Effect of Pramlintide on A_{1C} and Body Weight in Insulin-Treated African Americans and Hispanics With Type 2 Diabetes: A Pooled Post Hoc Analysis

D. Maggs, L. Shen, S. Strobel, D. Brown, O. Kolterman, and C. Weyer

An unresolved problem in the management of type 2 diabetes is that improvement of glycemic control with insulin, insulin secretagogues, and insulin sensitizers is often accompanied by undesired weight gain. This problem is of particular concern in ethnic groups with a high propensity for diabetes and obesity, such as African Americans and Hispanics. Two 1-year, randomized, double-blind, placebo-controlled clinical trials in insulin-treated patients with type 2 diabetes have shown that adjunctive therapy with pramlintide, an analog of the human β-cell hormone amylin, reduces A_{1C} with concomitant weight loss, rather than weight gain. To assess the effect of pramlintide in various ethnic groups with type 2 diabetes using insulin, we conducted a pooled post hoc analysis of the 2 trials, which included all Caucasian (n = 315), African American (n = 47), and Hispanic (n = 48) patients (age 57 years, A_{1C} 9.1%, body mass index [BMI] 33 kg/m^2, mean values) who completed 52 weeks of treatment with either pramlintide (120 μg twice daily or 150 μg 3 times a day) or placebo. Primary endpoints included changes from baseline to week 52 in A_{1C} and body weight. Collectively, pramlintide-treated patients achieved significant reductions from baseline in both A_{1C} and body weight (placebo-corrected treatment effects at week 52: −0.5% and −2.6 kg, respectively, both $P < .0001$). The simultaneous reduction in A_{1C} and body weight at week 52 was evident across all 3 ethnic groups and appeared to be most pronounced in African Americans (−0.7%, −4.1 kg), followed by Caucasians (−0.5%, −2.4 kg) and Hispanics (−0.3%, −2.3 kg). The glycemic improvement with pramlintide was not associated with an increased incidence of hypoglycemia over the entire study period (43% pramlintide *v* 40% placebo). Nausea, the most common adverse event associated with pramlintide treatment, was mostly mild and confined to the first 4 weeks of therapy (25% pramlintide *v* 16% placebo) with comparable patterns in the 3 ethnic groups. Thus, pending further experience, the combined improvement in glycemic and weight control with pramlintide treatment appears to be generalizable to a broad population of mixed ethnicity.

THE UNITED Kingdom Prospective Diabetes Study (UKPDS) has shown that intensified antihyperglycemic therapy, aimed at a reduction of A_{1C}, reduces the risk of long-term diabetic complications in patients with type 2 diabetes mellitus.[1,2] However, the UKPDS has also shown that type 2 diabetes is a progressive disease that is characterized by a steady decline in β-cell function and worsening hyperglycemia, despite the addition of multiple oral agents and insulin.[3] Even when treated with insulin, only 28% of the UKPDS participants achieved an A_{1C} value <7% after 9 years.[4] Among the barriers that hinder the attainment of glycemic goals with insulin in type 2 diabetes are an increased risk of hypoglycemia,[1] undesired weight gain,[1,5-8] and an inability to control excessive postprandial glucose excursions.[9,10]

These unresolved challenges with insulin therapy in type 2 diabetes are of particular concern in ethnic groups with a high propensity for diabetes and obesity, such as African Americans and Hispanics. Results from several community studies suggest that African American and Hispanic patients with type 2 diabetes have, on average, poorer glycemic control than Caucasians.[11-13] These findings were recently substantiated by results from the Third National Health and Nutrition Examination Survey (NHANES III), which found that as much as 50% of African American women and 45% of Hispanic men with type 2 diabetes had poor glycemic control (A_{1C} >8%) compared with 36% of Caucasians with the disease.[14] These ethnic differences in glycemic control did not appear to be attributable to differences in the use of oral agents or insulin.[14] In fact, poor glycemic control was particularly common in insulin-treated patients with type 2 diabetes.[14] Unfortunately, there is surprisingly little published data on ethnic differences in the response to different diabetes therapies. An ethnic comparison in the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM) suggested that African Americans and Caucasians may respond differently to intensification of insulin therapy.[15] This observation led the investigators to conclude that ethnic differences in glycemic response should be assessed when novel pharmacologic treatment modalities for type 2 diabetes emerge.[15]

