OBSERVATIONS

Rising Incidence of Type 1 Diabetes in Germany

12-Year trend analysis in children 0–14 years of age

Epidemiological studies from all parts of the world have reported increases in incidence of type 1 diabetes (1). In a 6-year population-based study that concluded in 1993 and was published in 1997, the incidence of type 1 diabetes in German children 0–14 years of age was reported to be 11.6 per 100,000 children a year (95% CI 10.9–12.2) (2). Using the Baden-Wuerttemberg (BW) incidence registry, data regarding 2,525 children with diabetes were analyzed over a 12-year period. Our objective was to determine the most recent trends in the incidence of childhood diabetes in Germany.

BW is a federal state in Southwest Germany. The total number of inhabitants was 10.4 million at the time of this research, and 1.8 million (16.9%) were younger than 15 years of age. This corresponds to 13.3% of the total child population in Germany. These population data were drawn from a national census in 1987 and the official yearly update thereafter.

Patients were registered according to European Diabetes (EURODIAB) Study criteria (3). They were included only if insulin treatment had begun before the 15th birthday and if the manifestation of disease occurred between 1 January 1987 and 31 December 1998.

All 31 pediatric departments in BW and 1 diabetes center participated in the study. Registration was done retrospectively for the time period between 1 January 1987 and 30 June 1997 and prospectively for the time period between 1 July 1997 and 31 December 1998. For the earlier time period, 2,121 hospital records were the primary data source. For the latter time period, 404 patients were registered prospectively. A separate secondary source of data was provided by a questionnaire distributed among members of the Diabetic Patients' Association (Deutscher Diabetiker Bund). The degree of ascertainment was calculated according to the capture-mark-recapture method (4) and resulted in 97.0% for the primary data source and 97.2% when both data sources were combined.

Sex and age standardization was done according to EURODIAB criteria. The 95% CI limits were calculated for all incidence rates assuming a Poisson distribution, or if n was higher than 100, assuming a normal distribution. Trend analysis was performed using the linear regression model, because this mathematical model seems to best describe the incidence development as a function of time. The correlation coefficient is given as R^2, and the probability was calculated using Fisher's test (represented as P).

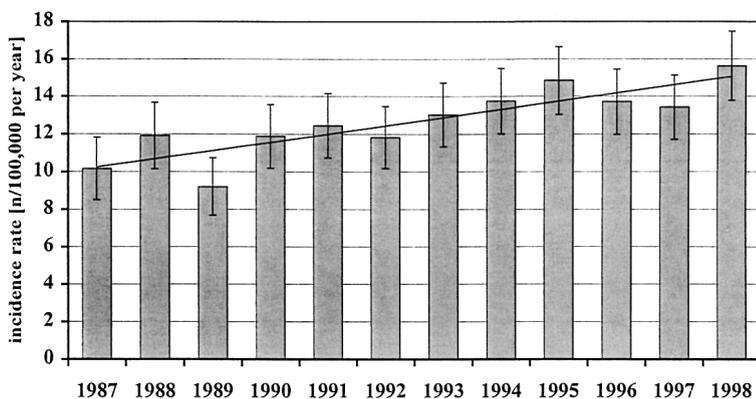The mean age and sex standardized incidence rate over 12 years was found to be 12.9 per 100,000 children a year (95% CI 12.4–13.4). The absolute increase in incidence was calculated with 0.44 per 100,000 children a year (0.26–0.62). This corresponds to an annual increase of 3.6%. Compared with the incidence in 1987, the overall increase in incidence over 12 years was 47.0%.

The mean incidence from 1987 to 1998 (12.9 per 100,000) was higher than that previously reported by the German Democratic Republic (7.4 per 100,000) (5) and by BW (2) in the early 1990s. For the children <15 years of age, incidence peaks up to 15.6 per 100,000 (Fig. 1) have not previously been seen in this region. In comparison with our earlier published incidence rate of 11.6 per 100,000 children a year (95% CI 10.9–12.2) from 1987 to 1993 in the same region, the incidence rate of 14.3 (13.5–15.0) from 1993 to 1998 was higher and clearly indicates the increasing incidence rate in German children during the last decade.

The increase of 3.6% per year in BW is higher than the international mean (2.5–3.0%), but similar numbers have been reported in Oxford, U.K. (3.7%), and in France (3.9%) (1).

As in most European countries, the increase in incidence cannot be easily explained. Whether environmental or genetic factors play a predominant role is a matter of controversial debate (6,7). Data on the incidence in the age-group ≥15 years of age are not available for our population. Thus, the observed trend may reflect a transition of the age at onset from children ≥15 years of age to children <15 years of age.

Knowing that a linear model may even underestimate the increase in incidence (1), one can make predictions by extrapolating the curve. Our calculations predict a doubling of the incidence rate within 20 years, reaching 24.7 per 100,000 children a year in the year 2020.

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Figure 1—*Trend in the incidence of diabetes in children 0–14 years of age in Germany (with 95% CIs). Regression equation: Incidence = 0.44 × year −860.06 (95% CI of the slope 0.26–0.62; $R^2 = 0.75$; P = 0.0003)*

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Prevalence of Maturity-Onset Diabetes of the Young Mutations in Brazilian Families With Autosomal-Dominant Early-Onset Type 2 Diabetes

The relative frequencies of the subtypes of maturity-onset diabetes of the young (MODY) were shown to vary greatly in studies from different populations (1–4). The Brazilian population has mixed ethnic background (African, Asian, European-Caucasian of several different countries of origin, and Indigenous), and little is known about the genetic determinants of diabetes in Brazilians. In this report, we describe the frequencies of the major MODY subtypes in a panel of 12 Brazilian families with autosomal-dominant early-onset type 2 diabetes (Fig. 1).

A total of 32 family members were studied. The age at diagnosis of diabetes was <25 years in at least one family member in 10 of the 12 families and was between 30 and 35 years in the two remaining families. The probands were five men and seven women with overt diabetes according to the revised criteria, aged 34 ± 18 years (mean $\pm$ SD), with age of diagnosis of 24 ± 13 years (range 8–50). The promoter and the coding regions of glucokinase (GCK/MODY2), hepatocyte nuclear factor 4α (HNF-4α/MODY1), and HNF-1α (MODY3) genes were screened for mutations by fluorescent-based single-strand conformational polymorphism (glucokinase only) and/or by direct sequencing. Three variants (C18R, Q59l, and D76N) in the insulin promoter factor 1 (IPF1/MODY4) gene previously found to be associated with familial diabetes were screened by polymerase chain reaction–restriction fragment–length polymorphism (5). IPF1, HNF-1β, and NeuroD1 genes were not systematically tested because they are very rare causes of MODY.

