OBSERVATIONS

Postprandial Hyperglycemia Is a Better Predictor of the Progression of Diabetic Retinopathy Than HbA_{1c} in Japanese Type 2 Diabetic Patients

It is well known that postchallenge and postprandial hyperglycemia are related to the progression of diabetic macroangiopathy (1–6). However, there is little information regarding the association between diabetic microangiopathy and postprandial hyperglycemia in human subjects. In this study, we performed a follow-up study to elucidate the relationship between diabetic retinopathy and postprandial glycemia or insulinemia.

We recruited 151 Japanese patients with type 2 diabetes (74 men, aged 58.1 ± 10.2 years, and 77 women, aged 57.9 ± 9.2 years) who were admitted to Osaka Prefectural General Hospital between 1 January 1995 and 31 December 1999. The mean duration of diabetes of these patients was 7.4 ± 6.7 years. The mean BMI and HbA_{1c} (A1C) were 25.7 ± 4.4 kg/m^2 and 8.15 ± 1.51%, respectively. Eighty-three patients were treated with diet alone and 65 with oral hypoglycemic agents. Two to 4 days before admission, patients were given an oral glucose load of 75 g and postchallenge plasma glucose and insulin levels were determined 2 h later. Within 2–4 days after admission, postprandial plasma glucose and insulin levels were determined 2 h after the intake of an isocaloric mixed breakfast (10 kcal/kg body wt; 57% carbohydrate, 15% fat, and 28% protein), representative of a standard Japanese breakfast. Within a week after admission, retinopathy was assessed through dilated pupils by ophthalmologists. One hundred twenty-one subjects showed no evidence of diabetic retinopathy, 23 simple diabetic retinopathy, and 7 preproliferative retinopathy or proliferative retinopathy. After discharge from the hospital, subjects were followed prospectively for 5.0 ± 1.5 years.

During the follow-up periods, diabetic retinopathy worsened in 34 patients. Since A1C, postprandial plasma glucose and insulin, postchallenge plasma glucose and insulin, fasting plasma glucose and insulin, and duration of diabetes are closely linked, we performed multiple logistic model analyses, including sex, smoking, blood pressure, and serum lipid profile, to identify the independent and important predictors of the progression of diabetic retinopathy. Also, it is noted that in multiple regression analyses, the significance of several factors can be lost when there is a very close correlation among these several factors in addition to another factor having a stronger correlation. Postprandial plasma glucose levels (odds ratio 1.008, $P = 0.016$) correlated with the progression of diabetic retinopathy, and the significance in correlation between A1C levels and the progression of retinopathy was lost in our multiple regression analyses. These results indicate that postprandial hyperglycemia is a stronger predictor of the progression of diabetic retinopathy than A1C in Japanese type 2 diabetic patients. In addition, postprandial plasma insulin levels independently correlated with the progression of diabetic retinopathy (0.918, $P < 0.0001$) (Fig. 1). Thus, we assume that the control of excessive glucose excursions, especially in the postprandial state, may provide clinical benefit on not only carotid atherosclerosis but also diabetic retinopathy (7).

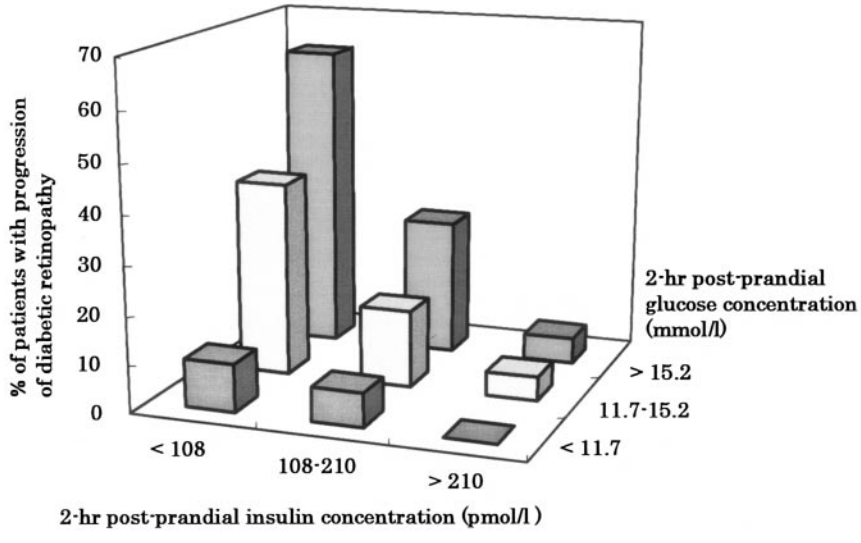

Figure 1—*Effects of 2-h postprandial insulin and glucose concentrations on the progression of diabetic retinopathy during a 5-year follow-up period according to tertiles of 2-h postprandial insulin and glucose concentrations.*

TOSHIHIKO SHIRAIWA, MD[1]
HIDEAKI KANETO, MD, PHD[1]
TAKESHI MIYATSUKA, MD, PHD[1]
KEN KATO, MD[1]
KAORU YAMAMOTO, MD[1]
AYAHA KAWASHIMA, MD[1]
TSUTOMU KANDA, MD, PHD[2]
MASAAKI SUZUKI, MD, PHD[2]
EIICHI IMANO, MD, PHD[2]
MUNEHIDE MATSUHISA, MD, PHD[1]
MASATSUGU HORI, MD, PHD[1]
YOSHIMITSU YAMASAKI, MD, PHD[1]

From the [1]Department of Internal Medicine and Therapeutics (A8), Osaka University Graduate School of Medicine, Suita City, Osaka, Japan; and the [2]Department of Gastroenterology and Metabolic Disease, Osaka Prefectural General Hospital, Sumiyoshi-ku, Osaka, Japan.

