OBSERVATIONS

Ethnic Differences in β-Cell Functional Reserve and Clinical Features in Patients With Ketosis-Prone Diabetes

Diabetic ketoacidosis (DKA) has been reported in subjects who lack the clinical characteristics of type 1 diabetes (1–3). In a preliminary analysis of the "types" of diabetes in patients presenting with DKA, we found that Hispanic patients had a significantly higher proportion with type 2 diabetes when compared with Caucasians and African Americans (1).

We performed a prospective analysis to compare demographic and clinical characteristics among ketosis-prone indigent subjects belonging to these three ethnic groups. We interviewed 271 consecutive patients at the time of admission for DKA over a 3-year period. Fasting serum C-peptide and glucose levels were measured in all patients after resolution of the ketoacidosis. Pearson's χ^2 test or one-way ANOVA were used, as appropriate, to evaluate group differences. Fasting serum C-peptide levels have been used to distinguish subjects with preserved β-cell function from those with absent β-cell function. We used a cutoff level of 0.33 nmol/l to separate these groups. This serum C-peptide concentration is widely accepted as a cutoff value in the literature (4), and we confirmed this by using receiver operator curve analysis in comparison with the area under the curve for C-peptide response to glucagon stimulation (3). A multivariate analysis was also performed to evaluate factors predictive of fasting C-peptide ≥0.33 nmol/l.

Of the 271 subjects admitted with DKA, 44% were African American, 40% Hispanic, and 16% Caucasian. The proportion of subjects admitted for DKA associated with new-onset diabetes was very similar among all three ethnic groups: 27–28%. However, only 44% of the Hispanic subjects were admitted with DKA secondary to noncompliance with the prescribed treatment for diabetes, as compared with 61% in the African Americans and 57% in the Caucasians (P = 0.01).

The Hispanic group had a significantly higher C-peptide level, 0.41 ± 0.35 nmol/l, compared with 0.25 ± 0.45 in the African American and 0.24 ± 0.32 in the Caucasian groups (P = 0.007). A significantly higher proportion of Hispanics (56%) compared with African Americans (29%) and Caucasians (32%) had a fasting plasma C-peptide level ≥0.33 nmol/l. The C-peptide–to–glucose ratios were 0.038 ± 0.021, 0.02 ± 0.029, and 0.024 ± 0.034 nmol/mmol, respectively, for the Hispanic, African-American, and Caucasian groups (P = 0.0004). In the multivariate analysis, Hispanic ethnicity (odds ratio 3.92, 95% CI: 1.96–8.12), duration of known diabetes <6 months (3.69, 1.57–8.76), and BMI ≥30 kg/m^2 (5.70, 2.61–13.04) were significant predictors of fasting plasma C-peptide ≥0.33 nmol/l.

In summary, this prospective analysis of ketosis-prone diabetes shows that, compared with Caucasian and African-American patients, Hispanic patients are more likely to have better preserved β-cell functional reserve, as assessed by a fasting serum C-peptide concentration ≥0.33 nmol/l and by the C-peptide–to–glucose ratio. These differences suggest that there is a higher frequency of ketosis-prone type 2 diabetes among Hispanics than among Caucasians and African Americans in this cohort of indigent subjects. Ethnic comparisons of β-cell function and insulin sensitivity in ketosis-prone diabetes are needed to better understand this syndrome.

MARIO R. MALDONADO, MD[1,2]
MAX E. OTINIANO, MD[1,2]
REBEKAH LEE, PA[1]
LUCILLE RODRIGUEZ, LVN[2]
ASHOK BALASUBRAMANYAM, MD[1,2]

From the [1]Department of Medicine/Endocrinology, Baylor College of Medicine, Houston, Texas; and [2]Endocrine Service, The Ben Taub General Hospital, Houston, Texas.

Address correspondence to Mario R. Maldonado, MD, Baylor College of Medicine, Department of Medicine/Endocrinology, 1 Baylor Plaza, Room 537E, Houston, TX 77030. E-mail: mariom@bcm.tmc.edu.

References

1. Balasubramanyam A, Zern JW, Hyman DJ, Pavlik V: New profiles of diabetic ketoacidosis: type 1 vs type 2 diabetes and the effect of ethnicity. *Arch Intern Med* 159:2317–2322, 1999
2. Umpierrez GE, DiGirolamo M, Tuvlin JA, Isaacs SD, Bhoola SM, Kokko JP: Differences in metabolic and hormonal milieu in diabetic- and alcohol-induced ketoacidosis. *J Crit Care* 15:52–59, 2000
3. Maldonado M, Hampe C, Iyer D, Rajan A, Hammerle L, Lermark A, Balasubramanyam A: Clinical and biologic heterogeneity of diabetes presenting with ketoacidosis (Abstract). *Diabetes* 50 (Suppl. 2):A262, 2001
4. Landin-Olsson M, Nilsson KO, Lernmark A, Sundkvist G: Islet cell antibodies and fasting C-peptide predict insulin requirement at diagnosis of diabetes mellitus. *Diabetologia* 33:561–568, 1990

Modulation of Oxidative and Antioxidative Status in Diabetes by Asphaltum Panjabinum

Oxidative stress in diabetes, a common metabolic disorder, damages organs, including the β-cells of the islets of Langerhans. In an ancient, traditional system of medicine, Asphaltum panjabinum (shilajit) (1) has been reported to possess an adaptogenic activity (2) (a rasayan), which reverts a pathological state to a physiological one with increased nonspecific resistance.

The present study was conducted in 61 diabetic subjects of either sex, aged 31–70 years, who were on unchanged dosages of glibenclamide and served as their own control subjects. Shilajit was administered as two capsules (500 mg each; Dabir India) twice daily for 30 days.

Treatment with shilajit exhibited a significant decrease in values of malondialdehyde (6.52 ± 1.68 nmol/ml plasma) compared with their higher pretreatment values (15.56 ± 5.40 nmol/ml plasma), whereas values of catalase in diabetic subjects (2,814.22 ± 737.49 μmol/ml hemolysate) were significantly increased after

treatment with shilajit (3,151.68 ± 158.41 μmol/ml hemolysate). However, values of superoxide dismutase (SOD) (8.55 ± 4.48 μmol/l hemolysate) and glutathione peroxidase (3.29 ± 1.02 μmol/ml hemolysate) in diabetic subjects were reduced after shilajit treatment (5.57 ± 3.26 μmol/l and 1.71 ± 0.28 μmol/ml hemolysate, respectively).

Shilajit has been reported to be a panacea for variety of diseases in Asian medicine (3). In humans, there is limited evidence concerning the role of free radicals and antioxidants in diabetes (4). This is the first clinical study with shilajit to show its effect on antioxidant activity in diabetic subjects. These observations are supported by in vitro (5) and liver homogenate (6) experimental models (in animals).

It appears that shilajit, being an adaptogen, reverses this process by resetting defective electron transport chain reactions. Thus, it decreases the increased turnover of superoxide anion, as is reflected by the decreased demand of SOD. Upregulation of catalase activity in the initial phases perhaps obviates the need for antioxidant enzymes in later steps.

Overall, shilajit results in the reduction of lipids per oxidation. Thus, processed shilajit may be of value as a dietary supplement for modulating diabetes status, as well as for the prevention of diabetes complications, which is a real challenge for the present-day diabetologist.

NIDHI SAXENA, PHD[1]
UPENDRA N. DWIVEDI, PHD[1]
RAJ K. SINGH, PHD[2]
ARVIND KUMAR, MD[3]
CHHAVI SAXENA, MSC, BAMS[4]
RAM C. SAXENA, MD[5]
MONA SAXENA, PHD[6]

From the [1]Department of Biochemistry, Lucknow University, Lucknow, Uttar Pradesh, India; the [2]Department of Biochemistry, CSSM Medical University, Lucknow, Uttar Pradesh, India; the [3]Department of Medicine, CSSM Medical University, Lucknow, Uttar Pradesh, India; the [4]State Ayurvedic Medical College, Lucknow University, Lucknow, Uttar Pradesh, India; the [5]Department of Pharmacology, Kothiwal Dental College and Research Center, Moradabad, Uttar Pradesh, India; and the [6]Center of Biomedical Magnetic Resonance, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India.

Address correspondence to Nidhi Saxena, MSc, PhD, Department of Biochemistry, 417/214, Ram Lodge, Newaz Ganj, Lucknow, Uttar Pradesh 226003, India. E-mail: rajendranidhi@yahoo.co.in.

References

1. Joshi JP: Shilajit vigyan. In *Vidhya Bhawan Granthmala No. 16*. Varanasi, India, Choukhambha Vidhya Bhawan, 1957 p. 1
2. Breakhman II, Dardimov IV: New substances of plant origin which increase non-specific resistance. *Ann Rev Pharmacol* 9:419, 1969
3. Ghosal S, Lal J, Singh SK: Shilajit part 8: the core structure of shilajit humus. *Soil Biol Biochem* 23:673–680, 1991
4. Singh RB, Rastogi SS: CHD in diabetes: pathogenesis: impact of diet and anti-oxidants. In *Postgraduate Medicine of Association of Physicians of India*. Vol. 12. Manoria PC, Ed. 1998, p. 40–49
5. Ghosal S, Bhattacharya S: Antioxidant defense by native and processed Shilajit: a comparative study. *Ind J Chem* 35:B127–B132, 1996
6. Tripathi YB, Shukla S, Chaurasia S: Antilipid peroxidative property of Shilajit. *Phytother Res* 10:269–270, 1996

The Use of Complementary and Alternative Medicine Therapies in Type 2 Diabetic Patients in Mexico

The growing utilization of complementary and alternative medicine (CAM) therapies represents one of the characteristic phenomena facing scientific medicine. Studies of the patient's opinions and attitudes toward CAM therapies are scarce. Among doctors, it is widely considered that the use of CAM therapies is only linked to a particular social or cultural background. We undertook a cross-sectional study designed to evaluate the spontaneous use of CAM therapies among 573 type 2 diabetic patients (aged 51.9 ± 10 years) in nine family medicine clinics in Mexico City, using a questionnaire form.

Almost 62% (353) of participants make use of CAM therapies, a higher percentage than that reported in the U.S. (8%) and Canada (37.3%). Our patients were younger, more likely to be women, less educated, and were all members of the public insurance system. Sixty-four percent did not disclose this practice to their physician, while 57% of American diabetic patients discussed CAM therapies with their physicians. Among Mexicans, the decision to use CAM therapies proceeded mainly from the patient's domestic environment (69%), while in only 8% of cases the treatment was recommended by physicians and nurses. Paradoxically, American diabetic subjects had CAM therapy recommended by their doctors and nurses in almost 43% of cases, a difference that reflects the general disregard of doctors who respect CAM therapies in Mexico, regardless of the local culture. Mexican patients who use CAM therapies prefer herbal remedies (332 [94.2%]), while the remaining 5.8% use other treatments. In Mexico the use of plants has a long historical tradition, while in the U.S. only 20% of diabetic subjects use herbal medicine (1). In Mexico, the cactus *Opuntia* is the favorite plant remedy among the majority of patients (73.1%) as a "traditional indigenous" treatment of type 2 diabetes. The *Opuntia* medicinal properties have already been scientifically evaluated and the hypoglycemic effect of its sap confirmed in clinical studies (2). Nevertheless, patients ignore the sum of effects that may occur during the simultaneous use of more than one hypoglycemic agent, or other potentially toxic effects (*Medicago sativa, Taraxacum officinale,* stigma of *Zea mays,* and *Equistem robustum* are considered diuretics; *Clematis dioca, Tamarindus indica*, *Rhamnus purshiana,* and *Carica papaya* are used as laxatives; and the leaves of *Physalis, Phoradedron,* and *Calea* are considered toxic but were used by 14 [4.2%] patients in this sample) (3).

This situation confirms that studies are required to determine the impact of CAM therapies, especially that of widespread popular herbal remedies, on diabetes management instead of ignoring the sociomedical phenomena taking place in our societies.

NICOLAS ARGÁEZ-LÓPEZ, MD[1]
NIELS H. WACHER, MD, MSC[1]
JESUS KUMATE-RODRÍGUEZ, MD, PHD[2]
MIGUEL CRUZ, PHD[2]
JUAN TALAVERA, MD, MSC[1]
ERIKA RIVERA-ARCE, PHD[3]
DR. XAVIER LOZOYA[3]
FOR THE DIMSS STUDY GROUP

From the [1]Unidad de Investigación Médica en Epidemiología Clínica, Hospital de Especialidades, Mexico City, Mexico; the [2]Unidad de Investigación Médica en Bioquímica, Hospital de Especialidades, Mexico City, Mexico; and the [3]Laboratorio de Plantas Medicinales, Hospital de Especialidades, Mexico City, Mexico.

Address correspondence to Niels Wacher, Unidad de Investigacion Medica en Epidemiologia Clinica, Hospital de Especialidades. CMN SXXI IMSS, Cuauhtemoc, Col, Doctores, Mexico. E-mail: nwacher@hotmail.com.