A missense mutation (GGA→GTA, G175V) in exon five and a variant in intron two (IVS2-8G→A) of the glucokinase gene were observed in the probands from kindred CAS and SAN, respectively. A missense mutation (CGG→CAG, R131Q) in exon two of the HNF-1α gene was detected in probands of two kindred (FRA and MAR). This mutation was already found to be associated with MODY in American and German kindred (6). A frameshift by the insertion of one nucleotide (P291fsinsC) in exon four of the HNF-1α gene was also observed in probands of two kindred (CAR and SES). This mutation is located in a mutational hotspot and seems to account for 20–25% of MODY3 mutations in several Caucasian populations (2,4,6). Mutations in the HNF-4α gene were not detected in our sample. The D76N variant in exon one of IPF1 was observed in the proband of kindred MAR, who also carried the HNF-1α R131Q mutation. It was suggested that the 76N allele has decreased transcriptional activity and could predispose to late-onset type 2 diabetes in a polygenic context (5), but these results were not confirmed in another study (7). The glucokinase and HNF-1α mutations were present in all subjects with hyperglycemia and in none of the normoglycemic relatives available for testing in the respective kindred (Fig. 1). The variant in intron two of the glucokinase gene and the IPF-1 D76N variant did not cosegregate with diabetes in kindred SAN and MAR. Regarding the clinical profile of the affected family members, MODY-X (no known mutation) subjects were more often treated by insulin or oral hypoglycemic agents than MODY2 and MODY3 subjects (86 vs. 18%; Fisher's exact test $P = 0.013$), suggesting that they might have more severe diabetes. Both mild (1) and severe (4) diabetes have been reported in MODY-X, which might suggest genetic heterogeneity.

The relative prevalences of MODY1, MODY2, MODY3, and MODY-X in our panel were 0, 8.3, 33.3, and 58.4%, respectively. Prevalences reported in the literature are heterogeneous, ranging from 0% (1) to 8% (4) for MODY1, 8% (3) to 63% (1) for MODY2, 21% (1) to 65% (2) for MODY3, and 16% (1) to 45% (3) for MODY-X. These heterogeneous results may reflect distinct genetic background, differences in the recruitment and ascertainment of families, or bias due to the small number of families in some of these investigations, including ours. Clinical misdiagnosis of MODY could explain the higher prevalence of MODY-X in our sample. If we apply a more stringent criterion, such as onset of diabetes before 25 years in at least two family members, the prevalences of the MODY subtypes would be 0, 12.5, 37.5 and 50%, respectively. However, the stringent criterion would have excluded the MODY3 kindred CAR.

In conclusion, mutations in the glucokinase and HNF-1α genes account for ~42% of the cases of MODY in a panel of Brazilian families, with MODY3 being the most frequent of the two subtypes. Our data suggest that the unknown MODY-X gene(s) could account for a large proportion of MODY cases in Brazil.

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Figure 1—*Pedigrees of the 12 families. Arrows identify the probands. Squares denote male family members, and circles denote female family members. Losangles and question marks (?) denote other family members of unknown glycemic status. Ages at diagnosis of diabetes are noted under the symbols. Wt and M stand for wild type and mutant alleles of glucokinase and HNF-1α genes. P (kindred SAN) stands for the IVS2-8G→A glucokinase polymorphism. D and N (kindred MAR) are alleles of the D76N variant of IPF1 gene.*

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Administration of Troglitazone, but Not Pioglitazone, Reduces Insulin Resistance Caused by Short-Term Dexamethasone (DXM) Treatment by Accelerating the Metabolism of DXM

Thiazolidine derivatives are newly developed insulin sensitizer agents that act to lower plasma glucose and reduce hyperinsulinemia (1), and they are being used to treat patients with type 2 diabetes accompanying insulin resistance. However, the precise molecular mechanism by which thiazolidines counteract general insulin resistance has yet to be clarified. Glucocorticoid induces gluconeogenesis and insulin resistance, resulting in the development of diabetes (2), but the precise molecular mechanisms remain to be elucidated. Recent studies showed that troglitazone, which was the first clinically applied drug of thiazolidine derivatives, improved dexamethasone (DXM)-induced insulin resistance in rats in a glucose clamp study (3) and that it had a good effect on patients with glucocorticoid-induced diabetes (4). In the present study, we examined the effects of troglitazone and pioglitazone, another insulin sensitizer, on insulin resistance induced by short-term DXM treatment, and compared their effects with those of metformin. Furthermore, troglitazone has been reported to reduce the plasma concentration of the oral contraceptives ethinylestradiol and norethindrone, which are metabolized by the liver enzyme CYP3A4 (5). Troglitazone is also believed to be an inducer of CYP3A4 like rifampicin and phenytoin, and it has been speculated that troglitazone may reduce the effects of glucocorticoid, which is metabolized by CYP3A4, by enhancing the activity of CYP3A4. In this study, we investigated the effects of troglitazone and pioglitazone on serum DXM concentrations.

A 75-g oral glucose tolerance test (OGTT) was administered to five healthy men in the following regimens: *1*) no pretreatment; *2*) after oral administration of 4 mg DXM daily for 3 days; and *3*) after oral administration of 400 mg troglitazone, 500 mg metformin, or 30 mg pioglitazone daily for 14 days, together with oral administration of 4 mg DXM daily for the last 3 days. Troglitazone administration reduced the DXM-induced increase of the mean area under the plasma and serum concentration time curve from 0 to 3 h [AUC(0–3)] for both the plasma glucose concentration and the serum insulin concentration during a 75-g OGTT (350.0 ± 24.7 vs. 433.9 ± 24.3 mg · dl^{-1} · h^{-1} and 127.9 ± 15.0 vs. 241.2 ± 16.8 μU · ml^{-1} · h^{-1}, respectively, $P < 0.05$), but metformin and pioglitazone administrations had no effects. Next, 2 mg DXM was administered to six healthy men, and their serum DXM concentrations were measured using radioimmunoassay methods during 24 h after DXM administration with and without preadministration of 400 mg troglitazone or 30 mg pioglitazone daily for 14 days. All serum concentrations of DXM, except that at 0.5 h, were significantly decreased ($P < 0.05$), and the AUC(0–24) of DXM was remarkably reduced by 49% after pretreatment with troglitazone (76.2 ± 10.2 vs. 150.1 ± 17.0 ng · ml^{-1} · h^{-1}, $P < 0.05$), but not after pretreatment with pioglitazone (Fig. 1).