Pramlintide, an analog of the β-cell hormone amylin, is currently in late-stage development as an adjunctive therapy to insulin for patients with type 1 and type 2 diabetes.[16-18] Amylin is normally cosecreted with insulin in response to meals; it complements the effects of insulin in postprandial glucose homeostasis and is deficient at mealtime in insulin-treated patients with type 1 and type 2 diabetes.[16-19] Short-term studies in patients with type 2 diabetes have shown that mealtime amylin replacement with pramlintide, as an adjunct to mealtime insulin replacement, leads to a marked reduction in postprandial glucose excursions.[20,21] This appears to be attributable to a correction of postprandial hyperglucagonemia[22] and a slowing of gastric emptying.[23] Two 1-year, randomized, double-blind, placebo-controlled US clinical studies in patients with type 2 diabetes have shown that the addition of pramlintide to preexisting insulin regimens facilitates a further reduction in A_{1C} that is accompanied by weight loss than weight gain.[24,25]

To assess whether these observations for pramlintide are also present in insulin-treated African Americans and Hispanics

From Amylin Pharmaceuticals, Inc, San Diego, CA.

Submitted April 11, 2003; accepted June 27, 2003.

Address reprint requests to Christian Weyer, MD, Amylin Pharmaceuticals, Inc, 9360 Towne Centre Dr, San Diego, CA 92121.

0026-0495/03/5212-0003$30.00/0
doi:10.1016/j.metabol.2003.06.003

Table 1. Baseline Demographic Characteristics and Concomitant Treatments

	Caucasian		African American		Hispanic	
	PBO	PRAM	PBO	PRAM	PBO	PRAM
N	164	151	21	26	26	22
Age* (yr)	58 ± 10	57 ± 9	58 ± 9	56 ± 9	51 ± 10	54 ± 12
Sex (% M/F)	60/40	58/42	29/71	46/54	50/50	32/68
Weight* (kg)	93.9 ± 18.8	96.9 ± 21.9	87.8 ± 16.8	97.8 ± 18.5	92.5 ± 17.9	88.8 ± 19.7
BMI* (kg/m^2)	31.5 ± 6.0	32.8 ± 7.1	31.6 ± 5.1	33.5 ± 6.1	33.7 ± 6.7	33.4 ± 6.0
A_{1C}* (%)	9.1 ± 1.2	8.9 ± 1.1	9.2 ± 1.8	9.7 ± 1.2	9.6 ± 1.1	9.3 ± 1.0
Diabetes duration* (yr)	12 ± 8	13 ± 8	11 ± 5	10 ± 6	13 ± 6	13 ± 7
Total daily insulin dose* (U)						
Baseline	67 ± 35	67 ± 35	53 ± 30	57 ± 31	77 ± 32	63 ± 24
Week 52	72 ± 37	70 ± 37	54 ± 32	56 ± 34	85 ± 39	69 ± 49
No. of daily injections†						
1	5 (3)	1 (0)	19 (10)	15 (912)	8 (0)	9 (9)
2	65 (62)	14 (12)	71 (76)	69 (73)	81 (81)	68 (59)
3+	29 (32)	83 (86)	10 (14)	15 (12)	12 (15)	23 (32)
Oral antihyperglycemic agents†						
MET only	9 (8)	5 (4)	10 (10)	8 (8)	15 (15)	14 (14)
SFU only	9 (9)	7 (7)	14 (14)	0 (0)	0 (4)	14 (14)
MET + SFU	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	14 (14)

*Data are mean ± SD.
†Percentage of patients, baseline (week 52).

with type 2 diabetes, we conducted a pooled, post hoc analysis examining the different ethnic groups in the 2 trials.