APPENDIX

The DIMSS Study Group: Margarita Jiménez, BSc,[A] José Halabe, MD, [A] Raúl Ariza, MD,[B] Héctor Fierro, MD,[A] Carlos Cuevas, MD,[A] Carlos Velasco, MD,[B] Moisés Mercado, MD,[A] Juan Garduño, MD, MSc,[C] Norma Juárez-Diaz, MD,[A] and Manuel de la Llata, MD,[D]; from UMF6: Anastasio Tapia, MD, and Elvira Rodriguez, MD; from UMF9: Luis Piñeiro, MD, Sandra Meléndez, MD, and Olivia Ruvalcaba, MD; from UMF11: Martin Gil Candelaria, MD, and Jesús Sánchez, MD; from UMF15: Laura Baillet, MD, and Antonio Gómez, MD; from UMF21: Martha Boijsseneau, MD, Bertha López-Castillejos, MD, and Maricela Garcia, MD; from UMF22: Mirella Gamiochipi, MSc; from UMF31: Patricia Vallejo, MD, and Mario Valencia, MD; from UMF34: Isabel Hernández, MD, Ida Báez-Toquiantzi, MD, and Rogelio Huerta, MD; and from UMF94: Ana Marin Cortés, MD, Rosa Ceja, MD, and Etelvina Zavala, MD.

[A]Hospital de Especialidades Centro Médica Nacional Siglo XXI; [B]Hospital de Especialidades Centro Médico "La Raza"; [C]Coordinación de Atención Médica, IMSS; [D]Hospital de Cardiologia "Luis Méndez" Centro Médico Siglo XXI.

References

1. Edge L, Ye X, Zheng D, Silverstein M: The prevalence and pattern of complimentary and alternative medicine use in individuals with diabetes. *Diabetes Care* 25:324–329, 2002
2. Frati A, Xilotl Diaz N, Altamirano P, Ariza R, Lopez-Ledesma R: The effect of two sequential doses of Opuntia streptacantha upon glycemia. *Arch Invest Med* 22:333–336, 1991
3. Gori M, Campbell R Natural products and diabetes treatment (Review Article). *Diabetes Educ* 24:201–202, 1998

Case Study: Metformin-Associated Lactic Acidosis

Could orlistat be relevant?

Lactic acidosis is a rare (1) but serious complication of metformin therapy with a high fatality rate (2). In the majority of reported cases there is a preexisting disease, most often a degree of renal impairment. We present a case of metformin-associated lactic acidosis (MALA) where drug interactions (orlistat in the long term and cimetidine over a short period of time) may have potentiated the condition.

A 59-year-old woman with type 2 diabetes for 14 years presented with a history of 3 months of vague abdominal pain and four to five loose bowel movements daily, which worsened over the 4 days before admission to hospital. On the day of admission she reported weakness, dizziness, and blurred vision. Her husband had noticed slurred speech and a reduced level of consciousness.

There was a past history of a healed duodenal ulcer and obesity. She had documented normal renal function 4 months before this admission (urea 5.7 mmol/l and creatinine 105 μmol/l). Her diabetes was well controlled on metformin at 500 mg t.i.d. for the past 8 years. Three months before admission she started orlistat at 120 mg t.i.d., which coincided with the onset of the abdominal pain and chronic diarrhea. During the 4 days before admission, as her abdominal pain worsened, cimetidine (400 mg b.i.d.) was prescribed on the presumption of reactivation of her duodenal ulcer.

Clinical examination showed an obese woman who was agitated and confused, with a Glasgow Coma Scale of 10/15. She was apyrexial, with a pulse of 70 bpm in sinus rhythm, blood pressure 85/40 mmHg, and O_2 saturation 97% on air. General examination was otherwise unremarkable; in particular there was no evidence of diabetic retinopathy or neuropathy.

Preliminary laboratory investigations showed a life-threatening metabolic acidosis with a pH of 6.5, bicarbonate of 2 mmol/l, and base excess of −38 mmol/l. The blood glucose was 5.6 and serum lactate 23.1 mmol/l. Her renal function was markedly impaired with a urea of 48.8 mmol/l and a creatinine of 753 μmol/l. Electrolytes, liver function, amylase, and inflammatory markers were normal. A blood metformin level measured 30 mg/l (therapeutic levels <2 mg/l).

The chest radiograph was normal, as was the electrocardiogram. A urinary catheter yielded a small amount of urine, which showed a trace of protein on dipstick testing. Central venous pressure was 1 cm H_2O. Renal ultrasound ruled out obstruction.

A diagnosis of metformin-associated lactic acidosis with cardiovascular collapse and acute prerenal renal failure was made.

She required vigorous rehydration, sodium bicarbonate infusion, inotropic support, and renal replacement therapy. All cultures of blood, urine, and feces were sterile. Three years after this episode she is dialysis independent and her renal function has stabilized with a creatinine of 250 μmol/l.

So, what could have triggered MALA in a patient with previously normal renal function? As the mechanism of this condition is not known, treatment options are supportive and usually aim to stop the drug, correct the acidosis, and treat contibutory underlying conditions, most often renal impairment (3). Renal replacement therapy not only removes lactate but also removes metformin from the blood. Metformin is absorbed relatively quickly at the intestinal level, is not metabolized, and 90% of the drug is eliminated by glomerulofiltration and tubular secretion (1). Its half-life is between 1.5 and 5 h. Compared with phenformin, it produces a minimal increase in lactate production—this appears to be via the extrahepatic splanchnic bed, with animal studies favoring the small intestine as site of origin (4). Metformin interacts with few other drugs, but a relevant interaction is its competitive inhibition for renal tubular secretion by cimetidine, resulting in decreased metformin renal clearance (5). Most cases of MALA occur in the setting of impaired renal function when plasma levels of metformin would be expected to rise (6). Intuitively, most studies relate the level of metformin to the degree of acidosis and to the outcome; recent work suggests that this is not necessarily the case (1,7).

The pharmacokinetic interactions of orlistat, a pancreatic lipase inhibitor that reduces intestinal absorbtion of dietary fat by up to 37% (8), have only recently been explored (9). With the exception of cyclosporine, there were no reported drug interactions. By far the most frequent adverse event during orlistat therapy is gastrointestinal upset (8,10). To date, there is one randomized-controlled study that compared orlistat with placebo in patients with type 2 diabetes on concurrent metformin therapy (11); the value of orlistat in achieving weight loss, alongside better glycemic control, lower cholesterol levels, and systolic blood pressure, is indisputable in both diabetic (11,12) and nondiabetic (8) patients. Of note are consistent gastrointestinal side effects reported by the orlistat group; however, no cases as extreme as our patient are reported.

We postulate two possible ways that orlistat could have played a role in the development of lactic acidosis in our patient:

1) It is possible that chronic diarrhea caused by orlistat may have led to a degree of renal impairment. Rising metformin levels may have increased the probability of intestinal upset of metformin itself (which also causes nausea, epigasrtic discomfort, and diarrhea), continuing a vicious circle of increasing renal failure. The final addition of cimetidine in an attempt to treat the gastrointestinal symptoms might have further impaired metformin excretion, precipitating the onset of lactic acidosis.

2) An alternative, though not exclusive, possibility is that orlistat affected intestinal handling of metformin and/or lactate. Metformin is concentrated more in the intestine than in the plasma, and it is known that there is a metformin-induced conversion of glucose to lactate in the intestinal mucosa (13,14). It is possible that orlistat, by affecting the fat absorption in the small intestine, may alter intestinal metformin levels, leading to either increased metformin absorption or driving the conversion of glucose to lactate. This process may have been exacerbated by cimetidine reducing the excretion of metformin.

In conclusion, the combination of metformin and orlistat (although safe in all studies reported so far) should be closely monitored, especially if the patient is also taking cimetidine.

DANA DAWSON, MBBS, MRCP[1]
CHRISTOPHER CONLON, MD, FRCP[2]

From the [1]Department of Cardiovascular Medicine, University of Oxford, John Radcliffe Hospital, Oxford, U.K.; and the [2]Nuffield Department of Medicine, University of Oxford, Oxford, U.K.

Address correspondence to Dana Dawson, MBBS, MRCP, Cardiovascular Department, Rm 5810, Level 5, John Radcliffe Hospital, Oxford, OX3 9DU, U.K. E-mail: dana.dawson@cardiov.ox.ac.uk and dana.dawson@doctors.org.uk.

References

1. Davidson MB, Peters AL: An overview of metformin in the treatment of type 2 diabetes mellitus (Review Article). *Am J Med* 102:99–110, 1997
2. Chan NN, Brain HP, Feher MD: Metformin-associated lactic acidosis: a rare or very rare clinical entity (Review Article) *Diabet Med* 16:273–281, 1999
3. Lalau JD, Race JM: Lactic acidosis in metformin therapy. *Drugs* 58 (Suppl. 1):55–60, 1999
4. Bailey CJ, Wilcock C, Day C: Effect of metformin on glucose metabolism in the splanchnic bed. *Br J Pharmacol* 105:1009–1013, 1992
5. Somogyi A, Stockley C, Keal J, Rolan P, Bochner F: Reduction of metformin renal tubular secretion by cimetidine in man. *Br J Clin Pharmacol* 23:545–551, 1987
6. Sulkin TV, Bosman D, Krentz AJ: Contraindications to metformin therapy in patients with NIDDM. *Diabetes Care* 20: 925–928, 1997
7. Lalau JD, Lacroix C, Compagnon P, de Cagny B, Rigaud JP, Bleichner G, Chauveau P, Dulbecco P, Guerin C, Haegy JM: Role of metformin accumulation in metformin-associated lactic acidosis. *Diabetes Care* 18:779–784, 1995
8. Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, Krempf M: Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients: European Multicentre Orlistat Study Group. *Lancet* 352:167–172, 1998
9. Zhi J, Moore R, Kanitra L, Mulligan TE: Pharmacokinetic evaluation of the possible interaction between selected concomitant medications and orlistat at steady state in healthy subjects. *J Clin Pharmacol* 42:1011–1019, 2002
10. Torgerson JS, Arlinger K, Kappi M, Sjostrom L: Principles for enhanced recruitment of subjects in a large clinical trial: the XENDOS (XENical in the prevention of Diabetes in Obese Subjects) study experience. *Control Clin Trials* 22:515–525, 2001
11. Miles JM, Leiter L, Hollander P, Wadden T, Anderson JW, Doyle M, Foreyt J, Aronne L, Klein S: Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. *Diabetes Care* 25:1123–1128, 2002
12. Kelley DE, Bray GA, Pi-Sunyer FX, Klein S, Hill J, Miles J, Hollander P: Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 25:1033–1041, 2002
13. Lalau JD, Race JM, Brinquin L: Lactic acidosis in metformin therapy: relationship between plasma metformin concentration and renal function (Letter). *Diabetes Care* 21:1366–1367, 1998
14. Lalau JD, Race JM, Andreelli F, Lacroix C, Canarelli JP: Metformin retention independent of renal failure in intestinal occlusion. *Diabetes Metab* 27:24–28, 2001

Subcutaneous Glucagon May Be Better Than Oral Glucose for Prehospital Treatment of Symptomatic Hypoglycemia

The optimal management of symptomatic hypoglycemia in the prehospital setting remains uncertain, particularly in the absence of intravenous access (1,2). We performed an audit in Toronto, ON, Canada, and compared prehospital patient care outcomes following administration of oral glucose gel versus subcutaneous glucagon. For the city's population of >2.5 million people, there is a single Emergency Medical Service system made up of both ambulance and fire services, which are directed by one base hospital.

Our study included all consecutive patients attended by primary care paramedics for symptomatic hypoglycemia, defined as a capillary glucose concentration <4.0 mmol/l (72 mg/dl). Initially, the primary care paramedics followed a standard protocol, using up to 20 g of 100% D-glucose gel, given orally in 50-ml doses. After a period of certified training, the primary care paramedics began to administer 1 mg subcutaneous glucagon,

Table 1—*Baseline characteristics and outcomes of individuals with symptomatic hypoglycemia who received subcutaneous glucagon versus oral glucose gel*

Characteristic/outcome	Subcutaneous glucagon	Oral glucose gel	Comparison of glucagon versus glucose therapy
n	233	282	
Age (years)	55.7 ± 20.7	57.4 ± 20.2	$P = 0.4$
Men	121 (51.9)	163 (57.8)	$P = 0.2$
Insulin use	189 (83.3)	202 (76.8)	$P = 0.1$
Initial CBGC [mmol/l (mg/dl)]	2.3 ± 0.8 [41 ± 14]	2.2 ± 0.7 [40 ± 13]	$P = 0.08$
Initial GCS	11 (8–13)	12 (10–14)	$P = 0.02$
Net increase in CBGC [mmol/l (mg/dl)]	1.4 ± 1.4 [25 ± 25]	0.5 ± 1.1 [9 ± 20]	Mean difference: 0.9 (95% CI 0.6–1.1) [16 (95% CI 11–20)]
Decline or no increase in GCS	34 (14.6)	149 (52.8)	RR 0.3 (0.2–0.4)
≥4 point increase in GCS	82 (35.2)	27 (9.6)	RR 3.7 (2.5–5.5)
Received more than one treatment dose	1 (0.4)	103 (36.7)	RR 0.01 (0.002–0.08)
Problems administering treatment	7 (3.0)	41 (14.5)	RR 0.2 (0.09–0.4)

Data are means ± SD, *n* (%), or median (25th–75th percentile). CBGC, capillary blood glucose concentration; RR, risk ratio.

stored in lyophilized form and reconstituted in 1 ml sterile water before administration. All other aspects of primary care paramedic training and patient care between periods remained otherwise unchanged. A repeat dose of either agent could be administered if the first dose was not effective after 10 min. Primary care paramedics were required to record each patient's initial capillary glucose concentration and 15-point Glasgow Coma Scale (GCS), and to reassess these parameters every 10 mins until arriving at the hospital. The Research Ethics Board of Sunnybrook and Women's College Health Sciences Center approved this study.