In the present study, we found that troglitazone preadministration decreased DXM-induced hyperglycemia and hyperinsulinemia and that pioglitazone and metformin did not. These findings suggest that the preadministration of troglitazone reverses glucose tolerance in healthy men receiving DXM. We speculated that these properties of troglitazone were independent of peroxisome proliferator–activated receptor-γ (PPARγ), because another PPARγ ligand, pioglitazone, induced no effects. There are two possible mechanisms for these troglitazone-induced effects. Troglitazone may have a direct beneficial effect on glucocorticoid-induced insulin resistance, and troglitazone may induce the rapid metabolism of DXM, resulting in a reduction of the general effect of glucocorticoid, including the induction of insulin resistance.

The precise molecular mechanism of glucocorticoid-induced insulin resistance remains unclear. Glucocorticoid reduces the translocation of GLUT4 from the cytosol into the membrane, while it increases the amount of GLUT4 protein itself (6,7). In vitro studies showed that troglitazone improved the impairment of 2-deoxyglucose uptake in 3T3-l1 adipocytes treated with DXM and in soleus muscle from DXM-treated rats (3,8). Therefore, it is possible that troglitazone may recover the glucocorticoid-impaired translocation of GLUT4. Alternatively, the reversal effect of troglitazone on
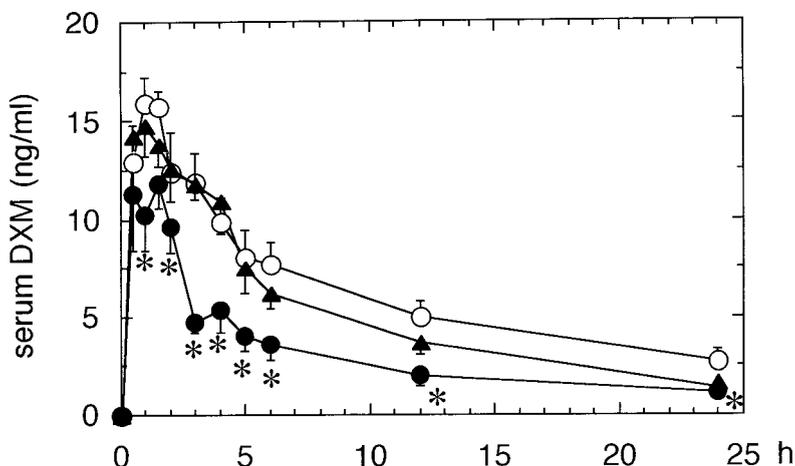
Figure 1—*Serum DXM concentrations before and after the oral administration of 2 mg DXM with and without pretreatment with 400 mg daily troglitazone or 30 mg daily pioglitazone for 14 days; ○, without pretreatment; ●, with pretreatment of 400 mg troglitazone daily for 14 days; ▲, with pretreatment of 30 mg pioglitazone daily for 14 days. Data are means ± SEM,* n = 6. **P < 0.05 vs. without pretreatment.*

DXM-induced insulin resistance may be attributable to inducement of the rapid metabolism of DXM. Troglitazone has recently been reported to reduce plasma concentrations of ethinylestradiol and norethindrone, oral contraceptives, which are metabolized by CYP3A4 (5); thus, using a higher dose of oral contraceptives or alternative methods of contraception during troglitazone therapy is recommended to prevent unplanned pregnancies. Troglitazone has also been reported to increase the urinary excretion of 6β-hydroxycortisol of CYP3A4 metabolites of cortisol in normal control subjects (9). The ratio of 24-h urinary 6β-hydroxycortisol to cortisol excretion can be evaluated as a noninvasive clinical test to detect enzyme activity of CYP3A4 substrates. Ramachandran et al. (10) showed that troglitazone increased the protein level and enzyme activity of CYP3A in primary cultures of human hepatocytes. These data suggest that troglitazone enhances the activity of CYP3A4 like rifampicin, phenytoin, phenobarbiturates, and carbamazepine. It is possible to improve diabetic control in nonoperable patients with Cushing's syndrome by the administration of troglitazone, and it has been reported that diabetic control was improved in diabetic patients who were given predonisolone by troglitazone administration (4). Because pioglitazone induced fewer effects on the pharmacokinetics of DXM in this study, it may also have fewer effects on the activity of CYP3A4. The reason for the difference between troglitazone and pioglitazone in the activity against CYP3A4 remains to be elucidated, but CYP3A4 inducers, such as rifampicin and phenobarbiturates, have recently been reported to be the ligands for an orphan nuclear receptor, pregnane X receptor (PXR), which is expressed in the liver and intestine (11). Thus, it would be interesting to assess whether troglitazone, but not pioglitazone, is a ligand for PXR.

In conclusion, the present study showed that DXM-induced insulin resistance was improved by troglitazone, but not by metformin or pioglitazone. Troglitazone administration reduced the serum concentration of orally administered DXM, indicating that the reversal effects of troglitazone on DXM-induced insulin resistance might have been mainly attributable to the rapid metabolism of DXM through the enhancement of the activity of CYP3A4 in vivo. In contrast, pioglita-

zone had fewer effects on the pharmacokinetics of DXM, and it was not an inducer of CYP3A4.

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Longitudinal Analysis of Blood Pressure, Lipid, and Glycemic Control in Diabetic Patients With Nephropathy Attending a Hospital Outpatient Clinic and Their Relationship to Renal Function, Mortality, and Cardiovascular Morbidity

Clinical trials have shown that optimal blood pressure (BP) control slows the deterioration of renal function in diabetic nephropathy (1), with specific renoprotection from ACE inhibition therapy (2). The benefit of glycemic control is less well established (3). Studies have demonstrated the efficacy of lipid control in the primary and secondary prevention of coronary heart disease in diabetic and nondiabetic people (4,5). Therefore, it is important that patients with diabetic nephropathy use a multiple risk-factor approach (6). Few data are available on BP, lipid, and glycemic control in the nontrial setting. We recently audited the use of therapies proven beneficial in a high-risk group of diabetic patients with overt nephropathy and completed a retrospective analysis of putative renal-failure progression factors from 1992 to 1999.

Data were extracted from our Diabetic Nephropathy Database (Microsoft Access 1997). Mean systolic BP (SBP), diastolic BP (DBP), HbA$_{1c}$, total serum cholesterol (TC), BMI, and serum creatinine

(CR) at baseline and follow-up, as well as demographic data including age, sex, age at diagnosis, duration of diabetes, diabetes type, length of follow-up, presence of retinopathy, smoking status, and date of death were documented for each patient. The number of patients from 1992 to 1999 with new ischemic heart disease (IHD), cerebrovascular disease (CVD), and peripheral vascular disease events with no previous history were also determined. Documented drug classes included statins, fibrates, β-blockers, calcium channel blockers, α-blockers, ACE-inhibitors (ACEI), angiotensin-II receptor antagonists, loop diuretics, thiazide diuretics, and aspirin. All patients with a CR >120 μmol/l, a positive dipstick proteinuria on at least three occasions (of which two were consecutive), and at least 2 years of follow-up data were selected from the database. Renal function for each patient was estimated using the inverse of serum CR (1/CR), and change in renal function was estimated as the rate of change of 1/CR (Δ1/CR). Two patient groups were created for comparison—deterioration in renal function versus stable or improved renal function. The British Hypertension Society recommendation of a BP ≤140/80 mmHg (7) defined optimal BP control, and the Joint British Society recommendation of a TC ≤5 mmol/l (8) defined optimal lipid control. An HbA$_{1c}$ ≤7.5% defined optimal glycemic control (9,10).

