetes clinic.

hood that they had more affordable access to a prudent diet containing reduced saturated fat and refined carbohydrates.

Their higher triglyceride levels, significant in men despite better glycemia, could reflect greater insulin resistance in these subjects who likely were less physically active than the less affluent subjects. By contrast total cholesterol levels may have risen significantly, if not dramatically, over two decades, reflecting a relatively small impact of westernization.

Our protocol revealed methodological limitations: the automated techniques for lipid assays differed in the 1976 study, the nonfasting collection of some serum samples may have influenced triglyceride concentrations, and the absence of formal dietary histories limited our interpretation of the lipid data. Nevertheless, these findings have implications for evolving CAD in Africans with type 2 diabetes. Their CAD prevalence remains low but may be increasing among urban dwellers (6). If subsequently confirmed, this suggests that prolonged exposure to only modest dyslipidemia, particularly when combined with other risk factors such as hypertension, smoking, and hypercoagulability, is the key atherogenic stimulus.

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Diabetes Is Still a Risk Factor for Restenosis After Drug-Eluting Stent in Coronary Arteries

We read with interest the meta-analysis of the effect of diabetes on restenosis rates among patients receiving coronary angioplasty stenting (1). This meta-analysis of six clinical trials showed that the odds ratio (OR) of coronary artery restenosis associated with diabetes was 1.61 (95% CI 1.21–2.14, $P = 0.004$) in univariate logistic regression models, but it decreased to 1.30 (0.99–1.70, $P = 0.055$) after age was controlled in multivariate models. All trials selected in this meta-analysis used classical bare-metal stents. However, drug-eluting stents (DESs) have been shown to improve outcomes among patients undergoing percutaneous coronary intervention by significantly reducing restenosis rates (2).

We performed a meta-analysis of the results from four recently published trials comparing bare-metal stents with DESs, two using sirolimus (RAVEL and SIRIUS) (3,4) and two using paclitaxel (TAXUS II and TAXUS IV) (5,6) (Fig. 1). These four trials comprised a significant proportion of diabetic patients (~20%) and provided figures that allowed us to recalculate the rate of restenosis after a follow-up of at least 6 months in both the diabetic and nondiabetic populations. The OR of in-stent restenosis in diabetic patients compared with control subjects averaged 1.94 (95% CI 1.46–2.58) in the groups receiving bare-metal stents ($P < 0.00001$). Unfortunately, none of the studies gave details about the respective ages of the diabetic and nondiabetic patients, so corrections for possible differences in age were not feasible (1). A similar OR was found when DESs were considered (OR 2.24 [1.39–3.61], $P = 0.0009$), suggesting that the use of new DESs does not allow to suppress differences between diabetic and nondiabetic patients. In both groups of patients, the rate of restenosis was markedly and significantly ($P < 0.00001$) higher with bare-metal stents compared with DESs, with an OR of 6.33 (4.57–8.76) in the nondiabetic population and 5.27 (3.36–8.28) in the diabetic population.

These results demonstrated the potential interest of DESs in patients at high risk of restenosis. Nevertheless, even when using DESs, the diabetes status remains a significant risk factor. This was recently confirmed in a large cohort of patients who benefited from unrestricted utilization of sirolimus-eluting stents compared with conventional bare-metal stent implantation in the "real world" (7). This research registry focused on a 1-year cumulative rate of major adverse cardiac events rather than on restenosis. It showed that the benefit of DESs did not reach statistical significance in diabetic patients (OR 0.72 [95% CI 0.30–1.77], $P = 0.50$). Furthermore, diabetes was a significant predictor of major adverse cardiac events (OR 1.62 [1.09–2.43], $P = 0.02$) and of clinically driven target vessel revascularization (OR 1.81 [1.10–2.99], $P = 0.02$) (Fig. 1).

In conclusion, diabetes remains a major risk factor for restenosis after both bare-metal stents and DESs. Considering the high prevalence and burden of coronary heart disease in diabetic patients, specific studies should be performed in this population in order to test the possibility of reducing the risk of restenosis and major cardiac events, including the use of more effective DESs (2).

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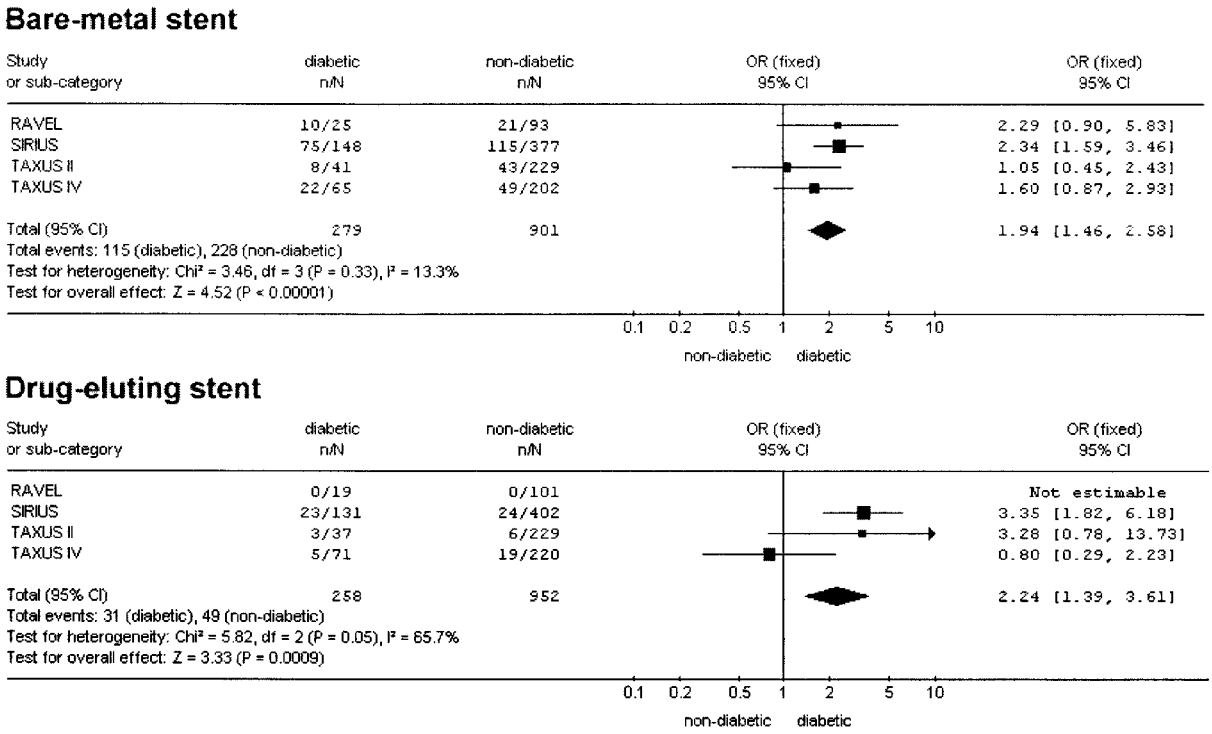

