OBSERVATIONS

Characteristics of 98 Children and Adolescents Diagnosed With Type 2 Diabetes by Their Health Care Provider at Initial Presentation

Although the number of children and youth with type 2 diabetes is increasing, a clear case definition that describes children with type 2 diabetes at presentation remains elusive. Most initial diagnoses are decided on the clinical picture at presentation (1). Characteristics and risk factors have been outlined in several review and clinical articles (2–4). The purpose of this study was to describe the characteristics of youth presenting for an initial visit to the outpatient clinic of a large tertiary children's care center and diagnosed with type 2 diabetes.

For this retrospective study, data were abstracted from a consecutive sample of 98 patients' medical records at Texas Children's Hospital starting 1 January 1998 and ending 31 October 2001. The sample's mean age at diagnosis was 13.6 years (SD 2.33; range 8.7–18.4 years). Fifty-one percent of the children were female and 49% were male (female: male ratio 1:1). For 43% race/ethnicity was not specified; the remaining participants were 28.6% African American, 22.4% Hispanic, 3.1% non-Hispanic white, and 3.1% Asian. Of those for whom data were available, a maternal history of type 2 diabetes was reported by 32.7% (18/55) and an unspecified type of diabetes by 12.7% (7/55). Twenty-seven percent (13/47) reported a father with type 2 diabetes and 21% (10/47) an unspecified type of diabetes.

Mean BMI was 34.67 kg/m^2 (SD 6.91). Ninety-three percent had a BMI ≥95th percentile. All but three of the individuals had BMIs ≥85th percentile. Of those for whom data were recorded, acanthosis nigricans was identified in 94% (48/51). A Tanner stage of 3, 4, or 5 was identified in 73.2% (49/67).

Blood pressure readings indicated that 49.4% (41/83) had a systolic (SBP) and 10.8% (9/83) a diastolic (DBP) ≥95th percentile for age, sex, and height (n = 83). Fifty-five percent (46/83) had SBP and 19.3% (16/83) DBP readings ≥90th percentile for blood pressure. Of 72 pulse rates recorded, 2.6% were ≥95th percentile for age. Average HbA_{1c} was 10.38 (SD 3.52) (n = 95).

Of those who had symptoms documented in the medical record, 83.6% (56/67) reported polyuria, 83.9% (52/62) polydipsia , and 61% (36/59) polyphagia. Seventy-five percent reported both polyuria and polydipsia (46/61). Of the cases available, 46.2% (24/52) reported all three of the polys at initial presentation, 46.8% (29/62) had weight loss, and 62.5% (30/48) had ketones. Of those for whom islet cell antibody data were recorded (50/98), 49 had JDF units <5. Fifty-three percent were started on insulin, 46.3% on oral agents, and 13.7% on both insulin and oral agent (n = 96). Initial mean insulin dose was 0.6 units/kg.

Our sample is similar to those described in previous reports except for a more even ratio of female to male subjects, a greater percent with elevated SBP and/or DBP, and more individuals reporting weight loss. We are the first to report blood pressure by the 95th and 90th percentiles and the first to report pulse rate. These data contribute to the growing body of clinical evidence defining the characteristics of youth with type 2 diabetes.

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Asymptomatic Bacteriuria and Leukocyturia in Type 1 Diabetic Children and Young Adults

In the study of Geerlings et al. (1), one of five type 1 diabetic women had asymptomatic bacteriuria (ASB). In the few studies of diabetic children a low prevalence of ~1% was found (2–4). Our clinical experience suggested a much higher prevalence; therefore, we decided to estimate the prevalence and possible risk factors of ASB in type 1 diabetic children.

There were 178 (86 male) type 1 diabetic children and young adults (age 15.1 ± 5.9 years) with diabetes duration of 6.2 (3.0–10.1) [median (interquartile range)] years who participated in this study.

The control group consisted of 194 (103 male) school children/medical students (14.4 ± 5.1 years). After careful cleaning, midstream voiding morning urine samples were collected and immediately cultured on 2 consecutive days.

ASB was defined as the presence of ≥10^5 colony-forming units/ml of one and

the same bacterial species in both samples without symptoms of urinary tract infection (UTI). In 140 diabetic patients and 191 control subjects, we had the possibility to evaluate the presence of leukocyturia by dip-slide method and/or microscopically (>5 cells/high-power field).

Student's *t* test, Mann-Whitney test, χ^2 test, and Fisher's exact test were used to assess statistically significant differences.

The prevalence of ASB was 10.1% (95% CI 5.7–14.5%), which was significantly higher than in the control group (2.6%, 0.35–4.8%) ($P = 0.003$) and tended to increase with age ($P = 0.064$). We did not find any difference in prevalence of ASB between diabetic male (9.3%) and female (10.9%) subjects ($P = 0.73$). The age, duration of diabetes, BMI, morning and mean daily blood glucose levels, urinary glucose excretion, HbA_{1c}, and albumin excretion rate (in the normal range) were similar in diabetic patients with and without ASB.

Leukocyturia tended to be more frequent in diabetic patients without ASB than in control subjects (14.4 vs. 7.6%; $P = 0.052$). Almost half (46.7%) of the diabetic children with ASB, but only 14.4% of those without ASB, had leukocyturia ($P = 0.002$).

In the 18 diabetic patients with ASB *S. agalactiae* ($n = 6$), *Enterococcus sp.* ($n = 5$), *E. coli* ($n = 4$), and *K. pneumoniae* ($n = 3$) were cultured. The proportion of leukocyturia in patients with Gram-positive and Gram-negative bacteria was 2/11 to 6/7 ($P = 0.041$), respectively. In control subjects, *E. coli* ($n = 2$), *S. agalactiae*, *K. pneumoniae*, and *P. vulgaris* ($n = 1$:1) were cultured.

In contrast to pediatric studies performed several decades ago (2–4), but in agreement with more recent adult observations (1) and textbook data (5), ASB in diabetic children occured with a higher frequency. Samples were collected by diabetes nurse specialists, and care was taken to avoid contamination. The increased prevalence of ASB is not readily explainable, particularly because our study could not demonstrate a relationship with ASB and hyperglycemia. Other possible reasons for the higher prevalence may include increased residual urine volume or impairment of several aspects of host defense mechanisms (e.g., cytokine secretion in the urinary tract), factors that are currently being investigated in our patients.

In UTI, the most common bacterium is *E. coli*, which was isolated in ~80–90% of positive cultures (6). In our diabetic patients with ASB, *E. coli* was found in only about a quarter of cases. Similarly low rates were found in adult type 1 diabetic women with ASB (1). It therefore seems that the spectrum of pathogenic bacteria causing ASB and UTI is different. The reason for this may be that the virulence factors are different in ASB and UTI.

In conclusion, we have found that the prevalence of ASB and leukocyturia was higher in diabetic children and young adults than in control subjects and that the spectrum of bacteria in ASB was different from the usual spectrum of UTI. As the treatment of ASB in adult type 1 diabetic women did not appear to prevent UTI (7) and may promote the invasion of more virulent pathogens (8), a careful follow-up of these pediatric patients is warranted before antibiotic therapy can be considered. This conclusion is underlined by a recent observation (9) that showed that women with type 1 diabetes and ASB had a tendency toward a decline in renal function.

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Low Birth Weight and Development of Type 2 Diabetes in a Japanese Population

According to epidemiological studies in the U. K. and other countries, individuals with low birth weights often develop insulin resistance–based disorders (1–5). Among Pima Indians and Taiwanese school children, a higher prevalence of type 2 diabetes was observed in individuals with both low and high birth weights (U-shaped relationship of birth weight and diabetes) (6,7). We conducted a study to examine the relation of low birth weight with type 2 diabetes and insulin resistance in Japanese type 2 diabetic patients.

