

use where stated was 1–8 months, and doses, stated in four reports, were 4 mg or 8 mg daily. Five patients had an associated hypertriglyceridemia, two had elevated cholesterol levels, and one a fall in total cholesterol levels. Two patients had angina or aggravated angina, and diabetes was aggravated in one. Concomitant medicines other than fibrates occurring more than once included sulfonylureas, metformin, ACE inhibitors (4), statins (4), and aspirin (2).

Spontaneous adverse reaction reports thus support the single published observation that rosiglitazone can lower HDL cholesterol whether or not a fibrate is prescribed. The occurrence of lowered HDL cholesterol with rosiglitazone in a patient who had experienced a similar reaction with bezafibrate suggests a common mechanism. Although small changes in HDL cholesterol measurements must be interpreted with caution, the New Zealand case report and others published indicate that the fall can be profound (1).

Vigibase also contains five reports of lowered HDL cholesterol with troglitazone and one with pioglitazone. Only one patient was also taking a fibrate. These reports contain incomplete information about response to medicine discontinuation but provide evidence for a therapeutic class effect that requires further confirmation.

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Fulminant Autoantibody-Negative and Type 1A Diabetes Phenotypes in a Korean HLA Identical Dizygotic Twin

Type 1 diabetes is a complex, heterogeneous autoimmune disease. Many genetic and environmental factors are thought to be involved in type 1 diabetes pathogenesis as shown in other autoimmune disorders. Although some immune-related genes such as HLA, AIRE, and CTLA-4 have been elucidated about their association in pathogenesis, the detailed genetic factors causing type 1 diabetes are unclear. In a study of twins with type 1 diabetes, significant subsets of monozygotic and dizygotic twins did not progress to clinical diabetes (1), suggesting that genetic heterogeneity and other random factors are crucial for type 1 diabetic pathogenesis, even in twins. Typically, type 1 diabetes is initiated by an autoimmune response against β -cells and followed by progressive defect of insulin secretion from β -cells. These results cause hyperglycemia and transient, usually partial remission, and finally lead to complete insulinopenia. Since Imagawa et al. (2) reported 11 cases of fulminant autoantibody (Ab)-negative type 1B diabetes as a novel subtype, ~200 additional cases have been described. Most of the cases were characterized as abrupt and severe onset, negative Abs, elevated exocrine pancreatic enzymes, and involvement of some specific HLA subtypes such as DRB1*0405 or DRB*0901, and DQA1*0303-DQB1*0401 or DQA1*0302-DQB1*0303. There is a lot of emerging evidence supporting the involvement of autoimmune mechanisms in the destruction of islet cells (3–5). In addition, HLA haplotypes associated with

fulminant Ab-negative type 1 diabetes are also closely correlated with those in type 1A diabetes (6,7).

Here, we report a dizygotic twin with different type 1 diabetic phenotypes; one brother has a fulminant Ab-negative, and the other shows type 1A.

A 35-year-old man (index case) was admitted to our hospital with diabetic ketoacidosis. He was relatively healthy and had suffered from flu-like symptoms for 7 days before admission. He complained of thirst and polydipsia for 2 days. His body weight was 66.2 kg (BMI 21.4 kg/m²). He did not take any medications. We found that serum glucose (39.6 mmol/l), BUN/Cr (28/1.5 mg/dl), amylase/lipase (187/254 units/l), and fructosamine (356 μ mol/l) levels in the patient were highly elevated, but HbA1c (A1C) (5.4%) was decreased. Both serum and urinary ketones were positive. According to arterial blood gas determination, the patient had mild metabolic acidosis. Both fasting serum and 24-h urine C-peptide levels were below the detection limit. After treatment with intravenous insulin and a large volume of fluid administration, his symptoms were rapidly improved, and laboratory parameters were close to near normal values. Any diabetes-related Abs, anti-insulin, GAD, islet cell, and thyroid Abs were not detected. The patient had HLA-DRB1*0405/*0701, DQA1*0303/*0201, and DQB1*0401/*0202 haplotypes. These haplotypes have also been previously reported about their association with fulminant Abs-negative and type 1A diabetes (2,6,8).