Figure 1—*Meta-analysis of four trials comparing the effects on restenosis of bare-metal stents and drug-eluting stents in diabetic and nondiabetic patients.*

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Major Diabetes Complications Have an Impact on Total Annual Medical Cost of Type 2 Diabetes

Brandle et al. (1) found that the occurrence of diabetes-related comorbidities in type 2 diabetic patients are associated with an increase in average annual medical cost.

To investigate the medical cost attributable to type 2 diabetes, we conducted a retrospective longitudinal cost-of-care study in a diabetologic center in Italy. A priori, we estimated to validly enroll 300 type 2 diabetic patients with at least 1 year of follow-up. To this aim, we randomly selected 315 type 2 diabetic patients from a base of ~2,000 diabetic patients attending the diabetologic center of Portogruaro during the period from January 2001 to August 2002.

Cost included hospitalizations, visits, diagnostics, and pharmacological therapies and were quantified in the perspective of the National Health Service. We ex-

tracted clinical and demographic information from the electronic database and performed extensive chart review, including the comorbidities retinopathy, cardiopathy (coronary heart disease), vasculopathy (other than coronary heart disease), and nephropathy.

We analyzed the association between diabetes-related comorbidities and average annual medical costs using univariate and multiple linear regression analyses. In the linear regression analysis, cost was transformed using the square-root transformation to better fit a Gaussian distribution.

Sixteen type 2 diabetic patients were excluded because it was found that their follow-up period was <1 year; the main reasons were premature mortality and loss to follow-up. A total of 299 type 2 diabetic patients were considered for this analysis and followed-up for an average of 476 days, totaling 520 person-years of observation. Their mean (±SD) age was 68.6 ± 8.8 years, and 201 (67.2%) were men. The mean systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, HbA_{1c}, and Hb levels were 152.5 ± 20.9 mmHg, 82.7 ± 10.0 mmHg, 195.5 ± 41.6 mg/dl, 50.2 ± 20.3 mg/dl, 7.1 ± 1.5%, and 13.9 ± 1.5 g/dl, respectively. The average annual cost of care was €1,909.67 (i.e., $2,425 U.S.; exchange rate, 1 Euro = $1.27 U.S.); 52% of costs were attributable to drugs, 28% to hospitalizations, 11% to diagnostics, and 9% to visits.

A total of 101 (33.8%) type 2 diabetic patients were free of diabetes-related comorbidities, 117 (39.1%) had one complication, and 81 (27.1%) had two or more complications. The more frequent complication was vasculopathy, which affected 89 (29.8%) type 2 diabetic patients, followed by cardiopathy (79 [26.4%]), retinopathy (66 [22.1%]), and nephropathy (65 [21.7%]).

The annual medical costs increased with the number of complications from €1,039.59 ($1,320 U.S.) to 1,808.17 ($2,296 U.S.) and to 3,141.21 ($3,989 U.S.) in type 2 diabetic patients with none, one, and two and more complications, respectively, with the association being statistically significant in both univariate (Kruskall-Wallis test, 73,035; $P < 0.0001$) and multiple linear regression analyses ($R^2 = 0.21$; F test 82.5, $P < 0.0001$).

We could not assess the impact of dialysis on cost, since the care of type 2 diabetic patients developing end-stage renal disease is not controlled by the diabetologic center.

We did not consider the cost of supplies for self-monitoring of blood glucose, which is, at any rate, minimal (~€100 · patient^{-1} · year^{-1}) and is not related to the type of complication.

Our study confirms the findings of Brandle et al. regarding the annual medical cost and its determinants in type 2 diabetic patients. Strategies aimed at preventing the onset of diabetes complications are likely to reduce medical costs in the long term, while improving patients' health.

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Normal Insulin Sensitivity During the Late Preclinical Stage of Type 1 Diabetes

In most cases, type 1 diabetes is the late consequence of a β-cell autoimmune destruction leading to absolute insulin deficiency (1). At onset of clinical diabetes, β-cell mass is thought to be reduced by 80–90% (2), and 73% of adult patients have ketosis or ketoacidosis at diagnosis (3). Patients with type 1 diabetes have major defects in insulin sensitivity at diagnosis of overt diabetes (4–8). However, the fact that pre-diabetic patients can maintain normal blood glucose levels in spite of dramatically low insulin secretory capacities suggests that their insulin sensitivity is normal.