PATIENTS AND METHODS

Study Design

The designs of the 2 long-term, randomized, placebo-controlled, double-blind studies included in this pooled post hoc analysis have been described in detail previously.[24,25] In brief, both studies included patients with type 2 diabetes and utilized an add-on design, ie, pramlintide or placebo (injected subcutaneously twice daily or 3 times a day before the major meals) were added to pre-existing insulin regimens. Study medication (placebo or pramlintide), but not insulin or oral medications, was provided to the study participants as part of the study. Both studies were of 52 weeks duration and had the same primary and secondary efficacy end points (see below), with repeated assessment of A_{1C}, body weight, total daily insulin doses (recorded in subject diaries), and safety parameters throughout the study.

For the present analysis, we pooled data from all patients categorized as Caucasian, African American, and Hispanic who had been randomized to placebo or pramlintide 120 μg twice daily or 150 μg 3 times a day, the dosing regimens that showed efficacy in the individual pivotal trials in patients with type 2 diabetes.[24,25] Other ethnic groups were not included because they comprised less than 1.5% of the study population, thus precluding meaningful analysis.

Statistical Methods

All efficacy and safety analyses were performed on the intent-to-treat (ITT) population (all randomized patients who received at least 1 dose of study medication). The main efficacy end points included the changes from baseline to week 52 for both A_{1C} and weight. For the overall population, differences in A_{1C} and weight between pramlintide and placebo groups were analyzed descriptively and parametrically. Because the 2 studies were not powered prospectively for ethnic comparisons, differences in A_{1C} and body weight between pramlintide and placebo in the individual ethnic groups were only analyzed descriptively.

RESULTS

Patient Disposition and Baseline Demographics

Of the 1,194 patients enrolled in the 2 studies, 410 (34%) were randomized to either placebo or pramlintide (120 μg twice daily and 150 μg 3 times a day) and had completed the study. Of those, 315 (77%) were Caucasian, 47 (11%) were African American, and 48 (12%) were Hispanic (Table 1).

Among the 3 ethnic groups, most of the key baseline demographics were well balanced. However, African Americans and Hispanics had a slightly higher mean baseline A_{1C} than Caucasians, and African Americans also tended to have a lower mean total daily insulin use than Caucasians and Hispanics. Within each ethnic group, there were some imbalances in gender distribution, weight, and A_{1C}. The vast majority of patients was on multiple injections of short- and long-acting insulin (Table 1), and the average body mass index (BMI) was >30 kg/m^2 (the cutoff for obesity, according to World Health Organization [WHO] criteria).[26]

A_{1C}

Collectively, pramlintide-treated patients achieved a significantly greater reduction from baseline in A_{1C} than placebo-treated patients (placebo-corrected treatment effect at week 52: -0.5%, $P < .0001$). The greater A_{1C} reduction was evident across all 3 ethnic groups and appeared to be somewhat more pronounced in African Americans (-0.7%) followed by Caucasians (-0.5%) and Hispanics (-0.3%) (Fig 1).

Weight

Collectively, pramlintide-treated patients achieved a significantly greater reduction from baseline in body weight than placebo-treated patients (placebo-corrected treatment effect at week 52: -2.6 kg, $P < .0001$). Again, the weight loss was