The proband's dizygotic twin mate also had type 1 diabetes, which has been well managed by regularly injecting NPH (0.13 units \cdot kg⁻¹ \cdot day⁻¹) before breakfast with near normal A1C levels. He had a high plasma glucose level (19.3 mmol/l) when he visited a local clinic and complained of polyuria and weight loss in February of 2002. At that time, he had 0.2 ng/ml serum C-peptide, 9.5% A1C, and positive anti-GAD antibodies (6.5, RR <1.0 unit/ml). All siblings, including a sister who has a normal glucose tolerance, revealed the same HLA II subtype. In consideration of all clinical and laboratory findings, we concluded that this dizygotic twin with the same HLA haplotype has different phenotypes of type 1 diabetes. One brother reveals fulminant Ab-negative, the other has type 1A phenotype.

Many previous reports suggest that

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Intramyocellular Lipid Is Not Significantly Increased in Healthy Young Insulin Resistant First-Degree Relatives of Diabetic Subjects

Insulin resistance is an early phenotypic feature of nondiabetic first-degree relatives of type 2 diabetic subjects (FDR) (1,2). While intramyocellular lipid (IMCL) is a marker of insulin resistance (3), how it develops is not completely understood. To study early defects accompanying insulin resistance, we characterized a population at high risk of type 2 diabetes (4,5). We studied young, healthy, sedentary, nonsmoking (age <45 years, BMI <36 kg/m²), normolipidemic, and normal glucose tolerant subjects. At-risk FDR subjects (14 female and 5 male) were compared with control subjects without family history of diabetes (12 female and 10 male).

To test the lipid supply hypothesis, we extended previous investigations in FDR (5) to determine whether IMCL is associated with insulin resistance and significantly greater in at-risk compared with control subjects in the prediabetes stage.

IMCL were determined in three muscles of differing fiber composition (biochemical determination of vastus lateralis

IMCL obtained from biopsy and soleus and tibialis anterior IMCL from magnetic resonance spectroscopy). Additional metabolic assessments were performed as previously reported (4–6). IMCL content of soleus and tibialis anterior muscles (ratio between proton resonance areas of intramyocellular CH₂ and creatine). Statistical analyses were performed using StatView 5 (SAS Institute, Cary, NC). Results are presented as means ± SE and *P* value <0.05 was considered significant.

At-risk and control subjects were similar for age, BMI, blood pressure, fasting glucose, leptin, adiponectin, and circulating lipid levels (4). At-risk subjects were 25% more insulin resistant than control subjects (51.8 ± 3.9 vs. 64.9 ± 4.6 μmol · min⁻¹ · kg⁻¹ fat-free mass, *P* = 0.04) (4).

IMCL triglyceride levels were slightly higher in the at-risk group in soleus (10.3 ± 1.1 vs. 8.6 ± 1.0 IMCH₂-to-creatine ratio, *P* = 0.25) and similar in tibialis anterior (5.6 ± 0.8 vs. 5.0 ± 0.8 IMCH₂-to-creatine ratio, *P* = 0.45) and vastus lateralis muscles (35.9 ± 5.2 vs. 32.1 ± 5.8 μmol/g dry weight, *P* = 0.63). As reported by Krssak and Roden (7), IMCL content of tibialis anterior was the best (and only) predictor of insulin sensitivity by euglycemic clamp in the entire cohort (tibialis anterior *r* = -0.39, *P* = 0.015; vastus lateralis *r* = 0.21, *P* = 0.20; soleus *r* = 0.07, *P* = 0.67) and also in the at-risk group alone (*r* = -0.58, *P* = 0.009). There was no significant sex difference in IMCL content (data not shown).

Thus, using an appropriate human model of early insulin resistance in prediabetes (healthy but insulin resistant, normoglycemic, normolipidemic diabetic relatives compared with matched subjects with no diabetic family history), ICML content in three different muscles was not significantly increased, nor related overall to insulin sensitivity (4–6).