To obtain data on birth weight, weight at age 20 years, maximum weight in the past, height, and other variables, we asked 2,471 employees (2,259 men and 212 women) of two companies in Tokyo and 815 patients (514 men and 301 women) with type 2 diabetes who were treated at Saiseikai Central Hospital, both ≥40 years of age, to complete a questionnaire in April 2001. Among them, we selected 1,960 male employees (occupational cohort) and 164 male diabetic patients (hospital cohort), both aged 40–59 years, who could provide their birth weights, either through maternal and child health notebook records (issued by each municipal office) or their mother's memory (if the notebook was missing), and who had agreed to participate in this study with informed consent. Birth

weights <2,500, 2,501–3,699, and >3,700 g were defined as low, normal, and high, respectively. In the occupational cohort, subjects with known type 2 diabetes and with HbA_{1c} >6.5% were defined as diabetic patients. In the hospital cohort, current use of antihypertensive agents was defined as hypertension. In both cohorts, subjects who had a diabetic parent, sibling, and/or offspring were considered to have a family history of diabetes. The significance of difference of the results in the different groups was tested by χ^2 analysis or Student's *t* test.

The prevalence of low birth weight in the 301 diabetic subjects, including those in the occupational cohort and the 1,823 nondiabetic subjects in the occupational cohort, was 18.6% (56 of 301) and 9.8% (178 of 1,823), respectively ($P < 0.001$), whereas the prevalence of high birth weight in the same groups was 9.3 and 11.6%, respectively (NS). Of the 56 diabetic subjects with low birth weight, 32 had a family history of diabetes (57.1%), and of the 178 corresponding nondiabetic subjects, only 25 had a family history of diabetes (14.0%) ($P < 0.0001$). Mean BMI at the age of 20 was 21.8 ± 3.3 and 20.6 ± 2.2 kg/m^2 ($P < 0.01$), and mean maximum BMI was 26.1 ± 3.3 and 24.8 ± 3.0 kg/m^2 ($P < 0.01$) in the same groups. The prevalence of hypertension in diabetic subjects with low and normal birth weight in the hospital cohort was 46.2% (18 of 39) and 23.4% (22 of 94) ($P < 0.01$), respectively, and the prevalence in those with high birth weight was 29.0% (9 of 31) (NS compared with low and normal weight groups), while mean BMI did not differ significantly among the three groups (23.0 ± 2.3, 23.9 ± 3.2, and 25.4 ± 4.2 kg/m^2).

Our results showed that low birth weight was also associated with the development of type 2 diabetes in Japanese subjects and that not only genetic influences but also higher BMI in adulthood seemed to be important in the development of type 2 diabetes in individuals with low birth weight. The significantly higher incidence of hypertension in diabetic subjects with low birth weight compared with diabetic subjects with normal birth weight suggests that insulin resistance might be stronger in the former. Further prospective studies with a large number of participants using more appropriate indices of insulin resistance are required to clarify this association between birth weight and insulin resistance in individuals with type 2 diabetes.

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Coffee Consumption and the Incidence of Type 2 Diabetes

There have been few reports of associations between coffee consumption and diabetes. In healthy subjects given an oral glucose tolerance test (OGTT), the 1-h glucose concentration was lower when the glucose load was given with coffee (1). There were no significant differences in the other time points in the test, nor in serum insulin concentration at any time point. In contrast, others have reported a deterioration of glucose tolerance after coffee ingestion (2,3). In healthy subjects a rise in blood glucose levels after caffeine intake was detected at the 2nd, 3rd, and 4th hours in comparison to those taking a placebo (4). Blood insulin levels were comparable after caffeine or placebo ingestion during the entire OGTT. Ingestion of coffee or the injection of caffeine is associated with elevated plasma catecholamines and free fatty acids, as well as decreased insulin sensitivity (5), all of which might be expected to increase the incidence of diabetes. Recently, coffee consumption was reported to decrease the incidence of type 2 diabetes in the Netherlands (6). Prompted by these inconsistent findings, we attempted to replicate the Dutch finding in the longitudinal population-based study of diabetes among the Pima Indians (7).

The average daily use of coffee was assessed by questionnaire from 1978 to 1992 in 2,680 nondiabetic individuals aged ≥15 years (mean age 27 years; 60% women) who had at least one follow-up examination by September 2002. Consumption was recorded as never, occasionally (less than one a day), one or two a day, three or more a day, or occasionally heavy. Diabetes was diagnosed by OGTT using the 1985 World Health Organization criteria (8).

During an average follow-up time of 11 years (range 1–23), 824 individuals developed diabetes. After adjustment for age, sex, and BMI in a time-dependent proportional hazards model, the risk of developing diabetes for those who reported drinking coffee compared with those who never drink coffee (referent category) was as follows: occasionally 1.09 (95% CI: 0.89–1.34), one or two a day 0.92 (0.74–1.13), three or more a day 1.01 (0.82–1.26), and occasionally heavy 0.81 (0.55–1.03). Overall, adjusted for age, sex, and BMI, there was no significant association between consumption categories and incidence of diabetes ($P = 0.6$). Tea consumption was also unrelated to the incidence of diabetes (not shown).

One strength of our study was the periodic use of an OGTT, as compared with the subjective self-reporting of diabetes

used in the Dutch study (6). In that study, coffee consumption was associated with lower socioeconomic status and less healthy behaviors, factors that might be associated with a lower likelihood of being tested for diabetes. Our study included nearly three times as many incident cases of diabetes as the Dutch study (824 vs. 306), resulting in a narrow 95% CI (0.84–1.18) around our estimate of the hazard rate ratio of 0.99 for any coffee consumption. In conclusion, our data provide no evidence for a relationship of coffee consumption and risk of type 2 diabetes.

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Impairment of Glucose Tolerance Over 10 Years in Middle-Aged Normal Glucose Tolerant Indians

We followed 191 normal glucose tolerant (NGT; 1985 World Health Organization criteria) nondiabetic subjects (115 men) as control subjects in the Wellcome Diabetes Study (1). Their mean age was 41 years (SD 11.2), BMI 23.6 kg/m^2 (34% >25 kg/m^2), and 31% had a first-degree relative with diabetes.

During the next 10 years, 8 (7 men) died, 40 were lost to follow up, 14 men and 8 women became impaired glucose tolerant (IGT), and 2 men and 4 women developed diabetes. Men whose glucose tolerance deteriorated were heavier at entry (71.8 vs. 62.3 kg, $P < 0.001$), more obese (BMI 25.3 vs. 22.6 kg/m^2, $P < 0.01$), and more centrally obese (waist circumferences 85.9 vs. 78.9 cm, $P < 0.01$) than those who remained NGT, all adjusted for age. They also had higher 2-h glycemia (oral glucose tolerance test, 6.6 vs. 5.9 mmol/l, $P < 0.05$), fasting triglyceridemia (1.6 vs. 1.1 mmol/l, $P < 0.01$), and fasting and 2-h insulinemia (95.1 vs. 47.9 and 929 vs. 515 pmol/l, $P < 0.05$ for both), which was reflected in insulin resistance (homeostasis model assessment [HOMA] 2.7 vs. 1.4, $P < 0.05$). Among women, triglyceridemia (1.5 vs. 0.9 mmol/l, $P < 0.01$) and higher systolic blood pressure (137 vs. 122 mmHg, $P < 0.05$) were predictive.

On multivariate analysis, after forcing in age, sex, and family history of diabetes, glucose tolerance deterioration (both sexes) was predicted by initial HOMA (odds ratio 1.38, 95% CI 1.01–1.85), 2-h plasma glucose (1.04, 1.00–1.08), fasting plasma triglyceride concentration (1.01, 1.00–1.02), and weight gain (1.2, 1.02–1.32).

These results, from a first prospective study of such duration among Indians in India, confirm studies from elsewhere (2) in associating deterioration of glucose tolerance in the NGT with obesity, weight gain, insulin resistance, higher circulating triglycerides, and 2-h glucose concentrations. Clearly, there is an excess of insulin resistance over B-cell deficiency markers. Finally, we wish to emphasize the relative thinness at which these effects were seen. The relative risk of deterioration of glucose tolerance during 10 years among the whole group was 2.4 (1.1–5.3) with BMI above and below 23 kg/m^2. This may reflect both the higher body fat percentage for a given BMI among Indians and their marked central adiposity (3). This has already prompted a reduction in the target BMI for obesity-related action among Asian Indians to 23 kg/m^2 (4).