Here we report that insulin sensitivity, measured by the glucose clamp method in nine patients, remains normal even during the very late preclinical stage of type 1 diabetes. None of these patients had clinical symptoms of overt diabetes, spontaneous weight loss, or ketosis before or at the time of the study. Mean age at entry in the study was 27 years (range 20–41). The mean BMI was 20.9 kg/m^2 (range 16.3–23.2). All patients were islet cell antibody positive, and seven of eight tested had at least one susceptibility HLA haplotype. Mean fasting glucose level was 7.2 ± 1.3 mmol/l (range 5–9.6). Of the eight patients who met the criteria for diabetes, four had fasting blood glucose level <7 mmol/l; in the ninth patient, oral glucose tolerance test disclosed impaired glucose tolerance. The mean HbA_{1c} level was 6.4 ± 0.8% (range 5.3–7.8; normal values 5.0 ± 0.5%). The sum of 1- and 3-min plasma insulin levels after the intravenous glucose tolerance test was 15.3 ± 5.8 mU/l (range 11–25).

Four patients were treated with insulin immediately after the metabolic explorations reported here. Four others have initiated permanent insulin therapy within 24 months of follow-up. The last patient was still non–insulin dependent when last seen 1 year after the study.

During clamp studies, the insulin dose-response curve of preclinical type 1 diabetic subjects was superimposable to that of 20 healthy control subjects. Maximal glucose infusion rate, at a plasma insulin level of 1,400 ± 120 mU/l, was 17.2 ± 1.6 mg · kg^{-1} · min^{-1} (Fig. 1). It was 16.4 ± 0.6 mg · kg^{-1} · min^{-1} in 20 control subjects at a similar plasma insulin level: 1,500 ± 100 mU/l. By contrast, the maximal glucose infusion rate was significantly lower in 15 patients with symptomatic diabetes of recent onset (11 ± 1.4 mg · kg^{-1} · min^{-1}, $P = 0.003$ by Mann-Whitney U test). These results confirm, at an even later stage of the natural history of the disease, those observed in a substudy of the Diabetes Prevention Trial-1 (9). Thus, the onset of overt clinical diabetes may be triggered by the addition of insu-

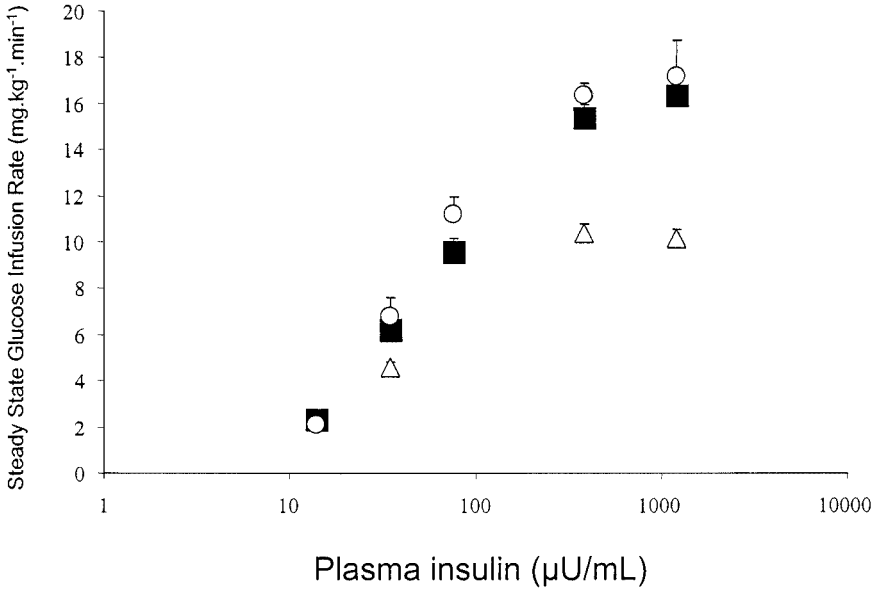

Figure 1—*Glucose clamp study. Dose-response curves obtained during the euglycemic-hyperinsulinemic clamps in patients with preclinical diabetes (○). For the purpose of comparison, results obtained in control subjects (■) and in patients with symptomatic diabetes studied within 1–3 week after diagnosis (△) are shown. The latter two are from ref. 7.*

lin resistance to insulin deficiency; the triggers may be external or internal factors. In this respect, the seasonal peaks of the incidence of diabetes (10) suggest that viral infections may play a role in the very final act of the preclinical phase by triggering insulin resistance and metabolic storm. The respective parts of insulin deficiency and insulin resistance may be determinants for the onset and duration of the honeymoon period.

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COMMENTS AND RESPONSES

Comparative Study of Prognostic Value for Coronary Disease Risk Between the U.K. Prospective Diabetes Study and Framingham Models

Response to Protopsaltis et al.

The comparison by Protopsaltis et al. (1) of the Framingham risk equations and the U.K. Prospective Diabetes Study (UKPDS) risk engine as predictors of coronary risk in diabetes is of interest, as previous analyses have shown that the Framingham equations can underestimate absolute coronary heart disease (CHD) risk in diabetic subjects by a factor of 2 or more (2,3). The sensitivity and specificity analyses presented by the authors, however, are difficult to interpret because of methodological concerns. They examined the incidence of coronary angiographically determined CHD but not "hard" CHD (defined as fatal or nonfatal myocardial infarction) as estimated by the UKPDS risk engine (4). Their use of a retrospective survivor cohort introduces bias, as patients with fatal CHD will have been excluded. This may explain the apparent poor performance of HbA_{1c} as a risk predictor, since myocardial infarction is more often fatal in those with higher HbA_{1c} (5). The use of a mixed cohort

of type 1 and type 2 diabetic subjects is problematic because the UKPDS risk engine, a type 2 diabetes–specific risk calculator, has not been evaluated in subjects with type 1 diabetes. The UKPDS analysis (6) cited by the authors shows that a 1% decrement in HbA_{1c} was associated with a 37% risk reduction in microvascular disease, not a 10-fold reduction (90%).

A full validation of a risk model requires a prospective study of a cohort to which the model is applicable. In the case of the risk engine, a cohort with type 2 diabetes and suitable demographic characteristics (3) is needed. Covariates should be measured at the beginning of follow-up, and the cohort should be monitored for the end points addressed by the model. In the case of the risk engine, these end points would be fatal and nonfatal myocardial infarction and sudden cardiac death. Publication of the observed rate of CHD in the cohort and of the mean predicted rate according to the model would then allow an evaluation of risk tools against true rates of heart disease. An ideal study would also adjust for assay differences, if appropriate, and for regression dilution and competing risks if necessary.