Address correspondence to Yoshimitsu Yamasaki, MD, PhD, Department of Internal Medicine and Therapeutics (A8), Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka, 565-0871, Japan. E-mail: yamasaki@medone.med.osaka-u.ac.jp.

References

1. Bonora E, Kiechi S, Oberhollenzer F, Egger G, Bonadonna RC, Muggeo M, Willeit J: Impaired glucose tolerance, type II diabetes and carotid atherosclerosis: prospective results from the Bruneck Study. *Diabetologia* 43:156–164, 2000
2. The DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–405, 2001
3. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL: Postchallenge hyperglycemia and mortality in a national

sample of U.S. adults. *Diabetes Care* 24: 1397–1402, 2001
4. The DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999
5. Bonora E, Muggeo M: Postprandial blood glucose as a risk factor for cardiovascular disease in type II diabetes: the epidemiological evidence. *Diabetologia* 44:2107–2114, 2001
6. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M, the STOP-NIDDM Trial Research Group: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003
7. Katherine Esposito, Dario Giugliano, Francesco Nappo, Raffaele Marfella, the Campanian Postprandial Hyperglycemia Study Group: Regression of carotid atherosclerosis by control of postprandial hyperglycemia in type 2 diabetes mellitus. *Circulation* 110:214–219, 2004

Glitazone in Diabetes

Relationship to patient dual public/private sector use

In its evidence-based guidelines for type 2 diabetes (1), the Veterans Health Administration (VHA) recommends a second-generation sulfonylurea or metformin as first-line drug therapy. Metformin or sulfonylurea is added to the first agent if HbA_{1c} (A1C) control is not satisfactory. Because of their modest effect on A1C, unknown long-term safety, and high cost, the VHA recommends reserving thiazolidinediones (glitazones) for selected patients. We compared community versus Veterans Affairs (VA) primary care providers regarding initiation of glitazone therapy and presence of contraindications in veterans, who frequently obtain care both within and outside the VHA.

Glitazone prescription at the Birmingham VA Medical Center (BVAMC) required endocrinology consultation in fiscal year 2002. Using the VHA's electronic medical record, we identified all consultations to the BVAMC endocrinology service in fiscal year 2002 and performed structured chart review. We assessed adherence to then-current guidelines for glitazone use, including *1*) failure of combination metformin-sulfonylurea therapy and patient refusal of insulin or *2*) insulin dose >75 units/day and A1C >1% above target.

We noted whether glitazone therapy was started by private physicians (110 patients) or by a request originating from within the VHA (65 patients). These two patient groups did not differ significantly in age, sex, or duration of diabetes. Insulin was tried before glitazone was initiated in 28% of patients treated within the VHA and 19% of those treated outside the VHA ($P = 0.178$). VHA physicians were more likely than community practitioners to have tried a metformin-sulfonylurea combination before rosiglitazone (74.4 vs. 44.4%, $P = 0.0005$). Of patients started on rosiglitazone within the VHA, 48.9% had A1C improvements of <0.5% (information unavailable for community physicians). However, VHA physicians used maximum rosiglitazone doses in only 17% of patients compared with 29% outside VHA. Heart failure was present in 12% of patients when rosiglitazone was requested, with no difference between community and VHA physicians in failing to recognize this contraindication ($P = 0.813$). From clinic notes, medication costs were the reason for seeking VHA care in 52% of patients whose glitazone had been initiated outside the VHA.

The differences between VHA and community physicians in initiating thiazolidinedione therapy may reflect differences in prescribing patterns across different systems. However, individuals treated in the community who found glitazones prohibitively expensive might have sought out the VHA. As we did, but in a more general population, Lederle and Parenti (2) documented that over half of veterans transferring to the VHA from community health care did so because of drug costs. Patients on less costly hypoglycemic regimens might be less likely to seek dual care. Therefore, we cannot easily extrapolate our findings to the entire private sector. Of note, medication costs contribute to poorer glycemic control in individuals with chronic illnesses (3). Piette et al. (4) found more medication underuse in patients with limited or no medication insurance than in VHA users.

In summary, we found that requests for initiating rosiglitazone were more guideline concordant when originating from within the VHA than from community physicians but that contraindications were not always recognized by either source. These expensive medications, the long-term safety of which is still unknown, may be significantly overused.

CHRISTINE M. HECKEMEYER, MD[1,2]
CATARINA I. KIEFE, MD, PHD[1,2,3]

From the [1]National Quality Scholars Program, Birmingham VA Medical Center, Birmingham, Alabama; the [2]Deep South Center on Effectiveness, Birmingham VA Medical Center, Birmingham, Alabama; and the [3]Division of Preventive Medicine, University of Alabama at Birmingham, Birmingham, Alabama.

Address correspondence to Christine M. Heckemeyer, MD, BVAMC Annex, Room 203, Mailbox no. B61, Birmingham VA Medical Center, 700 South 19th St., Birmingham, AL 35233. E-mail: christine.heckemeyer@med.va.gov.