A total of 260 patients had diabetic nephropathy with a mean ± SD BP of 146/72 ± 23/14 mmHg. Δ1/CR deteriorated in 61% of patients. In this group, SBP was higher (153 ± 24 vs. 136 ± 17 mmHg, P < 0.0001), more patients had a SBP >140 mmHg (70 vs. 40%, P < 0.001), and there were more deaths (33 vs. 15%, P = 0.001) compared with the patients in whom Δ1/CR remained stable or improved. In addition, 47 and 29% of patients achieved optimal glycemic and lipid control, respectively. Relatively few patients were taking aspirin (44%), lipid-lowering (20%), or ACEI (39%) therapy. Using simple regression, SBP was the strongest predictor of Δ1/CR (r = 0.23, P < 0.001), death (hazard ratio [HR] 95% CI 2.2 [1.6–4.1]), and IHD (HR 1.9 [1.4–3.4]). Using multiple regression, SBP was a strong predictor of death (HR 2.7 [1.5–4.9]) and IHD (HR 2.4 [1.7–5.5]), but not a strong predictor of Δ1/CR (P = NS). Using simple regression, DBP was a predictor of death (HR 1.7 [1.2–7.8]) and IHD (HR 1.5 [1.1–5.7]), but this signifi-cance was lost using multiple regression. TC was a predictor of IHD events using simple regression (HR 3.1 [2.2–6.8]) and multiple regression (HR 2.1 [1.5–5.7]). Lack of ACEI therapy was a predictor of death when using simple regression (odds ratio [OR] 95%CI 1.7 [1.2–3.9]), but not when using multiple regression. Using multiple regression, patients not on aspirin therapy had worse renal function (β = −232 × 10^{-6}, P = 0.002) and an increased risk of death (OR 2.8 [1.9–4.3]) and CVD (OR 2.2 [1.7–6.5]) compared with patients receiving aspirin treatment.

The mean ± SD BP of 146/72 ± 23/14 mmHg achieved in our patients is very close to the reported values in the tight BP arm of the UKPDS trial (144/82 ± 14/7 mmHg) (11), thus demonstrating that reasonable BP control can be achieved in routine clinical practice. Low use of therapies proven beneficial, unsatisfactory glycemic and lipid control, and the importance of SBP in determining renal function decline in our patients reinforced the need for multiple risk-factor intervention in patients with diabetic nephropathy.

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Microalbuminuria, High Blood Pressure Burden, and Nondipper Phenomenon

An interaction in normotensive type 1 diabetic patients

Type 1 diabetes is associated with hypertension and increased risk of morbidity and mortality attributable to cardiovascular disease and renal failure. Almost 40% of patients with type 1 diabetes will develop clinical diabetic nephropathy, defined as urinary albumin excretion rate (AER) >300 mg/24 h (1).

We studied 37 normotensive type 1 diabetic patients without macroalbuminuria, aged 26.5 ± 6.75 years and with 9.4 years (range 1–34) of disease, and 28 normotensive nondiabetic subjects with fasting glucose blood levels ≤ 100 mg/dl, aged 24.9 ± 6.81 years, who were matched to the diabetic group for age, sex, skin color, weight, height, and BMI. Albumin concentration was measured by double-antibody radioimmunoassay (DPC, Los Angeles, CA). Ambulatory blood pressure monitoring (ABPM) was performed during a working day using a portable automatic oscillometric recorder (SpaceLabs 90207). The recordings provided the mean 24-h, daytime, and nighttime values of systolic (sBP) and diastolic BP (dBP) and heart rate. Subjects with a nocturnal fall in either sBP or dBP of <10% of daytime values were classified as nondippers (2). We found higher means of ABPM in microalbuminuric diabetic patients than in normoalbuminuric and nondiabetic subjects. Nighttime BP values were higher in normoalbuminuric diabetic patients than in nondiabetic subjects. The BP burden was higher in microalbuminuric than in normoalbuminuric patients and nondiabetic subjects. No difference of BP burden was found between normoalbuminuric diabetic subjects and nondiabetic subjects. During the nighttime period, a higher frequency of systolic BP burden >50% and of diastolic BP burden >30% was found in microalbuminuric patients than in normoalbuminuric diabetic patients (4 of 9 vs. 1 of 28; $P = 0.008$). Nondiabetic subjects had a higher decline of sBP and dBP than microalbuminuric and normoalbuminuric patients. A high frequency of nondippers for sBP was observed among diabetic patients (30 of 37 vs. 12 of 30; $P = 0.001$), and a high frequency of microalbuminuria (5 of 9 vs. 5 of 28; $P = 0.04$) and a longer duration of disease (11.7 years [5–18] vs. 8.6 years [1–34]; $P < 0.05$) was observed in diabetic patients who were nondippers for dBP. In agreement with other studies (3,4), we found higher mean values and burden BP in microalbuminuric diabetic patients than in normoalbuminuric and nondiabetic subjects. Despite the demonstration in our study of an association between microalbuminuria and systolic BP burden >50% and diastolic >30% during the nighttime, the value of BP burden associated with microalbuminuria in diabetic patients has not been defined. We

observed a lower decline of nighttime BP in micro- and normoalbuminuric diabetic patients than in nondiabetic subjects, as noted in other studies (2,4). Although we did not evaluate autonomic function, the presence of a lower BP decline during the nighttime period in the diabetic group may suggest autonomic neuropathy (5). An interaction among poor glycemic control, higher BP during ABPM, and attenuated vagal activity in normoalbuminuric type 1 diabetic patients had been observed in patients with high-normal AER and impaired reduction in nocturnal dBP (6). The association between microalbuminuria and longer duration of diabetes with the nondipper status for dBP observed in our study has been related (4,7). Other studies have shown that type 1 diabetic patients who developed microalbuminuria had an impaired reduction in nocturnal dBP and higher AER compared with persistently normoalbuminuric patients (7), and that the nondipper status for dBP is a late alteration and is suggestive of microalbuminuria (4).

In conclusion, our study suggests that the impaired decline of BP was probably associated with diabetes itself and that higher BP burden and nondipper status for dBP were associated with microalbuminuria. Further prospective studies may determine whether an impaired nocturnal fall in BP and the nondipper phenomenon in normotensive type 1 diabetic patients could increase the risk of cardiovascular disease and nephropathy.

