OBSERVATIONS

Burden of Type 2 Diabetes in Young Korean Adults Owing to Obesity

Previous large-scale surveys reported that magnitudes of increase in type 2 diabetes and obesity are more remarkable among young adults than older ones, whereas prevalences of these are lower in young adults (1,2). These epidemiological findings have very important implications in clinical practice and public health policies. Despite its significance, however, there are few reports on the effects of obesity on the risk of disease in younger generations compared with older people.

We investigated the effects of BMI on the development of type 2 diabetes according to age-group in a large-scale, 10-year follow-up cohort, the Korea National Health Insurance Corporation (KNHIC) study. The KNHIC provides medical insurance to public servants, teachers, and their dependents. Of KNHIC members, 883,697 men and women aged 25–64 years in 1992 were selected as study subjects. All of the subjects were required to complete a medical questionnaire and have their general health status assessed every 2 years by the KNHIC. A more detailed description of the subjects has been published (3).

Type 2 diabetes was diagnosed when the fasting plasma glucose level is ≥126 mg/dl or subjects were treated for type 2 diabetes. BMI was categorized by 1-unit increments to examine the overall disease risks in detail with regard to the degree of obesity. In the analyses, the reference point was set as a BMI of 21 kg/m^2.

We found a significant linear dose-dependent relationship between BMI and type 2 diabetes in all age-groups (all $P <$ 0.05 for the linear trend), and these trends were more pronounced in the younger groups. The interaction between BMI and age-group was statistically significant ($P = 0.003$). With the reference BMI level of 21 kg/m^2, subjects with a BMI of 25 kg/m^2 who were between 20 and 29 years old had a relative risk of 2.24 (95% CI 1.95–2.49), while subjects aged 30–39, 40–49, and ≥50 years with this BMI had relative risks of 2.28 (2.13–2.43), 1.90 (1.78–2.02), and 1.80 (1.65–1.95), respectively. Subjects with a BMI of 30 kg/m^2 who were between 20 and 29 years old had a relative risk of 6.69 (4.52–8.33), while subjects aged 30–39, 40–49, and ≥50 years with this BMI had relative risks of 4.90 (4.11–5.58), 4.09 (3.47–4.62), and 2.67 (2.05–3.17), respectively. The discrepancy between these risks increased with BMI. We found steeper dose-dependent relationships between BMI and type 2 diabetes in the younger age-groups than in the older groups.

Because type 2 diabetes leads to long-term morbidity, the prevention of obesity in younger generations and the early identification of overt disease need to be considered as critical public health issues. Therefore, public effort is needed to control weight problems and obesity in young people to prevent future health problems before it is too late.

YEONG SOOK YOON, MD[1]
SOON-AE SHIN, MPH[2]
JUNG-HYUN NOH, MD, PHD[3]
SANG WOO OH, MD, PHD[1]

From the [1]Department of Family Medicine and Center for Health Promotion, Ilsan-Paik Hospital, Inje University, College of Medicine, Gyeonggi-Do, Republic of Korea; the [2]Division of Disease Prevention and Health Promotion, Korea National Health Insurance Corporation, Seoul, Republic of Korea; and the [3]Department of Internal Medicine, Ilsan-Paik Hospital, Inje University, College of Medicine, Gyeonggi-Do, Republic of Korea.

Address correspondence to Sang Woo Oh, MD, PhD, Department of Family Medicine and Center for Health Promotion, Inje University Ilsan-paik Hospital, Daewha-Dong, Ilsan-Gu, Goyang-Si, Gyeonggi-Do, 411-706, (South) Korea. E-mail: osw6021@yahoo.co.kr or osw6021@ilsanpaik.ac.kr.

References

1. Mokdad AH, Ford ES, Bowman BA, Nelson DE, Engelgau MM, Vinicor F, Marks JS: Diabetes trends in the U.S.: 1990–1998. *Diabetes Care* 23:1278–1283, 2000
2. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP: The spread of the obesity epidemic in the United States 1991–1998. *JAMA* 282: 1519–1522, 1999
3. Oh SW, Shin SA, Yun YH, Yoo T, Huh BY: Cut-off point of BMI and obesity-related comorbidities and mortality in middle-aged Koreans. *Obes Res* 12:2031–2040, 2004

Thiazolidinediones and Lowered HDL Cholesterol

Three publications, including two recently in Diabetes Care, have indicated that a combination of rosiglitazone and fibrates may lower serum HDL cholesterol in some patients (1–3). It is known that a paradoxical fall in HDL cholesterol may occur with fibrates.