Therefore, among Indians reduction in adiposity must be a prime target for diabetes prevention. This will have to start at levels that are accepted in the west without demur. This is necessary at all ages, but will be made difficult by our recent observation that central obesity and hyperinsulinemia are present in Indians at birth (5).

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Risk Factors of Autonomic and Sensory Nerve Dysfunction in Patients With Newly Diagnosed Type 1 Diabetes

Autonomic neuropathy (AN) in patients with newly diagnosed type 1 diabetes was first described by Fraser et al. (1). Of the six patients examined, two had evidence of AN. In this study, autonomic dysfunction detected during the initial metabolic derangement in newly diagnosed diabetic patients was not reversible after a prolonged period of improved control, indicating that established alterations may occur from the time of diagnosis onward. Other authors (2,3) have also shown that standard cardiovascular reflex tests are able to detect AN in newly diagnosed diabetic patients. A relationship between the severity of AN and prolongation of the corrected QT interval has also been noted (4).

According to the results of the EURODIAB IDDM Complications Study, the development of neuropathy is related to cardiovascular risk factors (5). The EURODIAB Prospective Complications Study (6) also confirms this finding.

However, there are no data regarding potential risk factors of nerve dysfunction in patients with newly diagnosed type 1 diabetes. We examined 40 patients with newly diagnosed type 1 diabetes with a mean (± SD) age of 34.7 ± 11.3 years. The control group comprised 25 healthy subjects (age 38.3 ± 14.8 years). The five standard tests of cardiovascular autonomic function were applied (7). Heart rate tests (heart rate responses to deep breathing, the 30:15 ratio, and the Valsalva ratio) mainly reflect parasympathetic function, while blood pressure responses to sustained handgrip and standing primarily allow the assessment of sympathetic integrity. The results of each of the five tests were scored as 0 (normal), 1 (borderline), or 2 (abnormal). A final score was calculated (range 0–10) to express the severity of the overall autonomic disorder. Patients with at least one abnormal or two borderline cardiovascular tests (score ≥2) were considered to have autonomic neuropathy. Peripheral sensory function was characterized by the evaluation of the current perception threshold (CPT), with a neuroselective diagnostic stimulator (Neurotron, Baltimore, MD), which permits transcutaneous testing (8) at three sinusoidal frequencies (2 kHz, 250 Hz, and 5 Hz). Median and peroneal nerves (digital branches) were studied. All tests were performed after 9 days (range 3–34) of insulin therapy.

As multiple comparisons increase the risk of the error of first kind, we considered results at $P \leq 0.01$ as statistically proven, while those at $P \leq 0.05$ were regarded as marginally significant.

Twelve diabetic patients (30%) had at least one abnormal autonomic function test. Parasympathetic neuropathy was found in six patients, sympathetic nerve dysfunction was observed in three patients, and three subjects had both parasympathetic and sympathetic damage. A significant decrease of the 30:15 ratio (mean ± SE) was found in diabetic patients compared with control subjects (1.28 ± 0.03 vs. 1.42 ± 0.03, $P = 0.003$). The autonomic score was higher in diabetic patients (1.08 ± 0.24) than in control subjects (0.17 ± 0.08, $P = 0.005$).

At least one abnormal sensory parameter was observed in 10 patients (25%). Higher CPT values indicating hypesthesia were found in the diabetic group compared with control subjects at peroneal nerve testing at 250 Hz (1.6 ± 0.1 vs. 1.1 ± 0.07 mA, $P = 0.03$) and 5 Hz (1.1 ± 0.09 vs. 0.6 ± 0.06, $P = 0.007$), just as at median nerve testing at 5 Hz (0.6 ± 0.03 vs. 0.49 ± 0.05, $P = 0.048$).

Analyzing the relationship between blood pressure and autonomic function in diabetic patients, the 30:15 ratio correlated significantly negatively with the diastolic blood pressure values ($r = 0.3240$, $P = 0.044$). There was a significant positive relationship between systolic blood pressure and the CPT values testing median nerve at 5 Hz ($r = 0.3988$, $P = 0.012$). The decrease of systolic blood pressure after standing correlated significantly negatively with CPT values at the peroneal nerve at 2 kHz ($r = -0.3436$, $P = 0.032$), 250 Hz ($r = -0.3893$, $P = 0.014$), and 5 Hz ($r = -0.3273$, $P = 0.042$).

Assessing the relationship between smoking and autonomic function, a significant negative correlation was found between the duration of smoking and the deep breathing test ($r = -0.3452$, $P = 0.006$). The duration of smoking correlated significantly positively with the parasympathetic score ($r = 0.3817$, $P = 0.002$), just as with the autonomic score ($r = 0.3398$, $P = 0.006$). There was a significant correlation between plasma cholesterol and the parasympathetic score ($r = 0.3937$, $P = 0.047$).

A significant negative correlation was observed between the deep breathing test and the CPT values testing the median nerve at 2 kHz ($r = -0.4452$, $P = 0.005$) as well as at 250 Hz ($r = -0.4048$, $P = 0.01$).

In conclusion, autonomic and sensory nerve dysfunction are quite frequent complications in newly diagnosed type 1 diabetic patients and seem to be related to each other. Our data suggest that traditional cardiovascular risk factors (smoking, hypertension, and serum cholesterol) should be considered as potential risk factors for the development of neuropathy, even in newly diagnosed type 1 diabetic patients. These observations may confirm the role of vascular factors in the pathogenesis of neuropathy and may be important for the development of risk reduction strategies.

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LDL Electronegativity Is Enhanced in Type 1 Diabetes

LDL particles exhibit heterogeneity in density, size, chemical composition, and charge (1). Lipoperoxidation, oxidation, and glycosylation increase the net negative charge and may enhance LDL atherogenicity with important metabolic consequences. A relevant role of more electronegative LDL in atherogenesis is supported by the observation that it is elevated in subjects at high risk, such as familial hypercholesterolemic and type 1 diabetic patients (2).

We reported the precise measurement of the electrophoretic mobility of LDL as an indicator of modification by capillary electrophoresis and the UV absorption at 234 nm that results from the formation of conjugated dienes in constituent polyenoic fatty acids in 14 type 1 diabetic patients (7 normoalbuminuric and 7 microalbuminuric patients) and in 6 nondiabetic subjects. In type 1 diabetic patients with normoalbuminuria (six men and one woman; mean age 38 ± 12 years) the mean duration of diabetes was 25 ± 7 years, and they were in stable glycemic control (HbA_{1c} = 7.1 ± 0.6%). The seven diabetic patients with microalbuminuria (six men and one woman; mean age 52 ± 9 years, $P < 0.01$ vs. normoalbuminuric patients) had a mean duration of diabetes of 22 ± 14 years and a mean HbA_{1c} value of 8.8 ± 1% ($P < 0.01$ vs. normoalbuminuric patients). Diabetic patients had significantly higher BMI (25 ± 2 kg/m^2) ($P < 0.01$ for normoalbuminuric subjects, 25 ± 3 kg/m^2; $P < 0.05$ for microalbuminuric vs. control group, 21 ± 2 kg/m^2) and fasting glucose levels (215 ± 83 mg/dl) ($P < 0.01$ for normoalbuminuric subjects, 197 ± 91 mg/dl; $P < 0.01$ for microalbuminuric vs. control group, 99 ± 18 mg/dl) than control subjects. There was no difference in triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol levels between diabetic subjects and the control group.

LDL was isolated by preparative sequential ultracentrifugation at the density of 1.063 g/ml. Dialyses, capillary electrophoresis (CE), and the electrophoretic mobility (μ) of LDL were performed as described by Stock and Miller (3). Migration of LDL particles was monitored at 200 and 234 nm. The amount of conjugated dienes is obtained from the percentage of the height of LDL peak at 234 nm related to the height of LDL peak at 200 nm. Student's *t* test and Pearson's correlation were used to assess statistical significance.

