poorly controlled insulin-dependent diabetes mellitus (IDDM) (1,2). Many drugs have been suggested as active treatment (clonidine, somatostatine, loperamide, calcium-channel blockers, intestinal antibiotics, tricyclic antidepressants, and anticholinergic agents), but clinical responses are often unsatisfactory, and diarrhea (with incontinence) may last for days or weeks despite medical efforts. Here we describe the case of a 48-year-old man, who has suffered from IDDM since he was 21. His HbA_{1c} ranged from 8.4 to 9.3% over the last 12 months, even though he was on multiple insulin injection therapy. His diabetes complications included background retinopathy, impotence, and peripheral and autonomic neuropathy (which was diagnosed through electromyogram and cardiovascular tests). Some months ago, he presented with several episodes of incontinence and diarrhea, which were treated at separate times with loperamide, rifamixine, verapamil, clonidine, amytriptiline, or anticholinergic drugs, without evidence of clinical relief.

The intermittent attacks (5–10 stools daily) lasted from 1 week to 10 days and were apparently unmodified by the prescribed therapy; then, bowel habit returned to normal or, more often, to constipation. Body mass index remained quite unchanged, and no pathological results were obtained on sequential collected coprocultures, abdomen ultrasonographic scan, X-ray enema, and fibrecolonoscopy. On the contrary, ano-rectal manometry showed impaired anal sensation. So, with the patient's informed consent, we prescribed ondasentron hydrochloride, an antagonist of 5-hydroxytryptamine (5-HT) type 3 receptors, which was suggested to prolong colonic transit in healthy volunteers (3) and was proposed in the treatment of diarrhea-predominant irritable bowel syndrome (4). Initially, ondasentron was administered in a dosage of 8 mg three times per day for 5 days; but, on other occasions, a prompt 2-day treatment was sufficient to abolish abdominal disorders. This observation suggests that rapid action on 5-HT type 3 receptors may be effective treatment for this diabetes complication and indicates the importance of serotonin as one of the putative noncholinergic alternative control systems of intestinal smooth muscle (5).

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References

1. Feldman M, Schiller LR: Disorders of gastrointestinal motility associated with diabetes mellitus. *Ann Intern Med* 98:378–384, 1983
2. Caviezel F, Bossi A, Baresi A, Salvini A: Ano-rectal manometry as an evaluating test for impaired ano-rectal function in diabetes mellitus. *Acta Diabetol Lat* 23:331–338, 1986
3. Talley NJ, Phillips SF, Haddad A, Miller LJ, Twomey C, Zinsmeister AR, MacCarthy RL, Ciociola A: GR 38032F (ondasentron), a selective 5HT3 receptor antagonist, slows colonic transit in healthy man. *Dig Dis Sci* 35:477–480, 1990
4. Steadman CJ, Talley NJ, Phillips SF, Zinsmeister AR: Selective 5-hydroxytryptamine type 3 receptor antagonism with ondasentron as treatment for diarrhea-predominant irritable bowel syndrome: a pilot study. *Mayo Clin Proc* 67: 732–738, 1992
5. Fozard JR: Neuronal 5-HT receptors in the periphery. *Neuropharmacology* 23:1473–1486, 1984

Autonomic Neuropathy and Corrected QT Interval Prolongation

There is a relationship

Bravenboer et al. (1) found no correlation between the corrected QT interval (QT_cI) and cardiovascular autonomic tests. During a 9-year-long study on the same topic, we examined 553 subjects; 162 patients (14–57 years of age, mean of 33.2 years, mean diabetes duration of 13 years) had insulin-dependent diabetes mellitus (IDDM), and 94 had non-insulin-dependent diabetes mellitus (NIDDM) (27–69 years of age, mean of 52 years, mean diabetes duration of 9 years). Because liver diseases are independent risk factors of autonomic neuropathy (AN) (2,3), chronic alcoholics were classified into three groups: 32 without liver disease (26–55 years of age, mean of 42.6 years), 48 with fatty liver (26–58 years of age, mean of 42.7 years), and 83 with alcohol-related cirrhosis (28–69 years of age, mean of 48.3 years). We also examined 49 patients (22–68 years of age, mean of 52 years) with chronic nonalcoholic liver disease and 85 healthy control subjects (14–66 years of age, mean of 41.7 years). Parasympathetic function was evaluated by heart-rate variation during deep breathing, standing (30:15 ratio), and Valsalva maneuver; sympathetic function was assessed by blood pressure response to standing and to the sustained handgrip test (4). QT_c was determined with Bazett's formula (5,6). The mean value of five subsequent sinus-beats was calculated.