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Comparative Study of Prognostic Value for Coronary Disease Risk Between the U.K. Prospective Diabetes Study and Framingham Models

Response to Stevens and Holman

We appreciate the comments of Stevens and Holman (1) regarding our analysis comparing the accuracy of the U.K. Prospective Diabetes Study (UKPDS) (2) and Framingham models in the prediction of 10-year risk for coronary artery disearse (CAD) in diabetic patients. In our letter, we mentioned that the diagnosis of CAD was established by coronary angiography. In addition, this study was performed in a cohort of patients with type 2 diabetes and included a 10-year follow-up. In the sample of cases with myocardial infarction who were examined during this analysis, fatal and nonfatal cases were included.

We agree that this analysis was retrospective with its disadvantages, and it is absolutely equitable that the variables used by both of these models should have been determined at the beginning of follow-up. However, it is obvious that this study was designed as a retrospective, since the UKPDS prediction model has recently constituted a useful cardiovascular disease (CVD) risk prognostic model. In the epidemiologic analysis of the UKPDS, Stratton et al. (3) showed that the effect of HbA_{1c} values on microvascular complications over a range of 5.5–11% was nearly 10-fold, whereas the effect of HbA_{1c} on myocardial infarction incidence, over the same range of HbA_{1c}, was 2-fold.

Regarding the effect of HbA_{1c} on myocardial infarction incidence, the range of HbA_{1c} was from 5.5 to 11%, so we can say that 11% (upper limit) is two times 5.5% or 1 more time 5.5% (lower limit). Therefore 1 refers to one time and not 1%. The percent symbol was added by mistake.

Moreover, as the UKPDS study showed, improved glycemic control had no significant impact in cardiovascular outcomes in patients with type 2 diabetes. The Veterans Affairs Cooperative Study (4) also showed a nonstatistical significant deterioration of CVD events in intensively treated patients compared with those receiving standard treatment.

The exception for reducing mortality from myocardial infarction was in the overweight UKPDS cohort patients treated with metformin (5). However, metformin use was not associated with lower blood glucose levels compared with insulin or sulfonylureas, so it can be assumed that the cardioprotective effects of metformin could be interpreted by its well-known actions in the atherothrombotic risk profile (6) and blood pressure levels through nonglycemic pathways.

Summarizing the previously epidemiologic data, since coronary heart disease is a multifactorial disease and glycemic control is not significantly associated (7,8) with reduced CVD risk in diabetic patients, it can be assumed that the small contribution of chronic hyperglycemia (HbA_{1c}) at the incidence of macrovascular complications has a respectively weak contribution on the calculation of coronary heart disease risk by the UKPDS mathematical model.

Finally, we absolutely agree with Stevens and Holman that prospective studies will be needed to determine the validity of the predictive value for both of these models.

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Dietary Antioxidant Intake and Risk of Type 2 Diabetes

Response to Montonen et al.

The results by Montonen et al. (1) regarding the potential role of dietary antioxidants in the prevention of type 2 diabetes are of considerable interest. The authors identify β-cryptoxanthin as a preventive factor, regardless of adjustment for other potential confounding factors, and point out that data support the hypothesis that "a sufficient intake of antioxidants plays a role in type 2 diabetes prevention."

Although the follow-up time and number of subjects are considerable, the nutritional and public health relevance on a population basis is uncertain, at least concerning β-cryptoxanthin. The authors report that dietary intake is on average <4 μg β-cryptoxanthin/day in both groups, with the lowest and highest quartiles <0.3 to >4.2 μg/day. However, regardless of the value obtained for the risk ratio (0.58 [95% CI 0.44–0.78]), these data should be interpreted in practical terms.

In developed countries, β-cryptoxanthin is mostly provided by citrus fruits, (2,3) and, after these major contributors are considered, dietary β-cryptoxanthin intake may be easily assessed, making misclassification of individuals unlikely, especially when considering extreme centiles. Also, β-cryptoxanthin content in fresh orange and mandarin is 120–1,300 μg/100 g (3,4). Thus, assuming the lowest end of this range, intake of β-cryptoxanthin in the highest quartile in Montonen et al.'s study (~5 μg/day) would be equivalent to the consumption of <5 g fresh orange or mandarin per day, which is less than one-twentieth of a standard portion.

In other European countries, median β-cryptoxanthin intake is 0.45–1.36 mg/day (2,3); the southern countries have higher intakes than those in the north, a difference that is also observed in their serum levels (5). Because there is a biological correlation between β-cryptoxanthin intake and serum concentrations, it is reasonable to assume that the lower the intake the lower the serum concentrations.

Considering these facts, in our opinion, it is very difficult to imagine any potential beneficial effects associated with the intake of such low amounts of β-cryptoxanthin as those reported by Montonen et al. (1), even when the statistical evidence is strong. Where nutritionally relevant population-based recommendations are concerned, we should not forget the multifactorial nature of the disease and that people, in the real world, consume foods and diets.

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Dietary Antioxidant Intake and Risk of Type 2 Diabetes

Response to Granado-Lorencio and Olmedilla-Alonso

We would like to express our warm thanks to Granado-Lorencio and Olmedilla-Alonso for carefully reading our article (1) and for their comments regarding the inverse association between β-cryptoxanthin intake and diabetes risk (2). Granado-Lorencio and Olmedilla-Alonso pointed out that the β-cryptoxanthin intake in our study population was exceptionally low; therefore, any potential beneficial effect associated with such low amounts of β-cryptoxanthin is difficult to imagine.