References

1. The pharmacologic management of type 2 diabetes mellitus [article online], 1999. Available from http://www.vapbm.org/archive/DIABET0001.pdf. Accessed 2 March 2005
2. Lederle FA, Parenti CM: Prescription drug costs as a reason for changing physicians. *J Gen Intern Med* 9:162–163, 1994
3. Soumerai Sb, Avorn J, Ross-Degnan D, Gortmaker S: Payment restrictions for prescription drugs under Medicaid: effects on therapy, cost, and equity. *N Engl J Med* 317:550–556, 1999
4. Piette JD, Wagner TH, Potter MB, Schillinger D: Health insurance status, cost-related medication underuse, and outcomes among diabetes patients in three systems of care. *Med Care* 42:102–109, 2004

Observations on Online Services for Diabetes Management

Kwon et al. (1) demonstrated that an Internet-based blood glucose monitoring system, which provided frequent and responsive interactions between patients and their physicians online, can be as effective as face-to-face diabetes follow-ups. Routine medical services typically include face-to-face patient education, in which each patient receives his/her education materials (such as goals to achieve and the knowledge and skills for self-management). To extend patient education for a lasting effect, we have developed a patient-oriented education management (POEM) system (available at www.dmc.idv.tw) (2).

In the system, we reorganize each patient's education materials, medication data, and laboratory test results at every visit and then present the information on the Web. The system also provides reminders for the next follow-up with e-mails and short messages via cell phone. This way, the patient or his/her family can easily access the materials after leaving the hospital and constantly review medical care data and education materials for improvement of his/her diabetes condition.

To evaluate the system, we conducted an 8-month follow-up study. A total of 274 patients with type 2 diabetes were randomly recruited from the hospital: 134 (57% men and 43% women) in the experimental group (using the POEM system) and 140 (46% men and 54% women) in the control group. Subjects were aged 66.0 ± 8.5 and 61.2 ± 12 years in the experimental and control groups, respectively. Diabetes duration was 5.28 ± 4.70 and 7.01 ± 5.44 years in the experimental and control groups, respectively. Improvements in diabetes condition were evaluated by laboratory test results, including fasting blood glucose, HbA_{1c} (A1C), total cholesterol level, triglycerides, and HDL.

The test results (means ± SD) at the first visit for patients' fasting blood glucose, A1C, total cholesterol level, triglycerides, and HDL were 187.54 ± 77.10 and 189.99 ± 73.49 mg/dl, 9.03 ± 2.79 and 8.95 ± 2.23%, 193.29 ± 47.93 and 202.52 ± 58.45 mg/dl, 152.48 ± 70.85 and 157.37 ± 74.88 mg/dl, and 44.97 ± 12.09 and 45.32 ± 12.08 mg/dl in the experimental and control groups, respectively. During 8-month follow-ups, the average results of their fasting blood glucose, A1C, total cholesterol level, triglycerides, and HDL were 114.87 ± 46.98 and 130.29 ± 42.31 mg/dl, 7.38 ± 1.37 and 8.03 ± 1.55%, 169.18 ± 29.46 and 180.50 ± 38.95 mg/dl, 129.06 ± 58.50 and 137.13 ± 64.65 mg/dl, and 45.09 ± 14.02 and 44.27 ± 11.67 mg/dl in the experimental and control groups, respectively.

We performed ANCOVA on the laboratory test results of two groups from the pre- to postintervention periods. The *F* values of fasting blood glucose, A1C, and total cholesterol level were 7.898 (P = 0.005), 7.345 (P = 0.007), and 4.139 (P = 0.043), respectively. The results showed significant changes between the two groups: patients in the experimental group had better control than those in the control group.

Additionally, we monitored the number of monthly logins by patients during this period. The number of logins started with 9.6 ± 2.9/month per patient, slowly decreased in the following 3 months to 8.5 ± 3.7, and thereafter remained at that level with slight changes. Therefore, the POEM system can motivate patients and enhance the effect of patient education. Consequently, patients can improve the management of their diabetes.

Chien-Tsai Liu, phd[1]
Yu-Ting Yeh, rn[2]
Ting-I Lee, md[3]
Yu-Chuan Li, md, phd[1]

From the [1]Graduate Institute of Medical Informatics, Taipei Medical University, Taipei, Taiwan; the [2]Graduate Institute of Medical Sciences, Taipei Medical University, Taipei, Taiwan; and [3]Taipei Medical University, Wanfang Hospital, Taipei, Taiwan.

Address correspondence to Dr. Chien-Tsai Liu, Associate Professor, Graduate Institute of Medical Informatics, Taipei Medical University, 250 Wu-Xing St., Taipei, Taiwan. E-mail: ctliu@tmu.edu.tw.