During the study period, primary care paramedics encountered 601 patients with confirmed hypoglycemia, of whom 86 were excluded, mostly because they did not receive any treatment or a posttreatment capillary blood glucose concentration was not recorded.

The baseline characteristics and outcomes of the remaining glucagon (n = 235) and glucose gel (n = 282) recipients are presented in Table 1. Those treated with subcutaneous glucagon had a significant 0.9 mmol/l (16 mg/dl) greater net increase in mean capillary glucose concentration than those who received oral glucose. Glucagon recipients displayed greater improvement in their GCS, required fewer repeat drug doses, and had fewer related safety or logistical problems than glucose gel recipients, such as patient treatment refusal or inability to swallow the gel (Table 1).

Incomplete or imprecise data recording or GCS assessment, as well as lack of masking between treatments and outcomes, likely biased this retrospective study. The novelty of subcutaneous glucagon might have carried with it a greater expectation about its potential efficacy in the eyes of the primary care paramedic, and may have enabled them to be more familiar with, and capable of, administering subcutaneous glucagon than oral glucose gel.

Our study and those of others (3,4) suggest that subcutaneous glucagon may be easier to administer than oral or intravenous glucose. While a randomized clinical trial may be more informative about the optimal method to treat serious hypoglycemia in a community setting, subcutaneous glucagon will likely remain a sensible and safe treatment option in the hands of a trained user.

Marian J. Vermeulen[1,2]
Michael Klompas[3]
Joel G. Ray[4]
Chris Mazza[5]
Laurie J. Morrison[1,2,6]

From the [1]Division of Prehospital Care, Department of Emergency Services, Sunnybrook and Women's College Health Sciences Center, Toronto, Canada; the [2]Department of Health Administration, University of Toronto, Toronto, Canada; the [3]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; the [4]Department of Medicine, St. Michael's Hospital and University of Toronto, Toronto, Canada; the [5]Ontario Air Ambulance Base Hospital Program, Toronto, Canada; and the [6]Division of Emergency Medicine, Department of Medicine, University of Toronto and Toronto Emergency Medical Services, Toronto, Canada.

Address correspondence to Marian Vermeulen, Institute for Clinical Evaluative Sciences, Sunnybrook and Women's College Health Sciences Centre, Room G111, 2075 Bayview Ave., Toronto, Ontario M4N 3M5, Canada. E-mail: marian.vermeulen@ices.on.ca.

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References

1. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
2. The Diabetes Control and Complications Trial Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997
3. Vukmir RB, Paris PM, Yealy DM: Glucagon: prehospital therapy for hypoglycemia. *Ann Emerg Med* 20:375–379, 1991
4. Jones JL, Ray VG, Gough JE, Garrison HG, Whitley TW: Determination of prehospital blood glucose: a prospective, controlled study. *J Emerg Med* 10:679–682, 1992

Usefulness of Home Blood Pressure Measurement in the Morning in Type 1 Diabetic Patients

Recently, we reported that home blood pressure (BP) measurement in the morning has a stronger predictive power for micro- and macrovascular complications in type 2 diabetic patients than casual/clinic BP measurement (1). Here we report the results examined in the study of type 1 diabetic patients.

We studied 53 type 1 diabetic patients who regularly visited our clinics. The number of female patients (36) was

twice that of male patients (17). The subjects were aged 23–81 years (mean 54 ± 17) and had a diabetes duration of 2–47 years (mean 17 ± 10). Their mean BMI was 22 ± 3 kg/m^2, HbA_{1c} 7.0 ± 0.9%, triglycerides 94 ± 44 mg/dl, total cholesterol 201 ± 32 mg/dl, LDL 107 ± 25 mg/dl, and HDL 75 ± 18 mg/dl. Of 53 patients, 38 (72%) were treated by multiple daily insulin injections and the remaining (28%) received subcutaneous continuous insulin infusion for diabetes. Twenty-two patients (42%) were treated with antihypertensive drugs at the beginning of the study.

The study design and analysis are the same as previously reported (1). BP was measured at the clinic during the day and at home after waking. Clinic hypertension and morning hypertension were defined as systolic BP (SBP) 130 mmHg and/or diastolic BP (DBP) 85 mmHg, whereas clinic normotension and morning normotension were SBP 130 mmHg and/or DBP 85 mmHg. Microalbuminuria and clinical albuminuria were defined as urinary albumin excretion 30 μg/mg creatinine and 300 μg/mg creatinine, respectively.

There were no significant differences in the prevalence of nephropathy ($n = 4$ in clinic hypertension vs. $n = 7$ in clinic normotension; odds ratio [OR] 1.3 [95% CI 0.3–5.1]) and retinopathy ($n = 5$ in clinic hypertension vs. $n = 8$ in clinic normotension; OR 1.5 [0.5–5.4]) between the two groups with clinic hypertension ($n = 17$) (mean SBP/DBP 152 ± 9/91 ± 17 mmHg) and with clinic normotension ($n = 36$) (mean SBP/DBP 118 ± 11/73 ± 11 mmHg). In contrast, the prevalence of nephropathy with eight microalbuminuria and three clinical albuminuria (mean albumin excretion 231 ± 437 μg/mg creatinine, $n = 11$) in the patients with morning hypertension (mean SBP/DBP 148 ± 16/82 ± 11 mmHg, $n = 14$) was significantly higher (OR 260 [12–5,404], $P < 0.001$) than that ($n = 0$) (mean albumin excretion 7.0 ± 6.1 μg/mg creatinine) with morning normotension (mean SBP/DBP 115 ± 12/70 ± 8 mmHg, $n = 39$). The prevalence of proliferative retinopathy ($n = 4$) in the patients with morning hypertension was significantly higher (OR 15.2 [1.5–152], $P < 0.001$) than that ($n = 1$) in those with morning normotension, although there was no significant difference in all types of retinopathy between two groups ($n = 5$ in morning hypertension and $n = 8$ in morning normotension). There was no occurrence of coronary heart disease or cerebral vascular disease in the two groups. Specifically, systolic morning hypertension made a significant ($r = 0.66$, $P = 0.001$) contribution to the occurrence of nephropathy by multiple regression analysis, whereas the difference is not related to age, sex, duration of diabetes, BMI, HbA_{1c}, and serum lipid concentrations or use of different methods of insulin therapy and antihypertensive drugs. Meanwhile, the duration of diabetes had a significant ($r = 0.4$, $P = 0.001$) contribution to the occurrence of retinopathy.

No relationships between SBP and DBP in home BP and clinic BP measurements were observed (morning SBP = 0.28, clinic SBP + 88 $r = 0.07$, $P = 0.06$ and morning DBP = 0.25, clinic DBP + 54 $r = 0.14$, $P = 0.005$). The area under the receiver-operating characteristic (ROC) curve (AUC) of morning SBP (0.99 ± 0.01) was significantly higher ($P < 0.001$) than that of clinic SBP (0.49 ± 0.10) in nephropathy. There was no statistical difference in AUC between them in other events. In nephropathy, sensitivities of 130-mmHg threshold in morning and clinic SBP were 1.0 (95% CI 1.0–1.0) and 0.55 (0.23–0.83), respectively, whereas those of 85-mmHg threshold in morning and clinic DBP were 0.64 (0.310.89) and 0.55 (0.23–0.83), respectively. Specificities of 130-mmHg threshold in morning and clinic SBP were 0.95 (0.84–0.99) and 0.48 (0.32–0.64), respectively, whereas those of 85-mmHg threshold in morning and clinic DBP were 0.14 (0.05–0.29) and 0.29 (0.16–0.45), respectively.

In type 1 diabetic patients, the prevalence of nephropathy in the patients with morning hypertension was significantly higher than in those without morning hypertension, even though they had clinic normotension (mean SBP/DBP 120 ± 11/75 ± 15 mmHg, $n = 8$). In contrast, the occurrence was not observed in those without morning hypertension, even though they had clinic hypertension (mean SBP/DBP 160 ± 8/85 ± 8 mmHg, $n = 11$). Specifically, nephropathy, including clinical albuminuria, was observed in patients with systolic morning hypertension but not in patients without morning hypertension. Analysis by ROC curves also indicates that home BP in the morning has a stronger predictive power than clinic BP, especially in nephropathy. The cut point of 130-mmHg morning SBP has higher sensitivity and higher specificity than that of clinic SBP. This finding indicates that nephropathy in type 1 diabetic patients may be strongly related to morning home BP rather than clinic BP, as in type 2 diabetic patients (1).

The reason may be explained by several factors, such as white coat hypertension, nondipper hypertension, and morning surge, as postulated in the type 2 diabetic patients (1). Particularly, an increase in nocturnal BP, as detected by ambulatory BP monitoring, in type 1 diabetes is related to the development of microalbuminuria (2,3). These phenomena are thought to be caused by many neuroendocrine and hematological factors, especially autonomic neuropathy (4–6). Although we did not measure 24-h ambulatory BP, the greater range in the relation of morning home BP and clinic BP may be partially explained by true and white coat hypertension, reverse-dipping hypertension, and the effects of treatment with antihypertensive drugs (1).

In contrast, the prevalence of retinopathy in type 1 diabetic patients did not relate to BP, including morning home BP, although the degree of retinopathy was strengthened by morning hypertension. The duration of diabetes contributed to retinopathy significantly. They support the hypothesis that sustained long-term hyperglycemia is the strongest predictor for developing retinopathy and that high morning home BP accelerates retinopathy (7).

In conclusion, elevations of morning home BP in type 1 diabetic patients are also strongly related to microvascular complications, especially nephropathy, and the control of morning hypertension may prevent vascular complications, as in type 2 diabetic patients (1).

Kyuzi Kamoi, md[1]
Youichi Imamura, md[2]
Masashi Miyakoshi, md[1,3]
Chiaki Kobayashi, md[1,3]

From the [1]Department of Medicine, Nagaoka Red Cross Hospital, Nagaoka, Niigata, Japan; the [2]Department of Endocrinology/Metabolism, Kurume University School of Medicine, Kurume, Japan; and the [3]Division of Endocrinology/Metabolism, Niigata University Graduate School of Medicine & Dental Science, Niigata, Japan.

Address correspondence to Kyuzi Kamoi, Department of Medicine, Nagaoka Red Cross Hospital, Nagaoka, Niigata, 940-2085, Japan. E-mail: kkamint@echigo.ne.jp.

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References

1. Kamoi K, Miyakoshi M, Soda S, Kaneko S, Nakagawa O: Usefulness of home blood pressure measurement in the morning in type 2 diabetic patients. *Diabetes Care* 25: 2218–2223, 2002
2. Moore WV, Donaldson DL, Chonko AM, Ideus P, Wiegmaon TB: Ambulatory blood pressure in type I diabetes mellitus: comparison to presence of incipient nephropathy in adolescents and young adults. *Diabetes* 41:1035–1041, 1992
3. Lurbe E, Redon J, Kesani A, Pascual JM, Tacons J, Alvarez J, Batlle D: Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. *N Engl J Med* 347:797–805, 2002
4. Spallone V, Bernardi L, Ricordi L, Solda P, Maiello MR, Calciati A, Gambardella S, Fratino P, Menzinger G: Relationship between the circadian rhythms of blood pressure and sympathovagal balance in diabetic autonomic neuropathy. *Diabetes* 42:1745–1752, 1993
5. Lafferty AR, Werther GA, Clarke CF: Ambulatory blood pressure, microalbuminuria, and autonomic neuropathy in adolescents with type 1 diabetes. *Diabetes Care* 23:533–538, 2000
6. Torbjornsdotter TB, Jaremko GA, Berg UB: Ambulatory blood pressure and heart rate in relation to kidney structure and metabolic control in adolescents with type I diabetes. *Diabetologia* 44:865–873, 2001
7. Fong DS, Aiello L, Gardner TW, King GL, Blankenship G, Cavallerano JD, Ferris FL 3rd, Klein R, for the American Diabetes Association: Diabetic retinopathy (Position Statement). *Diabetes Care* 26 (Suppl. 1):S99–S102, 2003

Homocysteinemia Is Not Changed by 3-Day Insulin-Induced Normoglycemia in Type 2 Diabetic Subjects

Diabetic patients have a two- to six-fold increase in the prevalence of cardiovascular diseases (CVDs) (1). Homocysteinemia is an independent risk factor for CVD (2). Genetic, age- and sex-related, nutritional, and hormonal factors leading to the abnormal regulation of homocysteinemia in diabetes play a role in CVD (3). The relation between homocysteinemia and cardiovascular morbidity remains unclear (4). Type 2 diabetes is the result of insulin resistance paired with a progressive loss of insulin secretion, and the resulting chronic hyperglycemia is associated with long-term CVD. In type 2 diabetes, a 3-day insulin-induced strict normoglycemia improves *1*) postprandial carbohydrate oxidation evaluated by indirect calorimetry (5) and 2) parameters of erythrocytic lipoperoxidation, such as malondialdehyde and vitamin E (6). Few studies have analyzed the relation between type 2 diabetes and homocysteinemia in regard to metabolic control. We studied the effect of a short period of normoglycemia (72 h), induced by an adapted infusion of insulin, on homocysteinemia.