At summarized statistical evaluation, heart-rate response to deep breathing ($P < 0.001$), Valsalva ratio ($P < 0.01$), sustained handgrip test ($P < 0.001$), and blood pressure response to standing ($P < 0.05$) showed a significant linear regression to aging, but the 30:15

Table 1—*QT_c-interval prolongation related to the severity of AN*

		Number of abnormal reflex tests on patient					
	n	0	1	2	3	4	5
IDDM	162						
QT_c (ms)		397 ± 24	422 ± 24	442 ± 22	451 ± 19	462 ± 19	489 ± 12
n		55	34	45	17	9	2
NIDDM	94						
QT_c (ms)		395 ± 15	415 ± 19	440 ± 15	456 ± 16	473 ± 17	—
n		24	23	18	21	8	0
Alcoholic patients	32						
No liver disease							
QT_c (ms)		392 ± 9	423 ± 9	442 ± 14	—	—	—
n		19	8	5	0	0	0
Fatty liver	48						
QT_c (ms)		404 ± 9	426 ± 14	442 ± 13	463 ± 17	477 ± 11	—
n		6	10	18	10	4	0
Cirrhosis	83						
QT_c (ms)		408 ± 21	430 ± 24	440 ± 15	458 ± 13	471 ± 12	497
n		7	14	19	27	15	1
Nonalcoholic patients	49						
QT_c (ms)		412 ± 19	421 ± 14	445 ± 20	457 ± 26	470 ± 12	—
n		9	15	10	11	4	0

Data are means ± SD.

ratio did not. Eighty-two control subjects had normal results in all five tests and a mean QT_c of 397 ± 21 (SD) ms. Patients were classified according to the severity of AN, which was based on the number of abnormal reflex indexes. Significant linear regression was found between QT_cI prolongation and severity of AN in all groups ($P < 0.001$) (Table 1). Abnormal QT_cI (>440 ms) was seen significantly more often in patients with AN than in those with normal autonomic function in IDDM, in NIDDM, in all three alcoholic groups ($P < 0.001$), and in nonalcoholic patients ($P < 0.01$). We also analyzed the relation between QT_c lengthening and changes of the five reflex indexes separately. In IDDM and in alcoholic cirrhotic patients, all five comparisons were significantly correlated with QT_cI ($P < 0.001$, except of the sustained handgrip test in IDDM: $P < 0.01$). Levels of significance in NIDDM were as follows: NS for Valsalva ratio, $P < 0.05$ for 30:15 ratio, and $P < 0.001$ for the three other tests. In alcoholic patients without liver disease and in those with fatty liver, QT_cI correlated significantly with deep breathing test ($P < 0.01$ and $P < 0.001$, respectively) and with the handgrip test ($P < 0.05$ in both groups). In nonalcoholic patients, significant correlation was found with the deep breathing test, 30:15 ratio (both $P < 0.05$), and the handgrip test ($P < 0.001$). Our data provide evidence of a relation between the presence and severity of AN and the degree of QT_cI prolongation in all groups examined. Thus, the changes in diabetic patients appear to be attributable to autonomic impairment rather than to diabetes per se. QT_cI prolongation correlated significantly with both parasympathetic and sympathetic test results, indicating that, besides the established role of sympathetic dysfunction, even parasympathetic damage may contribute to the development of QT_cI prolongation. We are in agreement with Bravenboer et al. (1) that QT_cI alone should not be used for the diagnosis of the severity of AN. However, evaluation of QT_cI may be a simple additional diagnostic aid to identify individuals with an increased cardiovascular risk. Myocardial infarction is the prime cause of death in diabetic patients. The prognostic importance of QT_cI at discharge after myocardial infarction has been proved (7).

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References

1. Bravenboer B, Hendriksen PH, Oey LP, Gispen WH, van Huffelen AC, Erkelens

DW: Is the corrected QT interval a reliable indicator of the severity of diabetic autonomic neuropathy? *Diabetes Care* 16: 1249–1253, 1993
2. Kempler P, Váradi A, Szalay F: Autonomic neuropathy in liver disease. *Lancet* II:1332, 1989
3. Kempler P, Váradi A, Tamás Gy: Autonomic neuropathy in newly diagnosed diabetes mellitus. *Diabetes Care* 16:848–849, 1993
4. Ewing DJ, Clarke BF: Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 285:916–918, 1982
5. Bazett HC: An analysis of time: relations of electrocardiograms. *Heart* 7:353–370, 1920
6. Gonin JM, Kadrofske M, Schmaltz S, Bastyr EJ, Vinik AI: Corrected QT interval prolongation as diagnostic tool for assessment of cardiac autonomic neuropathy in diabetes mellitus. *Diabetes Care* 13:68–71, 1990
7. Ahnve S, Gilpin E, Madsen EB, Froelicher V, Henning H, Ross J: Prognostic importance of QT_c interval at discharge after acute myocardial infarction: a multicenter study of 865 patients. *Am Heart J* 108:395–400, 1984