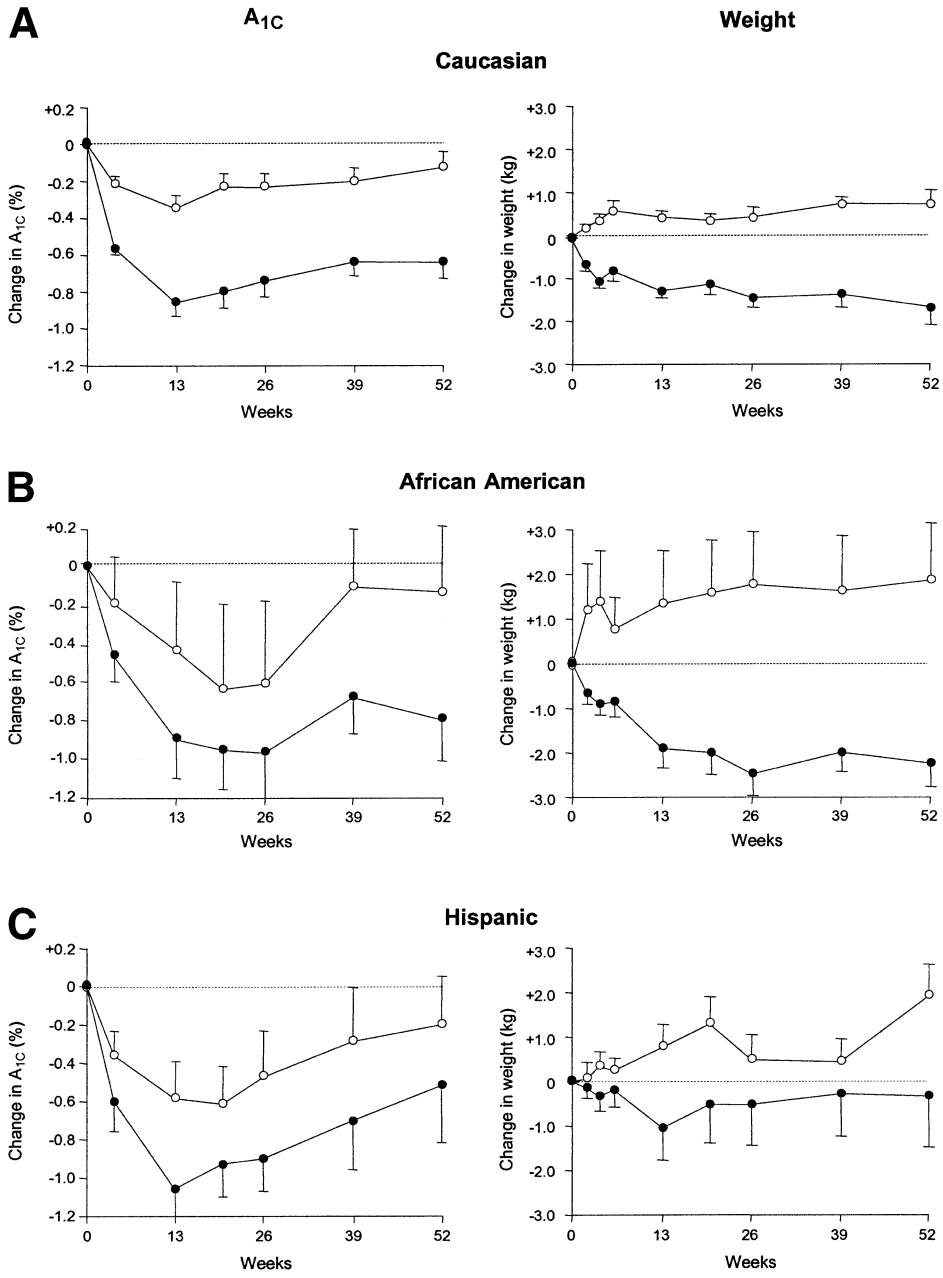

Fig 1. Change from baseline in A_{1C} and weight in insulin-treated (A) Caucasian, (B) African American, and (C) Hispanic patients with type 2 diabetes treated for 52 weeks with either pramlintide (●) or placebo (○). Error bars are ± SE.

evident across all 3 ethnic groups and appeared to be most pronounced in African Americans (−4.1 kg), followed by Caucasians (−2.4 kg) and Hispanics (−2.3 kg) (Fig 1).

Insulin and Concomitant Medications Use

The mean total daily insulin dose, as well as the percentages of patients using different insulin formulations, and taking 1, 2, or 3+ insulin injections/day, remained, for the most part, constant in all groups throughout the duration of the study. The percentage of patients using metformin (MET) only, sulfonylurea (SFU) only, or a combination of metformin and sulfonylurea, in addition to their usual insulin therapy also remained, for the most part, constant in each of the 3 ethnic groups (<4% change in any group).