With informed consent, the study included 12 (7 men and 5 women; aged 58.10 ± 3.20 years and BMI 29.71 ± 0.97 kg/m^2) poorly controlled (HbA_{1c} 10.1 ± 0.5%) type 2 diabetic subjects without renal insufficiency (creatinemia 85.80 ± 4.20 μmol/l). Oral antidiabetic treatment was continued. No vitamin supplements were taken. The intravenous insulin infusion rate (by electric syringe) was adapted every 2 h to capillary glucose assessment (our objective was 5.5 mmol/l). Venous blood was collected for biochemical assays. Glycemia was 6.7 ± 0.5, 6.0 ± 0.6, and 5.5 ± 0.5 mmol/l after 24, 48, and 72 h insulin infusion, respectively. Plasma total homocysteinemia was measured by competitive immunoassay coupled with chemiluminescence (DPC-France, La-Garenne-Colombes, France) on blood centrifuged at 4°C without delay. An unpaired *t* test was performed between control and diabetic subjects; paired *t* test and a two-tailed test were used for values before and after the infusion ($P < 0.05$). At $t = 0$, homocysteinemia was 9.26 ± 1.46 μmol/l in diabetic subjects, which was not significantly different versus that of the control group at 6.77 ± 1.13 μmol/l ($n = 7$; aged 47 ± 3 years and BMI 23.0 ± 1.3 kg/m^2). Homocysteinemia was also inversely correlated ($r = 0.65$) to glomerular filtration rate (Cockroft formula 97.10 ± 7.50 ml/min), as previously reported (7). At $t = 0$, no correlation was found between homocysteinemia and HbA_{1c} ($r = 0.24$) or insulin resistance ($r = 0.37$) evaluated by homeostasis model assessment (8). The 3-day treatment decreased triglyceridemia (−0.5 mmol/l). The major finding is that homocysteinemia, when measured 24 h after the end of insulin infusion (with insulinemia returned to the initial value), was statistically unchanged versus that at $t = 0$ (10.26 ± 1.90 μmol/l).

Improved glucose control with similar insulin levels did not modify homocysteinemia in our study. Homocysteinemia could be unchanged because the period of strict normoglycemia was too short compared with several weeks in rats, in which insulin induced an increase in the activities of enzymes implicated in the conversion of homocysteinemia (9). However, this 72-h normoglycemia induces a significant effect on carbohydrate metabolism (5), and it leads to better glucose control after 3.5 years in 45% of a type 2 diabetic population (10). On the other hand, 3-h hyperinsulinemia decreases homocysteinemia in normal subjects but not in insulin-resistant diabetic subjects under a euglycemic clamp (11), suggesting that this is the contribution of insulin resistance rather than hyperglycemia. No correlation between homocysteinemia and the degree of metabolic control was reported (12). Therefore, our results mainly suggest that homocysteinemia is highly independent of glycemic control in type 2 diabetes.

MARIE-CHRISTINE BEAUVIEUX, PD, PHD[1,2]
VINCENT RIGALLEAU, MD, PHD[2]
CAROLINE PERLEMOINE, MD[2]
LAURENCE BAILLET, MD[2]
HENRI GIN, MD, PHD[2]

From the [1]Laboratoire de Biochimie, Hôpital Haut-Lévêque, Pessac, France; and the [2]Service de Nutrition et Diabétologie, Hôpital Haut-Lévêque, Pessac, France.

Address correspondence to Marie-Christine Beauvieux, Laboratoire de Biochimie, Hôpital Haut-Lévêque, Avenue de Magellan, 33604 Pessac, France. E-mail: marie-christine.beauvieux@chu-bordeaux.fr.

References

1. Audelin MC, Genest J: Homocysteine and cardiovascular disease in diabetes mellitus. *Atherosclerosis* 159:497–511, 2001
2. Nehler MR, Taylor LM, Porter JM: Homocysteinemia as a risk factor for atherosclerosis: a review. *Cardiovasc Surg* 5:559–567, 1997
3. Asnasi S, Desouza C, Homan J, Murthy SN, McNamara DB, Fonseca V: Hormones and homocysteine. *Minerva Endocrinol* 27: 141–155, 2002
4. Yeromenko Y, Lavie L, Levy Y: Homocysteine and cardiovascular risk in patients with diabetes mellitus. *Nutr Metab Cardio-*

vasc Dis 2:108–116, 2001
5. Rigalleau V, Rabemanantsoa C, Gin H: A 3-day insulin-induced normoglycemia improves carbohydrates oxidation in type 2 diabetic subjects. *Metabolism* 51:1484–1488, 2002
6. Peuchant E, Delmas-Beauvieux MC, Couchouron A, Dubourg L, Thomas MJ, Perromat A, Clerc M, Gin H: Short-term insulin therapy and normoglycemia: effects on erythrocytes lipid peroxidation in NIDDM patients. *Diabetes Care* 20:202–207, 1997
7. Ozmen B, Ozmen D, Turgan N, Habif S, Mutaf I, Bayindir O: Association between homocysteinemia and renal function in patients with type 2 diabetes mellitus. *Ann Clin Lab Sci* 32:279–286, 2002
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC: Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28:412–419, 1985
9. Gursu MF, Baydas G, Cikim G, Canatan H: Insulin increases homocysteine levels in a dose-dependent manner in diabetic rats. *Arch Med Res* 33:305–307, 2002
10. Dupuy O, Mayaudon H, Palou M, Sarret D, Bordier L, Bauduceau B: Optimized transient insulin infusion in uncontrolled type 2 diabetes: evaluation of a pragmatic attitude. *Diabetes Metab* 26:371–375, 2000
11. Fonseca VA, Mudaliar S, Schmidt B, Fink LM, Kern PA, Henry RR: Plasma homocysteine concentrations are regulated by acute hyperinsulinemia in nondiabetic but not type 2 diabetic subjects. *Metabolism* 47:686–689, 1998
12. Hoogeven EK, Kostense PJ, Beks PJ, Mackaay AJ, Jakobs C, Bouter LM, Heine RJ, Stehouwer CDA: Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in non-insulin-dependent diabetes mellitus: a population-based study. *Arterioscler Thromb Vasc Biol* 18:133–138, 1998

Telemedicine Improves Eye Examination Rates in Individuals With Diabetes

A model for eye-care delivery in underserved communities

Diabetic retinopathy is the leading cause of impairment and blindness in the working population (1), yet little is known about eye examination rates in rural and ethnically diverse communities. We examined a model of health care delivery utilizing telemedicine in a primary care setting to improve retinal examination rates in a rural and ethnically diverse community in South Carolina.

A randomized clinical trial was conducted to formally evaluate the effectiveness of a telemedicine retinal screening program (TRSP) compared with usual care. TRSP involved use of a nonmydriatic retinal camera located in a rural, federally funded primary care practice. An ophthalmologist located at the university setting distant from the primary care practice site evaluated the retinal photograph and consulted with the patient using real-time video conferencing. The outcome of interest for this trial was the frequency of eye examinations. Selection criteria included adults aged >18 years with a physician diagnosis of diabetes of any duration and any form of treatment.

Participants ($n = 59$) included 53 African Americans (90%), and 21 participants (35.5%) had no insurance or were on a sliding scale. Of those randomized to the TRSP ($n = 30$), 23 (77%) obtained eye examinations compared with 4 of 29 usual care patients (14%), who obtained eye examinations through their eye-care providers (relative risk 5.56, 95% CI 2.19–14.10). Thus, patients who had the opportunity to receive their eye examination via telemedicine at the primary care practice site were approximately six times more likely to obtain a screening eye examination than those who were simply reminded to schedule examinations with their usual eye-care provider.

The importance of this finding is underscored by reported annual dilated eye examination rates <50% and by the fact that much of the blindness attributed to diabetic retinopathy is preventable by timely photocoagulation (2,3). The incidence rate of 14% in our standard care group is quite low but comparable with that in other similar community health centers in rural South Carolina.

This model of eye-care delivery bridges certain barriers, such as transportation and access, in that patients obtained retinal screening examinations in the familiar offices of their primary care physicians. Despite the small sample size, our TRSP elicited greater adherence to vision care guidelines for patients with diabetes living in an underserved and ethnically diverse community. Future translational research can evaluate the potential effectiveness of telemedicine technology to improve adherence to clinical practice guidelines for diabetes care.

Richard M. Davis, md
Stanley Fowler, md
Kim Bellis, md
Jeffrey Pockl, md
Vytautas al Pakalnis, md
Andrew Woldorf, md

From the Department of Ophthalmology, School of Medicine, University of South Carolina, Columbia, South Carolina.

Address correspondence to Richard M. Davis, MD, Department of Ophthalmology, School of Medicine, University of South Carolina, 4 Medical Park Dr., Suite 300, Columbia, SC 29203. E-mail: rdavis@medpark.sc.edu.

References
1. Klein R, Klein BEK: Vision disorders in diabetes. In *National Diabetes Data Group: Diabetes in America*. 2nd ed. Bethesda, MD, U.S. Dept. of Health and Human Services, 1995, p. 293–338
2. Brechner RJ, Cowie CC, Howie LJ, Herman WH, Will JC, Harris MI: Ophthalmic examination among adults with diagnosed diabetes mellitus. *JAMA* 270:1714–1718, 1993
3. Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 103:1796–1806, 1985

Interactions Between Peroxisome Proliferator–Activated Receptor Gene Polymorphism and Birth Length Influence Risk for Type 2 Diabetes

Type 2 diabetes has previously been shown to be associated with a small body size at birth, which is considered an indicator of the intrauterine environment. This inverse association has been observed between both birth weight and birth length (1,2). The peroxisome proliferator–activated receptor (PPAR) γ2 gene is associated with glucose and lipid metabolism and is therefore a major can-

didate gene for type 2 diabetes (3,4). We have previously reported that the effects of the Pro12Pro genotype of the PPAR γ2 gene on insulin sensitivity depends on birth size (5). In subjects whose birth weight was <3,500 g, the Pro12Pro genotype was associated with insulin resistance. In the present study, we have assessed the association between the PPAR γ2 gene polymorphism and birth length on manifest type 2 diabetes.

Of the measures of body size at birth, birth length predicts type 2 diabetes most strongly in this cohort (2,6). A total of 476 elderly subjects (mean age 70 ± 3 years) with data on birth size and who attended a clinical study, including a 75-g oral glucose tolerance test, participated in the present study. The PPAR γ genotype was unrelated to either birth weight or birth length. The Pro12Pro genotype was associated with higher fasting insulin concentrations than the Pro12Ala/Ala12Ala genotype (71 vs. 62 pmol/l, $P = 0.02$). This association was strongest in people who were short at birth ($P = 0.02$ for interaction between genotype and birth length). Ninety-four subjects in the cohort had type 2 diabetes. We examined the combined effects of the PPAR γ2 gene polymorphism and birth length on the occurrence of the disease. The Pro12Pro genotype was weakly associated with a higher incidence of type 2 diabetes ($P = 0.08$). However, this association was confined to people who were ≤49 cm in length at birth, among whom the cumulative incidence of type 2 diabetes was 24.5%, compared with those >49 cm in length at birth, whose cumulative incidence was 14.3% ($P = 0.02$). There were no interactions between genotype and adult body size on the incidence of type 2 diabetes.

The PPAR γ2 gene, which is known to be linked to insulin sensitivity, has only weak effects on the occurrence of type 2 diabetes. When the analysis was confined to people who had short body length at birth, the gene had somewhat stronger effects on disease rates. We suggest that this is a manifestation of gene-environmental interaction, whereby the genotype has different effects according to intrauterine growth, for which birth length serves as a marker. Our findings are consistent with the hypothesis that type 2 diabetes originates through an adverse environment during development, which influences gene expression and later disease risk.

JOHAN G. ERIKSSON, MD, PHD[1]
CLIVE OSMOND, PHD[1]
VIRPI LINDI, MSC[2]
MATTI UUSITUPA, MD, PHD[2]
TOM FORSEN, MD, PHD[1]
MARKKU LAAKSO, MD, PHD[3]
DAVID BARKER, FRC[1]

From the [1]MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, U.K.; the [2]Department of Medicine, University of Kuopio, Kuopio, Finland; and the [3]Department of Epidemiology and Health Promotion, Diabetes and Genetic Epidemiology Unit, National Public Health Institute, Helsinki, Finland.

Address correspondence to Johan G. Eriksson, National Public Health Institute, Department of Epidemiology and Health Promotion, Mannerheimintie 166, FIN-00300 Helsinki, Finland. E-mail: johan.eriksson@ktl.fi.