While our findings differ from Petersen et al. (8), we studied three muscles with two different methods (5,6) at an earlier stage of insulin resistance. However, as our subjects are mildly insulin resistant, possibly very small differences in muscle triglyceride levels may be undetectable by either state-of-the-art method. The implication remains that such small triglyceride accumulation is more likely to be secondary to a (putative) mitochondrial impairment (as proposed by Petersen et al.) than to be the primary cause for whole-body insulin insensitiv-

ity. In other words, increased muscle triglyceride appears unlikely to be the primary cause of established whole-body insulin resistance.

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Can Glargine Reduce the Number of Lung Infections in Patients With Cystic Fibrosis-Related Diabetes?

Incidence and prevalence of cystic fibrosis-related diabetes (CFRD) are rapidly increasing in recent years, according to the gradual increase in median survival age, which is now around 30 years (1). CFRD, with or without fasting hyperglycemia, may be chronic or intermittent, the latter in physically stressed patients. It is possible that the prediabetic state may have adverse effects on clinical status, nutrition, and lung function in patients with cystic fibrosis (2). As a matter of fact, impairment of lung function seems to appear up to 2-4 years before the clinical onset of diabetes. Insulin therapy was able to improve lung function in CFRD patients (3). Glargine is a recent long-acting insulin analog, which is a good candidate for basal insulinization, owing to a duration of action of 24 h without any peak and any hypoglycemic effect. Therefore, we speculated whether glargine treatment could exert beneficial effects in chronic or intermittent CFRD patients.

We analyzed eight CFRD patients (six females), aged 10-29 years, who were affected by pancreatic exocrine deficiency, had mean forced expiratory volume in 1 s (FEV1) of 77% (range 62-104), and were treated for 6 months with glargine. Four of eight patients were homozygous for the ΔF-508 mutation, two were heterozygous, one had a different CFTR mutation, and one was negative for known mutations. Patients were divided in two groups: Group A comprised four patients with chronic CFRD (three females, aged 15-29 years) treated with rapid insulin (0.9 units · kg⁻¹ · day⁻¹) in two or three doses in the last 1-3 years. Group B included four patients with intermittent CFRD (three females, aged 10-21 years) requiring insulin only during infections. Glargine was administered at 0.3 units · kg⁻¹ · day⁻¹ in all patients once a day.

Group A patients continued their preprandial rapid insulin administrations besides glargine. At the end of the study, BMI, FEV1 percentage, HbA_{1c} (A1C), and the number of lung infections were compared with baseline values. The control group comprised six patients with intermittent CFRD (four females, aged 14-18 years) who were affected by pancreatic exocrine deficiency and had a mean FEV1 of 71.8% (range 47-100); three of the patients were homozygous for the ΔF-508 mutation and three were heterozygous. All glargine-treated patients showed a good compliance with therapy; no hypoglycemic crises were recorded. The number of lung infections decreased in group A from 3.75 ± 0.5 to 1.75 ± 0.9 (P < 0.01) and in group B from 2.75 ± 0.50 to 1.25 ± 0.5 (P < 0.001), while no change was found in A1C and BMI. Moreover, the total dose of daily insulin did not change in group A. In the control group, the number of lung infections did not change during the same period of observation (3.3 ± 1.2 vs. 3.1 ± 0.4).

Our preliminary experience suggests that basal insulinization obtained not only in overt diabetic cystic fibrosis patients but also in prediabetic cystic fibrosis patients may play a pivotal role in reducing the number of lung infections. No hypoglycemic event occurred also in prediabetic patients, suggesting that—regardless of their fasting euglycemic status—they probably already required moderate basal insulin doses. The period of observation was probably too short to detect any positive change in BMI, FEV1, or any other health parameters. Further controlled studies should be encouraged in order to confirm the possible effects of glargine in preventing lung function impairment in cystic fibrosis patients.