The electrophoretic mobility (mean ± SD) for the diabetic LDL was $-1.249 \pm 0.065 \cdot 10^{-4} \cdot cm^2 \cdot vol^{-1} \cdot s^{-1}$, while that for the control LDL was –1.032 ± 0.121 ($P = 0.0001$). The diabetic group, subdivided into normoalbuminuric and microalbuminuric subjects, presented an electrophoretic mobility mean of –1.234 ± 0.068 and –1.263 ± $0.064 \cdot 10^{-4} \cdot cm^2 \cdot vol^{-1} \cdot s^{-1}$, respectively. When each group was compared with the control, the differences were always statistically significant in both cases ($P = 0.0032$ for normoalbuminuric patients vs. control subjects; $P = 0.0001$ for microalbuminuric patients vs. control subjects). Diabetic subjects have LDL with significantly higher migration rates, which were independent from microalbuminuria.

In LDL obtained from the diabetic patients the content of diene conjugates was not statistically different from the control group (6.22 ± 1.199% for diabetic subjects vs. 5.509 ± 0.219% for control subjects).

The difference between diabetic and control subjects was still not statistically significant when the content of diene conjugates in normoalbuminuric (6.235 ± 1.544%) and microalbuminuric (6.214 ± 0.854%) subjects was individually compared with that of the control group. In the diabetic group, the electrophoretic mobility was not significantly correlated with HbA_{1c}, duration of diabetes, the subjects' age, or fasting glucose levels.

The finding of electronegative LDL in type 1 diabetic subjects could be related to the increase of the so-called LDL(−), which is also detectable in normal subjects, although in small amounts (4). Capillary electrophoresis cannot separate the fraction LDL(−) from the bulk of plasma LDL. It gives an estimate of the algebraic sum of the electronegative charges distributed on the surface of LDL particles.

Nonenzymatic glycosylation should, surprisingly, be excluded as a cause of higher LDL electronegativity. In this regard, we found no significant correlation between electrophoretic mobility and HbA_{1c} and the fasting plasma glucose levels in the diabetic group. Furthermore, neither the duration of diabetes nor subject age had effects on LDL mobility. Thus, the increased negative charge could be related to compositional abnormalities or other modifications not evaluated in this report, such as an enrichment in sialic acid. Desialylated LDL is more resistant to copper oxidation than native LDL (5).

In conclusion, the finding of more electronegative LDL in diabetic subjects could be an additional risk factor for atherosclerosis in diabetes. Investigations are under way to assess if electrophoretic mobility of LDL in type 1 diabetes can be decreased by further lowering HbA_{1c} levels.

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Effect of Glimepiride on Serum Adiponectin Level in Subjects With Type 2 Diabetes

Sulfonylurea is known to lower glucose levels by stimulating pancreatic insulin secretion. Glimepiride, a new agent of sulfonylurea, is unique in that the glucose-lowering efficacy is similar but the ability to stimulate insulin secretion is lower in comparison with conventional sulfonylureas such as glibenclamide, glipizide, and gliclazide (1). Thus, glimepiride is hypothesized to have greater extrapancreatic effect, such as an improvement in insulin resistance (1). The previous report by Muller et al. (1) supports the hypothesis that insulin-resistant diabetic KK-Ay mice can be well controlled by glimepiride, but not by glibenclamide and gliclazide. Glimepiride is reported to increase insulin-stimulated glycogen synthesis in cultured human skeletal muscle cells. Very recently, Tsunekawa et al. (2) clearly demonstrated that glimepiride actually increases insulin sensitivity in type 2 diabetic patients. They also proposed that the increase in insulin sensitivity might be associated with increased adiponectinemia. Here we report our data regarding the effects of glimepiride on insulinemia, insulin sensitivity, and serum adiponectin levels in type 2 diabetic subjects. In addition, the effects of glimepiride are compared with those achieved by metformin, which has been proven to have little effect on body weight during glycemic control.

A total of 28 Japanese patients with type 2 diabetes (19 men and 9 women, aged 59 ± 2 years [mean ± SE], BMI 26.5 ± 0.8 kg/m^2) were investigated before and after treatment with glimepiride. The treatment duration was 3 months, and the daily dose of glimepiride was 1.9 ± 0.2 mg (range 1.0–3.0). Changes in indices were analyzed by Wilcoxon's sign-rank test. After the treatment, fasting plasma glucose (166 ± 7 vs. 147 ± 7 mg/dl, $P = 0.009$) and HbA_{1c} (7.9 ± 0.3 vs. 7.4 ± 0.2%, $P = 0.006$) levels fell significantly. Both fasting insulin (11.7 ± 1.5 vs. 9.4 ± 1.0 μU/ml, $P = 0.007$) and homeostasis model assessment for insulin resistance (HOMA-IR) (3) (5.0 ± 0.8 vs. 3.8 ± 0.6, $P = 0.005$) decreased, suggesting an amelioration of insulin resistance. Serum adiponectin concentration, measured by Linco RIA kits (St. Charles, MO), increased significantly (22.1 ± 2.7 vs. 28.5 ± 2.8 μg/ml, +29%, $P = 0.015$), whereas no significant change was observed in BMI (26.5 ± 0.9 vs. 26.5 ± 0.8 kg/m^2, $P = 0.748$). There was also no change in serum concentrations of total (214 ± 6 vs. 210 ± 6 mg/dl, $P = 0.125$) and HDL (54 ± 3 vs. 53 ± 3 mg/dl, $P = 0.438$) cholesterol and triglyceride (123 ± 10 vs. 120 ± 10 mg/dl, $P = 0.387$) before and after the treatment.

In a separate group of type 2 diabetic patients matched with the glimepiride group for sex, age, BMI, glycemia, and insulinemia (seven men and five women, aged 58 ± 3 years, and BMI 25.7 ± 0.7 kg/m^2), the effect of metformin (daily dose 750 mg) was evaluated. Three months of the metformin treatment also decreased both fasting glucose (159 ± 4 to 135 ± 4 mg/dl, $P = 0.006$) and HbA_{1c} (7.9 ± 0.2 to 7.1 ± 0.2%, $P = 0.013$) levels. In contrast to the glimepiride treatment, fasting insulin (12.4 ± 2.0 vs. 13.8 ± 4.3 μU/ml, $P = 0.689$) and HOMA-IR (4.8 ± 0.7 vs. 4.1 ± 1.0, $P = 0.695$) remained unchanged, whereas serum adiponectin concentration was increased slightly but significantly (18.7 ± 3.0 vs. 20.6 ± 3.3 μg/ml, +10%, $P = 0.034$). No significant change was observed in BMI and serum lipid concentrations (data not shown).

Our present finding supports the notion that one of the glucose-lowering mechanisms of glimepiride is to improve insulin resistance. In accordance with a recent article (2), the glimepiride treatment increased serum adiponectin levels without affecting BMI. In the present study, serum adiponectin levels were also increased by the treatment of metformin, which, unlike insulin-sensitizing thiazolidinediones, is known to not affect circulating adiponectin concentration (4). Therefore, it seems possible that the increase in adiponectinemia by the glimepiride treatment could be, in part, due to an effect of glycemic control per se. Another difference between the glimepiride and metformin groups is the change in insulinemia; fasting insulin was decreased in the former group and unchanged in the latter. Since insulin seems to suppress expression and secretion of adiponectin in both in vitro and in vivo studies (5,6), the decrease in insulinemia by glimepiride may conversely increase circulating adiponectin concentration.

We agree that the improvement in glycemic control, insulinemia, and adiponectinemia by glimepiride is of potential benefit to decrease risk factors of atherosclerosis in type 2 diabetic patients. The mechanisms of the increased adiponectinemia by glimepiride may be complex and multifactorial. It also remains to be elucidated whether conventional sulfonylureas would increase adiponectinemia in subjects with type 2 diabetes.

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Glargine Insulin Is Not an Alternative in Insulin Allergy

Allergy to insulin is rare with human recombinant insulin and is now reported for <1% of diabetic patients. Clinic symptoms are usually local and appear a few minutes after the injection (red blotch, induration, pruritus, and burning sensation at insulin injection sites) and are rarely general (from urticaria to anaphylactic shock). A decrease of the efficiency of the insulin is usually associated with these symptoms. Different methods have been proposed for the treatment of insulin allergy including the use of oral antihistaminics, the addition of glucocorticoids to insulin, and the change to human insulin analogues.