In epidemiologic studies, it is difficult to draw conclusions about the absolute amount of a specific nutritional com-

pound necessary for a beneficial health effect. One of the main reasons for this is the fact that nutrient composition tables are under continuing development. A common alternative technique, which we used in the present study, is to rank the study population according to the intakes. In such an approach, the validity of the results depends on the accuracy of the ranking, so absolute intake levels are less important.

In our analyses, the assessment of β-cryptoxanthin intake was based on analyzed values of Finnish foods available in the late 1980s. However, more recent estimates of the β-cryptoxanthin content of oranges have been shown to be much higher than those used in the present study (average orange intake 29 g/day). To ensure the accuracy of our analyses, we recalculated the β-cryptoxanthin intake using more recent published values (3,4). We calculated the κ coefficient between quartiles of the recalculated and the original variables and noted a high level of agreement between these two variables ($\kappa = 0.9$), suggesting that the study participants are very similarly ranked using either the original or the recalculated β-cryptoxanthin intake values. Thus, the inverse association between β-cryptoxanthin intake and diabetes risk presented in our article is justified.

In conclusion, we suggest that the significant inverse association between the intake of β-cryptoxanthin and the risk of type 2 diabetes observed in our study is a valid finding. The importance of this finding in the prevention of type 2 diabetes, however, remains to be established.

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Twice-Daily NPH or Mixture Insulins Versus Triple Therapy: Apples Versus Oranges

Response to Poulsen et al.

Poulsen et al. (1) recently demonstrated that triple therapy (metformin, rosiglitazone, and preprandial insulin aspart) lowered HbA_{1c} levels much better than twice-daily NPH or MIX insulin in type 2 diabetic patients. They then claim that the reason for this improvement, compared with the patients treated with insulin alone, is the superiority of specifically treating the three pathophysiological components of type 2 diabetes (peripheral insulin resistance, hepatic insulin resistance, and impaired glucose-stimulated insulin secretion). Given the design of the study, this conclusion is suspect for two reasons.

First, the glycemic goals for the two groups were different. The goals for patients receiving only insulin were a preprandial value of 5–7 mmo1/l. The goal for patients receiving triple therapy was a postprandial value of 5–7 mmol/l. Achieving a postprandial goal of 5–7 mmol/l will necessarily lead to better control than achieving the same goal preprandially (since in the latter situation the postprandial glucose concentrations will obviously be higher).

Second, twice-daily NPH injections are a poor insulin regimen to achieve near euglycemia because there is no short- or rapid-acting insulin to blunt postprandial hyperglycemia. (The authors acknowledge this in their discussion.) How many of the eight patients in the control group were on twice-daily NPH insulin? Even the ones on MIX insulin (I assume this is a premixed insulin) are not on an optimal insulin regimen for achieving near euglycemia. One example illustrates this point. How does one adjust the MIX insulin dose in a patient whose preprandial glucose concentrations before supper are in the lower part of the goal range but whose preprandial lunch values exceed the goal range?

For both of these reasons one would expect higher postprandial glucose concentrations in the control group receiving only insulin (which is borne out in Fig. 2*A*) and consequently higher HbA_{1c} levels. Hopefully these issues will not be ignored in subsequent long-term studies.

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The Combined Effect of Triple Therapy with Rosiglitazone, Metformin, and Insulin Aspart in Type 2 Diabetic Patients

Response to Poulsen et al.

I have some concerns regarding the results of Poulsen et al.'s (1) study, which suggested that triple therapy with insulin aspart, metformin, and rosiglitazone was superior to continuing treatment

with NPH insulin alone or NPH plus regular insulin (referred to as the control group). These results should be interpreted with caution because of several limitations in the study's design. First, I disagree with the authors for applying "identical" goals for metabolic control in both study groups. Although the glycemic target was similar in both arms, the timing of self-monitored blood glucose was different. Thus, the adjustment of the insulin dosage in the control group aimed at blood glucose levels between 5 and 7 mmol/l in the preprandial period, whereas in the triple therapy group, insulin adjustment targeted the same range of blood glucose but in the postprandial period. Clearly, setting a glycemic goal of 5–7 mmol/l for postprandial blood glucose was quite aggressive and substantially lower than the recommendations of the American Diabetes Association (<10.0 mmol/l) (2). This more stringent glycemic target in the triple therapy group compared with the control group may explain, at least in part, the superior metabolic control observed with the triple therapy regimen. In addition, the bias that favored the triple therapy group (e.g., providing closer follow-up and care) could not be excluded since the study was not blinded. Moreover, the investigators may have been reluctant to further increase insulin doses in the control group to achieve the study's preprandial glycemic goal because of the concern over hypoglycemia. Second, some patients in the control group received NPH twice daily and others received a mixture of NPH plus regular insulin. These two treatment regimens are different and should not be included in a single group because diabetic subjects receiving NPH alone may have inadequate plasma levels of postprandial insulin. Third, one limitation of triple therapy is the high cost of treatment and related laboratory tests, a factor that was not clarified in the study presumably because the three drugs were provided at no cost by the respective companies.

Despite these limitations, this pilot investigation addressed an attractive therapeutic approach that targeted the three main defects in the pathophysiology of type 2 diabetes. In this respect, the study's findings suggested that insulin resistance was probably the hardest abnormality to correct. Indeed, the combination of the two insulin-sensitizing agents, metformin and rosiglitazone, in maximum therapeutic doses resulted in only partial amelioration of insulin sensitivity after 6 months (1). It would be interesting to evaluate the long-term effects and cost-effectiveness of this form of triple therapy in type 2 diabetes in well-designed trials.

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The Combined Effect of Triple Therapy with Rosiglitazone, Metformin, and Insulin Aspart in Type 2 Diabetic Patients

Response to Davidson and Mikhail

We were not able to normalize HbA_{1c} values completely during triple therapy probably due to the fact that insulin action was not completely normalized by rosiglitazone and metformin, as stated by Davidson (1). Still, insulin-mediated glucose uptake was only 60% normal during triple therapy; however, a longer treatment period or a more potent insulin synthesizer may help in that respect. Another way to further reduce HbA_{1c} values is to use a more aggressive algorithm, increasing the Novorapid dose further before meals. However, this may induce more hypoglycemic attacks during the day time. The South Danish Diabetes Study, a newly initiated 2-year follow-up study that includes 400 subjects, will hopefully answer this question.