References

1. Kwon HS, Cho JH, Kim HS, Song BR, Ko SH, Lee JM, Kim SR, Chang SA, Kim HS, Cha BY, Lee KW, Son HY, Lee JH, Lee WC, Yoon KH: Establishment of blood glucose monitoring system using the Internet. *Diabetes Care* 27:478–483, 2004
2. Yeh YT, Lee TI, Hsu CY, Long AJ, Li YC, Liu CT: A framework for integrating information of clinical care into patient education for diabetes. *Journal of Taiwan Association for Medical Informatics* 14:15–24, 2005

Serum Vitamin C Levels in Type 2 Diabetic Nephropathy

Serum vitamin C concentrations have been reported to be low in diabetic patients (1). Diabetic nephropathy is known to develop in diabetic individuals, and decreased renal function and hypertension could reportedly accelerate atherosclerosis in patients with type 2 diabetes (2). Observational epidemiologic studies showed an inverse relation between the dietary intake or serum levels of vitamin C and blood pressure (3). Although reduced concentrations of vitamin C were reported in type 2 diabetic retinopathy (4), the concentrations of serum vitamin C in type 2 diabetic patients with diabetic nephropathy have not been previously reported. The aim of the present study is to determine whether the concentrations of serum vitamin C have any relation to type 2 diabetic nephropathy. Since diabetic nephropathy is associated with low-grade inflammation (5), we also examined the inflammatory marker of high-sensitivity C-reactive protein (hs-CRP).

Forty-one type 2 diabetic subjects (age 35–65 years [average 55]) and 15 age- and sex-matched control subjects participated in the study. Any subject who smoked, took vitamins or nonsteroidal anti-inflammatory agents, or was receiving hormone replacement therapy was ineligible for the study. In addition, any patient with a history of macrovascular disease was excluded. Although vitamin C intake did not differ between type 2 diabetic patients and control subjects, serum vitamin C levels were found to be low in type 2 diabetic patients compared with control subjects (4.9 ± 0.3 vs. 6.8 ± 0.4 μg/ml, $P < 0.005$). Serum vitamin C levels significantly correlated with serum creatinine ($r = -0.43$, $P < 0.005$), log hs-CRP ($r = -0.36$, $P < 0.05$), and diastolic blood pressure ($r = -0.33$, $P < 0.05$) in diabetic subjects. No correlation was found between serum vitamin C levels and urinary albumin excretion levels in patients with diabetes. A stepwise multiple regression analysis demonstrated that both creatinine levels ($\beta = -1.232$, F value = 9.09) and log hs-CRP ($\beta = -6.335$, F value = 4.12) were independent determinants of serum vitamin C levels.

In type 2 diabetic patients, low levels of serum vitamin C were closely associated with concomitant renal dysfunction and low-grade inflammation.

Kenzo Iino, md[1,2]
Takuko Fukui, md[1]
Keizo Anzai, md[1]
Masanori Iwase, md[2]
Kazuhiko Kogawa, md[1]
Masaro Ogimoto, md[1]
Junko Ono, md[1]
Takashi Asano, md[1]
Mitsuo Iida, md[2]
Kazuo Tamura, md[1]

From [1]The First Department of Internal Medicine, School of Medicine, Fukuoka University, Fukuoka, Japan; and the [2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Address correspondence to Kenzo Iino, MD, De-

partment of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan Maidashi 3-1-1, Higashi-ku, Fukuoka City, 812-8582, Japan. E-mail: iinok@mist.ocn.ne.jp.

References

1. Will JC, Byers T: Does diabetes mellitus increase the requirement for vitamin C? *Nutr Rev* 54:193–202, 1996
2. Ishimura E, Shoji T, Emoto M, Motoyama K, Shinohara K, Matsumoto N, Taniwaki H, Inaba M, Nishizawa Y: Renal insufficiency accelerates atherosclerosis in patients with type 2 diabetes mellitus. *Am J Kidney Dis* 38 (4 Suppl. 1):S186–S190, 2001
3. Jacques PF: A cross-sectional study of vitamin C intake and blood pressure in the elderly. *Int J Vitam Nutr Res* 62:252–255, 1992
4. Sinclair AJ, Girling AJ, Gray L, Le Guen C, Lunec J, Barnett AH: Disturbed handling of ascorbic acid in diabetic patients with and without microangiopathy during high dose ascorbate supplementation. *Diabetologia* 34:171–175, 1991
5. Stehouwer CD, Gall MA, Twisk JW, Knudsen E, Emeis JJ, Parving HH: Increased urinary albumin excretion, endothelial dysfunction, and chronic low-grade inflammation in type 2 diabetes: progressive, interrelated, and independently associated with risk of death. *Diabetes* 51:1157–1165, 2002

Should She or Shouldn't She?

The relationship between infant feeding practices and type 1 diabetes in the genetically at risk

Now more than ever, women with type 1 diabetes are able to bear healthy children. Nevertheless, the concern that early infant nutrition plays a role in subsequent diabetes development in the offspring remains an important issue. Though we still do not know the exact causes of type 1 diabetes, recent research indicates that both genetic and environmental issues are contributing factors.

A possible link between early infant nutrition and the risk of developing type 1 diabetes is a topic of recent interest. The Trial to Reduce Type 1 Diabetes in the Genetically at Risk (TRIGR) is the first international, nutritional intervention, primary prevention study for type 1 diabetes. Specifically, the TRIGR study addresses whether the early ingestion of intact foreign proteins contained in cow's milk may increase type 1 diabetes risk (1,2). The TRIGR has been designed to evaluate the hypothesis that weaning infants to an extensively hydrolyzed formula may delay or prevent the onset of type 1 diabetes in genetically susceptible children. Additional smaller studies (3,4) suggest that other food intake with variations in timing, quantity, and combination may be linked to type 1 diabetes autoimmunity in the high-risk infant.