To our knowledge, we report the first case of allergy to a new long-acting insulin analogue, insulin glargine

An 81-year-old man with type 2 diabetes was admitted for uncontrolled diabetes and insulin initiation. He had a coronary artery bypass 2 years previous and recently had a critical limb ischemia. The patient had no history of any allergy. He was first treated by Mixtard 30 twice daily (Innolet; Novo Nordisk). The patient presented local induration and pruritus at insulin injection site and general urticarian lesions from 10 to 15 min after the injection. An allergy to insulin was then suspected.

Skin-prick tests (5 UI/ml) were positive for human and porcine insulin and negative for all additives (protamine, paraben, metacresol, phenol, zinc, and isophane) using the Novo Insulin Allergy Kit (Novo Nordisk). These tests confirmed the allergy to insulin.

To test the possibility of treating the patient with rapid-acting insulin analogs, we examined skin reactions to aspart and lispro insulin. We have therefore performed additive skin-prick tests with aspart and lispro insulins. They were positive for lispro and negative for aspart insulin. Similar results with insulin analogues have been previously reported (1).

A treatment with subcutaneous continuous aspart insulin infusion was then initiated. No local reaction was observed, and glycemic control gradually improved. However, a prolonged treatment with an insulin pump was very difficult for this older patient. We therefore decided to test glargine insulin, a new long-acting human insulin analogue. Unfortunately, skin tests were very positive with glargine insulin. To our knowledge, we report the first case of allergy to this new insulin.

Human insulin analogues, lispro or aspart, have been proposed for the treatment of insulin allergy (1,2). Allergy to lispro, aspart, or both has been recently reported (1–3). In our observation, we establish a similar case with lispro but not with aspart insulins. However, to our knowledge, we report the first case of allergy with glargine insulin.

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Association Between Endothelial Nitric Oxide Synthase Glu298Asp Polymorphism and Postchallenge Insulin Levels in Nondiabetic Japanese Subjects

Endothelial nitric oxide synthase (eNOS) catalyzes NO production in vascular endothelial cells, and NO regulates local blood flow by inducing vasodilation (1). Enhancement of skeletal muscle glucose uptake occurs during elevation of muscle blood flow, which is induced by increased eNOS expression and activated by insulin stimulation (2–4). It was previously reported that low production of NO in eNOS knockout mice causes reduction of insulin-induced

blood flow and glucose uptake in whole body (5). These findings suggest that eNOS plays an important role in the regulation of insulin-induced glucose uptake in whole body.

Polymorphism in eNOS exon 7 with G→T conversion at nucleotide position 894 results in amino acid substitution of glutamic acid for aspartic acid in amino acid residue 298 (Glu298Asp). Structural alteration in this variant affects the susceptibility to cleavage and reduces activity of this enzyme (6,7). Dysfunction of eNOS by this polymorphism may cause reduction of insulin-induced blood flow and glucose uptake. It was recently demonstrated that insulin secretion and sensitivity could be assessed by 75-g oral glucose tolerance test (8,9). Therefore, we examined the association of this polymorphism with fasting and postchallenge glucose and insulin levels in nondiabetic Japanese subjects by the 75-g oral glucose tolerance test.

This study comprised 247 Japanese nondiabetic volunteers (69 men and 178 women). Written informed consent was obtained from all subjects enrolled in this study. A 75-g glucose tolerance test was performed early in the morning after fasting overnight. Venous sampling was obtained before loading (0 min), at 30 min, and 120 min after glucose loading, and blood glucose and insulin levels were measured. The serum insulin levels were measured with an EIA kit (Eiken insulin kit; EIA, Tokyo, Japan). All subjects were nondiabetic according to American Diabetes Association criteria (10). For assessing the substitution of G→T at position 894 (Glu298Asp), genomic DNA isolated from peripheral blood leukocytes was amplified by PCR and digested with *Ban*II restriction enzyme as previously described (11,12). Data are expressed as means ± SEM. Differences between each group were tested by two-tailed unpaired Student's *t* test. A $P < 0.05$ was considered as statistically significant.

The allele frequency was 0.927 for G and 0.073 for T in all subjects. Genotype distribution was 86.6% (214 of 247) for Glu/Glu, 12.2% (30 of 247) for Glu/Asp, and 1.2% (3 of 247) for Asp/Asp. The frequency and distribution are compatible with previous data (11,12). Because the number of homozygous mutants was too small, the combined data from homozygous and heterozygous individuals were used in the following analysis. There was no significant difference in age (53.8 ± 0.5 vs. 56.0 ± 1.6 years), BMI (23.4 ± 0.2 vs. 24.4 ± 0.7 kg/m^2), waist-to-hip ratio (1.01 ± 0.01 vs. 0.98 ± 0.04), systolic blood pressure (130.0 ± 1.3 vs. 130.1 ± 3.4 mmHg), diastolic blood pressure (77.6 ± 0.8 vs. 77.2 ± 2.0 mmHg), total cholesterol (5.46 ± 0.10 vs. 5.58 ± 0.21 mmol/l), triglyceride (1.28 ± 0.05 vs. 1.16 ± 0.10 mmol/l), HDL cholesterol (1.62 ± 0.03 vs. 1.63 ± 0.09 mmol/l), or HbA_{1c} (5.0 ± 0.1 vs. 5.0 ± 0.2%) between Glu/Glu and Glu/Asp + Asp/Asp. The results of the glucose tolerance test were as follows: plasma glucose in Glu/Glu was not significantly different from Glu/Asp + Asp/Asp at 0 min (5.07 ± 0.05 vs. 5.12 ± 0.12 mmol/l), 30 min (8.36 ± 0.16 vs. 8.94 ± 0.30 mmol/l), and 120 min (6.36 ± 0.18 vs. 6.93 ± 0.35 mmol/l). However, serum insulin levels were significantly increased in Glu/Asp + Asp/Asp compared with Glu/Glu at 30 min (309.6 ± 40.8 vs. 236.4 ± 9.6 pmol/l, $P < 0.02$) and 120 min (342.0 ± 36.0 vs. 220.2 ± 10.8 pmol/l, $P < 0.0005$). There was no significant difference in serum insulin levels at 0 min (35.2 ± 1.2 vs. 41.8 ± 3.0 pmol/l), homeostasis model assessment for insulin resistance (HOMA-IR) (1.36 ± 0.06 vs. 1.59 ± 0.12), and insulinogenic index ($\Delta I_{30}/\Delta G_{30}$, 1.09 ± 0.22 vs. 0.74 ± 0.12) between Glu/Glu and Glu/Asp + Asp/Asp.

In the present study, elevation of insulin levels at 30 and 120 min after glucose loading test was observed in subjects with Glu/Asp + Asp/Asp polymorphism compared with wild-type. However, the blood levels of glucose were not significantly different between these two groups. These data showed that there is a remarkable difference in postchallenge insulin levels between Glu/Glu and Glu/Asp + Asp/Asp groups. Subjects with Glu/Asp + Asp/Asp require more insulin to maintain the same glucose levels than subjects with Glu/Glu during glucose loading test. It was reported (8,9) that insulin level during postchallenge (120 min) is correlated with insulin sensitivity as measured by the glucose clamp method in nondiabetic subjects. Thus, one explanation for the elevated postchallenge (120 min) insulin levels may be reduced insulin sensitivity due to impaired insulin-mediated local blood flow in subjects with Glu/Asp + Asp/Asp polymorphism.

However, no significant difference was observed in HOMA-IR, a marker of insulin sensitivity, between subjects with Glu/Asp + Asp/Asp and those with Glu/Glu, suggesting that another mechanism in addition to insulin sensitivity may affect postchallenge insulin levels. It was previously observed (13) that decreased insulin-mediated blood flow in muscles is associated with reduction of insulin clearance in obese subjects with insulin resistance. Also, remarkable difference in blood flow and insulin clearance has been observed between lean and obese subjects in hyperinsulinemic conditions (13). These observations suggest that decreased insulin-mediated blood flow reduces insulin clearance, which leads to increased circulating insulin levels. Therefore, impairment of insulin-mediated vasodilation with subsequent reduction of insulin clearance may be another explanation for the changes of postchallenge insulin levels in subjects with the Glu/Asp + Asp/Asp polymorphism.