Davidson (1) and Mikhail (2) focus on the different ways of monitoring blood glucose values when using the two approaches. They claim that a focus on the postprandial values in the triple therapy group compared with preprandrial values in the control group favors the triple therapy group. However, self-monitored glucose values showed that the preprandial values were identical in the triple therapy group and the control group. Hence, the adjustment of the insulin dosage would have been identical only if the preprandrial blood glucose values were also used in the triple therapy group (as in the control group). The curve for self-monitored glucose in the triple therapy group is flat (no postprandial rise in blood glucose values), with a geometric mean of ~7 mmol/l, which is close to the findings in nondiabetic subjects. However, monitoring higher postprandial blood glucose values in the control group (NPH insulin alone) may have resulted in a further rise of the insulin dose, as proposed by Mikhail. We do not expect, however, to see a further effect of this on blood glucose values, since the 50% increase we already performed did not influence HbA_{1c} values (3), but this postulate is still not tested. The last argument against the criticism raised is that we aimed for the same HbA_{1c} values in both groups, which means that we did not rely on blood glucose values only. Thus, we cannot prove that monitoring the postprandial values in the control group also would have improved the glucose control in that group, but we showed that triple therapy was able to nearly normalize HbA_{1c} values in type 2 diabetic patients, which has never been the case when using NPH insulin treatment alone.

We conclude that this trial confirms our hypothesis that the key to the treatment of type 2 diabetic patients is to control postprandial blood glucose values by reconstructing the insulin peaks after meals and by improving insulin action in skeletal muscle, fat, and liver cells. Triple therapy seems to be a safe and effective treatment of hyperglycemia in type 2 diabetic patients, but further studies, especially of a longer duration, are needed.

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A Randomized Trial Evaluating a Predominantly Fetal Growth–Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

Response to Schaefer-Graf et al.

Schaefer-Graf et al. (1) rightly suggest that the management of women with gestational diabetes mellitus (GDM) should be based on more than glycemic factors alone. However, the study in which they conclude that strict glycemic control is not useful in the absence of the measurements of fetal overgrowth has two unusual features.

The authors' criteria for diagnosing GDM are lower than those of the World Health Organization or the American Diabetes Association, and they may be including women who could be considered normal. This is supported by the fact that there is little difference between the rate of large-for-gestional-age (LGA) babies in both their groups (12.1% above the 90th percentile) and that of the defining normal population (10%). These women may not have been equally represented in the two groups, as 30% more women in the ultrasound-defined group met their criteria for insulin therapy.

More importantly, the women with larger babies were treated more aggressively. Because their outcome was not different from less aggressively treated women without initially large babies, there is the possibility that the latter might have done better if they had been using the same glycemic targets as the women with large babies. They certainly had higher fasting glucose concentrations, and more of the LGA babies were born to women who did not receive insulin in either group. At the very least, the protocol favors the authors' hypothesis that insulin intervention before the onset of fetal overgrowth is not helpful.

Jovanovic (2) draws attention to the discrepancy in glucose targets but worries that her own policies, based on strict glycemic control and resulting in a lower macrosomia rate in her GDM population than in the local background population, may have achieved this at the cost of an increase in small-for-gestational-age (SGA) babies. For us, in a clinic of predominantly African and Carribean background, SGA is not an issue. Using Jovanovic's protocols in women diagnosed by World Health Organization criteria, our SGA rate is <5%. Because SGA is defined as babies in the lowest 10th percentile, our current rate is lower than that of the background population.

Schaefer-Graf et al.'s study supports the use of strict glycemic control in women with demonstrably large babies. This is valuable evidence that such problems may respond to intervention with insulin even after the onset of fetal overgrowth. Reassuringly, none of the differences in the rates of SGA in the study approached significance. We would not, therefore, support the authors' suggestion that we abandon glycemic indications for insulin therapy in our population until a randomized prospective trial using similarly strict glucose targets in all groups shows that it does more harm than good.

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A Randomized Trial Evaluating a Predominantly Fetal Growth–Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

Response to Amiel and Blott

We appreciate Amiel and Blott's (1) interest in our study (2) and thank them for their helpful discussion. They rightly pointed out that the diagnostic criteria used in Germany at the time of our study had been lower than those of the American Diabetes Association. We were also aware that we treated some women who would have been considered healthy in other countries. To demonstrate that the fetal growth–based approach is also safe for women with a more severe glucose intolerance, we repeated the analysis for a subgroup of women who fulfilled the diagnostic criteria of Carpenter and Coustan (3) (80% of our population). Again, there was no adverse outcome in the ultrasound group. The limitation to women who qualified for gestational diabetes mellitus (GDM) based on Carpenter and Coustan criteria diminished the difference in the rate of insulin therapy. Because of the higher degree of glucose intolerance in these women, more women qualified for insulin therapy in the standard group. We also

realized that in the whole population, the rate of women who met the criteria for insulin was higher in the ultrasound than in the standard group. However, this was not because of an unequal representation of fetal macrosomia, as suggested by the authors. The rate of an abdominal circumference of >75th percentile at entry was not different between both groups. It was more likely due to our low diagnostic criteria, which included women with a low degree of glucose intolerance and, therefore, less frequent need of insulin. The low rate of large-for-gestational-age (LGA) babies was an effect of intensive treatment. The studies of Langer et al. (4) and Buchanan et al. (5) demonstrate that a normal LGA rate can be achieved in GDM when we aim for a very tight control.

