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Brief report

Addition of exenatide or sitagliptin to insulin in new onset type 1 diabetes: A randomized, open label study☆,☆☆

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ABSTRACT

Incretin based therapies are known to have pleotropic benefits in type 2 diabetes but have not been studied in new onset type 1 diabetes. In this randomized, open label study, we investigated the effect of the addition of exenatide or sitagliptin to insulin in patients with new onset type 1 diabetes. Our data suggest that the addition of exenatide and sitagliptin decreases insulin requirements without increasing endogenous insulin production and hypoglycemic events.

1. Introduction

Type 1 diabetes mellitus (T1DM) is characterized by immune mediated β-cell destruction, with a residual functional tissue of 10–20% at the time of diagnosis [1]. Recent data suggest that residual β-cell function in T1DM persists for a long time after diagnosis [2–4]. Insulin remains the cornerstone in managing T1DM and a variety of immune mediated interventions have been studied with limited success [5–7]. Intensive insulin therapy can delay the onset of complications but is complicated by hypoglycemia and weight gain [8,9]. Incretin based therapies like glucagon like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitors have transformed the management of type 2 diabetes. Data from animal studies suggest that these compounds may preserve or regenerate β cell mass [2–4,10]. GLP-1 has pleotropic benefits in diabetes management supported by few observational studies in T1DM [11–14].

2. Materials and methods

This study (ClinicalTrials.gov number, NCT01235819) was conducted at a tertiary level referral center in India. Eighteen newly diagnosed adult type 1 diabetes patients (age > 18 years, positive for ketones and GAD antibody) were included in this randomized, open label, intervention study for a period of one

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year duration. Exclusion criteria were patients with any major illness or stimulated C peptide level <0.1 ng/ml.

The patients were divided randomly into 3 groups: Group 1 (Insulin alone), Group 2 (Insulin and Exenatide) and Group 3 (Insulin and Sitagliptin). Patients in all groups were advised similar diet and lifestyle modification. All patients were educated about self-monitoring of blood glucose and insulin dose adjustment as per blood glucose profile. Patients were started on twice daily premix insulin regime (25% Insulin Lispro and 75% Insulin Lispro Protamine) initially and later shifted to a three times daily premix regime depending on their glycemic profile. Patients in group 2 were instructed to inject 5 μg of exenatide s.c. twice daily for one month and the dose was increased to 10 μg twice daily from the second month onwards. Patients in group 3 were prescribed 100 mg orally of sitagliptin daily.

The primary outcome was change in insulin requirement from onset of T1DM and secondary outcomes were preservation of C-peptide secretion and risk of hypoglycemia at the end of one year observation. Stimulated C-peptide was assessed 2 h after consumption of a standardized mixed meal and the test was done twice (2nd week and end of 1 year). The local ethics committee approved the trial protocol and all patients provided written informed consent. Data are presented as mean ± SD and paired *t*-test was used for comparison of the data before and after intervention. Comparison between three groups was done using repeated measure ANOVA and a p value of less than 0.05 was considered significant. The statistical analysis and graph generation was done using Graph Pad Prism Software, Version 5 (Graph Pad Software, San Deigo, CA, USA).

3. Results

The study participants consisted of 13 males and 5 females with a mean age of 27.7 ± 5.4 years, mean duration of the diabetes was 1.1 ± 0.4 months, mean body weight of 57.3 ± 5.9 kg, mean BMI of 21.5 ± 2.9 kg/m^2 and a mean HbA1c 9.7 ± 0.8%. The comparison between baseline parameters and the data regarding outcomes are given in Table 1. The decrease in insulin requirement was 15.2 ± 9.5, 39.2 ± 20.1, 23.7 ± 13.9 units in groups 1, 2 and 3 respectively at the end of one year. Patients in groups 2 and 3 had significantly greater decreased insulin requirement at the end of study period ($p = 0.03$). Changes in body weight, insulin dose and stimulated C-peptide for each patient are shown in Fig. 1. Group 2 had the maximum percentage preservation in C peptide as shown in Table 2. The incidence of severe hypoglycemia was the same in all groups and none of the study participants had ketoacidosis during follow up. Two patients using exenatide had self limiting nausea in the initial two weeks of therapy and none of the participants discontinued the study drug.

Table 1 – Comparison between 3 groups about baseline parameters and outcomes.