In conclusion, the present study showed for the first time that eNOS Glu289Asp polymorphism affects postchallenge insulin levels in nondiabetic Japanese subjects.

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A Diabetic Subject With MELAS and Antiphospholipid Syndrome

Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome has been reported to coexist with autoimmune type 1 diabetes (1) and Graves' disease (2). We described, for the first time, a diabetic patient with MELAS syndrome, autoimmune hemolytic anemia, and antiphospholipid syndrome.

During routine health examination, a 38-year-old man was diagnosed with diabetes. There was no family history of diabetes. On 22 January 2001, he was admitted due to right hemiparesis, slurred speech, and headache. Magnetic resonance imaging of the brain revealed increased signal intensity on diffusion scan with decreased apparent diffusion coefficient confined to left middle cerebral arterial territory, which was compatible with acute ischemic infarct. For his young stroke, we checked carotid duplex, cardiac sonography, anti-nuclear antibodies, rheumatic factors, protein C, and protein S, which were all negative. The level of antiphospholipid antibodies was 14.7 phospholipid units/ml (normal <5, positive >15) and that of anticardiolipin antibodies was 17.5 phospholipid units/ml (normal <16, positive >21). He was then discharged in stable condition. Serum markers were repeated on 16 July 2001 and showed positivity for antiphospholipid antibodies (19.5 phospholipid units/ml) and anticardiolipin antibodies (22.4 phospholipid units/ml). Antiphospholipid syndrome was favored due to a history of vascular thrombosis and the presence of circulating antibodies. However, gradual loss of cognition and muscle power developed progressively. Bilateral hearing impairment was found, and the patient was once again admitted for hyperglycemia with metabolic acidosis on 11 July 2001. Serum lactic acid was high (6.95 mmol/l). The presence of lactic acidosis, bilateral hearing loss, progressive muscle weakness, young stroke, and diabetes prompted us to examine him for mitochondrial disease. MELAS syndrome was then diagnosed with a demonstration of an A-to-G point mutation at position 3243 of mitochondrial DNA. No such a mutation was found in his mother or siblings, indicating that a de novo mutation occurred in this subject. Besides, autoimmune hemolytic anemia was also found during admission (hemoglobin 9.0 g/dl, mean corpuscular volume 91.6 fl, reticulocyte count 10.81%, haptoglobin <5.83 mg/dl, direct Coombs test 2+, antinuclear antibodies [−] 1:160, and rheumatoid factor <20 IU/ml). His condition deteriorated progressively, and he died 5 months later of pneumonia.

It is difficult to distinguish patients with antiphospholipid syndrome from MELAS syndrome based on brain image studies. Patients with antiphospholipid syndrome may suffer from oxidant-mediated injury (3). Since the mitochondrial genome lacks a DNA repairing system and protecting proteins, it is susceptible to oxidative stress. Thus, the presence of antiphospholipid syndrome might be one of the causes of de novo mutation or may accelerate accumulation of mutated DNA, which may result in a rapidly deteriorating course such as that seen in this patient. We therefore suggest that patients with MELAS syndrome be examined for the presence of antiphospholipid syndrome, especially those presenting with vascular thrombosis.

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High Degree of Mitochondrial 3243 Mutation in Gastric Biopsy Specimen in a Patient With MELAS and Diabetes Complicated by Marked Gastrointestinal Abnormalities

A point mutation of mitochondrial DNA at nucleotide position 3243 has been shown to cause mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) (1). This mutation, however, is also found in maternally inherited diabetes and deafness (MIDD) (2), which accounts for ~1% of the diabetic population in Japan (3). The same point mutation of mitochondrial DNA causes a wide range of symptoms that have been suggested to be due to the difference in the degree of heteroplasmy; thus, the proportion of the mutant mitochondrial DNA is divergent among different tissues (4). Little evidence, however, is available due to difficulty in obtaining viable samples from active lesions associated with complications causing symptoms. In a diabetic patient with MELAS and severe gastrointestinal disease, including functional ileus, duodenal ulcer, and acute gastric mucosal lesions, which were resistant to treatment, we had a rare opportunity to investigate the degree of heteroplasmy of the 3243 mutation in a biopsy specimen of gastric mucosa, tissue with a major lesion that causes gastrointestinal complications, compared with peripheral white blood cells.

A 21-year-old woman had diabetes (HbA_{1c} 7.3%), bilateral hearing loss, muscle weakness, and several stroke-like episodes with high serum lactate and pyruvate levels (lactate 7.4 mmol/l and pyruvate 261 μmol/l). Neurological findings showed bilateral sensory hearing loss, bilateral external ophthalmoplegia and droopy eyelids, muscle weakness (proximal > distal), and cerebellar ataxia. Magnetic resonance imaging scans showed cerebellar atrophy and mild cerebral atrophy. Her mother, grandmother, and mother's brother also had hearing loss, but there was no obvious family history of diabetes. She also had functional ileus, duodenal ulcer, and acute gastric mucosal lesions, which were resistant to treatment. She was diagnosed as having MELAS with diabetes and gastrointestinal disease. DNA extracted from peripheral blood cells from the patient, her mother, and her elder sister was positive for the 3243 mutation. The proportion of the mutated allele in the proband (39%) was much higher than that in her sister (19%) and mother (10%). We also analyzed mitochondrial DNA of biopsy specimens of her gastric mucosa, which exhibited a higher proportion (57%) of the mutated allele than her peripheral white blood cells (39%), suggesting that her gastrointestinal complications were attributable to a high proportion of the mitochondrial variant in the gastrointestinal tract.

A high degree of mutated mitochondria in the gastrointestinal tract was previously reported in a case without typical clinical features of MELAS but with diabetes and gastrointestinal symptoms (5). There was 70% heteroplasmy of the mutation in his gastrointestinal tract, while that in peripheral white blood cells was 37% (5). Taking these findings together, it is likely that gastrointestinal symptoms in patients with the 3243 mutation, with either MELAS or MIDD, correlate with the degree of heteroplasmy in the gastrointestinal tract. These observations provide further evidence that the clinical diversity of symptoms related to mitochondrial 3243 mutation may be due to diversity in the proportion of the mutation in each organ.

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Frequency of Diabetes Transmission From Two Type 1 Diabetic Parents to Their Children

There is little information in the literature about the risk of diabetes in children of type 1 diabetic parents (mother and father affected), and evidence is based on small numbers (1). Analysis of a larger number of such trios could importantly contribute to the clar-

ification of type 1 diabetes inheritance. In the Karlsburg Clinic for Diabetes and Metabolic Diseases, 77 offspring of 61 pairs with type 1 diabetes have registered since 1955. Until 1989, the parents and their children (diabetic and nondiabetic) were repeatedly treated or checked for diabetes in our clinic; since 1990 some of the patients have visited the clinic or have been contacted as outpatients. The diagnosis of type 1 diabetes in the affected individuals is proofed by clinical and in many cases laboratory data (C-peptide, antibodies, and HLA), as is obvious from our previous study (2).

Here we present data of 58 offspring from 46 pairs with type 1 diabetes that were last contacted in December of 2001. There are 35 daughters and 23 sons born between 1955 and 1993. Until now, 25 of 58 (43%) descendants developed diabetes at ages 1–42 years (mean ± SD 11 ± 10). The diabetes incidence did not increase during the observation time in 10-year intervals [54 (7 of 13), 42 (5 of 12), and 50 (11 of 22), respectively, and so far 18% (2 of 11) in those born 1986–1995]. The difference in the diabetes affection of sons (12 of 23) and daughters (13 of 35) is not significant. A strong preponderance of female descendants (18 female and 7 male) was seen in children born before 1975, whereas the sex ratio is nearly one (18 female and 15 male) for those born after 1975.