We were very grateful that Lois Jovanovic's comment (6) emphasized the aspect of an increased risk for intrauterine growth retardation in some women with GDM. When we discuss treatment strategies for GDM, we always focus on how to reduce neonatal macrosomia. When we did a subanalysis comparing the outcome of women with hyperglycemia but normal fetal growth treated with (standard group) or without (ultrasound group) insulin, we also attempted to determine whether withholding insulin would increase the LGA and cesaerean section rates. We were surprised when we realized the high rate of SGA in the standard group. The overall rate of SGA was similar in both study groups. We did not conclude that the policy of strict glycemic control is harmful for the general population with GDM. We suggested the use of an additional test, the measurement of the fetal abdominal circumference, to decide who will benefit and for whom a tight glucose control might be harmful due to a reduction of the maternal fuel supply to the fetus. Although the differences between the groups were obvious, when we looked at the outcome of the women who were treated differently according to the study protocol, the small sample sizes resulting from the subanalysis impaired our possibilities of an adequate statistical analysis. In the future, we hope to initiate and cooperate in multicenter studies to gather more evidence to prove our results.

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Multiple Symmetric Lipomatosis: A Paradigm of Metabolically Innocent Obesity?

Response to Haap et al.

The study of Haap et al. (1) on two patients with multiple symmetric lipomatosis (MSL), also known as the Launois-Bensaude Syndrome, adds interesting new insights into a condition still poorly understood.

As for the conclusions drawn concerning insulin sensitivity in patient 1, we would like to suggest some caution. Our study group has also measured the insulin sensitivity index (ISI) in three subjects with MSL with the euglycemic-hyperinsulinemic clamp and found the ISI to be higher in one and lower in two male subjects in comparison with sex- and BMI-matched control subjects (2). The good insulin sensitivity in patient 1 in the study of Haap et al. may indeed be related to the low visceral fat mass in this very patient, but it is rather questionable whether this finding is typical in MSL. From five patients with MSL identified in our clinic, computed tomographies of the abdomen had been performed in two case subjects, and the degree of visceral fat was described as comparable with that of healthy subjects. In a systematic evaluation of the fat mass and deposition in 18 patients with MSL by computed tomography, Enzi et al. (3) also did not describe a distinct reduction of visceral fat in these patients. Given this and the considerable phenotypical and clinical variability in patients with MSL (4), the conclusion of a good insulin sensitivity in MSL patients should not be generalized. Studies in larger populations are mandatory, although not easily performed due to the rareness of the disease. In a literature search of our own, we identified about 400 cases published since the first description by Brodie in 1846 (5).

One further aspect on MSL seems worth mentioning: three of the five patients with MSL in our clinic had obstructive sleep apnea syndrome (OSAS). We recently identified (5) the presence of OSAS as an independent risk factor contributing to insulin resistance. Thus, the investigation for OSAS in MSL patients might also be useful in the discussion of insulin sensitivity and of other metabolic aspects of MSL.

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Multiple Symmetric Lipomatosis: A Paradigm of Metabolically Innocent Obesity?

Response to Harsch, Schahin, and Wiedmann

We have recently suggested (1) that patients with multiple symmetric lipomatosis (MSL) may represent a paradigm for metabolically innocent fat accumulation. Harsch and colleagues (2,3) raise some justified words of caution with respect to the generalization of this statement. It is probably true that we cannot make general metabolic inferences on the syndrome of MSL as such based on our rather limited sample size. But this was not our intention, and we welcome the opportunity to clarify our line of argument.

The original idea was to present a situation where a substantial increase in body fat mass was not accompanied by decreased insulin sensitivity, which is in much contrast to common belief. And in fact, fat accumulation, if confined to the subcutaneous compartment, was not associated with much insulin resistance. By selecting these two specific patients for argument's sake, we may have introduced a bias. But this is beside the point because even if everything we said held true for only these two subjects and no other patient with MSL, our findings would be no less interesting. And this is the reason why we specifically put "paradigm" in the title rather than the syndrome alone. Nevertheless, Harsch et al. (2) appropriately pointed out that fat accumulation in MSL need not necessarily be confined to the subcutaneous compartment and that, without doubt, if it included the visceral compartment, insulin resistance would be present.

Since our observation was accepted for publication, we were able to recruit two more patients with the clinical appearance of MSL and very little visceral fat. The whole-body fat volume of the two subjects was ~14 and 20 l, respectively. The subcutaneous-to-visceral abdominal fat ratio as measured by magnetic resonance imaging was 3.3 and 5.9, respectively, compared with BMI-, age-, and sex-matched control groups (1.6 and 1.4, respectively). Consistent with the small visceral fat mass, liver fat was much lower in both patients. Intramyocellular lipids in soleus and tibialis anterior muscles were also lower than those in the control groups. And again, both MSL patients were substantially more insulin sensitive than their respective control groups. For the sake of completeness we also came across a subject with clinical MSL and type 2 diabetes. But there are a number of reasons, which have little to do with our line of argument, for such a patient to acquire secondary types of diabetes, for example, via alcohol-induced pancreatitis.

Finally, the comment of Harsch et al. regarding a higher prevalence of obstructive sleep apnea syndrome (OSAS) among patients with MSL is interesting and valuable. OSAS seems to be an independent risk factor for insulin resistance (4). Upon reexamination of our small cohort, we indeed identified a man with documented OSAS (not among the ones reported). This patient appeared to be insulin sensitive and otherwise healthy, but due to his extreme obesity (BMI 64 kg/m^2) would not fit into the magnetom, and we were unable to assess his visceral fat mass. This aspect is not necessarily in conflict with our original hypothesis but just another mechanism to render someone insulin resistant. Probably, among two equally obese subjects with OSAS, the one with only subcutaneous fat accumulation is more insulin sensitive.

In conclusion, at some point the reasoning becomes circular and our way of presenting these selected patients with MSL may be just another way of demonstrating that subcutaneous fat is metabolically more innocent than visceral fat (5).

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Has RoboCop Got Diabetes?