These series of cases include only one case of HDL cholesterol lowering in a patient taking rosiglitazone without a fibrate (1). There are no published case reports of this reaction occurring with other thiazolidinediones, where the reaction resolved when the latter, rather than the fibrate, was withdrawn. Thus, confirmatory evidence of this reaction occurring with rosiglitazone alone and whether it is unique to rosiglitazone or a therapeutic class effect is needed.

The New Zealand Pharmacovigilance Centre recently received a report of HDL cholesterol lowering with rosiglitazone in the absence of a fibrate. A fall in HDL cholesterol from 0.8 to 0.2 mmol/l was described in a 64-year-old patient 3 weeks after starting rosiglitazone. When discontinued, recovery was rapid. Of note is that this patient had experienced a similar reaction to bezafibrate previously with the HDL cholesterol falling from 1.1 to 0.3 mmol/l.

Vigibase, the database of the WHO Collaborating Centre for International Drug Monitoring held at the Uppsala Monitoring Centre was searched for further cases.

There were 14 reports from three countries of lowered HDL cholesterol concentrations associated with rosiglitazone. The reporting of this drug/adverse reaction combination was disproportionately high compared with the background data (4). Five of the patients were not taking a fibrate. Outcome data were provided for all but three patients. Two patients recovered when rosiglitazone was withdrawn, and one of the patients was not taking a fibrate. In two others, rosiglitazone had not been discontinued at the time of reporting. Seven other patients recovered, but no information on drug withdrawal was given. There were eight males and five females aged 31–66 years (sex not stated in one report). Duration of

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.

RUTH L. SAVAGE, MBBS, MSC[1]
ANNE KIURU, MSC[2]

From the [1]Department of Preventive and Social Medicine, New Zealand Pharmacovigilance Centre, University of Otago, Dunedin, New Zealand; and the [2]Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden.

Address correspondence to Anne Kiuru, Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring, Stora Torget 3, Uppsala S-753 20, Sweden. E-mail: anne.kiuru@who-umc.org.

References

1. Sarker A, Semple RK, Dineen SF, O'Rahilly S, Martin SC: Severe hypo-α-lipoproteinemia during treatment with rosiglitazone. *Diabetes Care* 27:2577–2580, 2004
2. Normen L, Frohlich J, Montaner J, Harris M, Elliott T, Bondy G: Combination therapy with fenofibrate and rosiglitazone paradoxically lowers serum HDL cholesterol. *Diabetes Care* 27:2241–2242, 2004
3. Ebcioglu Z, Morgan J, Carey C, Capuzzi D: Paradoxical lowering of high-density lipoprotein cholesterol level in 2 patients receiving fenofibrate and a thiazolidinedione (Letter). *Ann Intern Med* 139:W80, 2003
4. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, DeFreitas RM: A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol* 54315–54321, 1998

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

Type 1 diabetes is a complex, heterogenous 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/m^2). 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 μmol/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 · kg^{-1} · 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

autoimmunity might be directly or indirectly involved in the development of fulminant type 1 diabetes. This dizygotic twin report also suggests that the immunogenetic mechanism is required for islet destruction in proband. The clinical courses among type 1 diabetes patients are different with respect to their onset age and ethnicity, suggesting that the presence of attacking or preventing genetic and environmental factors might determine the pathogenesis. Why are there different clinical courses between twin brothers who have the same HLA subtype? We need to further identify genetic and environmental factors determining these clinical variabilities in type 1 diabetes.