Safety

Pramlintide treatment was generally well tolerated, and there was no evidence of cardiovascular, pulmonary, hepatic, or renal toxicity or of drug-related idiosyncratic side effects associated with its use. As reported in the individual studies,[24,25] the most frequent adverse event more commonly reported with pramlintide than with placebo treatment was nausea, which was transient (confined primarily to the first 4 weeks of treatment), and mostly of mild-to-moderate inten-

sity. The incidence of nausea in the overall study population was 25% for pramlintide versus 16% for placebo, with comparable patterns in the 3 ethnic groups: 26% versus 17% in Caucasians, 23% versus 14% in African Americans, and 23% versus 12% in Hispanics. The incidence rates of hypoglycemia were similar between pramlintide and placebo: 43% versus 40% in the overall study population, 48% versus 43% in Caucasians, 31% versus 33% in African Americans, and 23% versus 27% in Hispanics.

Overall withdrawal rates in the placebo-treated group were 28% compared with 35% in the pramlintide-treated group with the percent withdrawal evenly represented across the 3 ethnic groups: 29% versus 35% in Caucasians, 30% versus 35% in African Americans, and 24% versus 31% in Hispanics. The main reasons for withdrawal in the placebo and pramlintide groups were withdrawal of consent (9% *v* 8%) and adverse events (9% *v* 15%).

DISCUSSION

It is well established that there are substantial ethnic differences in the prevalence and pathophysiology of type 2 diabetes. However, little is known about potential ethnic differences in the response to different antihyperglycemic therapies. The aim of the present post hoc analysis was to assess the long-term effect of pramlintide, an amylin analog in late-stage clinical development, on both A_{1C} and body weight in insulin-treated African Americans and Hispanics with type 2 diabetes, 2 ethnic groups with high propensities for diabetes and obesity.[27] The results indicate that the addition of pramlintide to insulin therapy leads to a combined and sustained improvement of both glycemic and weight control.

Although the present analysis was post hoc and not prospectively designed to perform statistical comparisons between the various ethnic groups, the data suggest that the glycemic effect of pramlintide was somewhat more pronounced in African Americans, who experienced a placebo-corrected A_{1C} reduction of 0.7%. Hispanics tended to have a somewhat lesser A_{1C} reduction, but nevertheless appeared to benefit from pramlintide treatment. In the interpretation of these A_{1C} reductions, it is noteworthy that pramlintide, when given before major meals, appears to reduce primarily postprandial glucose concentration. Interestingly, African Americans with type 2 diabetes have also been reported to respond better than Caucasians to intensification of insulin therapy.[15] In the 2 clinical trials that were pooled for the present analysis, patients were asked to keep their pre-existing insulin regimens constant. It would therefore be conceivable that African Americans and Hispanics might achieve even greater A_{1C} reductions if addition of pramlintide and intensification of insulin therapy were used in combination.

The mechanisms underlying pramlintide's postprandial glucose-lowering effects in type 2 diabetes are well characterized in human and in animal models and include a suppression of postprandial hyperglucagonemia[22] and a slowing of gastric emptying.[23] Unfortunately, there has been no systematic assessment of ethnic differences in postprandial glucagon secretion and gastric emptying rate in patients with type 2 diabetes. One study, however, reported that gastric emptying is accelerated in Hispanic compared with Caucasian patients with type 2 diabetes.[28] This underscores the need for further investigation into the metabolic abnormalities underlying postprandial hyperglycemia in ethnic groups with a high propensity for type 2 diabetes.