Serum Lipoprotein(a) Is Not Increased in NIDDM Patients With Microalbuminuria

Recently, much interest has been focused on lipoprotein(a) (Lp[a]) and diabetes (1). Particularly, contrasting data are available in the literature about the levels of Lp(a) in non-insulin-dependent diabetes mellitus (NIDDM) and its possible relationships with incipient diabetic nephropathy, i.e., with microalbuminuria (2–4). We determined Lp(a) levels and lipoprotein patterns in Caucasian NIDDM patients grouped according to their urinary albumin excretion (UAE) rate determined on three consecutive 24-h urine samples. Of the patients, 69 were microalbuminuric (UAE rate between 30 and 300 mg/24 h, median value and range: 66 [30–281] mg/24 h) and 60 were normoalbuminuric (UAE rate < 30 mg/24 h, 8.2 [5.0–27] mg/24 h). Sixty healthy individuals served as control subjects. The three groups of subjects were comparable for sex, age, duration of diabetes, prevalence of hypertension (47 vs. 61%), cardiopathy (26 vs. 30%), arteriopathy (14 vs. 14%), cardiovascular accidents (13 vs. 14%), retinopathy (24 vs. 18%), and glycometabolic control (Table 1). None of the diabetic patients or control subjects was affected by diseases or taking any medications known to influence Lp(a) levels. All diabetic patients were on diet and/or hypoglycemic agents.

Lp(a) serum concentrations were measured by a commercial ELISA sandwich method, using a polyclonal antibody (Biopool, Umea, Sweden) (interassay and intrassay coefficient of variation were 5 and 12%, respectively). The Mann-Whitney test was used to compare distributions. Correlations between parameters were looked at with the Kendall correlation test.

The median concentration of Lp(a) in microalbuminuric patients (9.2 mg/dl, range 0.1–116.8) was not significantly different with respect to that found in patients with normal UAE rates (8.0 mg/dl, range 0.3–69) (Table 1). Furthermore, the median Lp(a) concentration was not significantly different in the whole group of NIDDM patients (8.2 mg/dl, range 0.1–116.8) with respect to control subjects (9.2 mg/dl, range 1.6–64.5). We did not find any positive correlation between Lp(a) serum concentration and UAE rate in either normo- or microalbuminuric NIDDM patients or in the whole population of diabetic subjects. In both groups of diabetic patients, the mean HbA_{1c} and blood glucose levels did not show a positive correlation with serum Lp(a) concentrations in both the normoalbuminuric and microalbuminuric patients. Median concentrations of serum triglycerides and apolipoprotein B were significantly higher in microalbuminuric with respect to normoalbuminuric patients ($P < 0.001$ and $P < 0.05$, respectively), whereas the two groups did not show any significant difference in the median of other lipidic parameters.

Our findings are in contrast with those reported previously by Jenkins et al. (2): apolipoprotein A serum concentration in a relatively small sample of microalbuminuric NIDDM patients ($n = 26$) was higher than in normoalbuminuric subjects ($n = 56$). However, we included more than twice as many patients with an abnormal UAE rate compared with the previous study. Based on our data and taking into consideration the well-described ethnic influences on Lp(a) (5), it cannot be excluded that the discrepancies in the results between the two studies could be caused by genetic and/or racial differences of the populations studied. Another possible factor confounding interpretation of the results of Jenkins et al.'s (6) study may be the investigation of insulin-treated NIDDM.

In conclusion, we confirm another study (7) showing that NIDDM subjects do not have higher Lp(a) levels with respect to the general population. The main finding of our study is that Lp(a) levels were not associated with microalbuminuria in NIDDM patients treated with diet and hypoglycemic agents with relatively good glycometabolic control. Among NIDDM patients with normal UAE rates and with microalbuminuria, 16 and 17 subjects, respectively, had a serum Lp(a) concentration higher than 25 mg/dl, which is the usual cutoff value identifying subjects at high cardiovascular risk. Interestingly, in the microalbuminuric patients, the median Lp(a) concentration above this cut off was significantly higher than for normoalbuminuric patients (52 mg/dl, range 28.2–116.8 mg/dl vs. 32.7 mg/dl, range 26.2–69 mg/dl; $P < 0.05$). It could be hypothesized that only these latter patients may constitute the subgroup of diabetic