		Group 1 ($n = 6$)	Group 2 ($n = 6$)	Group 3 ($n = 6$)	P value
Age	Years	27.5 (4.9)	28.8 (7.6)	26.8 (3.8)	0.8289
Body Weight	Kg	58.3 (7.3)	56.2 (3.4)	57.5 (7)	0.8391
BMI	Kg/m^2	21.7 (3.4)	21.5 (1.7)	21.3 (3.7)	0.9752
DM duration	Days	35.9 (9.7)	29.6 (8.8)	30.8 (9.2)	0.4729
HbA1c	%	9.9 (0.9)	9.7 (0.8)	9.6 (0.8)	0.8203
Δ Insulin[a]	Units	15.2 (9.5)	39.2 (20.5)	23.7 (13.9)	**0.0311**
Δ C-peptide[b]	ng/mL	-0.05 (0.28)	0.097 (0.33)	0.0067 (0.19)	0.853
Hypoglycemia	Number	4	3	3	-
Off Insulin	Number	0	2	1	-

All P values less than 0.05 are given in bold.
Mean (S.D).
[a] Change in insulin requirement (Difference in the daily insulin dose between exit and entry point)
[b] Change in stimulated C-peptide (Difference in the C-peptide level between exit and entry in study)

Table 2 – Patient characteristics at baseline and after follow up in all three groups.

Feature	Group 1 ($N = 6$) (Insulin alone)		P value	Group 2 ($N = 6$) (Insulin + Exenatide)		P value	Group 3 ($N = 6$) (Insulin + Sitagliptin)		P value
	Before	After		Before	After		Before	After	
Weight (kg)	58.3(7.3)[c]	62.3(6.9)	**0.0006**	56.2(3.4)	55.7(2.9)	0.6560	57.5(7)	60.2(7.1)	**0.0171**
BMI (kg/m^2)	21.7(3.4)	23.2(3.4)	**0.0007**	21.5(1.7)	21.3(2)	0.6995	21.3(3.7)	22.3(3.6)	**0.0135**
HbA1c (%)	9.9(0.9)	7.9(0.4)	**0.0084**	9.7(0.8)	7.4(0.4)	**0.0036**	9.6(0.8)	7.5(0.4)	**0.0017**
Daily Insulin (U)[a]	59.3(13.1)	44.2(7)	**0.0114**	55.7(8.6)	16.5(15)	**0.0055**	47.8(11.5)	24.2(13.3)	**0.0088**
Insulin dose (U/Kg)	1.02 (0.2)	0.72 (0.17)	**0.0016**	0.994 (0.16)	0.295 (0.26)	**0.0041**	0.84 (0.23)	0.4 (0.21)	**0.0123**
C peptide[b] (ng/mL)	0.4(0.2)	0.35(0.15)	0.6828	0.48(0.25)	0.58(0.33)	0.5056	0.39(0.1)	0.4(0.12)	0.9368

All P values less than 0.05 are given in bold.
[a] Total insulin requirement per day.
[b] Stimulated C peptide value after a mixed meal.
[c] Mean (SD).