Jung H. Jung, MD[1]
Jong R. Hahm, MD[1,2]
Me A. Kim, MD[2,3]
Myoung H. Park, MD[4]
Deok R. Kim, PHD[2,5]
Tae S. Jung, MD[1]
Soon I. Chung, MD[1,2]

From the [1]Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea; the [2]Gyeongsang Institute of Health Sciences, Jinju, Republic of Korea; the [3]Department of Laboratory Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea; the [4]Department of Laboratory Medicine, Seoul National University Hospital, Seoul, Republic of Korea; and the [5]College of Medicine, Biochemistry, Gyeongsang National University, Jinju, Republic of Korea.

Address correspondence to Jong Ryeal Hahm, Gyeongsang National University Hospital, #90 Chilamdong, Jinju, Republic of Korea. E-mail: jrhahm@gshp.gsnu.ac.kr.

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References

1. Redondo MJ, Yu L, Hawa M, Mackenzie T, Pyke DA, Eisenbarth GS, Leslie RD: Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. *Diabetologia* 44:354–362, 2001
2. Imagawa A, Hanafusa T, Miyagawa JI, Matsuzawa Y, for the Osaka IDDM Study Group: A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. *N Engl J Med* 342:301–317, 2000
3. Tanaka S, Kobayashi T, Momotsu T: A novel subtype of type 1 diabetes mellitus. *N Engl J Med* 342:1835–1837, 2000
4. Shimada A, Morimoto J, Kodama K, Oikawa Y, Irie J, Nakagawa Y, Narumi S, Saruta T: T-cell-mediated autoimmunity may be involved in fulminant type 1 diabetes. *Diabetes Care* 25:635–636, 2002
5. Shimada A, Oikawa Y, Shigihara T, Senda T, Kodama K: A case of fulminant type 1 diabetes with strong evidence of autoimmunity. *Diabetes Care* 25:1482–1483, 2002
6. Tanaka S, Kobayashi T, Nakanishi K, Koyama R, Okubo M, Murase T, Odawara M, Inoko H: Association of HLA-DQ genotype in autoantibody-negative and rapid-onset type 1 diabetes. *Diabetes Care* 25: 2302–2307, 2002
7. Murao S, Makino H, Kaino Y, Konoue E, Ohashi J, Kida K, Fujii Y, Shimizu I, Kawasaki E, Fujiyama M, Kondo S, Tanaka K, Tarumi Y, Seto I, Kato K, Ohno K, Kusunoki Y, Ebisui O, Takada Y, Tanabe K, Takemoto K, Onuma H, Nishimiya T, Osawa H: Differences in the contribution of HLA-DR and -DQ haplotypes to susceptibility to adult- and childhood-onset type 1 diabetes in Japanese patients. *Diabetes* 53:2684–2690, 2004
8. Imagawa A, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, Maruyama T, Makino H: Different contribution of class II HLA in fulminant and typical autoimmune type 1 diabetes mellitus. *Diabetologia* 48: 294–300, 2005

Forty-Year Observation of 280 Japanese Patients With Congenital Rubella Syndrome

There was a rubella epidemic in 1964–1965 in Okinawa, Japan. By 2004, 280 subjects were diagnosed with congenital rubella syndrome (CRS). All 280 patients followed over this 40-year period developed cataracts, sensory deafness, and/or heart disease. We measured islet cell surface antibody (ICSA), islet cell antibody (ICA), and anti-GAD65, IA-2, and insulin antibodies. Three (1.1%) (patients 1, 2, and 3) of these 280 CRS patients developed type 1 diabetes (positive autoantibodies to pancreatic β-cells). Patients 1 and 2 had diabetic ketoacidosis and type 1 diabetes. Patient 3 was diagnosed with diabetes at 18 years of age and later found to have type 1 diabetes. Endogenous insulin response at the onset of diabetes was maintained in two patients (2 and 3). However, all three patients later required insulin administration. They had autoantibodies to pancreatic β-cells and developed type 1 diabetes.

Patient 1 is a 40-year-old woman born in 1965. She had cataracts, sensory deafness, and mutism. At 18 years of age, her fasting plasma glucose was 68 mg/dl. At 21 years of age, she developed diabetic ketoacidosis and was diagnosed with type 1 diabetes. She had ICSA, ICA, anti-GAD65Ab, and anti-IA2Ab, as well as goiter and thyroid-antibodies. She had Hashimoto's thyroiditis and developed hypothyroidism, for which she was treated with thyroxine.

