

Clinical Observations of Exenatide Treatment

Controlled clinical trials have demonstrated the effectiveness of exenatide in reducing glucose and weight (1–4). We herein report our initial clinical experience.

Clinic charts of the first 200 patients consecutively treated were retrospectively analyzed. Of these patients, 22% were lost to follow-up, noncompliant, or chose not to continue for reasons other than side effects. Thirteen percent discontinued treatment due to side effects including nausea (8%), urticaria (2%), jitteriness not associated with hypoglycemia (1.5%), abdominal pain (1%), and hypoglycemia (0.5%). In the single case of hypoglycemia, a self-monitored glucose of <60 mg/dl was documented and the patient was not taking a hypoglycemic medication. Urticaria was localized to the injection site; appearance and disappearance correlated with the time action of exenatide and resolved upon discontinuing the medication. One patient continued exenatide despite urticaria, and the urticaria became generalized.

For the 65% continuing treatment for at least 12 weeks, other diabetes concurrent medications were none (1.5%), thiazolidinedione (TZD) (45%), sulfonylurea (28%), metformin (40.5%), and insulin (21%). Mean weight loss at 12 weeks was 3.89 kg in the entire group and 4.23 kg in those on TZDs. The mean HbA_{1c} (A1C) decreased from 6.95 to 6.57% ($P < 0.005$). The mean diabetic concurrent medication dosages were reduced in those on sulfonylureas (64%), metformin (22%), TZDs (20%), and insulin (21%). In all cases, the reduction was significant ($P < 0.05$).

We believe the greater weight loss at 12 weeks compared with published studies at 30 weeks (1–4) (3.89 vs. 0.9–2.5 kg) is related to the encouragement and nutritional and activity support given to our patients. We are unsure whether one can expect the rate of weight loss to continue. The weight loss despite concurrent treatment with TZDs is encouraging since weight gain is a common problem with TZD treatment (5). Our results demonstrate not only a significant reduction in A1C but also the significant reduction in dosage of other antihyperglycemic concurrent

medications. The incidence of urticaria needs to be verified in larger observational studies.

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Prevalence of Diabetes in Patients With Multiple Sclerosis

Diabetes prevalence is unknown in patients with multiple sclerosis (MS). The objective of this study was to estimate the prevalence of both types of diabetes in MS patients. We reviewed the database from our MS center. A total of 1,206 patients were diagnosed and treated at the center for MS in a duration of 6 years (1991–1997). Of those patients, 92 were diagnosed as having diabetes. Health records were reviewed for

sex, race, type of diabetes (type 1 versus type 2), age of onset of MS and diabetes, and the presence of family history of diabetes (among first-degree relatives).

The diabetes prevalence was 7.7% in MS patients; 11 patients (0.92% [95% CI 0.38–1.46]) had type 1 diabetes, which is not significantly different from the general population ($P = 0.15$), and 6.75% (95% CI 6.74–6.76) had type 2 diabetes, which is higher than in the general population at that time ($P = 0.0054$).

The female-to-male ratio was 1.79 among the diabetic subjects. Among patients with type 2 diabetes, 35% developed diabetes before the diagnosis of MS. However, of those who developed diabetes after the diagnosis of MS, 41.5% were diagnosed in the first 5 years. The mean duration of MS before developing diabetes was 9.9 ± 9.03 (means \pm SD) years. We noted a positive family history of diabetes among first-degree relatives of 38% in those with type 2 diabetes and MS. Age distribution of type 2 diabetes shows a peak at the 5th and 6th decades of life. In type 1 diabetes, all patients had diabetes before onset of MS, except one case (diabetes 5 years after MS), with a mean duration of 16.8 ± 11.6 years of diabetes before diagnosis with MS. We also noted a positive family history of diabetes in 36% of patients with type 1 diabetes and MS.

The association of type 1 diabetes with MS may represent only a chance occurrence of two autoimmune diseases. However, both share epidemiological and immunological features and may be primed by virus-induced mechanisms (1). There is also a worldwide north-south prevalence gradient, more common in the northern zones of North America and Europe.

The prevalence of type 2 diabetes was higher in MS patients, probably because of muscle disease from nerve demyelination or use of ACTH and glucocorticoids as treatments. Several investigators have found some metabolic disorders linking both diseases, such as abnormalities in fat, calcium, and vitamin D metabolism. Also, there is evidence of disruption of myelin due to changes in glucose levels (2). Whether this observation has implications for a link between diabetes and MS is merely speculative, and further evidence of a relationship should be confirmed.

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Poor Glucose Control in the Year Before Admission as a Powerful Predictor of Amputation in Hospitalized Patients With Diabetic Foot Ulceration

Although there is a strong association between lower-extremity amputation (LEA) and HbA_{1c} (A1C) in diabetic patients (1,2), little information is available on glucose control in the period preceding and following LEA (3). Our objective was to evaluate the predictors of LEA and to examine the role of blood glucose control during the year before and the year after admission. A total of 122 diabetic patients (82 men and 40 women aged 69.7 ± 10.9 years, disease duration 19.7 ± 10.4 years) consecutively admitted for diabetic foot ulcers to the Medicine Department of United Hospitals of Bergamo between January 2003 and December 2004 were enrolled in our observational study and assigned to one of three groups.

The prevalence of long-term diabetes complications was similar in each group; >75% had peripheral polyneuropathy, nephropathy, retinopathy, and ischemic cardiomyopathy, and >90% had peripheral vascular disease. Glycemic control was evaluated before and after admission using the mean of three A1C levels mea-

sured in the year preceding admission and in the year following discharge. Patients were reevaluated 1 year after admission and assigned to one of three groups: group A, major amputation (n = 28); group B, minor amputation (n = 44); and group C, no amputation (n = 50). Major amputation was defined as amputation above the ankle, and minor amputation was defined as amputation below the ankle.