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Stockpiling of Ovarian Follicles and the Response to Rosiglitazone

A 46-year-old woman of Euroasian descent had been treated for 2 years with 500 mg metformin twice daily for polycystic ovarian disease (PCO). While menarche occurred at age 12 years, she had no more than two to three menstrual periods per year except on two occasions in her 20s when, following a 9- to 10-kg weight loss, she achieved regular menstrual periods, became pregnant, and delivered two healthy infants with no complications.

While being treated with metformin, the woman was diagnosed as having diabetes based on two fasting serum glucoses tests >7 mmol/l. She was switched to a combination tablet containing 2-mg rosiglitazone and 500 mg metformin twice daily. Following this change, her serum total testosterone dropped from 2.5 to 1.12 nmol/l and her menstrual periods became regular for 4 months, after which she became amenorrhic. Because of her age and history of PCO, this did not cause concern, even though she had no menopausal symptoms. Six months later, after presenting with abdominal pain, it was discovered by ultrasonography that she was 30 weeks' pregnant. Metformin and rosiglitazone were discontinued, and she was started on insulin therapy. At 36 weeks' gestation she became hypertensive and at 37 weeks delivered a healthy 3.4-kg baby girl without neonatal complications.

Spontaneous pregnancy in this age range is unusual and has been estimated

to be near 0% (1). The average age of last conception in a stable North American population (Hutterites) not practicing contraception was 40.9 years (1). This age-related decrease in fertility is attributed to loss of oocytes through years of ovulation. However, it has recently been noted that there is an increase in primary follicles in polycystic ovaries, a phenomenon described as “stockpiling,” possibly due to anovulation or stasis (2). We suggest that in PCO patients, even in the age range where the rate of spontaneous pregnancy is low, utilization of thiazolidinediones should be accompanied by concurrent contraceptive use. These patients may achieve a more favorable hormonal milieu for ovulation in the setting of “stockpiled” ovarian follicles.

This case is also unique in that the patient was older and the length of rosiglitazone exposure longer than in the previous two reports of rosiglitazone exposure during pregnancy. Despite the known presence of rosiglitazone in fetal tissue, three reports have now documented normal fetal outcomes (3–5).

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Detection of Associated Ocular Lesions During Screening of Diabetic Retinopathy

Diabetic retinopathy is the foremost cause of blindness in the working-age population in France (1). An increased incidence of diabetes combined with the lack of ophthalmologists and absence of optometrists makes screening inaccessible to the vast majority. In this setting, the digital fundus camera provides a rapid, sensitive, and cost-effective option (2). Since its installation in our hospital diabetes clinic, patients now routinely undergo photographic screening. Dilated multifield photography allowed good quality imaging of the posterior fundus, which enabled detection of other coexisting pathologies in addition to diabetic retinopathy.

Fundus photographs of 1,153 consecutive patients attending our screening clinic between November 2003 and October 2004 were recorded with the Topcon TRC NW6S camera (Topcon Europe, Capelle a/d IJssel, the Netherlands). Patients underwent five-field (45°) non-stereoscopic imaging through pharmacologically dilated pupils followed by interpretation by an experienced ophthalmologist. Presence of coexisting fundus lesions, apart from diabetic retinopathy, was noted, and patients were interrogated regarding relevant antecedent history. They were referred for further ophthalmological evaluation, the urgency depending on the diagnosis.

Patients (578 males and 575 females) of age 57 ± 16 years (mean \pm SD, range 16–92) had a duration of diabetes of 14 ± 11 years (range 0–57). For 124 patients (11%), this was their first fundus examination. Apart from diabetic retinopathy ($n = 622$, 54%), coexisting fundus pathologies were detected in 612 patients (53%). Among these, the most frequent were hypertensive retinopathy ($n = 205$, 18%), significant cataract ($n = 176$, 15%), age-related macular degeneration ($n = 66$, 6%), and disc cupping or atro-