Patient 2 is a 40-year-old woman born in 1965. She had cataracts, sensory deafness, and mutism. At 13 years of age, in May 1979, she complained of thirst and polyuria and developed diabetic ketoacidosis. She was treated with insulin. In September 1979, she again developed diabetic ketoacidosis. She was diagnosed with and treated for type 1 diabetes. She had ICSA.

Patient 3 is a 40-year-old man born in 1965. He had cataracts, sensory deafness, and mutism. He also had atrial septal defect. He was diagnosed with diabetes at 18 years of age. He later developed type 1 diabetes and is being treated with insulin. He had antibodies to ICSA and anti-GAD65Ab.

Patients 1 and 2 had diabetic ketoacidosis and were diagnosed with type 1 diabetes, and Patient 3 was found to have diabetes upon screening, later developed insulin-dependent diabetes, and now requires insulin. All three subjects developed type 1 diabetes. The age of diabetes onset was 21, 13, and 18 years, respectively. They had autoantibodies to pancreatic β-cells and type 1 diabetes. Total amount of insulin required ranged from 32 to 47 units per day. Patient 1 had Hashimoto's hypothyroidism.

Although the prevalence of diabetes in CRS was reported to be 20% in Caucasians (1), it is 1.1% in Japanese. The prevalence is 20 times higher in Caucasians than in Japanese in subjects with CRS, as seen in those without CRS (22–29 cases per 100,000 in Scandinavians, Canadians, and Scots and 1.5 per 100,000 in Japanese) (2). The present study was undertaken according to the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Nobuyuki Takasu, MD, PHD
Tomomi Ikema, MD, PHD
Ichiro Komiya, MD, PHD
Goro Mimura, MD, PHD

From the Department of Endocrinology and Metabolism (Second Department of Internal Medicine), University of the Ryukyus School of Medicine, Nishihara, Okinawa, Japan.

Address correspondence to Nobuyuki Takasu, MD, PhD, Department of Endocrinology and Metabolism (Second Department of Internal Medicine), University of the Ryukyus School of Medicine, Nishihara, Okinawa, 902-0215, Japan. E-mail: takasun@med.u-ryukyu.ac.jp.

References

1. Menser MA, Forrest JM, Bransby RD: Rubella infection and diabetes mellitus. *Lancet* 1:57–60, 1978
2. Patrick SL, Moy CS, LaPorte RE: The world of insulin-dependent diabetes mellitus: what international epidemiologic studies reveal about the etiology and natural history of IDDM. *Diabetes Metab Rev* 5:571–578, 1989

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/m^2), 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 CH_2 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 $\mu mol \cdot min^{-1} \cdot kg^{-1}$ 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 $IMCH_2$-to-creatine ratio, $P = 0.25$) and similar in tibialis anterior (5.6 ± 0.8 vs. 5.0 ± 0.8 $IMCH_2$-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 insensitivity. In other words, increased muscle triglyceride appears unlikely to be the primary cause of established whole-body insulin resistance.

ADAMANDIA D. KRIKETOS, PHD[1]
GARETH S. DENYER, PHD[2]
CAMPBELL H. THOMPSON, MD, DPHIL[3]
LESLEY V. CAMPBELL, MBBS, FRACP[1,4]

From the [1]Diabetes and Obesity Research Program, Garvan Institute of Medical Research, Sydney, Australia; the [2]School of Molecular and Microbial Sciences, University of Sydney, Sydney, Australia; the [3]Department of General Medicine, Flinders University of South Australia, Adelaide, Australia; and the [4]Diabetes Centre, St. Vincent's Hospital, Sydney, Australia.

Address correspondence to Prof. Lesley V. Campbell, Diabetes and Obesity Research Program, Garvan Institute of Medical Research, 384 Victoria St., Darlinghurst, Sydney, NSW 2010, Australia. E-mail: l.campbell@garvan.org.au..