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References

1. Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall C, Osmond C, Winter PD: Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 303:1019–1022, 1991
2. Forsén T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D: The fetal and childhood growth of persons who develop type 2 diabetes. *Ann Intern Med* 133: 176–182, 2000
3. Deeb SS, Fajas L, Nemoto M, Pihlajamäki J, Mykkänen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J: A Pro12Ala substitution in PPARgamma2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivity. *Nat Genet* 20:282–287, 1998
4. Altshuler D, Hirschorn JN, Klannemark M, Lindgreb CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES: The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* 26:76–80, 2000
5. Eriksson JG, Lindi V, Uusitupa M, Forsen TJ, Laakso M, Osmond C, Barker DJP: The effect of the Pro12Ala polymorphism of the peroxisome proliferator–activated receptor-γ2 gene on insulin sensitivity and insulin metabolism interact with size at birth. *Diabetes* 51:2321–2324, 2002
6. Eriksson JG, Forsén T, Tuomilehto J, Jaddoe VWV, Osmond C, Barker DJP: Effects of size at birth and childhood growth on the insulin resistance syndrome in elderly individuals. *Diabetologia* 45:342–348, 2002

A Novel Serotonin Blocker, Sarpogrelate, Increases Circulating Adiponectin Levels in Diabetic Patients With Arteriosclerosis Obliterans

The recent article by Tsunekawa et al. (1) demonstrates that adiponectin plays an important role in improving insulin resistance. Inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), are associated with the risk of development of arteriosclerosis among both diabetic and nondiabetic patients (2).

Low plasma adiponectin concentrations were clinically observed in patients with type 2 diabetes (3). These findings suggest that adiponectin might have anti-inflammatory properties and might act as an endogenous modulator for the development of obesity-related diseases.

Serotonin is a naturally occurring vasoactive substance and has also been involved with vascular inflammation leading to the atherosclerosis (4). Sarpogrelate hydrochloride is a serotonin 2A receptor antagonist and is clinically used for the cutaneous ulcer and ischemic change resulting from the arteriosclerosis.

Cryesthesia was defined as a feeling of cold in the feet and toes. We examined the grade (0–10) of cryesthesia by using a visual analog scale (5) and measured circulating adiponectin, high-sensitive CRP (hsCRP), IL-6, and lipid protein concentrations in eight diabetic patients with arteriosclerosis obliterans (ASO), who received a 3-month treatment course of a selective serotonin 2A receptor antagonist and sarpogrelate hydrochloride (100 mg three times a day). The changes in cryesthesia were considered the clinical outcome for the diabetic patients with ASO. Insulin resistance was evaluated by homeostasis model assessment = fasting insulin (μU/ml) × glucose (mmol/l)/22.5, as described elsewhere (6). Their mean ±

SD age was 64 ± 13 years, and the male-to-female ratio was three to one. Informed consent for participation was obtained from each individual. Written informed consent was obtained from all subjects. Sarpogrelate hydrochloride was supplied by Mitsubishi Pharma (Osaka, Japan). Blood samples were taken for all the enrolled individuals at baseline, 2 weeks, 1 month, 2 months, and 3 months after sarpogrelate hydrochloride treatment. Plasma adiponectin concentrations were determined with a radioimmunoassay kit according to the manufacturer's instructions (Linco Research, St. Charles, MO). Circulating IL-6 levels were measured by an enzyme-linked immunosorbent assay kit according to the manufacturer's guidelines (Amersham International, Tokyo, Japan). The concentrations of hsCRP and lipid proteins, including triglyceride, total cholesterol, and HDL cholesterol, were also examined with a standard method.

Data are expressed as means ± SD. The association between the baseline and the changes after sarpogrelate hydrochloride treatment were analyzed by the one-tailed ANOVA. A P value <0.05 was considered statistically significant.

Significantly decreased scales of cryesthesia in the lower extremities were observed in this study (0.7 ± 1.1 at 1 month vs. 10 ± 0 at baseline). Circulating adiponectin concentrations were significantly increased at the 2- and 3-month treatment courses after the sarpogrelate hydrochloride start (36.2 ± 10.8 and 34.5 ± 11.1 vs. 13.4 ± 9.8 μg/ml). The significant lower hsCRP values were found at 2 weeks, 1 month, and 3 months after the treatment (0.02 ± 0.01, 0.03 ± 0.03, and 0.03 ± 0.02 vs. 0.20 ± 0.13 mg/dl), whereas the IL-6 levels in blood were not significantly changed during the treatment course. The concentrations of lipid proteins, including triglyceride, total cholesterol, and HDL cholesterol, were not also significantly altered during the treatment. We found the decreased insulin resistance associated with the increase of adiponectin levels (4.5 ± 1.9 at 3 months vs. 15.8 ± 2.9 at baseline).

Sarpogrelate hydrochloride has recently been reported to be effective against diabetic nephropathy through the reduction of serotonin binding (7).

Plasma adiponectin concentrations were significantly increased in diabetic patients with ASO at 2 and 3 months after the sarpogrelate hydrochloride start, and the significant lower hsCRP values were found at 2 weeks, 1 month, and 3 months during the treatment. Our results suggest that sarpogrelate hydrochloride treatment might contribute to the inhibition of progression of ASO in diabetic patients.

JUN'ICHI YAMAKAWA, MD
TAKASHI TAKAHASHI, MD
TOHORU ITOH, MD
KAZUYA KUSAKA, MD
KEN KAWAURA, MD
XIN QUI WANG, MD
TSUGIYASU KANDA, MD

From the Department of General Medicine, Kanazawa Medical University, Ishikawa, Japan.

Address correspondence to Dr. Tsugiyasu Kanda, Department of General Medicine, Kanazawa Medical University, 1-1, Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa, 920-0293, Japan. E-mail: kandat@kanazawa-med.u.ac.jp.

Acknowledgments— This study was supported by the Science Research Promotion Fund of the Promotion and Mutual Aid Corporation for Private Schools of Japan.

References

1. Tsunekawa T, Hayashi T, Suzuki Y, Matsui-Hirai H, Kano H, Fukatsu A, Nomura N, Miyazaki A, Iguchi A: Plasma adiponectin plays an important role in improving insulin resistance with glimepiride in elderly type 2 diabetic subjects. *Diabetes Care* 26:285–289, 2003
2. Piol C, Fontbonne A, Sultan A, Rasamisoa M, Mariano-Goulant D, Davy JM, Monnier L, Avignon A: Inflammatory parameters are independent predictors of severe epicardial coronary stenosis in asymptomatic diabetic patients with silent myocardial ischemia. *Diabetes Care* 26:545–546, 2003
3. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 20:1595–1599, 2000
4. Katz MF, Farber HW, Dodds-Stitt Z, Cruikshank WW, Beer DJ: Serotonin-stimulated aortic endothelial cells secrete a novel T lymphocyte chemotactic and growth factor. *J Leukoc Biol* 55:567–573, 1994
5. Maxwell C: Sensitivity and accuracy of the visual analogue scale: a psycho-physical classroom experiment. *Br J Clin Pharmacol* 6:15–24, 1978
6. Hara K, Tobe K, Okada T, Kadowaki H, Akanuma Y, Ito C, Kimura S, Kadowaki T: A genetic variation in the *PGC-1* gene could confer insulin resistance and susceptibility to type II diabetes. *Diabetologia* 45:740–743, 2002
7. Takahashi T, Yano M, Minami J, Haraguchi T, Koga N, Higashi K, Kobori S: Sarpogrelate hydrochloride, a serotonin2A receptor antagonist, reduces albuminuria in diabetic patients with early-stage diabetic nephropathy. *Diabetes Res Clin Pract* 58:123–129, 2002

Comfort and Support Improve Painful Diabetic Neuropathy, Whereas Disappointment and Frustration Deteriorate the Metabolic and Neuropathic Status Despite an Intensive Diabetes Care Program

In this small series, we report a pilot study in which diabetic patients with painful neuropathy were closely monitored weekly by a physician skilled in intensified insulin delivery with and without the addition of alternative therapies for pain. Although the literature documents that a supportive health care team can improve diabetes control over and above the impact of simple medication adjustment, there is a paucity of reports on the impact of programs that fail to meet the expectations of patients and cause disappointment and stress. We therefore want to share our experience with five patients who were recruited as part of a pilot project to study the effect of alternative therapies in the treatment of painful diabetic neuropathy (1–5), specifically sessions with a healer and acupuncture, in which the acupuncture arm inadvertently failed.

Patients with long-standing diabetes may suffer complications, including neuropathy or nerve damage. To date, there is no specific treatment for this condition,

except analgesic medications (6–10). Although, the mainstay of therapy is to stabilize the glucose levels as near to normal as possible, many times the neuropathy pain is unresponsive. The purpose of this research was to evaluate the possible effects that alternative therapies may have on painful neuropathy in a population of diabetic patients requiring daily analgesia who participated in a program designed to normalize blood glucose levels.

The protocol called for three randomized groups: group 1: experimental (healing touch) plus medical intervention; group 2: acupuncture plus medical intervention; and group 3: medical intervention alone. The patients were instructed not to tell the diabetes specialist who provided the medical intervention their randomization group. The experimental group met twice weekly for an hour-long session with the healer. The healer touched one or more areas of the subjects' body that may have included the back, head, neck, shoulders, hands, or wrists. The touch was of light intensity, and each subject was treated sequentially. Soothing music was played in the background.

The acupuncture group was originally scheduled to receive acupuncture treatments but in fact acted as a true control and received no treatment due to a scheduling conflict. Since the patients were not allowed to reveal their randomization group to the physician, it was not discovered until after the study was completed that the acupuncture group not only did not receive treatments but also were highly irritated by the scheduling conflicts that arose.

At the beginning and end of the 6-week program, all subjects were evaluated for their metabolic and neuropathy status. Glucose and metabolic status were evaluated by measuring daily blood glucose concentrations (pre- and postprandially), glycosylated hemoglobin determination, insulin dosage, blood pressure, and weight. All five patients were seen weekly, and their medications were adjusted in an attempt to improve glucose control and to decrease the number of pain pills taken. The level of pain and neurological status were documented by pain analog scales, neurological examination for sensation, vibration, and position, as well as number of pain pills taken per day.

Table 1 shows the results of the first five patients recruited into the study. Although the sample size is small, it clearly shows that the patient who was disappointed because she did not receive the promised acupuncture treatments deteriorated, as shown by the increased number of pain pills and her lack of improved glucose control despite intensive care by both the physician and health care team. In comparison, the four other patients in the medical treatment alone and those who received the treatments from the healer improved in their objective and subjective measurements of pain and metabolic control. Of note, the indicators of sensation balance improved significantly in the patients in the healing group. In addition, both of these patients had a documented decrease in number of pain pills taken per day.

Table 1—*Metabolic parameters and analgesia taken at the beginning and end of the 6-week program*

	A1C pre	A1C post	Pain scale pre	Pain scale post	No. pain pills pre	No. pain pills post
Treatment group						
"Acupuncture" disappointed patient	8.0	8.7	1	10	3	5
Medical Rx alone	5.3	5.5	7	4	6	4
Medical Rx alone	7.2	5.4	2	1	3	0
Healing touch + medical	5.9	5.7	3	3	2	0
Healing touch + medical	5.7	5.9	3	0	7	5

Painful neuropathy is not only uncomfortable but also interferes with function and motivation to exercise and in all levels of diabetes care. Hyperglycemia is also associated with increasing pain. In a program designed to normalize blood glucose levels as part of a treatment strategy to improve painful neuropathy, alternative therapies for the treatment of pain were added. Inherent in our study design was the possibility that patients would have difficulty managing another care facility without specific guidance and support. In the case of the healing touch group, the system worked well; in the case of the acupuncture group, the system failed. When disappointment and failure are a part of the care system, it is clear that pain intensifies. It is also clear that adding a caring and soothing experience to the chore of weekly visits to a doctor to improve glucose control may increase the chances that the pain syndrome will improve. This small series does show that merely providing intensive diabetes care is not adequate in the care of diabetic patients with pain.

In conclusion, although the number of subjects who participated in this study was small, the results are very promising. Further research is indicated to evaluate the efficacy of alternative therapies for painful diabetic neuropathy. However, it is clear that when expectations are not met by the health care system, the best intentions do not result in improved care.

Gloria Kaye, phd
Alison Okada Wollitzer, phd
Lois Jovanovic, md

From the Sansum Medical Research Institute, Santa Barbara, California.

Address correspondence to Dr. Lois Jovanovic, Sansum Medical Research Institute, 2219 Bath St., Santa Barbara, CA 93105. E-mail: ljovanovic@sansum.org.