Studies in the general population of patients with diabetes have shown that weight gain is typical when glycemic control is improved using insulin alone.[5-7] It was therefore encouraging that the African American and Hispanic groups experienced weight loss during the 52 weeks they used pramlintide in addition to insulin therapy. Again, the effect of pramlintide appeared to be most pronounced in African Americans, who had achieved a placebo-corrected weight reduction of 4 kg at the end of the study. Hispanics also realized a weight loss of 2.3 kg with pramlintide treatment compared with placebo. These apparent ethnic differences in weight loss with pramlintide treatment should be interpreted with caution, however, considering the imbalances in gender and body weight in these 2 ethnic groups. The finding that pramlintide treatment leads to a further reduction in A_{1C} in conjunction with weight loss could prove useful for the treatment of these ethnic groups, who exhibit both a high prevalence of obesity and additional weight gain upon intensification of insulin therapy.[15] In the VA CSDM, for instance, African Americans experienced an increase in BMI from 30.5 to 33.8 kg/m^2 over 2 years upon intensification of insulin therapy.[15] As stated in earlier publications,[24,25] the weight loss with pramlintide in type 2 diabetes in the present analysis is not attributable to nausea (which was transient in nature and occurred in approximately 25% of pramlintide-treated patients and 16% of placebo-treated patients), but seems consistent with numerous preclinical studies indicating that amylin may have a role in the central regulation of food intake and body weight homeostasis.[29-31]

Although the proportion of African Americans and Hispanics in our analysis was too small for a conclusive comparison of the incidence of adverse events in various ethnic groups, the results indicate that the occurrence of nausea upon pramlintide treatment was similar for African Americans, Hispanics, and Caucasians. In all 3 ethnic groups, the vast majority of patients (approximately 75%) did not report any nausea during the 52 weeks. Compared with placebo, pramlintide treatment was not associated with an increased incidence of hypoglycemia in any of the ethnic groups. Whether the apparently lower incidence of hypoglycemia in African Americans and Hispanics was a statistical artifact (related to small sample sizes) or due to true physiologic reasons (such as a greater degree of insulin resistance) remains unknown.

In conclusion, the efficacy and safety results from this post hoc analysis showed no clear differences between African Americans and Hispanics compared with Caucasians. The combined improvement in glycemic and weight control with pramlintide treatment, pending further experience, appears to be generalizable to a broad population of mixed ethnicity.