Recent studies have also taken a closer look at breastfeeding newborns of diabetic mothers (5). Initial results indicate that newborns ingesting breast milk from their diabetic mothers may have a higher risk of becoming overweight and developing impaired glucose tolerance in childhood than if they were fed nondiabetic donor breast milk.

Substantiating the premise of linking diet during infancy to the development of type 1 diabetes in those with a genetic risk calls for a very large properly designed trial such as the TRIGR. Given the challenges of ascertaining eligible subjects in order to achieve the desired sample size of 2,032, it is crucial that all health providers who care for pregnant women who themselves have type 1 diabetes, or if the father or sibling of the baby has type 1 diabetes, help refer subjects to the TRIGR in order for the study to succeed (available at www.TRIGR.org). Then and only then will we be able to answer the very important question: "Should she or shouldn't she?"

LISA M. ROGERS, PHD, RD[1]
LOIS JOVANOVIC, MD[2]
DOROTHY J. BECKER, MD[3]

From the [1]Division of Neonatology and Developmental Biology, Department of Pediatrics, David Geffen School of Medicine at UCLA and Mattel Children's Hospital, Los Angeles, California; the [2]Sansum Diabetes Research Institute, Santa Barbara, California; and the [3]Division of Endocrinology, Department of Pediatrics, University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania.

Address correspondence to Dr. Lisa M. Rogers, 10833 Le Conte Ave., Room B2-375 MDCC, Los Angeles, CA 90095-1752. E-mail: lrogers@mednet.ucla.edu.

L.M.R. and D.J.B. have received grant/research support from Mead Johnson.

References

1. Virtanen SM, Rasanen L, Ylonen K, Aro A, Clayton D, Langholz B, Pitkaniemi J, Savilahti E, Lounamaa R, Tuomilehto J, Åkerblom HK, the Childhood Diabetes in Finland Study Group: Early introduction of dairy products associated with increased risk of IDDM in Finnish children. *Diabetes* 42:1786–1790, 1993
2. Åkerblom HK, Virtanen SM, Ilonen J, Savilahti E, Vaarala O, Reunanen A, Teramo K, Hämäläinen AM, Paronen J, Riikjärv MA, Ormisson A, Ludvigsson J, Dosch HM, Hakulinen T, Knip M, the Finnish TRIGR Study Group: Dietary manipulation of beta-cell autoimmunity in infants at increased risk for type 1 diabetes. *Diabetologia* 48:829–837, 2005
3. Ziegler A-G, Schmid S, Huber D, Hummel M, Bonifacio E: Early infant feeding and risk of developing type 1 diabetes-associated autoantibodies. *JAMA* 290:1721–1728, 2003
4. Norris JM, Barriga K, Klingensmith G, Hoffman M, Eisenbarth GS, Erlich HA, Rewers M: Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA* 290:1713–1720, 2003
5. Rodekamp E, Harder T, Kohlhoff R, Franke K, Dudenhausen JW, Plagemann A: Long-term impact of breast-feeding on body weight and glucose tolerance in children of diabetic mothers: role of the late neonatal period and early infancy. *Diabetes Care* 28:1457–1462, 2005

COMMENTS AND RESPONSES

Pancreatic Elastase-1 in Stools, a Marker of Exocrine Pancreas Function, Correlates With Both Residual β-Cell Secretion and Metabolic Control in Type 1 Diabetic Subjects

Response to Cavalot et al.

There is increasing evidence that exocrine pancreatic function may be impaired in patients with type 1 diabetes (1,2). Cavalot et al. (3) found that

fecal pancreatic elastase-1 (PE-1) was significantly lower in 37 consecutive type 1 diabetic subjects than in 20 healthy control subjects. PE-1 values were directly correlated to C-peptide values and inversely correlated to HbA_{1c} (A1C) and diabetes duration. No correlation between BMI and PE-1 was found. The authors therefore concluded that both residual insulin secretion and glycemic control have relevant effects on exocrine pancreatic function in type 1 diabetic patients.

In contrast to these findings, we found no association between PE-1 values and A1C in our study population. Sixteen consecutive patients with type 1 diabetes (9 men and 7 women) followed at our unit were studied (age 30.8 ± 6.8 years, BMI 24.1 ± 3.5 kg/m^2, duration of diabetes 14.3 ± 10.6 years, A1C 7.7 ± 1.2% [means ± SD]). In addition, 16 age-, sex-, and BMI-matched healthy control subjects were examined. PE-1 concentrations in stools were determined by enzyme-linked immunosorbent assay (intra-assay variance 5.8%, interassay variance 7.7%; ScheBo-Tech). PE-1 concentrations >200 μg/g stools indicate normal exocrine pancreatic function, concentrations between 100 and 200 μg/g indicate mild exocrine pancreatic insufficiency, and concentrations <100 μg/g indicate severe exocrine pancreatic insufficiency.

The PE-1 concentrations of patients with type 1 diabetes were significantly reduced compared with control subjects (244.1 ± 192.6 vs. 515.1 ± 174.2 μg/g stools, $P < 0.003$). Six patients (four men and two women) had PE-1 concentrations between 100 and 200 μg/g stools, three patients (one man and two women) had PE-1 levels <100 μg/g stools, and one patient had PE-1 levels <200 μg/g stools. In diabetic patients, there were no correlations between PE-1-values and diabetes duration ($r = 0.07$, $P = 0.79$), age ($r = -0.20$, $P = 0.47$), A1C ($r = -0.26$, $P = 0.32$), or BMI ($r = 0.27$, $P = 0.30$). In patients with A1C >8% ($n = 5$), PE-1 did not differ from those with A1C ≤8% ($n = 11$) (214.6 ± 263.6 vs. 257.4 ± 165.1 μg/g stools, $P = 0.69$). Among patients with A1C >8%, 4 of 5 patients had PE-1 concentrations <200 μg/g stools compared with 5 of 11 with A1C <8% ($P = 0.59$).