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Bone Mineral Density, Type 1 Diabetes, and Celiac Disease

Correspondence in *Diabetes Care* has highlighted the importance of two secondary causes of reduced bone mineral density (BMD) in type 1 diabetes, namely thyrotoxicosis and primary hyperparathyroidism (1,2). We describe another secondary cause of reduced BMD. Celiac disease is associated with reduced BMD and reversible secondary osteoporosis in the general population (3,4). Celiac disease is not uncommon in type 1 diabetes, with a prevalence of 1–7.8% (5). The association between celiac disease, type 1 diabetes, and osteopenia has been discussed in *Diabetes Care* (6), but the impact of celiac disease on BMD in type 1 diabetes has not been quantified.

We undertook a population-based study of BMD in 99 women with type 1 diabetes using dual-energy X-ray absorptiometry, as previously described (7). Although multiple clinical determinants of BMD were assessed, no subject had diagnosed celiac disease, and we did not undertake any screening tests for undiagnosed celiac disease at the time of the ini-

tial study. After the completion of the study, women with a reduced BMD (*Z* score of −1 or less) were investigated for secondary causes of osteopenia, and four women were found to have celiac disease. Ethics committee approval was then obtained to screen the remaining women for celiac disease using the IgA endomysial antibody (EMA) serological test.

A total of 10 of the 99 subjects were EMA positive, and all 10 subjects had features of celiac disease on small bowel biopsy. Seven subjects had minor gastrointestinal symptoms that resolved after the introduction of a gluten-free diet. The remaining three subjects were asymptomatic. The 10 women with a new diagnosis of celiac disease were younger than the 89 women without celiac disease (mean age 37 and 43 years, respectively); therefore, BMD was adjusted for age. The mean age-adjusted (standard deviation) *Z* score at the lumbar spine was −0.98 for the 10 subjects with celiac disease, compared with −0.12 for the 89 subjects with diabetes alone (*P* = 0.03). The corresponding mean *Z* scores at the femoral neck were −0.72 and −0.06, respectively (*P* = 0.11). The *Z* score for all 99 women studied was −0.21 at the lumbar spine and −0.12 at the femoral neck (7), thus the impact of removing the 10 subjects with celiac disease from the calculation of the study population's mean BMD was negligible.

The above results from women with type 1 diabetes are consistent with the previously described finding in the general population, which shows an association between untreated celiac disease and reduced BMD. Celiac disease should be considered as a possible secondary cause of osteopenia in type 1 diabetic patients found to have a reduced BMD. We recommend that future studies examining determinants of osteopenia in type 1 diabetes include a sceening test for celiac disease. The presence of celiac disease had minimal impact on the mean BMD of the population studied, thus the results do not support the hypothesis that celiac disease is the principal cause of the reduced BMD described in association with type 1 diabetes.

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Serious Hypoglycemia: Munchausen's Syndrome?

Hypoglycemia presents important diagnostic and therapeutic problems. Severe and repetitive hypoglycemic episodes in patients without treatment may be difficult to explain. Failure to identify factitious hypoglycemia may lead to laparatomy or pancreatectomy. Hypoglycemia factitia is assessed as a manifestation of Munchausen's syndrome (1), which is characterized by factitious illness associated with hospital peregrination, mythomanic discourse that includes

medical elements, and passivity and dependence at examinations. Munchausen's syndrome was first described in relation to laparotomophilia migrans patients, whose stories were dramatic and untruthful.

Between January 1997 and 30 November 1999, we searched for the presence of a sulfonylurea-related oral hypoglycemic agent in 129 patients who had unexplained severe hypoglycemia. The patients were recruited from all over France during a 35-month period. To detect the presence of sulfonylurea, we developed a chromatographic liquid method with UV detection.

In 22 patients (17%), a second generation of the sulfonylurea oral hypoglycemic agent was detected: glibenclamide was detected in 19 patients, and gliclazide was detected in 3 patients. The study population comprised 13 women (mean age ± SD 40 ± 18 years) and 9 men (64 ± 11 years). The plasmatic concentrations are usually superior to the therapeutic ones, and in seven cases, they were five times more, with a maximum of 18 times the therapeutic degrees. All of these patients had only one hypoglycemic agent. Diagnosing the patients was difficult, because the patients remained on their medication during their hospitalization stay, which was aimed at identifying an etiology. The search for hypoglycemic agents is made through a surveillance of glycemia. In a 28-year-old patient, we identified glibenclamide concentrations of 338 μg/l at 1:00 P.M. (therapeutic concentration 25–50 μg/l), of 141 μg/l at 10:00 P.M., and of 211 μg/l at 2:00 A.M. over a 2-day period. Few patients have family members who require treatment with hypoglycemic medication, but interrogation is usually difficult. In most cases, an insulinoma was suggested and sometimes a pancreatectomy was planned.

This study is the first to be conducted in order to evaluate the impact of Munchausen's syndrome on hypoglycemia.

Only a few cases of hypoglycemia factitia with oral hypoglycemic agent have been published (2–5), yet the lack of publications must not result in neglect and underevaluation of the risk. Hypoglycemia factitia with sulfonylurea should be considered in the differential diagnosis of insulinoma. They can be excluded only by analyzing the patients' blood for sulfonylurea drugs.

The etiologic diagnosis of severe hy-

poglycemia is difficult. The hidden absorption of one or more hypoglycemic agents must be tracked.

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Serum Leptin Concentrations in Young Smokers With Type 1 Diabetes

Several studies have reported that serum levels of leptin, an adipocyte-secreted hormone, increase exponentially with increasing body fat mass (1). However, there is considerable variability in leptin levels at a given level of adiposity, suggesting that other factors may influence circulating leptin levels. In this context, there is little and somewhat conflicting information regarding the effects of diabetic state per se on leptin levels, particularly in type 1 diabetes. Serum leptin concentrations have been found to be normal (2,3) or higher (4) in type 1 diabetic patients compared with control subjects. Moreover, although significantly lower serum leptin levels have been demonstrated in nondiabetic smokers

versus nonsmokers (1,5–7), to our knowledge, there is a lack of available data regarding the impact of smoking on leptin levels in young adults with type 1 diabetes. On the other hand, the clarification of smoking's impact may have important implications for risk management and our understanding of the pathophysiological mechanisms of weight gain after smoking cessation. Thus, the main purposes of the present study were to compare serum leptin levels in nondiabetic subjects and type 1 diabetic patients and to assess the effects of chronic smoking on leptin levels in type 1 diabetic patients.