References

1. Eriksson J, Franssila-Kallunki A, Ekstrand A, Saloranta C, Widen E, Schalin C, Groop L: Early metabolic defects in persons at increased risk for non-insulin dependent diabetes mellitus. *N Engl J Med* 321:337–343, 1989
2. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic patients. *Ann Intern Med* 13:909–915, 1990
3. Lillioja SL, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennet PH, Bogardus C: Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: prospective studies of Pima Indians. *N Engl J Med* 329:1988–1992, 1993
4. Kriketos AD, Greenfield JR, Peake PW, Furler SM, Denyer GS, Charlesworth JA, Campbell LV: Inflammation, insulin resistance, and adiposity. *Diabetes Care* 27: 2033–2040, 2004
5. Kriketos AD, Milner KL, Denyer G, Campbell LV: Is postprandial hypertriglyceridaemia in relatives of type 2 diabetic subjects a consequence of insulin resistance? *Eur J Clin Invest* 35:117–125, 2005
6. Gan SK, Kriketos AD, Ellis BA, Maclean EL, Thompson CH, Kraegen EW, Chisholm DJ: Changes in aerobic capacity and visceral fat but not myocyte lipid levels predict increased insulin action after increased exercise in overweight males. *Diabetes Care* 26:1706–1713, 2003
7. Krssak M, Roden M: The role of lipid accumulation in liver and muscle for insulin resistance and type 2 diabetes mellitus in

humans. *Rev Endocrin Metab Disord* 5:127–134, 2004
8. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI: Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med* 350:664–671, 2004

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.

ADRIANA FRANZESE, MD[1]
MARIA IMMACOLATA SPAGNUOLO, MD, PHD[1]
ANGELA SEPE, MD[1]
GIULIANA VALERIO, MD, PHD[2]
ENZA MOZZILLO, MD[1]
VALERIA RAIA, MD[1]

From the [1]Department of Pediatrics, Federico II University, Naples, Italy; and the [2]School of Movement Sciences (DiSIST), Parthenope University, Naples, Italy.

Address correspondence to Adriana Franzese, Department of Pediatrics, University Federico II, Naples, Italy, V S Pansini, 5, 80131 Naples, Italy. E-mail: franzese@unina.it.

References
1. Koch C, Rainisio M, Madessani U, Harms HK, Hodson ME, Mastella G, McKenzie SG, Navarro J, Strandvik B: Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function in patiens with cystic fibrosis: data from European Epidemiologic Registry of Cystic Fibrosis. *Paediatr Pulmonol* 32.343–350, 2001
2. Moran A, Milla C: Abnormal glucose tolerance in cystic fibrosis: why should patients be screened? *J Pediatr* 142:97–99, 2003
3. Lanng S, Thorsteinsson B, Nerup J, Koch C: Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr* 83:849–853, 1994

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 amenorrheic. 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).

TOM BROOKS VAUGHAN, MD
DAVID S.H. BELL, MD

From the Department of Medicine, University of Alabama Birmingham, Division of Endocrinology, Birmingham, Alabama.

Address correspondence to Tom Brooks Vaughan, UAB Department of Medicine, Division of Endocrinology, Faculty Office Tower, Suite 758, 510 20th St. S., Birmingham, AL 35294. E-mail: brooks@uab.edu.

References

1. Tarlatzis B, Zepiridis L: Perimenopausal conception. *Ann N Y Acad Sci* 997:93–104, 2003
2. Maciel G, Baracat E, Benda J, Markham S, Hensinger K, Chang J, Erickson G: Stockpiling of transitional and classic primary follicles in ovaries of women with polycystic ovary syndrome. *J Clin End Met* 89: 5321–5327, 2004
3. Yaris F, Yaris E, Kadioglu M, Ulku C, Kesim M, Kalyoncu N: Normal pregnancy outcome following inadvertent exposure ot rosiglitazone, gliclazide, and atorvostatin in a diabetic and hypertensive woman. *Reprod Toxicol* 18:619–621, 2004
4. Kalyoncu N, Yaris F, Ulku C, Kadioglu M, Kesim M, Unsal M, Dikici M, Yaris E: A case of rosiglitazone exposure in the second trimester of pregnancy. *Reprod Toxicol* 19:563–564, 2005
5. Chan L, Yeung J, Lau T: Placental transfer of rosiglitazone in the first trimester of human pregnancy. *Fertil Steril* 83:955–958, 2005

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°) nonstereoscopic 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 ± 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 atrophy (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.