We observed a dramatic decrease in the age of diabetes onset. Children born during 1955–1975 developed the disease at 1–42 years (mean 15.1 ± 12.1), and children born during 1975–1995 developed the disease at 2–13 years (7.3 ± 5.2) ($P = 0.0449$). The mean age of mothers when they gave birth to their children was 24 years in both periods.

In children born before 1975 the mean age of diabetes manifestation (15.1 ± 12.1 years) is not different from that of their parents (fathers 16 ± 4.9 years and mothers 16.2 ± 7.4 years), but in children born after 1976 (7.3 ± 5.2) it is significantly ($P = 0.014$) younger than that of their fathers (13.6 ± 5.9 years) but not of their mothers (11 ± 6.8 years).

The constant diabetes incidence of >40% over >40 years of observation time implies the definite role of a genetic background for type 1 diabetes development. The high diabetes frequency of 43% (near half) in a representative number of children of two type 1 diabetic parents points, according to Mendelian laws, to a small number of responsible genes. On the other hand, we believe that these data demonstrate the influence of the altered environment over time. We previously described (3) a disturbed proportion of male to female (1:2) in children of diabetic mothers, but not of fathers. We now show that this shifted sex ratio does not exist in offspring of diabetic mothers (and fathers) born in the last 20 years. As most children were born in the Karlsburg hospital, we know that the therapeutical principles of diabetes treatment during pregnancy changed to normoglycemia in the late 1970s (4,5). As described in the Swedish study (6), we also confirm the dramatic shift to younger age at diagnosis for this subgroup of German diabetic children.

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Putting Diabetes to the Test

Analyzing glycemic control based on patients' diabetes knowledge

Diabetes has reached epidemic proportions. Most of the morbidity, mortality, and cost of type 2 diabetes is related to cardiovascular complications (1). These complications can be decreased by improving glycemic control (2,3). However, one problem in diabetes care is the poor translation of knowledge derived from research to clinical practice (4). A lack of patients understanding the long-term ramifications of poor glycemic control may play a role in this. To further test this hypothesis, we performed the following study to determine whether patient diabetes knowledge was related to glycemic control.

Diabetes knowledge was measured using the Michigan Diabetes Knowledge Test (J.T. Fitzgerald, University of Michigan, Ann Arbor, MI) (5). Only questions pertaining to type 2 diabetes were used. HbA_{1c} values were determined. Data were analyzed using SAS software version 6.1 (SAS, Cary, NC). Logistic regression analysis was done using Pearson's correlation coefficient.

Seventy-seven subjects completed the study. The average number of questions answered correctly was 8.5 ± 2.3. The mean HbA_{1c} value was 8.05 ± 1.6%. Regression analysis demonstrated an inverse correlation between the number of correct responses and HbA_{1c} values. For each increase in the number of questions answered correctly, HbA_{1c} decreased by 0.239 ($r = -0.337$, $P < 0.003$).

These results suggest that improved diabetes knowledge improves glycemic control. Other studies have shown that patient educational interventions lower HbA_{1c} values (6). Patient education

should be part of the diabetes treatment plan as this provides another modality for reaching glycemic targets. Patient empowerment is a strong tool that can be attained through knowledge of disease processes.

In conclusion, we have shown that improved diabetes knowledge is associated with better glycemic control. Empowering diabetic patients with knowledge of their disease may help combat this financially draining epidemic.

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Ethnic Differences in Diabetes Symptoms Among People Without Known Diabetes in New Zealand

National diabetes awareness programs often emphasize the importance of symptoms in undiagnosed diabetes. Here we describe the frequency of diabetes symptoms in a multiethnic community in New Zealand.

Randomly selected nondiabetic European, Maori, and Pacific residents were asked if any of six cardinal symptoms of hyperglycemia (thirst, weight loss, polyuria, boils, tiredness, and blurred vision) were present. Subjects were screened using random venous blood sampling as previously described (6). Those with a random glucose ≥6.5 mmol/l within 2 h of a meal, or ≥6.0 2 h after a meal, and a random 20% of others were invited to attend a 75-g, 2-h oral glucose tolerance test (OGTT) (1999 World Health Organization criteria for diabetes, impaired glucose tolerance [IGT], and impaired fasting glucose [IFG]). Those diagnosed elsewhere, or with no OGTT but a random glucose of ≥11.1 mmol/l, have been included in the undiagnosed diabetes group. Odds ratios (ORs) and 95% CIs are shown.

Of the 2,423 people invited to participate, 1,585 (65.4%) were interviewed. Overall (and after removing those with new diabetes), Maori and Pacific individuals were significantly more likely to have more than two symptoms (Europeans 4.2% [3.8%] vs. 14.3% [13.5%] and 9.4% [9.0%], both $P < 0.001$, respectively). Each of the individual symptoms was present significantly less frequently among Europeans.

Of the 786 invited to the 75-g OGTT, 534 (67.9%) attended. Symptoms were uncommon among those with new diabetes, but still 2.6-fold (1.4–4.8) as likely when compared with IGT/IFG or normal subjects (e.g., more than two symptoms present in 16.9% vs. 6.5% and 7.5%, respectively, $P < 0.001$). This is a similar frequency to that found in the Australian Diabetes Screening Study (2) but less than in the Hoorn study (3). IGT/IFG and normal subjects had very similar symptom frequencies. A logistic regression for each symptom revealed that after adjusting for ethnicity, age, sex, and BMI, only thirst was significantly associated with hyperglycemia, and then only at ≥17.0 mmol/l vs. <5.0 mmol/l, OR = 9.2 (3.2–26.6). In a similar analysis, more than two symptoms were 3.5-fold (1.2–10.1) more common among those with a random glucose ≥11.0 mmol/l. When diabetes replaced random glucose in each regression, thirst (2.0 [1.0–4.0]), polyuria (1.8 [1.0–3.2]), tiredness (1.9 [1.0–3.4]), and having two symptoms (1.9 [1.1–3.4]) were significant entrants. Obesity was not associated with excess symptoms.

We conclude that few individuals with undiagnosed diabetes had symptoms, and that symptoms were only marginally increased in undiagnosed diabetes. Furthermore, symptoms were not increased in IGT/IFG. Ethnic differences in symptoms exist, confounding their interpretation in some settings. Our data suggest that unless a patient presents acutely, using prompted symptomatology to decide who should be screened for dysglycemia using blood testing is futile.

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COMMENTS AND RESPONSES

Hyperglycemia After Myocardial Infarction

In their article on hyperglycemia in subjects admitted with myocardial infarction, Dandona, Aljada, and Bandyopadhyay (1) summarize much of the current knowledge about the anti-inflammatory effects of insulin. They propose mechanisms to explain the decreased morbidity and mortality seen in subjects on insulin infusions with tight blood glucose control. This may explain the results seen in another trial (2) in the intensive care population.

However, the authors fail to mention another of the possible effects of insulin. One of the systemic responses to critical illness is acute protein breakdown. This is thought to permit release of amino acids from skeletal muscle for high-priority use in threatened tissues. This protein breakdown may be due to the catabolic actions of the counter regulatory hormones and/or through the actions of a variety of cytokines (3). The insulin resistance that occurs as a result of these excess hormones and cytokines may reduce the inhibitory effect that insulin has on the ATP-ubiquitin proteasome proteolytic pathway, thus leading to an increase in skeletal muscle protein loss (4). This breakdown occurs despite the provision of adequate enteral or parenteral nutrition (5).

The protein breakdown seen in critical illness is analogous to the situation seen during prolonged insulin deprivation in subjects with type 1 diabetes. Insulin has been shown to prevent this breakdown from occurring (6,7). Thus, one of the reasons for the improved outcomes in the intensive care population on insulin may be that they lose less protein. The anti-catabolic action of insulin in these patients results in fewer complications due to the maintenance of immunocompetence, reduced incidence of infection, normalized wound healing, less muscle weakness, and lower mortality seen in the hyperglycemic critically ill (8).