phy ($n = 33$, 3%). Twenty patients (2%) had previously undiagnosed sight-threatening lesions needing immediate ophthalmic referral. These included age-related macular degeneration ($n = 4$, 2 with submacular membranes), retinal vein occlusions ($n = 4$), severe hypertensive retinopathy ($n = 3$), retinal macroaneurysms ($n = 2$), macular hole ($n = 1$), and rhegmatogenous retinal detachment ($n = 1$). Presence of an intraocular neoplasm (choroidal mass lesion) was suspected in one patient. Optic nerve lesions requiring referral comprised optic atrophy ($n = 2$, 1 with pituitary tumor and 1 with anterior optic neuropathy), papilloedema (in 1 patient with metastatic thyroid carcinoma), and advanced glaucomatous cupping ($n = 1$). Other rare ophthalmic conditions discovered were atypical choroidal nevus ($n = 2$), congenital disc anomalies ($n = 2$), retinitis pigmentosa ($n = 1$), bilateral choroidal folds ($n = 1$), and oculodermal melanocytosis ($n = 1$).

Multiple cases with coexistent fundus pathologies including some with potential vision-threatening consequences were detected during diabetic retinopathy screening. This, to our knowledge, has not yet been reported in literature. This underlines the importance of periodic ophthalmologic check up, especially in the elderly population. A study carried out at a diabetic retinopathy screening clinic in Paris revealed that 30% of patients never had a fundus examination (3). Due to a decreasing number of ophthalmologists in France, a consultation often involves a waiting period of several months. Screening with the digital fundus camera, which consumes less time and manpower, is therefore becoming increasingly popular in hospital practice. In addition to diabetic retinopathy screening, expert interpretation and timely referral provides a secondary benefit of general ophthalmic surveillance to the diabetic community. Considering its easy, quality, and cost-effective functioning, this could find application in mass ophthalmic screening.

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Acknowledgments—We thank the Direction Régionale de la Recherche Clinique (Prof. H. Decousus) for funding the hospital research project (Grant: Regional Clinical Hospital Research Trial 2003-28/04).

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COMMENTS AND RESPONSES

Are Fatty Acids a Link Between Diabetes and Lowered Cognitive Performance?

Response to Brands et al.

In a meta-analysis of the literature, Brands et al. (1) found that type 1 diabetic patients had lowered cognitive performance. Compared with a control group, the type 1 diabetic group had lowered intelligence, speed of information processing, psychomotor efficiency, visual and sustained attention, cognitive flexibility, and visual perception. Brands et al. discussed

possible causes, including levels of glycemic control, microvascular complications, and depression. The role of altered fatty acid profiles in type 1 diabetic patients should be considered as well.

Decsi et al. (2) found that type 1 diabetic patients have lower levels of long-chain polyunsaturated fatty acids (LCPUFAs). They speculate that this is because type 1 diabetic patients synthesize less LCPUFAs. Obtaining sufficient amounts of ω -3 LCPUFAs is important for cognitive performance (3,4). Kalmijn et al. (3) found that greater consumption of ω -3 LCPUFAs reduced the risk of impaired overall cognitive function and speed in middle-aged individuals. Rats that are deficient in ω -3 fatty acids display impaired spatial task performance (4). Achieving optimal levels of ω -3 LCPUFAs may improve brain function through better cardiovascular health, changes in gene expression in the brain, membrane biophysics, and biosyntheses of eicosanoids (3,5,6).

If type 1 diabetic patients are synthesizing less LCPUFAs, they will need to get more of it from their diets. The possibility that decreased levels of LCPUFAs are partially responsible for the lowered cognitive performance in type 1 diabetic patients is worth exploring.

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Are Fatty Acids a Link Between Diabetes and Lowered Cognitive Performance?

Response to Ross

We thank Dr. Ross (1) for her comments on our recent paper on cognition and type 1 diabetes (2). We agree that many questions remain open with regard to the etiology underlying impaired cognitive performance in patients with type 1 diabetes.