The main finding of our study is that PE-1 is significantly lower in type 1 diabetic subjects and confirms the frequent occurrence of an exocrine pancreas deficiency in these patients. These results are consistent with those of Cavalot et al.; however, we did not find any association between PE-1 values and A1C and diabetes duration. There is no mention of comedication with antihypertensive agents or other medications in the Cavalot et al. study. Recent data demonstrate the existence of an islet angiotensin-generating system of potential importance on exocrine pancreatic function (4). Therefore, antihypertensive agents interfering with the angiotensin system could influence exocrine pancreatic function (5). In our study, 5 of 16 patients were treated with antihypertensive agents (ACE inhibitors in 4 and an angiotensin II receptor blocker in 1). These five subjects had lower PE-1 values than patients without such treatment (121.1 ± 83.3 vs. 299.9 ± 204 μg/g stools), although the difference was not statistically significant ($P = 0.088$).

Bruno Mueller, md
Fajfr Radko, md
Peter Diem, md

From the Endocrine and Diabetes Division, University of Bern, Inselspital, Bern, Switzerland.

Address correspondence to Bruno Mueller, MD, Endocrine and Diabetes Division, University of Bern, Inselspital, 3010 Bern, Switzerland. E-mail: bruno.mueller@insel.ch.

References

1. Icks A, Haastert B, Giani G, Rathmann W: Low fecal elastase-1 in type 1 diabetes mellitus. *Z Gastroenterol* 39:823–830, 2001
2. Hardt PD, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, Bretzel RG, Hollenhorst M, Kloer HU, the S2453112/S2453113 Study Group: High prevalence of exocrine pancreatic insufficiency in diabetes mellitus: a multicenter study screening fecal elastase 1 concentrations in 1,021 diabetic patients. *Pancreatology* 3:395–402, 2003
3. Cavalot F, Bonomo K, Perna P, Bacillo E, Salacone P, Gallo M, Mattiello L, Trovati M, Gaia E: Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual β-cell secretion and metabolic control in type 1 diabetic subjects (Brief Report). *Diabetes Care* 27:2052–2054, 2004
4. Leung PS, Chappell MC: A local pancreatic renin-angiotensin system: endocrine and exocrine rolls. *Int J Biochem Cell Biol* 35:838–846, 2003
5. Lau T, Carlsson PO, Leung PS: Evidence for a local angiotensin-generating system and dose-dependent inhibition of glucose-stimulated insulin release by angiotensin II in isolated pancreatic islets. *Diabetologia* 47:240–248, 2004

Pancreatic Elastase-1 in Stools, a Marker of Exocrine Pancreas Function, Correlates With Both Residual β-Cell Secretion and Metabolic Control in Type 1 Diabetic Subjects

Response to Mueller et al.

We thank Mueller et al. (1) for their interest in our article (2), in which we demonstrated that type 1 diabetic patients present low fecal pancreatic elastase-1 (PE-1) and that PE-1 correlates with C-peptide, HbA_{1c} (A1C), and diabetes duration. In 16 type 1 diabetic patients, they found that PE-1 concentrations were low compared with control subjects but did not correlate with A1C and diabetes duration.

Furthermore, Mueller et al. observed that patients on drugs interfering with the angiotensin system show a further reduction of PE-1. Since we did not mention treatment with these drugs in our report, we now provide this information. Eight of our 37 type 1 diabetic patients were on ACE inhibitors. PE-1 was lower in patients on ACE inhibitors (135.2 ± 25.9 vs. 297.9 ± 35.3 μg/g stools, $P = 0.0211$), confirming the observation of Mueller et al. Also, in patients not on ACE inhibitors, PE-1 correlated with A1C ($r = -0.490$, $P = 0.007$), diabetes duration ($r = -0.400$, $P = 0.0325$), and C-peptide ($r = 0.540$, $P = 0.0028$).

Thus, we confirm in this subgroup the correlation between A1C and PE-1 already described in our whole series (2). On the other hand, it is interesting to observe that in the series of Mueller et al., 4 of the 5 patients with A1C >8% presented PE-1 <200 μg/g stools compared with 5 of the 11 patients with A1C <8% (i.e., 80 vs. 45%), suggesting that blood glucose control also influenced, in some way, PE-1 in their patients. But why did patients on ACE inhibitors show low PE-1 values? Mueller et al. suggest a role for the inhibition of the local angiotensin-

generating system, which has been described in pancreas (3). This hypothesis is intriguing. It should not be forgotten, however, that ACE inhibitors are prescribed to cure hypertension and/or microalbuminuria, which depend at least in part on diabetes duration and glycemic control, which influence PE-1 per se. When our 8 patients on ACE inhibitors were compared with the other 29, they presented a longer diabetes duration (15.8 ± 3.2 vs. 8.9 ± 1.3 years, $P = 0.0388$) and a trend to higher A1C (8.9 ± 0.53 vs. 7.9 ± 0.26%, $P = 0.07$) and lower C-peptide (0.08 ± 0.023 vs. 0.36 ± 0.089 ng/ml, $P = 0.46$). Their lower PE-1 values, therefore, could also be attributed to these factors and not only to a putative inhibitory effect of ACE inhibitors on exocrine pancreas function. In conclusion, we provide further evidence that in our series, PE-1 correlates with A1C. Furthermore, we confirm that type 1 diabetic patients on ACE inhibitors show lower PE-1 concentrations and thank Mueller et al. for their interest in our work and for the intriguing suggestion concerning the relationship between PE-1 and ACE inhibition.