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Hyperglycemia After Myocardial Infarction

Response to Dhatariya

We appreciate the comments of Dhatariya (1) in this issue of *Diabetes Care*. Clearly, insulin is the ultimate anabolic hormone that may not only keep inflammation at bay, but also regulate the appropriate utilization of metabolites such that it conserves protein and fat and prevents their breakdown. Its usefulness in preventing protein catabolism in the clinical setting was demonstrated in the 1980s. The key studies of Nair and colleagues (2,3) referred to by Dhatariya provide the scientific basis for this important insulin action. The next challenge is to determine how inflammation induces a state of protein catabolism and exactly how insulin exerts its beneficial effects against the background of inflammation.

It is also worth mentioning two other key actions of insulin described recently: *1)* apo $E^{-/-}$ mice that develop atherosclerosis suppress this process when given insulin (4), and 2) insulin suppresses reperfusion-induced myocardial damage following ischemia in isolated rat heart, as well as reduces myocardial apoptosis (5).

We believe this is just the beginning of a new era in understanding insulin action beyond the conventional biochemical/metabolic paradigm that we have been accustomed to for the first 80 years of its life. As discussed in our commentary, as we understand more about these novel actions of insulin, its clinical application will expand.

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Clinical and Genetic Heterogeneity of Latent Autoimmune Diabetes in Adults

We read with great interest the recent article by Hosszufalusi et al. (1) reporting that latent autoimmune diabetes in adults (LADA) manifests clinical features similar to those of adult-onset type 1 diabetes with rapid progression, and that prevalences of predisposing alleles and haplotypes did not differ between these two forms of autoimmune diabetes. Patients with LADA have been found to be heterogeneous in their clinical attributes (2). Some patients develop insulin deficiency within a few years (LADA-type 1), while others show clinical and metabolic markers similar to patterns in antibody-negative type 2 diabetes (LADA-type 2). As the authors noted, selection bias may have been present among the patients with LADA in their study because they tested for antibodies against islet cell cytoplasma (ICA) only in patients clinically suspected to have LADA. Therefore, patients with LADA in their study were not representative of all LADA patients, but represented only a subgroup, namely LADA-type 1. As a result, patient characteristics and prevalences of predisposing alleles and haplotypes were similar to those seen in adult-onset type 1 diabetes. We previously reported that HLA-DRB1 alleles influenced the prognosis of Japanese patients with diabetes who were positive for antibodies to GAD (3). Patients with LADA who later developed insulin deficiency showed increased prevalence of one of the predisposing alleles. Notably, patients with LADA who did not develop insulin deficiency were more likely to have protective alleles and less likely to have predisposing alleles than patients with type 1 diabetes showing rapid progression.

In addition, the authors diagnosed type 1 diabetes when patients had typical diabetes symptoms, were ketosis-prone, and required prompt insulin treatment at the time of diagnosis. The median and upper interquartile fasting concentrations of C-peptide (0.46 and 1.05 nmol/l, respectively) in the subjects with type 1 diabetes were somewhat higher than we expected, given their tendency toward ketosis and immediate need for insulin treatment. One suspects that patients who required insulin within 6 months of diagnosis as opposed to the time of diagnosis may have been included in the type 1 diabetes category. We propose that those patients should be placed in another subgroup, given their clinical differences from typical type 1 diabetic patients.

Demonstrating that ICA detected at diagnosis disappeared in six LADA patients with a relatively long disease course, the authors speculated that the tendency of ICA to disappear with increasing disease duration was similar in LADA and type 1 diabetes. In fact, the meaning of this disappearance may differ between LADA and type 1 diabetes. ICA positivity has been reported to persist in LADA (4), in contrast to the disappearance during the course of type 1 diabetes. Low levels of antibodies to GAD in patients with LADA declined to undetectable levels in our study (5), which suggests the possibility of pseudopositivity of antibodies to GAD.

In conclusion, patients with LADA constitute a clinically and genetically heterogeneous group. A more precise classification of autoimmune diabetes in adults is needed to define differences between forms of autoimmune diabetes in adults.

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Clinical and Genetic Heterogeneity of Latent Autoimmune Diabetes in Adults

Response to Fukui et al.

We read with interest the comments of Fukui et al. (1) in this issue of *Diabetes Care* regarding our recent article (2). They claim that patients with latent autoimmune diabetes in adults (LADA) are heterogeneous in their clinical attributes and that the LADA patients in our study represented the LADA type 1 subgroup. Because of this, we observed that their clinical and genetic characteristics resembled patients having rapidly progressive adult-onset type 1 diabetes. We agree that LADA patients may show heterogeneous clinical features, but we feel that our patients with LADA are representative of the whole LADA group: 25% of our LADA patients belonged to the overweight category based on their BMI, and the same percentage of patients had lipid abnormalities. The median of the insulin-free period after the diagnosis of diabetes was 3.0 years (1.0–6.0), despite the fact that we initiated insulin therapy in 23 of our 54 patients with LADA during the first year after diagnosis. The indication of insulin treatment in these patients was their autoantibody positivity and not their metabolic status. We suspect that LADA type 1 and LADA type 2 subgroups may not represent different clinical entities. Instead we think that a certain proportion of patients with LADA, mainly with aging, develop clinical features of metabolic syndrome beside their autoimmune diabetes.

We agree with Palmer and Hirsch (3) that phenotypically there are at least three separate populations of autoimmune diabetes in adults: adult-onset type 1 diabetes, LADA, and obese phenotypic type 2 diabetes with autoantibody positivity. In the study of Fukui et al. (4) anti–GAD-positive type 2 diabetic patients with secondary failure of sulfonylurea therapy ($n = 44$, we think that these are the LADA patients) showed an increased prevalence of one of the predisposing alleles, while the anti–GAD-positive and well-controlled type 2 diabetic patients ($n = 22$, we think that they represent type 2 diabetes with autoantibody positivity) were more likely to have protective alleles and less likely to have predisposing alleles compared with type 1 diabetes showing rapid progression. Notably, the type 1 diabetic group from their study instead represents childhood-onset diabetes (age at onset was 14.5 ± 12.9 years). Another explanation could be the ethnic differences between the Japanese and Hungarian populations.

The unexpected high level of fasting C-peptide at onset in the type 1 diabetic group, (median 0.46 nmol/l [range 0.24–1.05]) was also surprising. However, Mallone et al. (5) also reported a wide range of fasting plasma C-peptide levels in newly diagnosed type 1 diabetes, even with childhood onset (median 0.44 ng/ml [0–5.70]) . Since the diagnosis of type 1 diabetes was established according to the World Health Organization criteria, and the decision of prompt insulin therapy was based on the clinical picture (presence of ketonuria or ketoacidosis) in our study, we do not think that another subgroup of type 1 diabetic patients should have been formed on the basis of the fasting C-peptide level. As a result of the comments by Fukui et al., we noticed a regrettable typing error in Table 1 of our report (1): fasting C-peptide in adult-onset type 1 diabetes 1–10 years after onset is 0.40 nmol/l (0.24–0.62) instead of 0.40 nmol/l (0.24–1.05).

We reported that the islet cell antibody (ICA) positivity documented earlier disappeared in six patients having LADA with longer disease course. There was a considerable interval between the positive and the negative ICA tests (6–11 years). The data regarding persistence of ICA in LADA are controversial. In the cited study (6), ICA either persisted ($n = 18$) or disappeared ($n = 9$) and anti-GAD antibody persisted ($n = 10$) in patients having type 2 diabetes with further insulin requirement. Further studies are necessary to evaluate the long-term characteristics of ICA in patients with LADA.

Regarding the classification of autoimmune diabetes, we would divide it into two or three subtypes. One subtype would be the childhood-onset type 1 diabetes (age at onset <20 years), showing the highest prevalence of the predisposing genotypes and the most aggressive β-cell destruction. Another subtype could be adult-onset type 1 diabetes, which has two forms: rapidly and slowly progressive. The latter should be called LADA without age restriction. The problem of obese phenotypic type 2 diabetes with autoantibody positivity remains unsolved; it needs to be decided whether this group belongs to type 1 or type 2 diabetes, represents a mixture of type 1 and type 2 diabetes, represents a distinct clinical entity, or is merely a laboratory bias.

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