We received a picture series from Becton Dickinson (Fig. 1*A*, here transformed to black and white and translated from Swedish) showing how syringes look after one, three, and five injections. We were astonished at how deformed the syringes were after a few injections.

To test the reproducibility of the syringe deformation, one physician and two nurses, all with ordinary builds and without scars or metal implants, tested Becton Dickinson's insulin pen syringes Micro-Fine+ 31 gauge × 8 mm. We used the syringes 1, 3, 5, and 10 times for injections in the abdominal fat. One syringe was thereafter used to penetrate an ordinary rubber mousepad 100 times, then to cut into a wooden computer table, and, finally, to cut a metal lamp foot. Pictures were taken of the syringes with a Zeiss Axioscope 2.5× lens with a lateral light source and a Canon 10D camera with 6.2 mpx resolution. The only syringe that looked similar to the used syringes in Becton Dickinson's picture series was the one that cut into a metal lamp foot. The syringes used 0, 1, 3, 5, 10, and 100 times are without distortion of the tip (Fig. 1*B*).

Hence, Becton Dickinson has improved the quality of their insulin syringes dramatically since the pictures were published, the syringes have been manipulated to produce false evidence of syringe defects, or Robocop was used as a test subject.

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Has RoboCop Got Diabetes?

Response to Berger et al.

We thank Berger et al. (1) for raising questions about the serious issue of reusing insulin syringes and pen needles. The source of the photographs used by Becton Dickinson is an independent study conducted in 1997 by Dr. Jacques Garden, Chairman of the Department of Metallurgy at the University of Grenoble, France (unpublished observation).

In Garden's study, 80 diabetic patients from the Diabetes Service of Dr. Dieter Look returned their used pen needles and indicated the number of times each specific needle had been used. All needles were used in a customary fashion and spanned the range of manufacturer types, gauges, and needle lengths. Needles were used from 2 to 38 times. Needle tips were then resterilized for safety reasons and examined by electron microscopy (2).

The tip damage found by Garden ranged from mild bending of the extreme tip to a hook-like distortion of the entire distal shaft of the needle. Loss of the tip was seen on one occasion. Some needles appeared undamaged, even after many reuses. (In this regard Garden's findings agree with those of Berger et al.) However, a clear association was seen between the severity of tip damage and the number of needle reuses.

Among the needles, some looked just like the ones provided by Berger et al. Some were much worse than the ones we have chosen to show the public. We are unsure why the results of Berger et al. differ from our own. Among the possible causes are *1*) the magnification used was

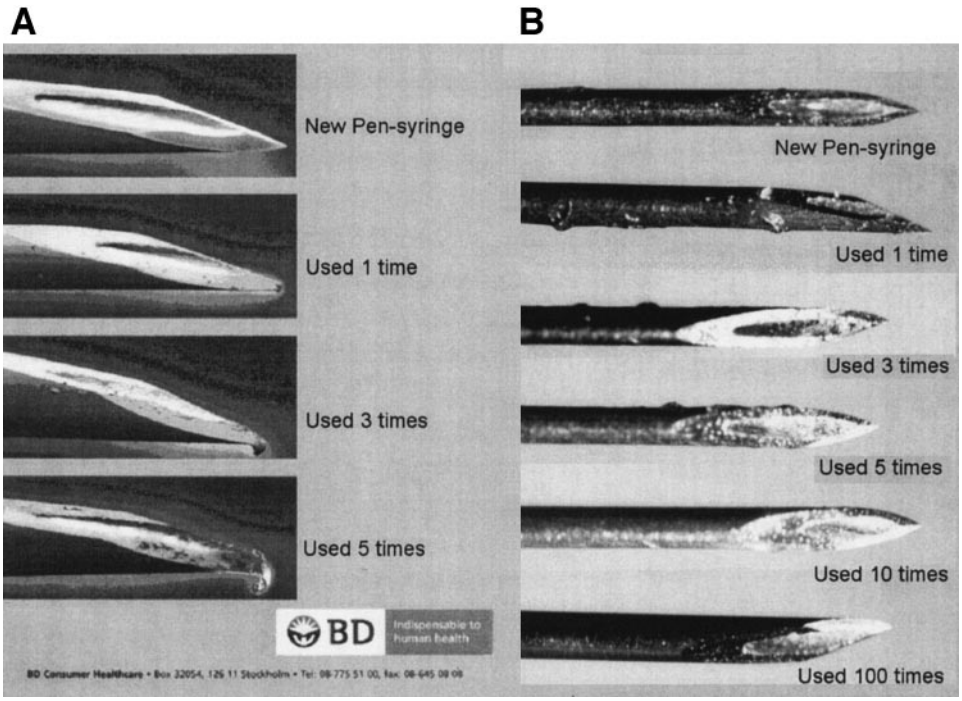

Figure 1—The picture series distributed by Becton Dickinson (*A*), and our own pictures of used syringes (*B*).

at least an order of magnitude less than that of Garden (>300×), 2) the health care professionals in their study may be more careful than patients when performing injections or may use different techniques, or 3) they viewed fewer samples, and sampling error may have resulted. We would welcome a full discussion of this study with Berger et al.

We advise against pen needle and insulin syringe reuse for a number of reasons. First, the syringes may become hooked, as we have previously described. The "hook" at the tip of the syringe may break off and become lodged in the skin, and the pain of injection with a syringe increases with each reuse.

Second, studies conducted by a series of nurses in Europe have shown significant increases in lipodystrophy in patients who reuse insulin syringes and pen needles (3). Third, there are reports of increased infections from reuse of insulin syringes (4). Finally, reusing syringes can lead to suboptimal therapy. With syringes, the patient can bring significant amounts of NPH into the regular or lispro vial. With pens, leaving the needle on between uses can lead to incomplete injections, which may cause the patient to underdose themselves and receive as little as 35% of the expected dose (5).

We believe the issue of insulin syringe and pen needle reuse to be serious, with real safety concerns that have not been fully explored in the past. We welcome a more complete scientific discussion of this issue.

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