We measured serum leptin concentrations (RIA-kit; Linco Research, St Louis, MO) in 54 young type 1 diabetic patients without clinical evidence of macroangiopathy and in 20 healthy control subjects who were matched for age (31.6 ± 1.3 vs. 31.8 ± 1.3 years), sex (M/F = 30/24 vs. 12/8), BMI (23.8 ± 0.6 vs. 23.3 ± 0.7 kg/m^2), systolic blood pressure (125 ± 2 vs. 122 ± 2 mmHg), diastolic blood pressure (81 ± 1 vs. 80 ± 1 mmHg), and smoking status (smokers $n = 20$ vs. 10). The average glycometabolic control of diabetic patients was fairly good (HbA$_{1c}$ $6.7 \pm 0.1\%$); the diabetes duration was 14.8 ± 0.2 years. More details on clinical and biochemical characteristics of the subjects have been reported previously (8). Type 1 diabetic patients had leptin concentrations substantially similar to the healthy control subjects (mean $\pm$ SEM 4.13 ± 0.5 vs. 4.36 ± 0.7 ng/ml). After stratification by smoking status, diabetic smokers ($n = 34$) had values for age, sex, BMI, lipids, blood pressure, glycometabolic control, creatinine, diabetes duration, and its microvascular complications (i.e., presence of retinopathy and/or microalbuminuria) that were superimposable upon their nonsmoking counterparts ($n = 20$). Nevertheless, serum leptin levels were markedly reduced in diabetic smokers versus nonsmokers (2.62 ± 0.4 vs. 4.91 ± 0.7 ng/ml; $P < 0.01$). Similarly, healthy subjects who smoked had significantly lower leptin levels than healthy nonsmokers (3.7 ± 1.1 vs. 5.7 ± 0.8 ng/ml; $P < 0.05$). Leptin levels decreased markedly with the increase in the number of cigarettes smoked daily in both diabetic patients (nonsmokers vs. <11 cigarettes/day vs. >11 cigarettes/day: 4.91 ± 0.7 vs. 3.1 ± 0.7 vs. 2.3 ± 0.6 ng/ml, respectively; $P < 0.02$ for comparison by one-way analysis

of variance) and control subjects, although this trend did not achieve a statistical significance ($P = 0.058$). The dose-response relationship found in diabetic patients between leptin levels and the number of cigarettes smoked per day remained statistically significant even after adjustment for potential confounders, such as age, sex, BMI, glycometabolic control, lipids, diabetes duration, and complication status.

Overall, therefore, the evidence from this study and other studies (2,3) suggests that type 1 diabetic patients have serum leptin levels similar to those of healthy control subjects with comparable BMI, and that chronic cigarette smoking itself may be one of the major life-style determinants of leptin levels in both normal subjects (5–7) and type 1 diabetic individuals. Although no straightforward explanation is available, cigarette smoking may directly or indirectly modify the sensitivity of hypothalamic leptin receptors and, consequently, modulate leptin synthesis (5).

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An Avoidable Cause of False Home Glucose Measurements

In patients with type 2 diabetes, tight control of blood glucose reduces complications and improves outcomes. As a result, increasing numbers of elderly patients with type 2 diabetes are being advised to measure blood glucose at home. For these elderly patients, who are at risk to have impaired cognition, vision, and dexterity, it is especially important that their home glucose meters provide accurate, reliable results and are simple to operate. We report a case of an elderly patient who suffered falsely elevated home glucose measurements for an interesting and avoidable cause.

An 89-year-old man with type 2 diabetes had been managed for many years with low daily doses of insulin. After an adjustment of his insulin schedule, he suffered an episode of symptomatic hypoglycemia. Because he was on small doses of insulin and his glucose control had

been excellent (glycohemoglobin 6.0%), he was advised to stop all insulin administration and to carefully monitor blood glucose levels at home for a period of time.

Three days after receiving this advice, his wife called the office nurse, stating that earlier in the day the patient had a blood glucose level of 561 mg/dl, without any other untoward effects. She "sent him outside to work it off," and when he came back his blood glucose was 175 mg/dl. They were advised to continue monitoring the blood glucose.

Two days later, the patient's wife again called to state that earlier in the day he had a blood glucose of 591 mg/dl, and again she advised him to increase his exercise. His blood glucose 2 h later was 180 mg/dl. The patient and his wife were asked to come to the clinic and to bring his home glucose meter for further investigation of these wildly fluctuating blood glucose measurements in a previously stable individual.

During the clinic visit, it was determined that the home glucose meter was working properly. The patient's 56-year-old daughter, an accountant, arrived in the meanwhile to state that she had discovered the problem. Inspecting a digital display of a calculator, she determined that the number 165 read upside down was 591, and the number 195 read upside down was 561. She concluded that the patient and his wife had been reading the glucose meter upside down.

By using a commercially available digital calculator, we have determined that the digits 0, 1, 2, 5, and 8 appear as the same numbers whether read right way up or upside down. The digit six may appear to be a nine when read upside down, and the digit nine may appear to be a six when read upside down. Thus, combinations of these digits result in the potential for a patient to turn a home glucose monitor upside down and obtain a false glucose reading.

Many commercially available home glucose meters will provide digital readings of up to 600. Thus, glucose values in the 100s, 200s, or 500s could represent the patient's actual blood glucose at the time, or they could represent the upside down reading phenomenon.

Patients should be clearly informed which is the top and which is the bottom of their glucose meters, and companies should be sure that their devices are very

clearly labeled in this regard to prevent incidents similar to the one reported here. In addition, health care personnel who deal with patients with diabetes should be aware of this potential problem in interpreting home glucose meter readings.

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COMMENTS AND RESPONSES

Do All Women Require Intensive Retinal Surveillance During Pregnancy?

The Diabetes Control and Complications Trial (DCCT) Research Group is to be congratulated on its careful analysis of the retinal changes in pregnancy in women who participated in the trial (1). This analysis was able to demonstrate both a genuine "pregnancy effect" and an "early worsening effect" of tightening glycemic control as independent contributors to the well-recognized phenomenon of deterioration in retinopathy during pregnancy. Because comparable data are unlikely to ever be accumulated, this letter will probably stand as the last word on the subject.

However, one important point was not addressed in the article: whether women who had no retinopathy immediately before or early in pregnancy ever developed in later pregnancy or postpartum retinopathy of sufficient severity to warrant intervention by an ophthalmologist. Other prospective studies have found that, although up to 33% of such women develop background changes during pregnancy, the retinopathy is mild in degree, does not require intervention, and regresses postpartum (2–8).

Thus, the injunction in the DCCT Research Group's article, that all women with type 1 diabetes should have intensive retinal surveillance during pregnancy and postpartum (1), does not seem to have sound evidence to support it—even though it accords with the recommendations of an earlier review (9). It is important that all diabetic women have their eyes examined in early pregnancy, but the literature suggests that only those who have retinopathy detected before or early in pregnancy and those who are without retinopathy but have particularly poor glycemic control require intensive ophthalmologic surveillance.