NILANJANA DEB-JOARDAR, MD, FRCSED[1]
NATACHA GERMAIN, MD[2]
GILLES THURET, MD, PHD[1]
ANNE-FREDERIQUE GARCIN, MD[1]
PIERRE MANOLI, MD[1]
BRUNO ESTOUR, MD[2]
PHILIPPE GAIN, MD, PHD[1]

From the [1]Department of Ophthalmology, University Hospital Bellevue, Saint-Etienne, France; and the [2]Department of Endocrinology, University Hospital Bellevue, Saint-Etienne, France.

Address correspondence to Prof. Philippe Gain, MD, PhD, Service d'Ophtalmologie (pavillon 50A), CHRU de Bellevue, 25 Boulevard Pasteur, F 42055 Saint-Etienne Cedex 2, France. E-mail: philippe.gain@univ-st-etienne.fr.

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References

1. Deb N, Thuret G, Estour B, Massin P, Gain P: Screening for diabetic retinopathy in France. *Diabetes Metab* 30:140–145, 2004
2. Massin P, Erginay A, Ben Mehidi A, Vicaut E, Quentel G, Victor Z, Marre M, Guillausseau PJ, Gaudric A: Evaluation of a new non-mydriatic digital camera for detection of diabetic retinopathy. *Diabet Med* 20:635–641, 2003
3. Massin P, Aubert JP, Erginay A, Bourovitch JC, Benmehidi A, Audran G, Bernit B, Jamet M, Collet C, Laloi-Michelin M, Guillausseau PJ, Gaudric A, Marre M: Screening for diabetic retinopathy: the first telemedical approach in a primary care setting in France. *Diabetes Metab* 30: 451–457, 2004

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.

CELIA M. ROSS, MS

Address correspondence to Celia M. Ross, M.S., 36 Ridgewood Circle, Wilmington, DE 19809. E-mail: celiamaryross@aol.com.

References

1. Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP: The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care* 28:726–735, 2005
2. Decsi T, Minda H, Hermann R, Kozari A, Erhardt E, Burus I, Molnar S, Soltesz G: Polyunsaturated fatty acids in plasma and erythrocyte membrane lipids of diabetic children. *Prostaglandins Leukot Essent Fatty Acids* 67:203–210, 2002
3. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ: Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology* 62:275–280, 2004
4. Moriguchi T, Salem N Jr: Recovery of brain docosahexaenoate leads to recovery of spatial task performance. *J Neurochem* 87:297–309, 2003
5. Kitajka K, Sinclair AJ, Weisinger RS, Weisinger HS, Mathai M, Jayasooriya AP, Halver JE, Puskas LG: Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. *Proc Natl Acad Sci U S A* 101:10931–10936, 2004
6. Philbrick DJ, Mahadevappa VG, Ackman RG, Holub BJ: Ingestion of fish oil or a derived n-3 fatty acid concentrate containing eicosapentaenoic acid (EPA) affects fatty acid compositions of individual phospholipids of rat brain, sciatic nerve and retina. *J Nutr* 117:1663–1670, 1987

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.

AUGUSTINA M.A. BRANDS, MSC[1,2,3]
GEERT JAN BIESSELS, PHD, MD[1]
EDWARD H.F. DE HAAN, PHD[1,3]
L. JAAP KAPPELLE, PHD, MD[1]
ROY P.C. KESSELS, PHD[1,3]

From the [1]Department of Neurology, University Medical Center, Utrecht, the Netherlands; the [2]Department of Neuropsychology, Hofpoort Hospital/RPC, Woerden, the Netherlands; and [3]Helmholtz Instituut, Utrecht University, the Netherlands.

Address correspondence to Augustina M.A. Brands, Department of Neuropsychology, Hofpoort Hospital, Blekerijlaan 3, 3447 AC Woerden, The Netherlands. E-mail: i.brands@altrecht.nl.

References

1. Ross CM: Are fatty acids a link between diabetes and lowered cognitive performance? (Letter). *Diabetes Care* 28:2335, 2005
2. Brands AMA, Biessels GJ, de Haan EHF, Kappelle LJ, Kessels RPC: The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care* 28:726–735, 2005
3. Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ: Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology* 62:275–280, 2004
4. Tisserand DJ, Jolles J: On the involvement of prefrontal networks in cognitive ageing. *Cortex* 39:1107–1128, 2003

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 results 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.

