

## OBSERVATIONS

## Ethnic Differences in $\beta$ -Cell Functional Reserve and Clinical Features in Patients With Ketosis-Prone Diabetes

**D**iabetic 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  $\chi^2$  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  $\beta$ -cell function from those with absent  $\beta$ -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  $\geq 0.33$  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,  $0.41 \pm 0.35$  nmol/l, compared with  $0.25 \pm 0.45$  in the African American and  $0.24 \pm 0.32$  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  $\geq 0.33$  nmol/l. The C-peptide-to-glucose ratios were  $0.038 \pm 0.021$ ,  $0.02 \pm 0.029$ , and  $0.024 \pm 0.034$  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  $\geq 30$  kg/m<sup>2</sup> (5.70, 2.61–13.04) were significant predictors of fasting plasma C-peptide  $\geq 0.33$  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  $\beta$ -cell functional reserve, as assessed by a fasting serum C-peptide concentration  $\geq 0.33$  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  $\beta$ -cell function and insulin sensitivity in ketosis-prone diabetes are needed to better understand this syndrome.

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## Modulation of Oxidative and Antioxidative Status in Diabetes by Asphaltum Panjabinum

**O**xidative stress in diabetes, a common metabolic disorder, damages organs, including the  $\beta$ -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 ( $6.52 \pm 1.68$  nmol/ml plasma) compared with their higher pretreatment values ( $15.56 \pm 5.40$  nmol/ml plasma), whereas values of catalase in diabetic subjects ( $2,814.22 \pm 737.49$   $\mu$ mol/ml hemolysate) were significantly increased after

treatment with shilajit ( $3,151.68 \pm 158.41 \mu\text{mol/ml}$  hemolysate). However, values of superoxide dismutase (SOD) ( $8.55 \pm 4.48 \mu\text{mol/l}$  hemolysate) and glutathione peroxidase ( $3.29 \pm 1.02 \mu\text{mol/ml}$  hemolysate) in diabetic subjects were reduced after shilajit treatment ( $5.57 \pm 3.26 \mu\text{mol/l}$  and  $1.71 \pm 0.28 \mu\text{mol/ml}$  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.

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## 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  $51.9 \pm 10$  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*, *Phoradendron*, 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.

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## 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 pre-existing 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  $\mu$ mol/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 reactivity 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 afebrile, with a pulse of 70 bpm in sinus rhythm, blood pressure 85/40 mmHg, and O<sub>2</sub> 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  $\mu$ mol/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<sub>2</sub>O. 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  $\mu$ mol/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 contributory 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 absorption 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, epigastric 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.

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## 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
<i>n</i>	233	282	
Age (years)	55.7 ± 20.7	57.4 ± 20.2	<i>P</i> = 0.4
Men	121 (51.9)	163 (57.8)	<i>P</i> = 0.2
Insulin use	189 (83.3)	202 (76.8)	<i>P</i> = 0.1
Initial CBGC [mmol/l (mg/dl)]	2.3 ± 0.8 [41 ± 14]	2.2 ± 0.7 [40 ± 13]	<i>P</i> = 0.08
Initial GCS	11 (8–13)	12 (10–14)	<i>P</i> = 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.

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## 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  $54 \pm 17$ ) and had a diabetes duration of 2–47 years (mean  $17 \pm 10$ ). Their mean BMI was  $22 \pm 3$  kg/m<sup>2</sup>, HbA<sub>1c</sub>  $7.0 \pm 0.9\%$ , triglycerides  $94 \pm 44$  mg/dl, total cholesterol  $201 \pm 32$  mg/dl, LDL  $107 \pm 25$  mg/dl, and HDL  $75 \pm 18$  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  $30 \mu\text{g}/\text{mg}$  creatinine and  $300 \mu\text{g}/\text{mg}$  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  $152 \pm 9/91 \pm 17$  mmHg) and with clinic normotension ( $n = 36$ ) (mean SBP/DBP  $118 \pm 11/73 \pm 11$  mmHg). In contrast, the prevalence of nephropathy with eight microalbuminuria and three clinical albuminuria (mean albumin excretion  $231 \pm 437 \mu\text{g}/\text{mg}$  creatinine,  $n = 11$ ) in the patients with morning hypertension (mean SBP/DBP  $148 \pm 16/82 \pm 11$  mmHg,  $n = 14$ ) was significantly higher (OR 260 [12–5,404],  $P < 0.001$ ) than that ( $n = 0$ ) (mean albumin excretion  $7.0 \pm 6.1 \mu\text{g}/\text{mg}$  creatinine) with morning normotension (mean SBP/DBP  $115 \pm 12/70 \pm 8$  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 morn-

ing 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<sub>1c</sub>, 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 ( $0.99 \pm 0.01$ ) was significantly higher ( $P < 0.001$ ) than that of clinic SBP ( $0.49 \pm 0.10$ ) 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  $120 \pm 11/75 \pm 15$  mmHg,  $n = 8$ ). In contrast, the occurrence was not observed in those without morning hypertension, even though they had clinic hypertension (mean SBP/DBP  $160 \pm 8/85 \pm 8$  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 specific-

ity 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).