FRANCO CAVALOT, MD[1]
KATIA BONOMO, MD[1]
ELISA FIORA, MD[1]
EZIO GAIA, MD[2]
MARIELLA TROVATI, MD[1]

From the [1]Diabetes Unit, Department of Clinical and Biological Sciences, University of Turin, San Luigi Gonzaga Hospital, Orbassano (Turin), Italy; and the [2]Gastroenterology Unit, Department of Internal Medicine, San Luigi Gonzaga Hospital, Orbassano (Turin), Italy.

Address correspondence to Prof. Mariella Trovati, MD, Diabetes Unit, Department of Clinical and Biological Sciences of the University of Turin, San Luigi Gonzaga Hospital, 10043 Orbassano (Turin), Italy. E-mail: mariella.trovati@unito.it.

References

1. Mueller B, Radko F, Diem P: Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual β-cell secretion and metabolic control in type 1 diabetic subjects (Letter). *Diabetes Care* 28:2809–2810, 2005
2. Cavalot F, Bonomo K, Perna P, Bacillo E, Salacone P, Gallo M, Mattiello L, Trovati M, Gaia E: Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual β-cell secretion and metabolic control in type 1 diabetic subjects (Brief Report). *Diabetes Care* 27:2052–2054, 2004
3. Leung PS, Chappell MC: A local pancreatic renin-angiotensin system: endocrine and exocrine roles. *Int J Biochem Cell Biol* 35:838–846, 2003

Initiation of Insulin Therapy in Patients With Type 2 Diabetes Failing Oral Therapy

Response to Mikhail and Cope and to Janka

In a recent editorial (1), Davidson commented on two studies (2,3) in which insulin initiation using a basal insulin analog was compared with either a human insulin premix or an analog insulin premix. These articles have prompted further correspondence concerning the design and results of these studies (4,5).

Mikhail and Cope (4) and Janka (5) commented that the greater HbA_{1c} reduction observed in patients taking biphasic insulin aspart 70/30 (BIAsp 70/30), as compared with insulin glargine, may be attributed to a greater dose of BIAsp 70/30. They suggested that glargine was not titrated to the fullest extent in the INITIATE study. However, the fasting blood glucose values achieved with titration of the evening dose of glargine were the same in the INITIATE, Treat-to-Target (6), zand Janka et al. (2) studies (from 117 to 115 mg/dl). These blood glucose values, as well as those for the BIAsp 70/30 in INITIATE, were slightly above the targeted fasting glucose values and suggest a reluctance by clinicians to titrate insulin to the fullest extent. It is not surprising that there was a greater BIAsp 70/30 dose, as there was a second insulin injection to titrate. The administration of twice-daily BIAsp 70/30 during INITIATE provided coverage of postprandial glycemia during breakfast and the evening meal, often the biggest meals of the day. With the growing acceptance of the importance of postprandial glycemia on overall glycemic control, a premix analog insulin has the advantage over a single basal injection of targeting and reducing postprandial glucose excursions.

With a greater insulin dose, more hypoglycemia and weight gain might be expected. However, no subjects in the BIAsp 70/30 group had a major hypoglycemic episode, nor did any withdraw from the study because of hypoglycemia. Therefore, hypoglycemia was not an impediment to the pursuit of glycemic control for the BIAsp 70/30 group, which had a greater percentage of patients reach the target HbA_{1c} of <7%, compared with the glargine group (66 vs. 40%, respectively).

As aptly stated in the Davidson editorial, the most important factor in initiating insulin therapy is to "intensify the approach until targets are achieved and then to maintain them." With the success rate observed in the INITIATE study, the premixed formulation of BIAsp 70/30 clearly is a viable option for initiating insulin therapy and for achieving glycemic targets in a majority of insulin-naïve patients with type 2 diabetes.

PHILIP RASKIN, MD

From the Department of Internal Medicine, Southwestern Medical Center at Dallas, University of Texas, Dallas, Texas.

Address correspondence to Dr. Philip Raskin, University of Texas, Southwestern Medical Center at Dallas, Department of Internal Medicine, 5323 Harry Hines Blvd., Dallas, TX 75235-8858. E-mail: philip.raskin@utsouthwestern.edu.