References

1. Goodnick PJ, Breakstone K, Wen XL, Kumar A: Acupuncture and neuropathy. *Am J Psychiatry* 157:1342–1343, 2000
2. Abuaisha BB, Costanzi JB, Boulton AJ: Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. *Diabetes Res Clin Pract* 39:115–121, 1998
3. Totka JP, Kachoyeanos MK, Friedhoff M: Pain management for children with insulin-dependent diabetes. *Diabetes Educ* 19: 481, 483–4, 1993
4. Fotopuolos SS, Sunderland WP: Biofeedback in the treatment of psychophysiologic disorders. *Biofeedback Self Regul* 3: 331–361, 1978
5. Kaptchuk TJ, Eisenberg DM: Varieties of healing. 2. A taxonomy of unconventional healing practices. *Ann Intern Med* 135: 196–204, 2001
6. Simmons Z, Feldman EL: Update on diabetic neuropathy. *Curr Opin Neurol* 15: 595–603, 2002
7. Calcutt NA: Potential mechanisms of neu-

ropathic pain in diabetes. *Int Rev Neurobiol* 50:205–228, 2002
8. Rossi P, Morano S, Serrao M, Gbriele A, DiMario U, Monocutti C, Pozzesere G: Pre-perceptual pain sensory responses (N1 component) in type 1 diabetes mellitus. *Neuroreport* 13:1009–1012, 2002
9. Vrethem M, Boivie J, Arnqvist H, Holmgren H, Lindstrom T: Painful polyneuropathy in patients with and without diabetes: clinical, neurophysiologic, and quantitative sensory characteristics. *Clin J Pain* 18:122–127, 2002
10. Jensen PG, Lanson JR: Management of painful diabetic neuropathy. *Drugs Aging* 18:737–749, 2001

Reduced Level of Opioid Peptides, Hemorphin-7 Peptides, in Serum of Diabetic Patients

Hemorphins are endogenous peptides belonging to the family of atypical opioid peptides (1) that are released from sequentially hydrolyzed hemoglobin, the first sequence implicating a hemoglobin cathepsin D proteolysis (2). They were isolated as naturally occurring peptides in various tissues and biological fluids and many of their biological effects have been described (1). Until now, no study had been performed concerning the consequence of the hemoglobin glycosylation on the hemorphin generation in diabetes.

In the present study, the ability of cathepsin D to liberate hemorphin-7 peptides from glycated hemoglobin was performed. To accomplish this, bovine hemoglobin was glycated in vitro and then hydrolyzed by cathepsin D. The hemorphins released (LVV-Hemorphin-7 and VV-Hemorphin-7) were quantified by high-pressure liquid chromatography and compared with the hemorphin level liberated from nonglycated hemoglobin. Moreover hemorphin-7 peptides serum levels between diabetic and nondiabetic patients were compared. Serums from 31 diabetic (aged 47 ± 17 years with a mean HbA_{1c} 8.4 ± 1.7%) and 25 nondiabetic (aged 39 ± 15 years) patients were estimated by an enzyme-linked immunosorbent assay procedure (3).

Results demonstrated that liberation of LVV-Hemorphin-7 and VV-Hemorphin-7 from in vitro glycated hemoglobin decreased three and five times, respectively, in comparison with normal hemoglobin. Moreover, compared with the control subjects, diabetic patients exhibited significantly lower levels of serum hemorphin-7 peptides (0.8 ± 0.94 vs. 4.09 ± 1.05 μmol/l, $P < 0.0001$). Nevertheless, no correlation was found between HbA_{1c} and hemorphin levels.

Consequently, in vivo release of hemorphins from hemoglobin hydrolysis is probably altered by glycosylation, as the present results indicate that the hemoglobin glycosylation reduces its degradation by cathepsin D.

With regards to the many effects attributed to hemorphins in the organism (among which are antihypertensive [4] and opioid-like effects [5]), the results from this study cause one to wonder about the consequence of their reduced level in diabetic patients. Does the diminution of hemorphins released from diabetic serum contribute to the decreased pain threshold to exogeneous or endogeneous nociceptive stimuli? Because the cause of pain in diabetic neuropathy remains uncertain and because its control is the most difficult management issue (6), further studies are required to explore the relation between reduced hemorphin levels and the hyperalgesic forms of peripheral neuropathy.

INGRID I. FRUITER-ARNAUDIN, PHD[1]
MARIE M. COHEN, PHD[1]
SOLANGE S. NERVI, PHD[2]
STEPHANIE S. BORDENAVE, PHD[1]
FREDERIC F. SANNIER, PHD[1]
JEAN-MARIE J.M. PIOT, PHD[1]

From the [1]Laboratoire de Génie Protéique et Cellulaire, La Rochelle, France; and the [2]Service de Nutrition, Maladies Métaboliques et Endocrinologie, Centre Hospitalo, Universitaire de Marseille, Hôpital Sainte-Marguerite, Marseille, France.

Address correspondence to Dr. Ingrid Fruiter-Arnaudin, University of La Rochelle, Laboratory Cellular & Protein Engineering, Avenue Michel Crepeau, Marie Curie Building, 17042 La Rochelle Cedex 1, 17042, France. E-mail: ifruitie@univ-lr.fr.

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References
1. Nyberg F, Sanderson K, Glamsta EL: The hemorphins: a new class of opioid peptides derived from the blood protein hemoglobin. *Biopolymers* 43:147–156, 1997
2. Fruitier I, Garreau I, Piot JM: Cathepsin D is a good candidate for the specific release of a stable hemorphin from hemoglobin in vivo: VV-hemorphin-7. *Biochem Biophys Res Commun* 246:719–724, 1998
3. Cohen M, Fruitier-Arnaudin I, Garreau-Balandier I, Piot JM: Quantification of hemorphin-7 peptides by enzyme linked immunosorbent assay with secondary antibody. *Analytica Chimica Acta* 461:229–233, 2002
4. Zhao Q, Sannier F, Garreau I, Guillochon D, Piot JM: Inhibition and inhibition kinetics of angiotensin converting enzyme activity by hemorphins, isolated from a peptic bovine hemoglobin hydrolysate. *Biochem Biophys Res Commun* 204:216–223, 1994
5. Zhao Q, Garreau I, Sannier F, Piot JM: Opioid peptides derived from hemoglobin: hemorphins. *Biopolymers* 43:75–98, 1997
6. Vinik AI: Diabetic neuropathy: pathogenesis and therapy (Review). *Am J Med* 107 (Suppl.):S17–S26, 1999

Prolonged Corrected QT Interval Is Associated With Acute and Chronic Hyperinsulinemia in Nondiabetic Subjects

Foussas et al. (1) observed that in type 2 diabetic patients intensive insulin treatment during acute coronary syndrome was associated with decreased QT dispersion, while the heart rate–corrected QT (QTc) interval tended to increase. This may be of concern because QTc prolongation is known to increase the risk of ventricular arrhythmia and sudden death. However, prognosis of diabetic patients with acute myocardial infarction can be improved by treatment of hyperglycemia with insulin (2).

Apart from myocardial ischemia and infarction, different factors in diabetic patients contribute to the duration of QTc interval, such as insulin resistance, glucose tolerance, glycemic control, and diabetes complications (3–5). Thus, QTc prolongation in the diabetic heart is likely

of multifactorial origin. The results of Foussas et al. suggest that hyperinsulinemia related to insulin treatment may also contribute to myocardial repolarization. We have conducted a study that deals with insulin-induced QTc prolongation and focuses on the associations between QTc and acute and chronic hyperinsulinemia in nondiabetic subjects.

We studied 35 nondiabetic offspring of type 2 diabetic patients with a wide range of insulin sensitivity and fasting plasma insulin concentration and 19 control subjects as described in detail elsewhere (6). Acute hyperinsulinemia was produced with the euglycemic-hyperinsulinemic clamp technique. Plasma insulin was raised to the desired level, where it was maintained by a continuous insulin infusion at a rate of 480 pmol · m body surface area^{-2} · min^{-1}. Blood glucose was clamped at 5.0 mmol/l by infusing glucose at varying rates. Average QT and QTc (QT/R-R interval$^{-0.5}$) intervals were assessed from 30-min electrocardiogram recordings at baseline and at steady state during the clamp by using a computerized method.

We found that QT and QTc intervals were comparable in subjects with and without family history of type 2 diabetes. Compared with men, women had longer QT (415 ± 7 vs. 389 ± 6 ms, $P < 0.01$) and QTc intervals (425 ± 5 vs. 400 ± 5 ms, $P < 0.001$). After adjustment for sex, QTc interval correlated with the rates of whole-body glucose uptake ($r = -0.32$, $P < 0.05$) and with fasting plasma insulin concentration ($r = 0.33$, $P < 0.05$). During acute hyperinsulinemia, heartbeat interval decreased significantly (956 ± 18 to 894 ± 15 ms, $P < 0.001$) and QT interval remained unchanged (404 ± 5 vs. 406 ± 5 ms, NS), whereas QTc interval increased (414 ± 4 to 430 ± 4 ms, $P < 0.001$).

Our findings suggest that repolarization of the myocardium is also influenced by acute hyperinsulinemia in nondiabetic subjects. Thus, this phenomenon is not restricted to the diabetic heart. Although significant change in QTc interval was observed in response to acute hyperinsulinemia, there were also relations between QTc interval and fasting plasma insulin concentration and insulin sensitivity, suggesting that insulin contributes to myocardial repolarization in physiological conditions. These interrelations highlight the diverse effects of insulin on the cardiovascular system.

Tomi Laitinen, md[1]
Ilkka Vauhkonen, md[2]
Leo Niskanen, md[2]
Juha Hartikainen, md[2]
Matti Uusitupa, md[3]
Markku Laakso, md[2]

From the [1]Department of Clinical Physiology, Kuopio University Hospital, Kuopio, Finland; the [2]Department of Medicine, Kuopio University Hospital, Kuopio, Finland; and the [3]Department of Clinical Nutrition, Kuopio University Hospital, Kuopio, Finland.

Address correspondence to Tomi Laitinen, Department of Clinical Physiology, Kuopio University Hospital, P.O. Box 1777, FIN-70211, Kuopio, Finland. E-mail: tomi.laitinen@kuh.fi.

References

1. Foussas S, Stefanidis A, Melidonis A, Tournis S, Michail P, Dosios T, Asimacopoulos P: Intensive insulin treatment and QT-interval (Letter). *Diabetes Care* 26: 954–955, 2003
2. Malmberg K, Norhammar A, Wedel H, Ryden L: Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. *Circulation* 99:2626–2632, 1999
3. Veglio M, Borra M, Stevens LK, Fuller JH, Perin PC: The relation between QTc interval prolongation and diabetic complications: the EURODIAB IDDM Complication Study Group. *Diabetologia* 42:68–75, 1999
4. Festa A, D'Agostino R Jr, Rautaharju P, Mykkanen L, Haffner SM: Relation of systemic blood pressure, left ventricular mass, insulin sensitivity, and coronary artery disease to QT interval duration in nondiabetic and type 2 diabetic subjects. *Am J Cardiol* 86:1117–1122, 2000
5. Brown DW, Giles WH, Greenlund KJ, Valdez R, Croft JB: Impaired fasting glucose, diabetes mellitus, and cardiovascular disease risk factors are associated with prolonged QTc duration: results from the Third National Health and Nutrition Examination Survey. *J Cardiovasc Risk* 8: 227–233, 2001
6. Laitinen T, Vauhkonen IKJ, Niskanen LK, Hartikainen JEK, Länsimies EA, Uusitupa MIJ, Laakso M: Power spectral analysis of heart rate variability during hyperinsulinemia in nondiabetic offspring of type 2 diabetic patients: evidence for possible early autonomic dysfunction in insulin-resistant subjects. *Diabetes* 48:1295–1299, 1999

Long-Term, Randomized Clinical Trial of Two Diets in the Metabolic Syndrome and Type 2 Diabetes

The best dietary balance of fatty acids, protein, and carbohydrate in patients with both glucose and lipid metabolism disorders remains unclear (1). Substitution of carbohydrates for saturated fatty acids frequently leads to increased triglyceride and decreased HDL cholesterol (2), adverse effects not seen with increased dietary monounsaturated fatty acids (MUFAs) (3). Moderate hyperglycemia can contribute to increased turnover of protein, suggesting increased need for protein in type 2 diabetes (4).

Between January 2000 and February 2001, we randomized 35 patients with the metabolic syndrome or type 2 diabetes to the contemporary American Heart Association (AHA) diet (15% of calories from protein, 30% fat, and 15% MUFAs) or a diet higher in protein, total fat, and MUFAs (25, 40, and 22% of calories, respectively; HiPro-HiMono diet). Enrollment criteria for the 42-week trial were BMI ≥25 kg/m^2, elevated fasting glucose (6.1–6.9 mmol/l [110–125 mg/dl] for impaired fasting glucose and ≥6.9 mmol/l [≥126 mg/dl] for diabetes), calculated LDL cholesterol >2.8 mmol/l, and fasting triglyceride ≥1.7 mmol/l. (The trial preceded the National Cholesterol Education Program's clinical definition of the metabolic syndrome.) These risk factors were also the trial end points.

Patients were given a scale to weigh portions and prepared their own food, with the exception of almonds, which were given to the HiPro-HiMono group to replace other primary sources of MUFAs during the last 24 weeks. All patients were taught their diet and to self-monitor food intake and weight by using password-protected web pages with individualized meal plans, menus, and messages from a dietitian.