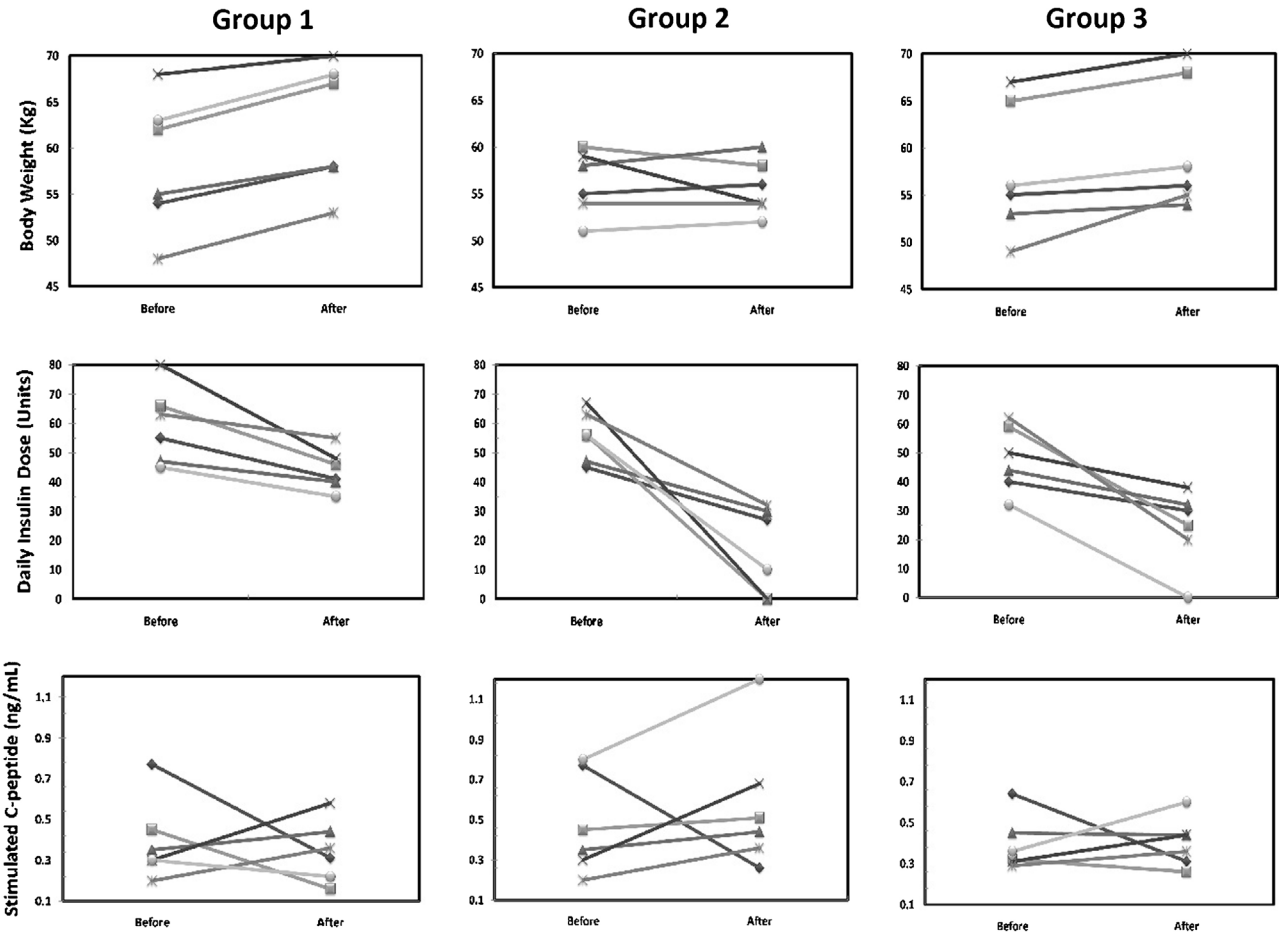

Fig. 1 – Changes in body weight, dose of insulin and C-peptide in all study participants.

4. Discussion

Our data show that the addition of exenatide or sitagliptin soon after diagnosis of T1DM decreases insulin requirement. The additional benefits were lack of weight gain and similar risk of hypoglycemia. Our study did not show any significant difference regarding preservation of endogenous insulin secretion with use of exenatide or sitagliptin. Previous studies suggest that GLP-1 action is deficient in T1DM patients [15]. Hence, any drugs which augment the incretin response may help in the control of diabetes and may support the use of incretin modulators in T1DM patients. Similar results have been reported with the use of liraglutide, exenatide and various gliptins in a spectrum of type 1 diabetes patients [12–14,16].

GLP-1 receptor agonists lead to weight loss in type 2 diabetes coupled with improvement in glycemic control [17] while gliptins are weight neutral in type 2 diabetes [18]. Our study showed a small but insignificant weight loss with exenatide compared with significant weight gain in the other two groups. The complete lack of insulin requirement in three patients (two in the exenatide and one in the sitagliptin group) could be due to the honeymoon phase of type 1 diabetes [19]. However there may be a role of incretin modulators in determining and/or prolonging this honeymoon phase. The beneficial effects of incretin modulators in T1DM could be explained by immune and non immune mediated mechanisms. Immune mediated mechanisms include reducing insulitis, increasing $CD4^+$, $CD25^+$ regulatory T cells and stimulating β-cell replication [20]. Non immune mediated mechanisms include reducing glucagon, delaying gastric emptying and decreasing appetite by central GLP-1 receptor mediated actions [11].

The greater beneficial effect of exenatide over sitagliptin could be due to multiple factors including clinical differences at the start of the study, less weight gain during the study, greater GLP-1 effect and less insulin resistance. Sitagliptin requires adequate levels of native GLP-1 for its action and previous studies have shown reduced GLP-1 levels in T1DM [15]. The limitations of our study are the small sample size and short duration of the observation period.

In conclusion, the addition of exenatide or sitagliptin reduced insulin requirements in new onset type 1 diabetes patients. The use of exenatide resulted in significant weight loss in comparison to sitagliptin. The addition of either medication did not alter the risk of hypoglycemia or affect endogenous insulin preservation.

Conflict of Interest

None declared.

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