Intensive surveillance is demanding. A recent review (9) suggests that it should involve a complete eye examination at least every trimester and within 3 months postpartum. Women with type 1 diabetes already have a lot to contend with during pregnancy. Should those that do not need intensive surveillance be burdened with resource-consuming and, arguably, unnecessary visits for retinal examination? This group is not trivial in number—more than half of the intensively treated patients in the DCCT study had no retinopathy on their first examination (1).

The American Diabetes Association's Clinical Practice Recommendations seem ambiguous on this point. The position statement on preconception care states that follow-up ophthalmologic examinations should be "anticipated" during pregnancy for all women with diabetes (10); yet, the position statement on diabetic retinopathy states that the frequency of follow-up should depend on the result of the first trimester examination (11).

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Response to Cundy

We thank Dr. Cundy (1) for his interest in and careful reading of the article of the Diabetes Control and Complications Trial (DCCT) Research Group that focused on the risk for developing progressive retinopathy during and after pregnancy (2). Given the relatively small number of women who became pregnant ($n = 180$) and the even smaller number of pregnant women who developed severe retinopathy in the DCCT (defined as proliferative or severe nonproliferative retinopathy, $n = 13$), we were hesitant to make any specific recommendations that could potentially jeopardize patient safety. Moreover, both the frequent follow-up of DCCT volunteers with standardized research-quality stereoscopic fundus photography and the generally low level of mean HbA_{1c} before pregnancy (7.4 and 8.1% in the intensive and conventional treatment groups, respectively) (3) made translation of our results to the nonresearch population problematic and further tempered our recommendations.

On the other hand, we must ask Dr. Cundy whether the relationship between baseline retinopathy status before pregnancy and the risk of progressive retinopathy during and after pregnancy can help to refine current recommendations regarding the need to screen diabetic women frequently during and after pregnancy. Specifically, did any of the women who developed severe retinopathy during or after pregnancy have no or only minimal retinopathy before pregnancy? With a large enough group of women who became pregnant with no retinopathy at baseline, we should be able to cast some light on whether such patients are at any substantive risk for developing severe retinopathy during and shortly after pregnancy. Furthermore, we should be able to determine the need for frequent ophthalmologic surveillance.

Of 270 pregnancies in the DCCT, 183 were in women who showed no or only minimal retinopathy (microaneurysms only) at the examination immediately preceding the pregnancy. Three (1.6%) developed severe retinopathy. Conversely, of the 13 patients who developed severe retinopathy during their pregnancies, none had no retinopathy, 3 had retinopathy, and 10 had mild to moderately severe nonproliferative retinopathy before their pregnancies. The small number of patients with severe retinopathy associated with pregnancy precludes any detailed analyses or conclusive determinations. However, on the basis that only three cases of severe retinopathy developed during 183 pregnancies that showed no or only minimal retinopathy before pregnancy, we can hypothesize that the risk in such women is quite low.

In summary, the major findings of our study are the following: pregnancy increases the risk for progressive retinopathy during and in the first year after pregnancy; the risk cannot be explained entirely by the transient worsening associated with intensification of therapy, although intensification of therapy did

impact the risk (4); and the adverse effects of pregnancy on retinopathy appear to dissipate and generally do not affect long-term outcome. We have previously demonstrated that the degree of baseline retinopathy affects the risk of progressive retinopathy in nonpregnant patients. (5) Similarly, a low level of retinopathy before pregnancy appears to be associated with low risk for developing severe retinopathy during or shortly after pregnancy; however, the relatively small subset of DCCT participants who became pregnant prevents us from concluding that ophthalmologic screening during pregnancy is unnecessary—even in women with little or no retinopathy before their pregnancy.

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Oral Glucose Tolerance Test Indexes for Insulin Sensitivity and Secretion Based on Various Availabilities of Sampling Times

We have recently proposed a series of indexes for β-cell function and insulin sensitivity to be calculated from glucose and insulin concentrations obtained during a classic World Health Organization oral glucose tolerance test (OGTT) (1). The models were validated by the euglycemic-hyperinsulinemic and the hyperglycemic clamp technique, respectively. The generation of these indexes was based on simple statistical models using stepwise linear regression analysis. The variables in the model assumed the availability of determina-

Table 1—*Estimates of insulin sensitivity based on availability of sampling time points in nondiabetic subjects*

Sampling times	Estimated insulin sensitivity index (μmol $\cdot$ kg^{-1} $\cdot$ min^{-1} $\cdot$ pmol/l)	Estimated metabolic clearance rate (ml $\cdot$ kg^{-1} $\cdot$ min^{-1})
0 and 120 min	$0.156 - 0.0000459 \times \text{Ins}_{120} - 0.000321 \times \text{Ins}_0 - 0.00541 \times \text{Gluc}_{120}$ $r = 0.69$	$13.273 - 0.00384 \times \text{Ins}_{120} - 0.0232 \times \text{Ins}_0 - 0.463 \times \text{Gluc}_{120}$ $r = 0.68$
0, 60, and 120 min	$0.156 - 0.0000459 \times \text{Ins}_{120} - 0.000321 \times \text{Ins}_0 - 0.00541 \times \text{Gluc}_{120}$ $r = 0.69$	$13.273 - 0.00384 \times \text{Ins}_{120} - 0.0232 \times \text{Ins}_0 - 0.463 \times \text{Gluc}_{120}$ $r = 0.68$
0 and 30 min	$0.205 - 0.000437 \times \text{Ins}_0 - 0.0185 \times \text{Gluc}_0$ $r = 0.62$	$15.841 - 0.0341 \times \text{Ins}_0 - 1.262 \times \text{Gluc}_0$ $r = 0.59$
0, 30, and 60 min	$0.149 - 0.000467 \times \text{Ins}_0 - 0.00466 \times \text{Gluc}_{60}$ $r = 0.65$	$12.464 - 0.0357 \times \text{Ins}_0 - 0.376 \times \text{Gluc}_{60}$ $r = 0.62$
0 and 120 min*	$0.222 - 0.00333 \times \text{BMI} - 0.0000779 \times \text{Ins}_{120} - 0.000422 \times \text{Age}$ $r = 0.79$	$19.240 - 0.281 \times \text{BMI} - 0.00498 \times \text{Ins}_{120} - 0.333 \times \text{Gluc}_{120}$ $r = 0.79$
0, 60, and 120 min*	$0.222 - 0.00333 \times \text{BMI} - 0.0000779 \times \text{Ins}_{120} - 0.000422 \times \text{Age}$ $r = 0.79$	$19.240 - 0.281 \times \text{BMI} - 0.00498 \times \text{Ins}_{120} - 0.333 \times \text{Gluc}_{120}$ $r = 0.79$
0 and 30 min*	$0.213 - 0.00305 \times \text{BMI} - 0.000308 \times \text{Ins}_0 - 0.000640 \times \text{Age}$ $r = 0.75$	$18.078 - 0.267 \times \text{BMI} - 0.0214 \times \text{Ins}_0 - 0.0501 \times \text{Age}$ $r = 0.75$
0, 30, and 60 min*	$0.231 - 0.00296 \times \text{BMI} - 0.000284 \times \text{Ins}_0 - 0.000506 \times \text{Age} - 0.00318 \times \text{Gluc}_{60}$ $r = 0.78$	$19.487 - 0.260 \times \text{BMI} - 0.254 \times \text{Gluc}_{60} - 0.0195 \times \text{Ins}_0 - 0.0394 \times \text{Age}$ $r = 0.77$