References

1. Davidson MB: Starting insulin therapy in type 2 diabetic patients: does it really matter how? (Editorial). *Diabetes Care* 28:494–495, 2005
2. Janka HU, Plewe G, Riddle MC, Kliebe-Frisch C, Schweitzer MA, Yki-Järvinen H: Comparison of basal insulin added to oral agents versus twice-daily premixed insulin as initial insulin therapy for type 2 diabetes. *Diabetes Care* 28:254–259, 2005
3. Raskin P, Allen E, Hollander P, Lewin A, Gabbay RA, Hu P, Bode B, Garber A, the INITIATE Study Group: Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 28:260–265, 2005
4. Mikhail NE, Cope D: Initiation of insulin in patients with type 2 diabetes failing oral therapy (Letter). *Diabetes Care* 28:1537–1538, 2005
5. Janka HU: Initiation of insulin in patients with type 2 diabetes failing oral therapy (Letter). *Diabetes Care* 28:1538, 2005
6. Riddle MC, Rosenstock J, Gerich J, the Insulin Glargine 4002 Study Investigators: The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 26:3080–3086, 2003

No Independent Association of Alanine Aminotransferase With Risk of Future Type 2 Diabetes in the Hoorn Study

We read with great interest the article by Nannipieri et al. (1), which reported no association between aspartate aminotransferase, alanine aminotransferase (ALT), or alkaline phosphatase and the 7-year incidence of impaired glucose tolerance and type 2 diabetes. Interestingly, γ-glutamyltransferase was, but ALT was not, a significant predictor of impaired glucose tolerance or type 2 diabetes. This is, as the authors stated, in contrast to previously published papers that found significant prospective associations of ALT with incident type 2 diabetes after adjustment for obesity, insulin sensitivity, or inflammation (C-reactive protein) (2–4). We studied the baseline ALT enzyme activity in relation to 6-year incident type 2 diabetes in the Hoorn Study, a population-based cohort study of glucose tolerance among Caucasian men and women (5). Glucose tolerance was assessed by oral glucose tolerance test at baseline and after 6.4 years of follow-up. The study methods were similar to the Mexico City Diabetes Study described by Nannipieri et al. (1), with the exception that the participants of the Hoorn Study were ~15 years older at baseline (5). Of the 1,289 subjects free of type 2 diabetes at baseline, 123 developed type 2 diabetes during follow-up. We found that ALT was a significant predictor of type 2 diabetes only in the models adjusted for age, sex, and follow-up duration, with an odds ratio of 2.18 (95% CI 1.29–3.69) for subjects in the upper tertile versus those in the lower tertile. However, after additional adjustment for waist circumference, BMI, alcohol consumption, fasting plasma insulin levels, and 2-h postload glucose levels, the association attenuated and lost significance (1.18 [0.66–2.11]). The other liver enzymes were not determined in the Hoorn Study.

Thus, in accordance with the report by Nannipieri et al. (1), but in contrast to the findings by others, we found that ALT was not an independent predictor of incident type 2 diabetes in the Hoorn study. We think it is important to report these findings, since we cannot exclude the possibility of publication bias leading to overrepresentation of studies showing an independent relationship between liver enzymes and risk of type 2 diabetes. The observed association between ALT and incident type 2 diabetes in several published reports may be explained by the fact that these studies were performed in selected populations, i.e., in high-risk populations and may not be representative for the general population. An alternative explanation is that the applied models overadjust for potential mediating variables such as insulin and 2-h glucose, factors that might be directly related to liver fat. To increase the insight into the role of liver fat in the pathophysiology of the metabolic syndrome and type 2 diabetes, further studies are needed to assess the underlying mechanisms. The role of oxidative stress, as hypothesized by Nannipieri et al. (1), as well as the contribution of inflammation should be explored in large-scaled prospective studies.

ROGER K. SCHINDHELM, BSC, MD[1]
JACQUELINE M. DEKKER, PHD[2]
GIEL NIJPELS, MD, PHD[2,3]
ROBERT J. HEINE, MD, PHD[1,2]
MICHAELA DIAMANT, MD, PHD[1]

From the [1]Department of Endocrinology, VU University Medical Center, Amsterdam, the Netherlands; the [2]Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, the Netherlands; and the [3]Department of General Practice, VU University Medical Center, Amsterdam, the Netherlands.

Address correspondence to Roger K. Schindhelm, VU University Medical Center, Department of Endocrinology, P.O. Box 7007, 1007 MB Amsterdam, Netherlands. E-mail: rk.schindhelm@vumc.nl.

References

1. Nannipieri M, Gonzales C, Baldi S, Posadas R, Williams K, Haffner SM, Stern MP, Ferrannini E: Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico City Diabetes Study. *Diabetes Care* 28:1757–1762, 2005
2. Vozarova B, Stefan N, Lindsay RS, Saremi A, Pratley RE, Bogardus C, Tataranni PA: High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 51:1889–1895, 2002
3. Hanley AJ, Williams K, Festa A, Wagenknecht LE, D'Agostino RB Jr, Kempf J, Zinman B, Haffner SM: Elevations in markers of liver injury and risk of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. *Diabetes* 53:2623–2632, 2004
4. Sattar N, Scherbakova O, Ford I, O'Reilly DS, Stanley A, Forrest E, Macfarlane PW, Packard CJ, Cobbe SM, Shepherd J: Elevated alanine aminotransferase predicts new-onset type 2 diabetes independently of classical risk factors, metabolic syndrome, and C-reactive protein in the West of Scotland Coronary Prevention Study. *Diabetes* 53:2855–2860, 2004
5. Mooy JM, Grootenhuis PA, de Vries H, Valkenburg HA, Bouter LM, Kostense PJ, Heine RJ: Prevalence and determinants of glucose intolerance in a Dutch Caucasian population: the Hoorn Study. *Diabetes Care* 18:1270–1273, 1995