REFERENCES

1. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 352:837-853, 1998
2. UK Prospective Diabetes Study Group: Effect of intensive blood glucose control on metformin with complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854-865, 1998
3. UK Prospective Diabetes Study Group: Overview of 6 years' therapy of type II diabetes: A progressive disease. Diabetes 44:1249-1258, 1995
4. Turner RC, Cull CA, Frighi V, et al: Glycemic control with diet, sulphonylureas, metformin, or insulin in patients with type 2 diabetes mellitus (UKPDS 49). JAMA 281:2005-2012, 1999
5. Purnell J, Weyer C: Weight effect of current and experimental drugs for diabetes mellitus: From promotion to alleviation of obesity. Treat Endocrinol 2:33-47, 2003
6. Riddle MC: Should obese type 2 diabetic patients be treated with insulin. in Gill GV, Pickup JC, Williams G, (eds): Difficult Diabetes. Oxford, UK, Blackwell Science, 2001, pp 94-112
7. Henry RR, Gumbiner B, Ditzler T, et al: Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. Diabetes Care 16:21-31, 1993
8. DeFronzo RA: Pharmacologic therapy for type 2 diabetes mellitus. Ann Intern Med 131:281-303, 1999
9. Del Prato S: Post-prandial hyperglycaemia—the necessity for better control. Int J Clin Pract Suppl 112:3-8, 2000
10. Lebovitz HE: Postprandial hyperglycaemic state: Importance and consequences. Diabetes Res Clin Pract 40:S27-S28, 1998
11. Eberhardt MS, Lackland DT, Wheeler FC, et al: Is race related to glycemic control? An assessment of glycosylated hemoglobin in two South Carolina communities. J Clin Epidemiol 47:1181-1189, 1994
12. Weatherspoon LJ, Kumanyika SK, Ludlow R, et al: Glycemic control in a sample of black and white clinic patients with NIDDM. Diabetes Care 17:1148-1153, 1994
13. Wisdom K, Gryzek JP, Havstad SL, et al: Comparison of laboratory test frequency and test results between African-Americans and Caucasians with diabetes: Opportunity for improvement. Diabetes Care 20:971-977, 1997
14. Harris MI, Eastman RC, Cowie CC, et al: Racial and ethnic differences in glycemic control of adults with type 2 diabetes. Diabetes Care 22:403-408, 1999
15. Agrawal L, Emanuele NV, Abraira C, et al: Ethnic differences in the glycemic response to exogenous insulin treatment in the Veterans Affairs Cooperative Study in type 2 diabetes mellitus (VA CSDM). Diabetes Care 21:510-515, 1998
16. Weyer C, Maggs DG, Young AA, et al: Amylin replacement with pramlintide as an adjunct to insulin therapy in type 1 and type 2 diabetes mellitus: A physiological approach toward improved metabolic control. Curr Pharm Des 7:1353-1373, 2001
17. Edelman SV, Weyer C: Unresolved challenges with insulin therapy in type 1 and type 2 diabetes: Potential benefit of replacing amylin, a second b-cell hormone. Diabetes Technol Ther 4:175-189, 2002
18. Buse JB, Weyer C, Maggs DG: Amylin replacement with pramlintide in type 1 and type 2 diabetes: A physiological approach to overcome barriers with insulin therapy. Clin Diabetes 20:137-144, 2002
19. Koda JE, Fineman M, Rink TJ, et al: Amylin concentrations and glucose control. Lancet 339:1179-1180, 1992
20. Thompson RG, Gottlieb A, Organ K, et al: Pramlintide: A human amylin analogue reduced postprandial plasma glucose, insulin and C-peptide concentrations in patients with type 2 diabetes. Diabet Med 14:547-555, 1997
21. Maggs D, Weyer C, Crean J, et al: Mealtime amylin replacement with pramlintide markedly improves postprandial glucose excursions when added to insulin lispro in patients with type 2 diabetes: A dose-timing study. Diabetologia 45:A264, 2002 (suppl 2, abstr)
22. Fineman M, Weyer C, Maggs DG, et al: The human amylin analog, pramlintide, reduces postprandial hyperglucagonemia in patients with type 2 diabetes mellitus. Horm Metab Res 9:504-508, 2002
23. Lee JS, Vella A, Camilleri M, et al: Vagal inhibition in the retardation of gastric emptying of solids by the amylin analog, pramlintide, in diabetes mellitus. Gastroenterology 118:A624, 2000
24. Hollander PA, Levy P, Fineman M, et al: Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes mellitus: A one year randomized controlled trial. Diabetes Care 26:784-790, 2003
25. Ratner RE, Want LL, Fineman MS, et al: Adjunctive therapy with the amylin analogue pramlintide leads to a combined improvement in glycemic and weight control in insulin-treated patients with type 2 diabetes. Diabetes Technol Ther 4:51-61, 2002
26. World Health Organization: Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation. WHO Tech Ref Series No. 894, Geneva, 2000
27. Raymond NR, E'eramo-melkus G: Non-insulin-dependent diabetes and obesity in the black and Hispanic population: Culturally sensitive management. Diabetes Educ 19:313-317, 1993
28. Schwartz JG, McMahan CA, Green GM, et al: Gastric emptying in Mexican Americans compared to non-Hispanic whites. Dig Dis Sci 40:624-630, 1995
29. Bhavsar S, Watkins J, Young A: Comparison of central and peripheral administration of amylin on reduction of food intake in rats. Diabetologia 40:A302, 1997
30. Rushing PA, Hagan MM, Seeley RJ, et al: Amylin: A novel action in the brain to reduce body weight. Endocrinology 141:850-853, 2000
31. Lutz TA, Mollet A, Rushing PA, et al: The anorectic effect of a chronic peripheral infusion of amylin is abolished in area postrema/nucleus of the solitary tract (AP/NTS) lesioned rats. Int J Obes Relat Metab Disord 25:1005-1011, 2001