Twelve patients withdrew within 6 weeks (because of inability to attend

clinic, computer problems, and/or health reasons). An additional six patients had one to two missing observations during the follow-up period. Multilevel models were used to describe the dietary effects and permitted the use of all collected data in the statistical analyses, including incomplete cases. At 42 weeks, although trends in risk factors slightly favored the HiPro-HiMono diet, changes were not significantly different between the AHA and HiPro-HiMono groups for weight (−5.9 vs. −9.1 kg; $P = 0.768$), triglyceride (−0.8 vs. −1.1 mmol/l; $P = 0.920$), fasting glucose (−2.2 vs. −3.2 mmol/l; $P = 0.153$), and LDL cholesterol (0.23 vs. 0.18 mmol/l; $P = 0.217$). The preponderance of patients improved their glycemic control. At 42 weeks, glycemic control was normalized in all 10 patients with impaired fasting glucose; it was also normalized in 2 and reduced to impaired fasting glucose in 3 of 7 patients with diabetes. Food record analyses to evaluate compliance showed that changes from the baseline diets to assigned levels of carbohydrate and total, saturated, and monounsaturated fats were significantly different between the groups, in keeping with different dietary goals. In a similar study (5), with slightly different diets, subjects at the end of 18 months were consuming diets of similar composition.

Our long-term study, enabled by our Internet Management System, was limited by small sample size. The power to detect a 10% difference between groups at $\alpha = 0.05$ with the observed SDs was <18% for LDL cholesterol, triglyceride, and fasting glucose. Weight loss was a potential confounding factor in the analyses. Nevertheless, the study's trends support the hypothesis that a diet high in protein and MUFAs may be advantageous in correcting glucose and lipid metabolism abnormalities. Large, randomized, multicenter trials are needed.

LYNNE W. SCOTT, MA[1]
ASHOK BALASUBRAMANYAM, MD[1]
KAY T. KIMBALL, PHD[2]
AMY K. AHERNS, MS[1]
C. MICHAEL FORDIS, JR., MD[3]
CHRISTIE M. BALLANTYNE, MD[1]

From the [1]Department of Medicine, Baylor College of Medicine, Houston, Texas; [2]Statistical Design and Analysis, Austin, Texas; and the [3]Center for Collaborative and Interactive Technologies, Baylor College of Medicine, Houston, Texas.

Address correspondence to Lynne W. Scott, MA, RD, Baylor College of Medicine, 6550 Fannin, Smith Tower 1271, Houston, TX 77030. E-mail: lscott@bcm.tmc.edu.

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References

1. Grundy SM, Abate N, Chandalia M: Diet composition and the metabolic syndrome: what is the optimal fat intake? *Am J Med* 113 (Suppl 9B):25S–29S, 2002
2. Turley ML, Skeaff CM, Mann JI, Cox B: The effect of a low-fat, high-carbohydrate diet on serum high density lipoprotein cholesterol and triglyceride. *Eur J Clin Nutr* 52:728–732, 1998
3. Garg A: High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis. *Am J Clin Nutr* 67 (Suppl.): 577S–582S, 1998
4. Gougeon R, Pencharz PB, Marliss EB: Effect of NIDDM on the kinetics of whole-body protein metabolism. *Diabetes* 43: 318–328, 1994
5. Milne MM, Mann JI, Chisholm AW, Williams SM: Long-term comparison of three dietary prescriptions in the treatment of NIDDM. *Diabetes Care* 17:74–80, 1994

Fenofibrate Monotherapy Induced Rhabdomyolysis

Fenofibrate (TriCor; Abbott Pharmaceuticals, Abbott Park, IL), a fibric acid derivative, was introduced in the U.S. in 1998. It is frequently used to treat diabetic dyslipidemia and hypertriglyceridemia alone or in combination with statins. Despite reports of rhabdomyolysis with the use of statins or statin-fibrate combinations, there have been no cases of rhabdomyolysis reported in the U.S. when fenofibrate was used alone to treat a patient with normal baseline creatinine. Here, we present the first case of a patient with a normal creatinine who developed life-threatening rhabdomyolysis while under the treatment of fenofibrate monotherapy.

A 56-year-old woman with a medical history significant for type 2 diabetes, peripheral vascular disease, hypertension, hyperlipidemia, and polyneuropathy presented with a complaint of the new onset of diffuse myalgia. She had no recent viral illness or other complaints. Ten days before presentation she was started on 200 mg fenofibrate daily. Before fenofibrate therapy, her serum creatinine was 1.3 mg/dl, thyroid-stimulating hormone was normal, and liver function was normal. Her medications included NPH insulin, metformin 500 mg q.d., amitriptyline 25 mg q.h.s., pioglitazone 30 mg q.d., quinapril 10 mg q.d., fenofibrate 200 mg q.d., and daily aspirin. Physical examination was unremarkable except for diffuse generalized muscle tenderness.

Because of the patient's presenting symptoms and recent initiation of fenofibrate therapy, her creatine phosphokinase (CPK) level was checked and found to be 5,632 units/l. Fenofibrate was discontinued. She was admitted to the hospital with a presumptive diagnosis of rhabdomyolysis. Her admission labs were also remarkable for elevated transaminases and a creatinine of 2.0 mg/dl. Because of the creatinine elevation, metformin was also discontinued.

Following hydration and bicarbonate therapy, the patient's myalgia resolved. She was discharged with fluid intake encouraged. Although her CPK peaked to >23,000 units/l, it returned to baseline (86 units/l) within weeks of discharge. Her renal function also improved gradually within months of hospitalization.

The fibric acid agents have long been shown to be of benefit in the treatment of hyperlipidemia. Early fibrates such as clofibrate and even gemfibrozil have rarely been associated with rhabdomyolysis. Fenofibrate has been one of the newer fibrates to show great promise since its release, with few if any reports of rhabdomyolysis outside the U.S. Taken once daily with a meal, fenofibrate is more effective than gemfibrozil in lowering serum LDL cholesterol and triglyceride concentrations (1,2). It has also been shown to be of benefit in raising the serum concentration of HDL cholesterol and in lowering dense LDL cholesterol. Fenofibrate in combination with low-dose 3-hydroxy-3 methylglutaryl conenzyme A (HMG-CoA) reducatse inhibitors are being used more frequently in the treatment of combined hyperlipidemia and to lower non-HDL cholesterol to

<130 mg/dl (1–7). However, there are still risks with the usage of fenofibrate in combination and even alone, as was evidenced by our patient.

In summary, rhabdomyolysis in patients with normal baseline creatinine on fenofibrate monotherapy has not been previously reported in the U.S. Physicians should be aware of the potential toxicities of this agent. Thus, we advocate close supervision of patients treated with this agent, patient education about potential side effects, and prompt treatment should problems arise.

Billie J. Barker, MD[1]
Roger R. Goodenough, MD[2]
James M. Falko, MD[1]

From the [1]Department of Internal Medicine, Riverside Methodist Hospital, Columbus, Ohio; and the [2]Department of Family Medicine, Upper Valley Medical Center, Troy, Ohio.

Address correspondence to Dr. Falko, Medical Education, Riverside Methodist Hospital, 3535 Olentangy River Rd., Columbus, OH, 43214. E-mail: falkoj@ohiohealth.com.

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References

1. Jen SL, Chen JW, Lee WL, Wang SP: Efficacy and safety of fenofibrate or gemfibrozil on serum lipid profiles in Chinese patients with type IIb hyperlipidemia: a single-blind, randomized, and cross-over study. *Chinese Medical Journal* 59:217–224, 1997
2. Insua A, Massari F, Rodriguez Moncalvo JJ, Ruben Zanchetta J, Insua AM: Fenofibrate or gemfibrozil for treatment of types IIa and IIb primary hyperlipoproteinemia: a randomized, double-blind, crossover study. *Endocr Pract* 8:96–101, 2002
3. Choice of lipid-regulating drugs. *Med Letter* 43:43–48, 2001
4. Despres J: Increasing high-density lipoprotein cholesterol: an update on fenofibrate. *Am J Cardiol* 88:30N–236N, 2001
5. Ellen RL, McPherson R: Long-term efficacy and safety of fenofibrate and a statin in the treatment of combined hyperlipidemia. *Am J Cardiol* 81:60B–65B, 1998
6. Diabetes Atherosclerosis Intervention Study Investigators: Effect of fenofibrate on progression of coronary artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomized study. *Lancet* 357:905–910, 2001
7. Brown WV: Fenofibrate, a third-generation fibric acid derivative. *Am J Med* 83: 1–2, 1987

Insulin Injection Abscesses Caused by *Mycobacterium Chelonae*

Insulin injection abscesses occur in patients with diabetes and are mainly due to *Staphylococcus aureus*. However, we need to look for other organisms that can cause problems so that appropriate treatment can be given. Here we report a case of injection abscesses due to an atypical mycobacterium, *Mycobacterium chelonae*.

A 43-year-old woman with diabetes presented with a 5-month history of abscesses on her thighs and abdomen at injection sites. She used a pen device three times daily (reusing the needle) and a syringe and needle in the evening. With an HbA_{1c} of 14%, her diabetes control was far from ideal. She had a 23-year history of diabetes and had been admitted to the hospital on a few occasions for seizures during episodes of hypoglycemia.

The abscesses had been treated with several courses of oral flucloxacillin but continued to enlarge with the development of new lesions. The largest abscess on her right thigh was incised and drained by the general surgeons and continued to drain pus after the procedure. No infecting organism had been isolated from charcoal swabs of the lesions.

On presentation, she had a large abscess draining pus on the left thigh with smaller nodules on the right thigh and a carbuncle on her anterior abdominal wall. She was well, apyrexial, and her diabetes control had not changed significantly since the abscesses had appeared.

After discussion with the microbiology department with reference to the obvious pus but apparently sterile culture taken from the swabs, pus was aspirated from the abscess on the thigh and sent for culture. A skin biopsy was also taken and sent for histological assessment and culture. The biopsy showed a deep dermal abscess with inflammation. Microscopy of the pus did not show acid and alcohol fast bacilli (AFBs). After being cultured for 6 weeks at 30°C, *M. chelonae* was isolated from the pus. This was sent to the reference laboratory where the diagnosis was confirmed and the *M. chelonae* was found to be sensitive to clarithromycin and ciprofloxacin. The cultures of the patient's needles and pen device did not reveal any *M. chelonae*.

The patient was started on 500 mg b.d. clarithromycin and 250 mg t.d.s. ciprofloxacin, which cleared the abscesses over the next few months. Toward the end of treatment a new nodule appeared on the right thigh away from injection sites, which was completely excised. The histology showed granulomatous inflammation in the deep dermis and subcutis. A single well-formed AFB was identified by a modified Zeil-Neilsen stain. Treatment was continued for 6 months after the lesions cleared, and the patient has remained well and has not developed any new lesions.

M. chelonae is a fast-growing, atypical mycobacterium of Runyon group IV. It is considered fast growing as it grows in 3–7 days at 25°C to 40°C compared with other groups that require 2 weeks to grow. Despite this, *M. chelonae* is difficult to culture.

It is widespread in the environment and has been reported to survive on the skin for 6 h. It is contracted from the environment rather than by human-to-human transmission but rarely causes human disease. Primary cutaneous infections have been reported after injections in patients with diabetes on insulin (2,3) and in postoperative patients. In immunocompetent patients there is usually a known portal of entry, but cutaneous disease can follow dissemination from an endogenous source (4). Disseminated disease is more likely to occur in immunosuppressed patients, such as those on long term steroids or after a renal transplant (5). In a study of 100 cases of cutaneous disease, 35% had localized infections following trauma and, of these, 3 had diabetes (6)

The presentation of cutaneous infection includes localized cellulitis, granulomatous nodules, abscesses, and ulcers (7). Lesions have been noted to exhibit spirotrichoid spread (8). This is lymphangitic spread with nodules ascending proximally along lymphatic vessels. Extracutaneous lesions include osteomyelitis, endocarditis, and keratitis following surgery and may be related to catheters,

renal dialysis catheters, and tracheostomy tubes.

M. chelonae is resistant to usual antituberculous treatment but may be sensitive to clarithromycin and ciprofloxacin. It may also respond to imipenem and linezolid. This case reinforces the need to consider atypical infections in cases of persistant cutaneous infection, especially in patients who are relatively immunocompromised.

KATHERINE FINUCANE, BMBCH[1]
PHIL AMBREY, MRCP[2]
SHALINI NARAYAN, MRCP[3]
CLIVE B. ARCHER, MD, PHD[3]
COLIN DAYAN, FRCP, PHD[4]

From the [1]Weston General Hospital, Dermatology, Bristol, U.K.; the [2]Weston General Hospital, Medicine, Bristol, U.K.; the [3]Bristol Royal Infirmary, Dermatology, Bristol, U.K.; and the [4]University of Bristol, Medicine, Bristol, U.K.

Address correspondence to Dr. Katherine Finucane, 21 Elmgrove Rd., Redland, Bristol, BS6 6AJ, U.K. E-mail: cjbur@globalnet.co.uk.