Data are shown as means ± SD. Categorical variables were compared by χ^2 test, continuous variables by ANOVA.

In the year before admission, mean A1C levels were significantly higher in groups A (9.7 ± 1.5%) and B (9.1 ± 1.9%) than in the group C (7.9 ± 1.3%, P < 0.001 vs. A and P < 0.05 vs. B). Similarly at admission, A1C levels were higher in groups A (10.1%) and B (9.4 ± 1.8%) than in the group C (8.1 ± 1.5%, P < 0.001). A1C levels decreased in all groups after 1 year of follow-up: 8.4 ± 1% in group A, 7.9 ± 1.3% in group B, and 7.5 ± 1.2% in group C (P < 0.05 vs. A).

At admission, patients in groups A and B had a higher ulceration grade according to Wagner's classification (3.9 ± 0.4 and 3.7 ± 0.4, respectively) than those in group C (2.7 ± 1.1, P < 0.001). The prevalence of patients with LDL cholesterol levels <100 mg/dl was significantly lower in groups A (38%) and B (40%) than in group C (65%; P < 0.01 vs. A and P < 0.05 vs. B). More patients in group C (75%, P < 0.05) were on aspirin therapy than in groups A (61%) and B (59%). The frequency of optimal blood pressure control (\leq 130/80 mmHg) was ~50% in all groups. Patients in group A (21%, P < 0.001 vs. B and C) received less follow-up with a specialist in a diabetes clinic than patients in the groups B (50%) and C (56%).

Although hypertension and cholesterol levels were inadequately treated, and aspirin therapy underused in a large number of these patients, multivariate logistic regression analysis revealed that only A1C level and ulceration grade were independently associated with LEA.

In conclusion, poor metabolic control and inadequate treatment of modifiable risk factors are powerful predictors of LEA in patients hospitalized for diabetic foot ulcers. We suggest that all diabetic patients with poor metabolic control and risk factors associated with cardiovascular disease receive early referral for education

and aggressive treatment with a diabetes clinic.

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Type 1 Diabetes and Autism Association Seems to Be Linked to the Incidence of Diabetes

We read with interest the article of Freeman et al. (1) reporting a higher prevalence of autism spectrum disorder in pediatric patients with type 1 diabetes in Toronto than in the general population (0.9% [95% CI 0.3–1.5 vs. 0.34–0.67]).

The finding was, however, not confirmed by Harijutsalo and Tuomilehto (2), who reported a prevalence of autism spectrum disorders in type 1 diabetic patients similar to that in the population aged <18 years in northern Finland

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Stability of Body Weight in Type 2 Diabetes

Response to Chaudhry et al.

In a recent volume in this journal, Chaudhry et al. (1) reported their findings of weight change in 205 men with diabetes. They conclude that over the course of at least 5 years, modest weight gain is the norm in men with diabetes. In contrast, we have previously published data (2) on 816 adult Pima Indians with diabetes, which showed that the general pattern of weight change after a diagnosis of diabetes was weight loss. These apparently discrepant findings may reflect ethnic differences, but there are a number of other potential reasons for the differences.

The Chaudhry et al. study was limited to men, while our study included men and women. We found no difference in patterns of weight change between the sexes; therefore, that does not seem to explain the divergent results. We also found that the pattern of weight change varied at different durations of diabetes, with weight gain being predominant in the first 2 years after diagnosis, followed by continuing weight loss. Diabetes duration was not a factor that was analyzed in the Chaudhry et al. study, but all subjects had a minimum duration of diabetes of 5 years; thus, it seems an unlikely reason for the differing results. A more likely explanation is the difference in treatments reported. In our study, the majority of subjects were receiving no pharmacological agents for diabetes, and there was a greater degree of weight stability among those receiving insulin or oral agents; in fact, among those taking insulin, there was a tendency toward weight gain in some of the duration groups. The Chaudhry et al. study only includes sub-

jects receiving either oral agents or insulin. They reported weight loss among subjects taking metformin. If the majority of our subjects had been receiving metformin, that might explain the weight loss we reported among the subjects taking oral agents. However, at the time of our study, metformin was not as widely used as it is today, and not enough patients received metformin to allow for a subanalysis of this group, which primarily consisted of people taking sulfonylureas. Finally, the criteria for enrollment in the two studies were very different. In the Chaudhry et al. study, only men who had attended annual examinations over the study period were included, with data taken only from the baseline and final examination. In our study, we only required that a subject had attended two or more research examinations (after being diagnosed with diabetes) with no regard to how regularly they attended hospital appointments. It would be interesting to know whether the Chaudhry et al. findings would differ if they had included all possible subjects, regardless of clinic attendance or pharmacologic therapy.

In summary, the pattern of weight change in type 2 diabetes is not well understood and may be quite variable according to patient characteristics.

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Stability of Body Weight in Type 2 Diabetes

Response to Looker et al.

We thank Looker et al. (1) for their comments regarding our study (2). We also appreciate the authors calling attention to their study (3) regarding weight change in Pima Indians before and after the diagnosis of diabetes. As Looker et al. point out, the two study populations are very different in regard to age, sex, and genetic background. The study design, the study inclusion criteria, and the treatment categories were all different, and the number of times the subjects were observed during the study period was different. Therefore, it is difficult for us to compare our results with those published previously by Looker et al. Nevertheless, our own data, as well as the data obtained in Pima Indians, indicate that rapid weight gain is not a characteristic of most people with type 2 diabetes.

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