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## Telemedicine Improves Eye Examination Rates in Individuals With Diabetes

A model for eye-care delivery in underserved communities

**D** iabetic 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 com-

munities. 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 po-

tential effectiveness of telemedicine technology to improve adherence to clinical practice guidelines for diabetes care.

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

**T**ype 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)  $\gamma$ 2 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  $\gamma$ 2 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  $\gamma$ 2 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  $70 \pm 3$  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  $\gamma$  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  $\gamma$ 2 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  $\leq 49$  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  $\gamma$ 2 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.

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**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 ( $\mu$ U/ml)  $\times$  glucose (mmol/l)/22.5, as described elsewhere (6). Their mean  $\pm$

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SD age was  $64 \pm 13$  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  $\pm$  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 ( $0.7 \pm 1.1$  at 1 month vs.  $10 \pm 0$  at baseline). Circulating adiponectin concentrations were significantly increased at the 2- and 3-month treatment courses after the sarpogrelate hydrochloride start ( $36.2 \pm 10.8$  and  $34.5 \pm 11.1$  vs.  $13.4 \pm 9.8$   $\mu\text{g/ml}$ ). The significant lower hsCRP values were found at 2 weeks, 1 month, and 3 months after the treatment ( $0.02 \pm 0.01$ ,  $0.03 \pm 0.03$ , and  $0.03 \pm 0.02$  vs.  $0.20 \pm 0.13$  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 ( $4.5 \pm 1.9$  at 3 months vs.  $15.8 \pm 2.9$  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.

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## 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

**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

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.

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.

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## 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 glycosylated hemoglobin was performed. To accomplish this, bovine hemoglobin was glycosylated 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 nonglycosylated hemoglobin. Moreover hemorphin-7 peptides serum levels between diabetic and nondiabetic patients were compared. Serums from 31 diabetic (aged  $47 \pm 17$  years with a mean  $HbA_{1c}$   $8.4 \pm 1.7\%$ ) and 25 nondiabetic (aged  $39 \pm 15$  years) patients were estimated by an enzyme-linked immunosorbent assay procedure (3).

Results demonstrated that liberation of LVV-Hemorphin-7 and VV-Hemor-

phin-7 from in vitro glycosylated 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 ( $0.8 \pm 0.94$  vs.  $4.09 \pm 1.05 \mu\text{mol/l}$ ,  $P < 0.0001$ ). 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 exogenous or endogenous 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.

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## 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  $480 \text{ pmol} \cdot \text{m}^2 \cdot \text{min}^{-1}$ . Blood glucose was clamped at  $5.0 \text{ mmol/l}$  by infusing glucose at varying rates. Average QT and QTc (QT/R-R interval<sup>-0.5</sup>) 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 ( $415 \pm 7$  vs.  $389 \pm 6$  ms,  $P < 0.01$ ) and QTc intervals ( $425 \pm 5$  vs.  $400 \pm 5$  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 ( $956 \pm 18$  to  $894 \pm 15$  ms,  $P < 0.001$ ) and QT interval remained unchanged ( $404 \pm 5$  vs.  $406 \pm 5$  ms, NS), whereas QTc interval increased ( $414 \pm 4$  to  $430 \pm 4$  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.

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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  $\geq 25 \text{ kg/m}^2$ , elevated fasting glucose ( $6.1\text{--}6.9 \text{ mmol/l}$  [ $110\text{--}125 \text{ mg/dl}$ ] for impaired fasting glucose and  $\geq 6.9 \text{ mmol/l}$  [ $\geq 126 \text{ mg/dl}$ ] for diabetes), calculated LDL cholesterol  $>2.8 \text{ mmol/l}$ , and fasting triglyceride  $\geq 1.7 \text{ mmol/l}$ . (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.

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## Fenofibrate Monotherapy Induced Rhabdomyolysis

**F**enofibrate (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 coenzyme A (HMG-CoA) reductase inhibitors are being used more frequently in the treatment of combined hyperlipidemia and to lower non-HDL cholesterol to





renal dialysis catheters, and tracheostomy tubes.

*M. chelonae* is resistant to usual anti-tuberculous 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 persistent cutaneous infection, especially in patients who are relatively immunocompromised.

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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.

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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  $\beta$ -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).

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## 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.”

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## 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 separately 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.

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