ALI A. RIZVI, MD

From the Division of Endocrinology, Diabetes, and Metabolism, University of South Carolina School of Medicine, Columbia, South Carolina.

Address correspondence to Dr. Ali A. Rizvi, University of South Carolina School of Medicine, Division of Endocrinology, Diabetes, and Metabolism, 2 Medical Park, Suite 502, Columbia, SC 29203-6840. E-mail: arizvi@gw.mp.sc.edu.

References

1. Baldwin D, Villaneuva G, McNutt R, Bhatnagar S: Eliminating inpatient sliding-scale insulin: a reeducation project with medical house staff. *Diabetes Care* 28:1008–1011, 2005
2. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, Hirsch IB, the American Diabetes Association Diabetes in Hospitals Writing Committee: Management of diabetes and hyperglycemia in hospitals (Review). *Diabetes Care* 27:553–591, 2004

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

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-

tios or sensitivity factors. We are not sure that these are practical for busy general medical wards.

Our approach of using NPH and regular insulin twice daily (BID) is a basal-bolus approach to subcutaneous insulin therapy. BID NPH provides basal insulin and the bolus for lunch. BID regular insulin provides bolus insulin for breakfast and supper. This approach is completely different from sliding-scale regular insulin given every 6 h where basal insulin is never provided. Since we performed our study, the use of once-daily insulin glargine as basal insulin and three rapid-acting insulin analog mealtime boluses has become more commonly used. However, this regimen has been studied largely in type 1 diabetes. About 95% of our subjects and indeed most inpatients with hyperglycemia have type 2 diabetes.

Our blood glucose targets are described in the RESEARCH DESIGN AND METHODS section of our work. Dr. Rizvi misinterprets the use of HbA_{1c} (A1C) in our inpatients. As shown in Table 3 of our original article, the mean A1C in our study patients was 8.7% (2). An important goal of the teaching program with our residents was to use the opportunity presented by the hospitalization to improve diabetic therapy in all inpatients with A1C >7%. With our approach, we increased the percentage of patients who were discharged on improved therapy from 32 to 80%. This was associated with an improved A1C after 1 year, as seen in Fig. 3 in our original article. If sliding-scale regular insulin were the only regimen used for inpatient control of hyperglycemia, it would be impossible to titrate a new improved diabetic regimen (oral agent or insulin) on which to safely discharge the patient.

We have recently completed two studies of insulin glargine use in inpatients (3,4), and its applicability is promising. We are currently comparing the use of aspart versus regular insulin in an ongoing study of medical inpatients.

DAVID BALDWIN, MD
GRISELDA VILLANUEVA, ND
ROBERT MCNUTT, MD
SARIKA BHATNAGAR, MD

From the Section of Endocrinology, Rush University Medical Center, Chicago, Illinois.

Address correspondence to David Baldwin, MD, Section of Endocrinology, Rush University Medical Center, Suite 250, 1725 W. Harrison St., Chicago, IL 60612. E-mail: david_baldwin@rush.edu.

References

1. Rizvi AA: Eliminating inpatient sliding-scale insulin: a reeducation project with medical house staff (Letter). *Diabetes Care* 28:2336, 2005
2. Baldwin D, Villaneuva G, McNutt R, Bhatnagar S: Eliminating inpatient sliding-scale insulin: a reeducation project with medical house staff. *Diabetes Care* 28: 1008–1011, 2005
3. Baldwin D, Qaadir A, Villanueva G: Once daily insulin glargine vs. six hourly sliding scale regular insulin for control of hyperglycemia after bariatric surgery (Abstract). *Diabetes* 54 (Suppl. 1):A68, 2005
4. Yeldandi RR, Lurie A, Baldwin J, Baldwin D: Comparison of once daily glargine insulin with twice daily NPH/regular insulin for control of hyperglycemia in inpatients after cardiovascular surgery (Abstract). *Diabetes* 54 (Suppl. 1):A126, 2005