Although it seems clear that the underlying pathophysiology is a multifactorial process, the exact nature and the relative contribution of different underlying mechanisms is not yet understood. Indeed, outside the field of diabetes, there is growing evidence for a possible protective role of long-chain polyunsaturated fatty acids (LCPUFAs) on cognitive function (3). However, until now the possible role of altered fatty acid profiles on cognition in type 1 diabetic patients has not been systematically investigated and, as such, was beyond the scope of our meta-analysis. The profile of cognitive disturbances (e.g., reduced overall cognitive performance and lowered processing speed) in middle-aged persons with lowered intake of ω -3 LCPUFAs (3) resembles the cognitive pattern described in our meta-analysis (2).

Still, one has to notice that this cognitive profile is not unique for lowered levels of LCPUFAs but has, for example, also been described in studies addressing cognitive performance in normal aging (4). Therefore, the possible protective role of LCPUFAs warrants further investigation.

A first step would be to examine the relation between LCPUFA levels, as well as other potentially relevant etiologic factors that are discussed in our review (2),

and impaired cognition in patients with type 1 diabetes. Considering the limited effect sizes of cognitive impairments found in our meta-analysis and the relatively large interindividual variation, this will require large, preferentially prospective, population-based study designs. Also, highly sensitive neuropsychological tests should be used in order to detect even subtle cognitive changes.

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Eliminating Inpatient Sliding-Scale Insulin: A Reeducation Project With Medical House Staff

Response to Baldwin et al.

The study by Baldwin et al. (1) had the laudable intention of training house staff in moving away from inpatient sliding-scale insulin in favor of a

basal-bolus approach or active titration of oral agents. However, some key points in their report remain unexplained. The authors state that in insulin-treated patients, the premeal short-acting insulin (usually regular) in combination with a basal insulin (usually NPH) was used. However, no details are given as to how the NPH was titrated and what parameters, if any, were used for adjustment. Even more notable is the lack of information about adjustment of short acting insulin. How were the initial doses of regular insulin arrived at, and what end point was the basis for periodic alterations of the premeal dose of bolus insulin? Were 2-h postprandial blood glucoses measured, and was the insulin-to-carbohydrate ratio and sensitivity factor utilized? If a best-guess approach was used, how is that much different from, or superior to, a sliding scale? The authors state that premeal regular insulin was administered twice daily, whereas for true prandial coverage, usually three and sometimes more injections are necessary. Thus the claim that the basal-bolus insulin was used in the study patients is not entirely true. Simply vowing to eliminate sliding-scale insulin without replacing it with a rational, scientific, and target-based alternative insulin regimen does not solve the problem. It is entirely possible that the HbA_{1c} improvement seen in the study was due to intensive escalation of insulin or oral-agent therapy secondary to the increased attention provided by the twice-daily watchful eye of an endocrinologist and had very little to do with refusing to write sliding-scale orders per se.

The endocrine service at our institution utilizes a basal-bolus insulin regimen designed to overcome the above drawbacks. Daily adjustments of basal insulin are made based on fasting, premeal, and periodic 3:00 A.M. blood glucose readings. Two-hour postprandial readings, insulin-to-carbohydrate ratios, and sensitivity factor calculations dictate initiation and fine tuning of short-acting premeal insulin (2). It has required a reeducation of nurses, trainees, other health care professionals, and patients. We have attempted to involve persons from various disciplines to try to change the mindset vis-à-vis inpatient diabetes control through a collaborative effort. Although we are still in the midst of evaluating the efficacy of our inpatient subcutaneous insulin orders, we have been pleased with the re-

sults so far and feel that this approach is on a more scientific footing.

The optimal method of using subcutaneous insulin in the hospital remains to be determined. However, we feel that the only enduring philosophy is one that tailors both basal and short-acting insulin to the needs of the patient by means of a rational approach that has inherent flexibility.

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Response to Rizvi

We thank Dr. Rizvi (1) for his comments about our study (2). Unfortunately, due to space constraints, we were not able to include all of the details for insulin initiation and titration in the main body of the article. As indicated in the fifth paragraph of the RESEARCH DESIGN AND METHODS section, these details are contained in an online appendix for the article (available at <http://care.diabetesjournals.org>). We did not measure 2-h postprandial blood glucoses nor use any insulin-to-carbohydrate ra-