References

1. Kane C, Vincent A, Greene J, Sandin R: Disseminated cutaneous *Mycobacterium chelonae* infection. *Cancer Control* 7:181–184, 2000
2. Jackson PG, Keen H, Noble CJ, Simmons NA: Injection abscesses in a diabetic due to *Mycobacterium chelonei var abscessus. BMJ* 281:1105–1106, 1980
3. Kelly SE: Multiple injection abcesses in a diabetic caused by *Mycobacterium chelonei*. *Clin Exp Dermatol* 12:48–49, 1987
4. Kelley L, Deering K, Kaye E: Cutaneous *Mycobacterium chelonei* presenting in an immunocompetant host: case report and review of the literature. *Cutis* 56:293–295, 1995
5. Endzweig CH, Strauss E, Murphy F, Rao BK: A case of cutaneous *Mycobacterium chelonae abscessus* infection in a renal transplant patient. *J Cutan Med Surg* 5:28–32, 2001
6. Wallace R, Brown B, Onyi G: Skin, soft tissue, and bone infections due to *Mycobacterium chelonae chelonae:* importance of prior corticosteroid therapy, frequency of disseminated infections and resistance to oral antimicrobials other than clarithromycin. *J Infect Dis* 166:405–412, 1992
7. Kullavanijaya P: Atypical mycobacterial cutaneous infection. *Clin Dermato* 17:153–158, 1999
8. Higgins E, Lawrence CM: Spirotrichoid spread of *Mycobacterium chelonei. Clin Exp Dermatol* 13:234–236, 1988

COMMENTS AND RESPONSES

Clarification of Statements in 2003 Clinical Practice Recommendations

In the 2003 American Diabetes Association Clinical Practice Recommendations, some statements in the Position Statement "Hyperglycemic Crises in Patients With Diabetes Mellitus" (1) lack support in the literature.

1) On p. S109, the authors write "The combination of insulin deficiency and increased counterregulatory hormones in DKA also leads to the release of free fatty acids into the circulation from adipose tissue (lipolysis) and to unrestrained hepatic fatty acid oxidation to ketone bodies. . . with resulting ketonemia and metabolic acidosis." According to Mayes (2) and Watkins et al. (3), there is no relationship between the plasmatic levels of free fatty acids and ketone bodies.

2) On p. S110, the authors write "Successful treatment of DKA. . . requires correction of hyperglycemia. . ." Both Watkins et. al. (3) and Malchoff et al. (4) have observed no correlation between serum glucose and serum ketoacid concentrations in acutely decompensated diabetic patients. In other words, serum ketoacid concentration is glucose independent, and, thus, not influenced by the decrease of hyperglycemia toward normal values.

An explanation for the readers of *Diabetes Care* would be useful.

VIKTOR ROSIVAL, PHD

From the Department of Clinical Biochemistry, Dérer's Hospital, Bratislava, Slovakia.

Address correspondence to Viktor Rosival, Department of Clinical Biochemistry, Dérer's Hospital, Limbová 5, SK-833 05 Bratislava, Slovakia. E-mail: rosivalv@hotmail.com.

References

1. American Diabetes Association: Hyperglycemic Crises in Patients With Diabetes Mellitus. *Diabetes Care* 26 (Suppl. 1):S109–S117, 2003
2. Mayes PA: Absence of a relation between lipogenesis and ketogenesis in vivo. *Nature* 183:540–541, 1959
3. Watkins PJ, Hill DM, Fitzgerald MG, Malins JM: Ketonaemia in uncontrolled diabetes mellitus. *BMJ* 4:522–525, 1970
4. Malchoff CD, Pohl SL, Kaiser DL, Carey RM: Determinants of glucose and ketoacid concentrations in acutely hyperglycemic diabetic patients. *Am J Med* 77:275–285, 1984

Clarification of Statements in 2003 Clinical Practice Recommendations

Response to Rosival

The comments of Rosival (1) on the American Diabetes Association Position Statement regarding hyperglycemic crises (2) in this issue of *Diabetes Care* are appreciated. We offer the following responses:

1) The studies cited by Rosival regarding regulations of free fatty acids to β-oxidation and ketogenesis are at least 20 years old. More updated studies on the mechanism were discussed in our technical review (3), on the basis of which the Position Statement on hyperglycemic crises was written.

2) Regarding successful treatment of diabetic ketoacidosis (DKA), Rosival has misinterpreted our statement, as we did not mention anything regarding correlation of blood glucose with ketones. Our statement was about "Successful treatment of DKA and HHS requires correction of dehydration, hyperglycemia, and electrolyte imbalances. . ." (3).

ABBAS E. KITABCHI, PHD, MD

From the Division of Endocrinology, Diabetes & Metabolism, the University of Tennessee Health Science Center, Memphis, Tennessee.

Address correspondence to Abbas E. Kitabchi, PhD, MD, Director, Division of Endocrinology, Diabetes & Metabolism, The University of Tennessee Health Science Center, 951 Court Ave., Room 335M, Memphis, TN 38163. E-mail: akitabchi@utmem.edu.

References

1. Rosival V: Clarification of statements in 2003 Clinical Practice Recommendations (Letter). *Diabetes Care* 26:2484, 2003
2. American Diabetes Association: Hyperglycemic crises in patients with diabetes mellitus (Position Statement). *Diabetes*

Care 26 (Suppl. 1):S109–S117, 2003
3. Kitabchi AE, Umpierrez GE, Murphy MB, Barrett EJ, Kreisberg RA, Malone JI, Wall BM: Management of hyperglycemic crises in patients with diabetes (Technical Review). *Diabetes Care* 24:131–153, 2001

Insulin Pump Therapy: a Meta-Analysis

Response to Weissberg-Benchell et al.

Weissberg-Benchell et al. (1) conclude, based on their meta-analysis on the efficacy of continuous subcutaneous insulin infusion (CSII) versus multiple daily injection (MDI) or conventional therapy (CT), that glycohemoglobin is significantly lower with CSII than with injection therapy. It is stated that "the weighted summary mean difference comparing the effect of CSII with MDI/CT was 0.95, with a 95% CI of 0.8–1.1, indicating that there was a significant difference between the two treatment approaches." This is concluded from a meta-analysis of 11 studies with a parallel design. However, 5 of these 11 studies were not randomized, and therefore open to selection bias. Furthermore, two of these nonrandomized studies are interpreted to show the largest effect sizes, ~2.5 and 4.5%. This will result in an overestimation of the weighted mean effect size, whereas the other studies show effect sizes between 0.25 and 0.75%. Effect sizes in this range are much more in agreement with a recent meta-analysis by Pickup et al. (2) that only included randomized studies and concluded that the effect of CSII on glycohemoglobin was 0.51%, as compared with injection therapy. Therefore, the large difference presented between insulin pump and injection therapy of 0.95% glycated hemoglobin is untenable from a methodological point of view. The mean effect size of CSII as found by Pickup et al. is consistent with a recent statement from Schade and Valentine (3): "the health care team must determine which treatment modality has the greatest potential for benefit in each diabetic patient."

J. Hans DeVries, MD[1]
Robert J. Heine, MD, PhD[2]

From the [1]Academic Medical Center, Internal Medicine, Amsterdam, the Netherlands; and the VU Medical Center, Endocrinology, Amsterdam, the Netherlands.

Address correspondence to Dr. J. DeVries, Academic Medical Center, Internal Medicine, P.O. Box 22660, Amsterdam, 1100 AD, The Netherlands. E-mail: j.h.devries@amc.uva.nl.

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References
1. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R: Insulin pump therapy: a meta-analysis. *Diabetes Care* 26:1079–1087, 2003
2. Pickup J, Mattock M, Kerry S: Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 324:705, 2002
3. Schade DS, Valentine V: Response to Cersosimo (Letter). *Diabetes Care* 26:967–968, 2003

Insulin Pump Therapy: a Meta-Analysis

Response to DeVries et al.

We thank DeVries et al. (1) for their letter in this issue of *Diabetes Care*. We acknowledge that nonrandomized parallel design studies have an inherent selection bias that could exaggerate group differences. Regarding the design of our study, we wanted to be as inclusive as possible in our review; therefore, we analyzed all the studies that met the criteria listed in the introduction of the article. We also clearly informed the readers that some of the parallel design studies (2–12) did not follow a randomized design, which is a methodological issue that we incorporated in subsequent discussions pertaining to the results.

The test for homogeneity for all 11 studies was not statistically significant ($P = 0.99$), implying that there was no evidence to indicate the studies were different. We reran the analyses for the parallel design studies, separating the randomized and nonrandomized studies. For the randomized studies, a Q-statistic of 3.92 ($P = 0.73$) suggests the studies are homogeneous. The weighted summary mean difference was 0.375, with a 95% CI of 0.14–0.61, indicating that there was a significant difference between the two treatment approaches. For the nonrandomized studies, a Q-statistic of 24.99 ($P > 0.99$) suggests the studies are homogeneous. The weighted summary mean difference was 1.32, with a 95% CI of 1.13–1.51, indicating that there was a significant difference between the two treatment approaches. In sum, both sets of studies show a significant difference between continuous subcutaneous insulin infusion therapy and multiple daily injection or conventional therapy, although as expected, the average difference in means is larger for the nonrandomized studies.

In addition, the meta-analyses were separetely conducted on parallel ($n = 11$) and paired designs ($n = 41$) separately. We arrived at the same conclusions for both sets of analyses. Our discussion and recommendations are based on both analyses and take into account all methodological and quantitative observations made with respect to the studies involved in the meta-analysis.

Jill Weissberg-Benchell, PhD, CDE[1]
Jeanne Antisdel-Lomaglio, PhD[2]
Roopa Seshadri, PhD[3]

From the [1]Department of Child and Adolescent Psychiatry, Children's Memorial Hospital, Chicago, Illinois; the [2]Cancer Support Center, Homewood, Illinois; and the [3]Children's Research Institution, Children's Memorial Hospital, Chicago, Illinois.

Address correspondence to Dr. Jill Weissberg-Benchell, Children's Memorial Hospital, Department of Child & Adolescent Psychiatry, 2300 Childrens Plaza, Box 10, Chicago, Illinois 60614. E-mail: jwbenchell@childrensmemorial.org.

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References
1. DeVries JH, Heine RJ: Insulin pump therapy: a meta-analysis (Letter). *Diabetes Care* 26:2485, 2003
2. Bell DS, Ackerson C, Cutter G, Clements RS Jr: Factors associated with discontinuation of continuous subcutaneous insulin infusion. *Am J Med Sci* 295:23–28, 1988
3. Beck-Nielsen H, Richelsen B, Schwartz Sorensen N, Hother Nielsen O: Insulin pump treatment: effect on glucose homeostasis, metabolites, hormones, insulin antibodies and quality of life. *Diabetes Res* 2:37–43, 1985
4. Knight G, Boulton AJ, Drury J, Ward JD: Long term glycaemic control by alternative regimens in a feasibility study of con-

tinuous subcutaneous insulin infusion. *Diabetes Res* 3:355–358, 1986
5. Goicolea Opacua I, Hernandez Colau I, Vazquez Garcia JA: Comparative study between the subcutaneous continuous insulin infusion pump and optimized conventional treatment: effects at 6 months (article in Spanish). *Rev Clin Esp* 179:3–7, 1986
6. Olsen T, Richelsen B, Ehlers N, Beck-Nielsen H: Diabetic retinopathy after 3 years' treatment with continuous subcutaneous insulin infusion (CSII). *Acta Ophthalmol (Copenh)* 65:185–189, 1987
7. Edelmann E, Walter H, Biermann E, Schleicher E, Bachmann W, Mehnert H: Sustained normoglycemia and remission phase in newly diagnosed type I diabetic subjects: comparison between continuous subcutaneous insulin infusion and conventional therapy during a one year follow-up. *Horm Metab Res* 19:419–421, 1987
8. Dahl JS, Toriesen P, Hanssen K, Sandvik L, Aagenes O: Increase in insulin antibodies during continuous subcutaneous insulin infusion and multiple-injection therapy in contrast to conventional treatment. *Diabetes* 36:1–5, 1987
9. Bibergeil H, Huttl I, Felsing W, Felsing U, Seidlein I, Herfurth S, Dabels J, Reichel G, Luder C, Albrecht G, et al: Thirty six months continuous subcutaneous insulin infusion (CSII) in insulin dependent diabetes (IDDM): influence on early stages of retinopathy, nephropathy and neuropathy: psychological analysis. *Exp Clin Endocrinol* 9:51–61, 1987
10. Tubiana-Rufi N, de Lonlay P, Bloch J, Czernichow P: Remission of severe hypoglycemic incidents in young diabetic children treated with subcutaneous infusion (article in French). *Arch Pediatr* 3:969–976, 1996
11. Guerci B, Meyer L, Delbachian I, Kolopp M, Ziegler O, Drouin P: Blood glucose control on Sunday in IDDM patients: intensified conventional insulin therapy versus continuous subcutaneous insulin infusion. *Diabetes Res Clin Pract* 40:175–80, 1998
12. Boland, EA, Grey M, Oesterle A, Frederickson L, Tamborlane WV: Continuous subcutaneous insulin infusion: a new way to lower risk of severe hypoglycemia, improve metabolic control, and enhance coping in adolescents with type 1 diabetes. *Diabetes Care* 22:1779–1784, 1999