Insulin (Ins) measured in picomoles per liter; glucose (Gluc) measured in millimoles per liter. *Inclusion of demographic parameters (age, sex, BMI, and waist-to-hip ratio) in model. All P values < 0.001.

Table 2—*Estimates of β-cell function based on availability of sampling time points in nondiabetic subjects*

Sampling times	Estimated first phase (pmol/l)	Estimated second phase (pmol/l)
0 and 120 min	$2{,}503 + 6.476 \times \mathrm{Ins}_0 - 126.5 \times \mathrm{Gluc}_{120} + 0.954 \times \mathrm{Ins}_{120} - 239.3 \times \mathrm{Gluc}_0$ $r = 0.65$	$393 + 1.163 \times \mathrm{Ins}_0 - 40.72 \times \mathrm{Gluc}_{120} + 0.313 \times \mathrm{Ins}_{120}$ $r = 0.70$
0, 60, and 120 min	$1{,}194 + 4.724 \times \mathrm{Ins}_0 - 117.0 \times \mathrm{Gluc}_{60} + 1.414 \times \mathrm{Ins}_{60}$ $r = 0.71$	$295 + 0.349 \times \mathrm{Ins}_{60} - 25.72 \times \mathrm{Gluc}_{60} + 1.107 \times \mathrm{Ins}_0$ $r = 0.75$
0 and 30 min	$1{,}283 + 1.829 \times \mathrm{Ins}_{30} - 138.7 \times \mathrm{Gluc}_{30} + 3.772 \times \mathrm{Ins}_0$ $r = 0.78$	$286 + 0.416 \times \mathrm{Ins}_{30} - 25.94 \times \mathrm{Gluc}_{30} + 0.926 \times \mathrm{Ins}_0$ $r = 0.79$
0, 30, and 60 min	$1{,}283 + 1.829 \times \mathrm{Ins}_{30} - 138.7 \times \mathrm{Gluc}_{30} + 3.772 \times \mathrm{Ins}_0$ $r = 0.78$	$286 + 0.416 \times \mathrm{Ins}_{30} - 25.94 \times \mathrm{Gluc}_{30} + 0.926 \times \mathrm{Ins}_0$ $r = 0.79$
0 and 120 min*	$2{,}032 + 4.681 \times \mathrm{Ins}_0 - 135.0 \times \mathrm{Gluc}_{120} + 0.995 \times \mathrm{Ins}_{120} + 27.99 \times \mathrm{BMI} - 269.1 \times \mathrm{Gluc}_0$ $r = 0.68$	$277 + 0.800 \times \mathrm{Ins}_0 - 42.79 \times \mathrm{Gluc}_{120} + 0.321 \times \mathrm{Ins}_{120} + 5.338 \times \mathrm{BMI}$ $r = 0.73$
0, 60, and 120 min*	$728 + 3.537 \times \mathrm{Ins}_0 - 120.3 \times \mathrm{Gluc}_{60} + 1.341 \times \mathrm{Ins}_{60} + 21.27 \times \mathrm{BMI}$ $r = 0.73$	$208 + 0.335 \times \mathrm{Ins}_{60} - 26.33 \times \mathrm{Gluc}_{60} + 0.887 \times \mathrm{Ins}_0 + 3.933 \times \mathrm{BMI}$ $r = 0.76$
0 and 30 min*	$1{,}283 + 1.829 \times \mathrm{Ins}_{30} - 138.7 \times \mathrm{Gluc}_{30} + 3.772 \times \mathrm{Ins}_0$ $r = 0.78$	$286 + 0.416 \times \mathrm{Ins}_{30} - 25.94 \times \mathrm{Gluc}_{30} + 0.926 \times \mathrm{Ins}_0$ $r = 0.79$
0, 30, and 60 min*	$1{,}283 + 1.829 \times \mathrm{Ins}_{30} - 138.7 \times \mathrm{Gluc}_{30} + 3.772 \times \mathrm{Ins}_0$ $r = 0.78$	$286 + 0.416 \times \mathrm{Ins}_{30} - 25.94 \times \mathrm{Gluc}_{30} + 0.926 \times \mathrm{Ins}_0$ $r = 0.79$

Insulin (Ins) measured in picomoles per liter; glucose (Gluc) measured in millimoles per liter. *Inclusion of demographic parameters (age, sex, BMI, and waist-to-hip ratio) in model. All P values < 0.001.

tions at 0, 30, 60, 90, and 120 min. Since the publication of this article, we have been contacted repeatedly by potential users of the indexes who do not have at their disposal all of the time points required for the various indexes.

Therefore, we returned to the original database of OGTTs and euglycemic and hyperglycemic clamps in the 104 nondiabetic subjects (normal glucose tolerance, $n = 65$; impaired glucose tolerance, $n = 39$) and generated the equations for different sets of time points. The exact same procedures were applied as previously described (1), except the indicated variables only were entered in the model. The equations were generated using both pure OGTT data and OGTT data plus demographic data (BMI, age, and waist-to-hip ratio). The resulting equations with the variables remaining in the equations are

shown in Tables 1 and 2. The r values for the insulin secretion parameters ranged from 0.65 to 0.79 and for insulin sensitivity from 0.59 to 0.79. For comparison, the homeostasis model assessment (HOMA) resistance index was reasonably well correlated with the insulin sensitivity index ($r = -0.59$, $P < 0.001$) and the metabolic clearance rate ($r = -0.56$, $P < 0.001$), and the HOMA secretion index was reasonably well correlated with first-phase ($r = 0.57$, $P < 0.001$) and second-phase insulin release ($r = 0.62$, $P < 0.001$), as previously reported (1).

In conclusion, given many variations in oral glucose tolerance, reasonable estimates for insulin secretion and insulin sensitivity can be made. The optimal sampling constellation appears to be 0, 30, and 120 min, including age and BMI (all r values >0.78).

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